Creating an Effective Routine Surveillance System for Drug-Resistant Tuberculosis Among Previously Treated Patients in Tanzania

By

Basra Esmail Doulla

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy by

Liverpool School of Tropical Medicine

January 2021

Institutions

1. National Tuberculosis and Leprosy Programme, Dar es Salaam, Tanzania

2. Liverpool School of Tropical Medicine, Liverpool, United Kingdom

3. National Institute for Medical Research- Muhimbili, Dar es Salaam, Tanzania

Research Team

S/N	Name	Institution	Position
1.	Ms. Basra E. Doulla	National Tuberculosis and Leprosy Programme	Team leader (PhD Student)
2.	Prof Bertie Squire	Liverpool School of Tropical Medicine	Lead Supervisor
3.	Dr Eleanor Macpherson	Liverpool School of Tropical Medicine	Co-Supervisor
4.	Dr Esther Ngadaya	National Institute for Medical Research- Muhimbili	Co-Supervisor
5	Dr Ivor Langley	Liverpool School of Tropical Medicine	Senior Supervisor

Declaration

I confirm that the material presented in this thesis is as a result of my work and has not been presented, nor is it currently being presented, either in part or wholly as part of any other degree or another qualification.

Statement of contribution

This study is comprised of my original work. I received tremendous support from all my supervisors. This included technical support, training and guidance throughout the study in areas such as qualitative research methods and thesis design.

I trained a research assistant who undertook the staff and stakeholder interviews. Transcribed interviews were reviewed with the support of social research scientists from the National Institute for Medical Research and the Ifakara Health Institute. I received assistance on data analysis including working closely with a statistician to interpret the findings. My supervisors reviewed the analysed data and provided relevant inputs on the interpretation that enabled me to finalize and generate an appropriate outcome of the study.

This thesis has been written exclusively by the PhD candidate, Basra Esmail Doulla. At no previous time was this work been submitted for a degree. All quotations have been distinguished by quotation marks and sources of information recognised.

Basra Doulla
Date 30.01.2021

Acknowledgement

This study would not have been possible without the financial support from the Swiss Tropical and Public Health Institute in Geneva and the Ministry of Health under the East African Public Health Laboratory in Tanzania. I would like to thank my supervisors, Prof. Squire and Dr Langley from the Department of Clinical Science at Liverpool School of Tropical Medicine, Liverpool, United Kingdom. The door to Dr Langley was always open and reachable whenever I ran into a troubling issue or had a question about my research or writing, he was also the second reader of this thesis, and I am gratefully indebted to his very valuable comments. He consistently allowed this study to be my own work but steered me in the right direction whenever he thought I needed it. The time I spent with Prof. Squire was very productive and he helped solve many of my problems and encouraged me to do the right thing from the beginning. I appreciated his tireless technical support throughout the study. I also extend my gratitude to Dr McPherson whose useful teaching on qualitative methods made my work much easier.

Many thanks also go to the in-country supervisor Dr Ngadaya, for close follow up on my day-to-day work. This would not have been easy without the strong support that I received from the National Tuberculosis and Leprosy Programme Manager Dr Mutayoba, who permitted me to use the routine Programme data and provided advice on the design. Concurrently, my gratitude also goes to the Mwanza Administrative Office for allowing me to carry out the study in their region. I am incredibly grateful to my Advisory Panel, Dr Obasi and Dr Parry, from the Liverpool School of Tropical Medicine for their encouragement and input, which led me in the right direction. Sincere thanks go to all regional and district health care workers at the study sites, TB Programme staff, partners supporting the Programme and senior Ministry of Health staff for their willingness to participate, cooperate and contribute to the study. I would also like to thank the experts who were involved in this study in one way or the other: Mr. Malewo for conducting supportive supervision throughout the study period and make sure that the primary data are collected and recorded properly. Mr. Shirima, Mr. Mbegu and Mr. Mwinyikae of the Central Tuberculosis

Reference Laboratory for routine data collection and validation which facilitated selection and design layout of the study; Mr. Shamtandulo of the National Institute for Medical Research and Mr. Mohamed from the Ifakara Health Institute for analysing the objectives of this study. Likewise, I acknowledge the staff from the Liverpool School of Tropical Medicine, Clinical Science Department for the availability of their support whenever I needed it. All this could not have been accomplished without support from my family, especially my husband, Dr Doulla, and my children, Dr Saphia, Ashalulu, Najma, Nassir and Yusuph all of whom constantly encouraged and supported me during throughout my studies. I was also fortunate to be surrounded by good friends and family throughout my stay at Liverpool School of Tropical Medicine (LSTM). I would love to recognise tremendous encouragement and support received from Mrs Liz Langley and my sisters living in United Kingdom; Anab, Khurthum, Filsan and Zamzam for their constant moral support throughout my studying.

Abstract

Creating an Effective Routine Surveillance System for Drug-Resistant Tuberculosis Among Previously Treated Patients in Tanzania.

Basra Esmail Doulla

Introduction: Tuberculosis routine surveillance is an essential tool for scrutinising the effectiveness of TB Programmes and especially for monitoring drug resistance. This study sought to understand the effectiveness of the existing Routine Surveillance System for drug-resistant Tuberculosis amongst previously treated TB patients in Tanzania, identify weaknesses and interventions leading to improvements, and then pilot these interventions.

Methods: Both quantitative and qualitative methods were used to gather the current Routine Surveillance System information among previously treated tuberculosis patients. Quantitative data were collected from the routine laboratory databases over a three-year period (2011-2013). Qualitative data were collected using key informant interviews and focus group discussions. Based on the results, an intervention to improve the Routine Surveillance System was designed and a pilot study was implemented in Mwanza region. The intervention considered the implementation of rapid molecular techniques such as Xpert MTB/RIF and Line Probe Assay at the Central Tuberculosis Reference Laboratory. Revised communication measures and request form completion strategies were also included. A further qualitative study was undertaken for comparison after implementation.

Results: The initial quantitative analysis showed that, over the surveyed period, 2,750 specimens were received at the reference laboratory from across the country. This was only 32% of the anticipated numbers, although it reached 61% in 2013. The median and interquartile ranges of turnaround times for microscopy, culture and drug sensitivity testing were: 1(1, 1), 61(43, 71) and 129(72, 170) days respectively. Contamination was evident in both culture and susceptibility testing. The qualitative

analysis showed a mixed picture; the system of sending specimens via post was seen to be efficient, though many challenges were noted, in particular: inadequate supplies, poor completion of forms, staff shortages and demotivation. Delays in the transportation of specimens were associated with inadequate funding, training and poor supervision. A revised routine surveillance system for drug-resistant tuberculosis amongst previously treated tuberculosis patients in Tanzania was designed to address many of the identified shortfalls. The revised system, piloted in Mwanza, increased the volume of specimens received from 75 in 2016 to 185 in 2017. The system reduced the time it took for specimens to reach the reference laboratory by 22% (from 9 to 7 days). The median time for results getting back to the requesters was shortened by 36% (from 11 to 7 days). Overall, the number of drug resistant cases increased by 67% (from 12 to 20). In the qualitative analysis undertaken following the pilot, stakeholders identified earlier diagnosis, timely feedback of results, strengthened communication and reliable specimen transportation arrangements as key gains.

Conclusion: The routine surveillance system is critical to the effectiveness of the Tuberculosis Programme in Tanzania. The existing routine surveillance policy was poorly executed and lacked new technology, which led to long delays, specimen inertness, discontentment and compromised patient care. A revised routine surveillance system can overcome these weaknesses and increase MDR-TB detection. These lessons are highly relevant to other resource-limited settings, including elsewhere in sub-Saharan Africa.

Word count 483

Short title: Routine surveillance for control of tuberculosis drug resistance in Tanzania

Keywords: Tuberculosis; Surveillance; Drug resistance; Tanzania, Central TB Reference laboratory

Table of contents

List of papers and presentation

The following papers (published, submitted or to be submitted) and presentations are outcomes of this research.

Publications

1) Title: Routine surveillance for the identification of drug resistant tuberculosis in Tanzania; A cross-sectional study of stakeholder's perceptions Doulla BE, Squire SB, MacPherson E, Ngadaya ES, Mutayoba BK, Langley I. PLoS One. 2019 Feb 22;14(2): e0212421. doi: 10.1371/journal.pone.0212421. eCollection 2019. PMID: 30794620

Note: This publication is based on chapters 3 and 4 of the thesis.

2) Title: Reducing delay to Multidrug-Resistant Tuberculosis case detection through a revised routine surveillance system. Doulla BE, Squire SB; MacPherson E; Ngadaya ES; Mutayoba BK; Langley I Submitted to BMC Infectious Diseases in March 2019. Currently under review.

Note: This publication is based on chapters on chapter 5 of this thesis.

3) Title: Utility of a revised routine surveillance system for previously treated cases in Mwanza, Tanzania: A before and after qualitative study Manuscript under preparation

Note: This manuscript will be based on chapter 6 of this thesis.

List of figures

List of tables

List of Appendices

Abbreviations

AFB	Acid Fast Bacilli
AIDS	Acquired immunodeficiency syndrome
CRL	Central Reference Laboratory
CTRL	Central Tuberculosis Reference Laboratory
CPC	Cetylpyridinium Chloride
DDC	District Diagnostic Centres
DOT	Directly Observed Treatment
DR	Drug Resistant
DRS	Drug Resistant Survey
DR-TB	Drug Resistant Tuberculosis
DST	Drug Susceptibility Testing
DTLC	District Tuberculosis and Leprosy Coordinator
EMS	Expedited Mail Services
EPTB	Extra Pulmonary Tuberculosis
FDG	Focus Group Discussion
FLDs	First Line Drugs
Gx	GeneXpert
HIV	Human immunodeficiency virus

HR	Isoniazid Resistance
IDI	In Depth Interview
IHI	Ifakara Health Institute
KII	Key Informants Interview
LED	Light Emitting Diode
LJ	Lowenstein Jensen
LPA	Line Probe Assay
LSTM	Liverpool School of Tropical Medicine
MDG	Millennium Development Goals
MDR- TB	Multi-drug resistant tuberculosis
MTB	Mycobacterium tuberculosis
MTBC	Mycobacterium Tuberculosis Complex
NIMR	National Institute for Medical Research
NTM	Non-Tuberculous Mycobacteria
NTLP	National Tuberculosis /Leprosy Programme
NTP	National Tuberculosis Programme
PI	Principal Investigator
PST	Prevalence Survey Tuberculosis
PTB	Pulmonary Tuberculosis

RA	Researcher Assistant
Retreatment	Previously Treated TB Case
RLS	Resource Limited Settings
RSS	Routine Surveillance System
RR	Rifampicin Resistance
RR TB	Rifampicin Resistance Tuberculosis
RTLC	Regional Tuberculosis and Leprosy Coordinator
SDGs	Sustainable Development Goals
TB	Tuberculosis
WHO	World Health Organization
XDR	Extensively Drug Resistance
XPERT	GeneXpert MTB/RIF
ZN	Ziehl Neelsen

Definitions

Drug susceptibility testing: Refers to in vitro testing using either phenotypic methods to determine susceptibility or molecular techniques to detect resistance. This entails testing to find out which drugs will be effective against certain TB bacteria.

Drug Susceptible Tuberculosis: If someone is infected with TB bacteria that are fully susceptible, it means that all the TB drugs will be effective so long as they are taken properly.

Drug Resistant Tuberculosis: Is the resistance to anti-TB drugs, meaning that the disease does not respond to standard TB drug treatment. This can occur when first-line drugs are misused or mismanaged.

Extensively drug resistant TB (XDR-TB): Is a rare type of MDR-TB that is resistant to isoniazid and rifampicin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

Extra-Pulmonary Tuberculosis: Extra-pulmonary tuberculosis (EPTB) occurs when the bacteria spread outside of the lung and cause disease. Except for laryngeal TB, EPTB is not usually infectious. Patients with EPTB disease often also have TB disease in the lungs. EPTB usually occurs in people with weak immune systems such as those who are PLHIV, DM or infants.

Genotypic DST (molecular DST): Genotypic testing detects mutations in the TB genome associated with specific drug resistance. (Note: genotypic testing is also used to identify M. tuberculosis by detecting the presence of TB-specific mycobacterial DNA).

Molecular Detection of Drug Resistance: Is a method to identify multidrug-resistant TB (MDR-TB) rapidly. This service uses Deoxyribonucleic Acid (DNA) sequencing for detection of mutations most often associated with rifampicin and isoniazid drug resistance. Added testing will be conducted to identify mutations associated with resistance to the most effective second-line drugs; fluoroquinolones, amikacin, kanamycin and capreomycin.

Mono-resistance: resistance to one first-line anti-TB drug only.

Multidrug-Resistant Tuberculosis (MDR-TB): is a form of TB caused by organisms that are resistant to at least two of the most effective anti TB drugs, isoniazid and rifampicin.

New case: Is a newly registered episode of TB in a patient who had never been treated for TB or reports having taken anti-TB drugs for less than one month.

Phenotypic DST (conventional DST): Phenotypic testing determines if an isolate is resistant to an anti-TB drug by evaluating growth (or metabolic activity) in the presence of the drug.

Poly-resistance: resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin.

Presumptive TB case: a patient who presents with symptoms or signs suggestive of TB.

Previously-treated case: Is a registered patient who has reported having received one month or more of anti-TB drugs in the past. Previously treated cases (also referred to as "retreatment cases") are a heterogeneous group composed of several subcategories. i.e. Relapse, Treatment after failure, Treatment after loss to follow-up and Previously-treated other.

Proportion method: is used for testing the susceptibility of M. TB complex isolates. It differentiates the proportion of resistant organisms within a particular strain that is used to determine clinically significant in particular anti TB drugs.

Pulmonary Tuberculosis (PTB): This is the most frequent type, accounting for about 80% of TB cases. PTB is infectious. Symptoms include a cough for two or more weeks and sputum production. Patients may have cavities in the lung that are rich in bacilli.

Purposive sampling (also known as judgment, selective or subjective sampling): is a sampling technique in which researcher relies on his or her own judgment when choosing members of population to participate in the study.

Rifampicin resistance (RR): resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. This includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR.

Relapse patients: have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment and have now been diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).

Routine Surveillance System: Is a surveillance system based on routine drug susceptibility testing of TB cases.

Sampling: is a process used in statistical analysis in which a predetermined number of observations are taken from a larger population. The methodology used to sample from a larger population depends on the type of analysis being performed, but it may include simple random sampling or systematic sampling.

Surveillance systems based on routine drug susceptibility testing: A surveillance system based on routine DST of all TB cases is able to provide continuous information on drug resistance patterns among patient groups, and is therefore able to accurately detect trends, as well as localized outbreaks.

Transit time: the time from specimen collection in the peripheral health facilities to the time the specimen is received at a site where DST can take place time.

Treatment after failure: patients are those who have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment.

Treatment after loss to follow-up: patients have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment (previously known as treatment after default patients).

Tuberculosis (TB): is a disease caused by bacteria Mycobacterium tuberculosis that is spread from person to person through airborne particles aspirated by an infected individual.

Turnaround time (TAT): The time from specimen receipt at the CTRL to the time the DST results are sent back to the requesting clinician

Xpert MTB/RIF (Xpert): a rapid molecular technology for detection of MTB and rifampicin resistance (RR). The assay operates on the GeneXpert system (Cepheid, CA, USA)

Chapter 1 Introduction

1.1 Global Tuberculosis burden

Tuberculosis (TB) is a leading cause of morbidity and mortality worldwide (1). The disease remains a global emergency which was first declared by the World Health Organisation (WHO) in 1993 and endorsed by the Africa Union through the Maputo declaration in 2005 (2). TB is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* (MTB). It typically affects the lungs (pulmonary TB or PTB) but can also affect other parts of the body (extrapulmonary TB or EPTB). The mode of transmission of the bacilli is mainly by infected aerosol in tiny droplets when talking, coughing, laughing or sneezing (3,4). Between 2000 and 2017 there was significant progress in global TB control and in fighting the disease (5,6). TB treatment alone averted an estimated 45 million deaths and TB treatment supported by Antiretroviral Therapy (ART) averted an additional 9 million deaths among Human Immunodeficiency Virus (HIV) positive people (5,6). According to WHO estimates, there were 10.0 million new incident cases of TB disease in 2017, of which 5.8 million were men, 3.2 million were women and 1.0 million were children (aged< 15 years). People living with HIV accounted for an estimated 9% total (7). In addition, about one-quarter of the world's population has latent TB. This refers to people who have been infected by TB bacteria but who have not (yet) become ill with the disease and cannot transmit the disease (8). People infected with TB bacteria have about 5 to 15% lifetime risk of falling ill with TB. People with compromised immune systems, such as people living with HIV, malnutrition or diabetes, or people who use tobacco, have a much higher risk of falling ill (8).

The emergence and global spread of Multidrug-Resistant TB (MDR-TB) has become a priority public health issue (9). MDR-TB is TB disease that is resistant to at least isoniazid (INH) and rifampicin (RIF), the two most potent first line drugs (FLD) for TB treatment. According to the 2016 WHO Global Report there were an estimated 480,000 cases of MDR-TB globally. It can be argued these figures are an underestimate of the true burden of MDR-TB (9). It is because these estimates are based on the number of notifications, but in resource constrained settings many TB and MDR-TB cases are still missed for a long time. There are many factors attributed to the missing cases such as inefficient

routine surveillance, diagnosis, and lack of robust data leading to the WHO inability to accurately estimate the burden.

Furthermore, nearly one in ten of the MDR-TB cases are categorised as Extensively Drug-Resistant TB (XDR-TB). Most recently, totally drug-resistant TB (TDR-TB) has emerged in various parts of the world. XDR-TB is a rare type of MDR TB that is resistant to INH and RIF, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). Both MDR-TB and XDR-TB require long-term treatment regimens with toxic second-line anti-TB drugs that are associated with serious side effects leading to non-adherence and high mortality (9).

Effective TB control measures require early identification of the TB infected persons followed by timely tailored therapies (10). In resource-constrained countries there are often many patient and healthcare system-related delays between the onset of TB symptoms and diagnosis and treatment. Such delays provide more opportunities for transmission of the disease, which adversely affects the public (11,12).

Diagnosis of active TB in Low-and Middle-Income Countries (LMIC) is still mainly based on the detection of MTB through sputum smear microscopy examination and occasionally culture (10). Culture methods are more sensitive and specific than microscopy but are slower (e.g. 3-8 weeks in the Löwenstein-Jensen (LJ) medium and 2-3 weeks for liquid culture) and prone to contamination. Both methods are complex requiring skilled personnel, good laboratory standards and infrastructure (Biosafety level 2 for solid culture and level 3 for liquid culture), and continuous power supply (13,14).

Difficulty in specimen transportation between remote locations and reference laboratories are also contributing factors to diagnostic delay, particularly for drug resistance testing (8,15). In 2010, the WHO endorsed the use of the Xpert MTB/RIF (Xpert) assay, a rapid molecular technology for detection of MTB and rifampicin resistance (RR). The assay operates on the GeneXpert system (Cepheid, CA, USA), and has the potential to revolutionise the detection of TB and MDR-TB in LMIC (15,16). TB programmes need to make the right decision about which of these new tools to implement and where in the diagnostic algorithm to apply them most effectively (17). These

decisions are difficult as the new tools are often expensive to implement and use, and until recently the health system and patient effects were uncertain (17). The need for reliable drug-susceptibility testing (DST) has increased with the growth in the prevalence of MDR-TB. This has also lead to an increased demand for appropriate treatment for MDR-TB and an expansion of anti-TB Drug Resistance Surveys (DRS) (18).

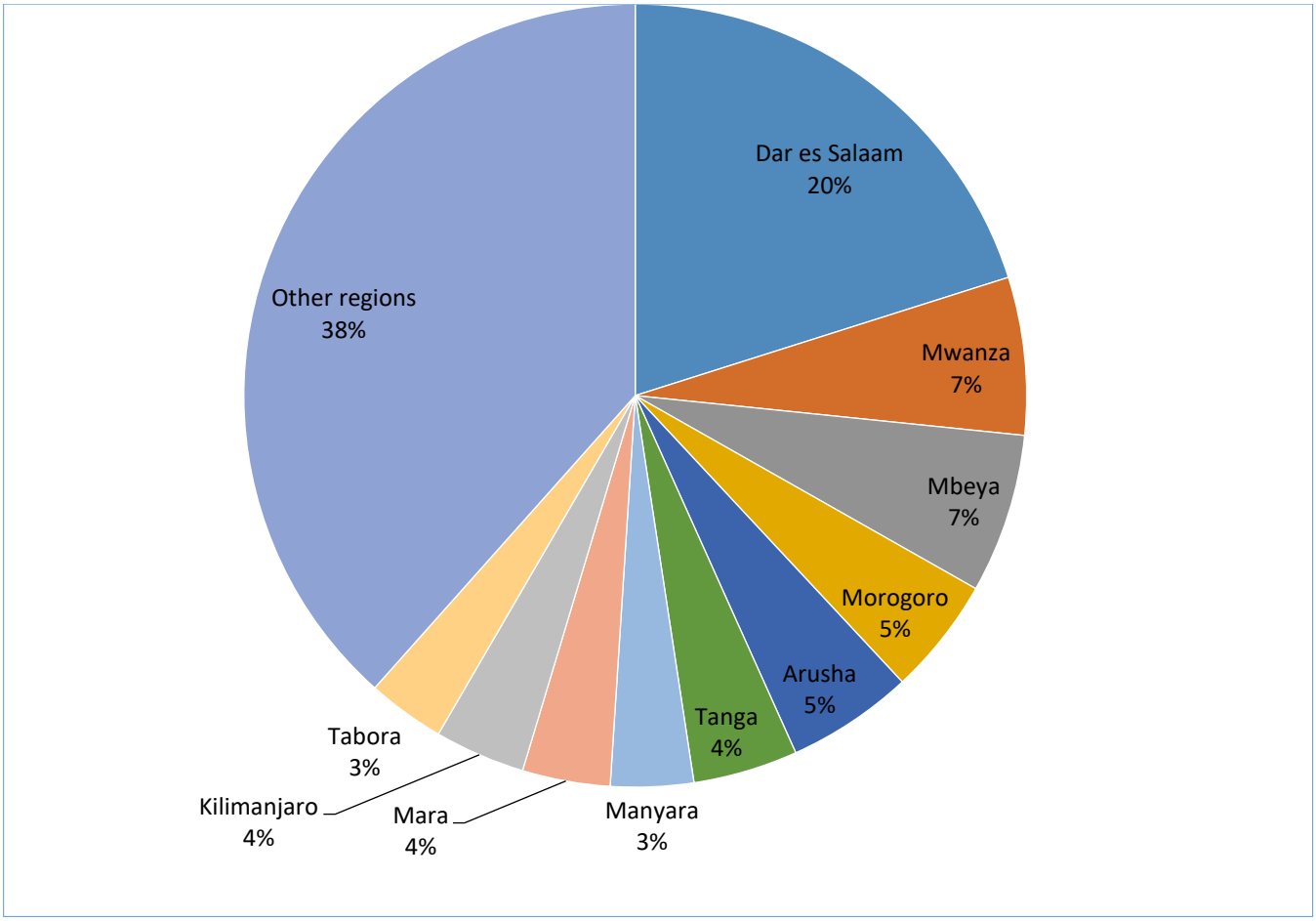
In summary, urgent action is required to improve the quality of diagnosis, treatment and care for people with DR-TB, which requires higher coverage of accurate DST and prompt feedback of results, alongside the overall reduction of under-diagnosis of all forms of TB (19).

1.2 TB and MDR-TB burden in Tanzania

In Tanzania, TB closely follows HIV and Malaria in the major causes of morbidity and mortality from an infectious disease, especially among adults (20). According to the WHO report, Tanzania is among the 30 countries with the highest TB burden (6). The national Prevalence Survey of TB (PST) completed in November 2012 revealed a higher TB burden than previous estimates had predicted. The survey showed a TB prevalence of 295 per 100,000 population among adults ≥ 15 years and a case detection rate of 42% – 54% (21). The WHO estimated that TB incidence was 269/100,000 in 2017, which implies 154,000 people became infected with TB in Tanzania whereas only a total of 69,623 TB cases were notified, equivalent to a 45.2% case detection rate. Overall this implies that approximately 84,000 TB cases were missed (19).

In addition, TB cases notified in Tanzania had only increased from 62,100 in 2006 to 65,902 cases in 2016 (22,23). The National TB and Leprosy Programme (NTLP) annual report of 2016 further reveals the distribution of notified cases of TB (all forms). This showed that Dar es Salaam city is the largest contributor representing 20% of all cases notified, as shown in Figure 1.

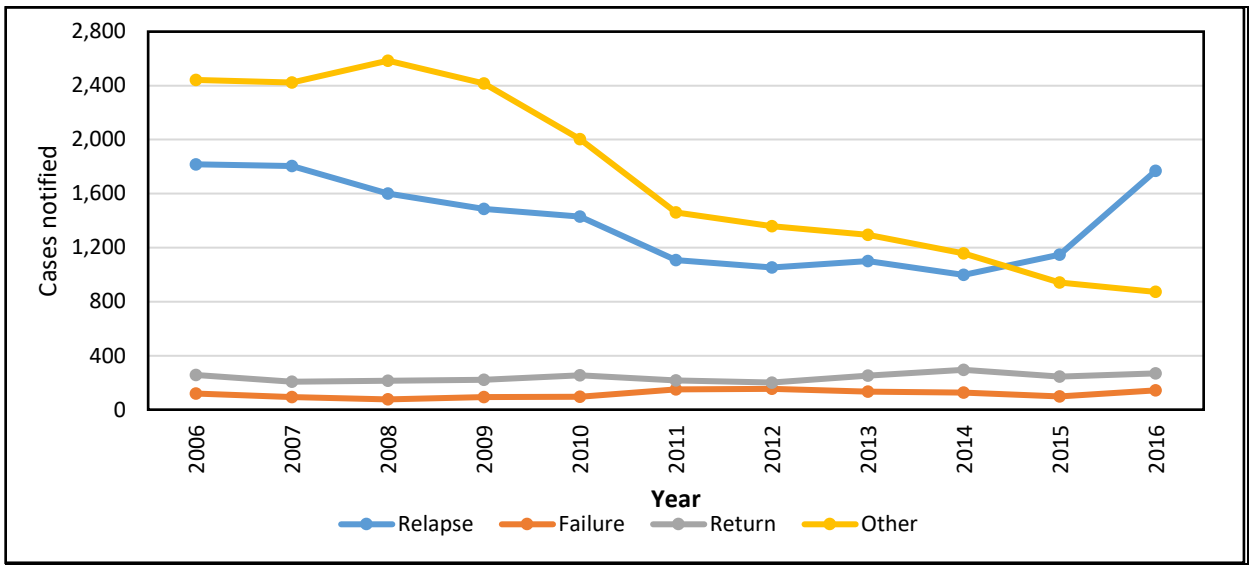
Figure 1 Distribution of TB cases notified by region



Source NTLP annual report 2016

The total previously treated TB cases notified in Tanzania from 2006 to 2016 were 38,200 with 3,051 cases in 2016 representing 4.6 % of all cases notified in the country in that year. Previously-treated TB cases are made up of relapse, failures, lost to follow-up and other. Figure 2 shows the trend of recorded previously-treated cases, which may be impacted by changes in definitions effecting how these have been recorded (23,24)

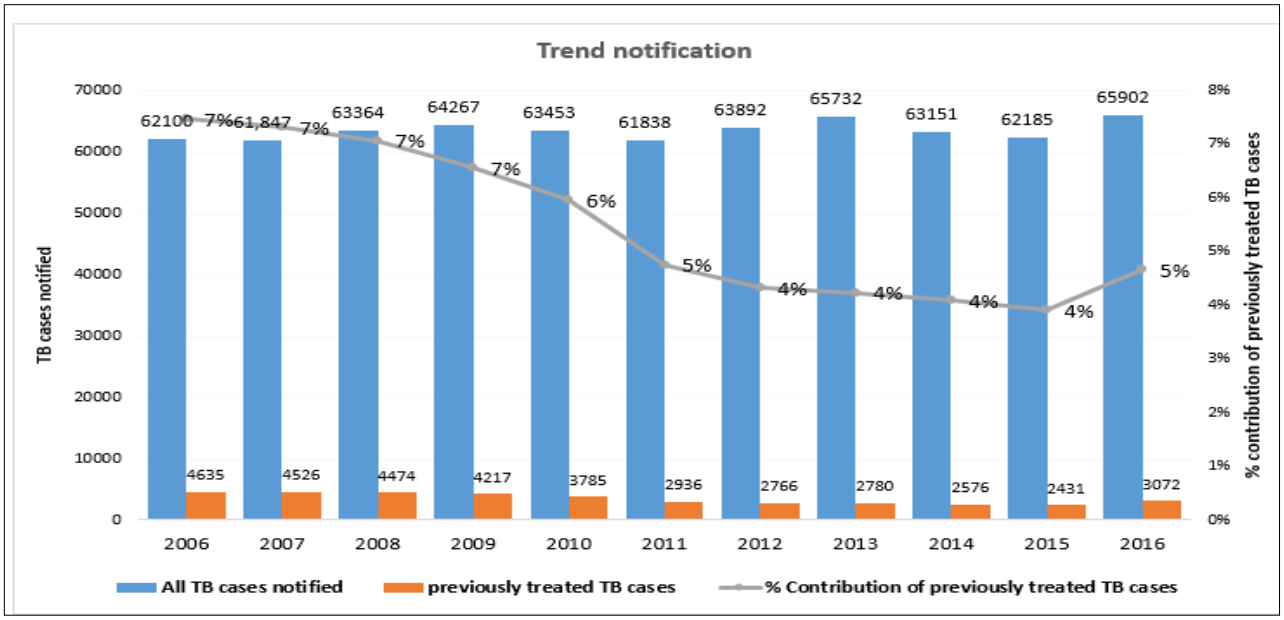
Figure 2 Trend Previously-treated TB cases notified



Source NTLP annual report 2016

Figure 3 shows the trend of new TB case notified compared to the contributions from previously-treated TB cases. This shows the level of Previously-treated TB cases as a proportion of all forms of TB has remained constant between 2011 and 2016 at around (4 to 5%).

Figure 3: Trend of All TB notification and Previously-treated TB cases 2006 - 2016

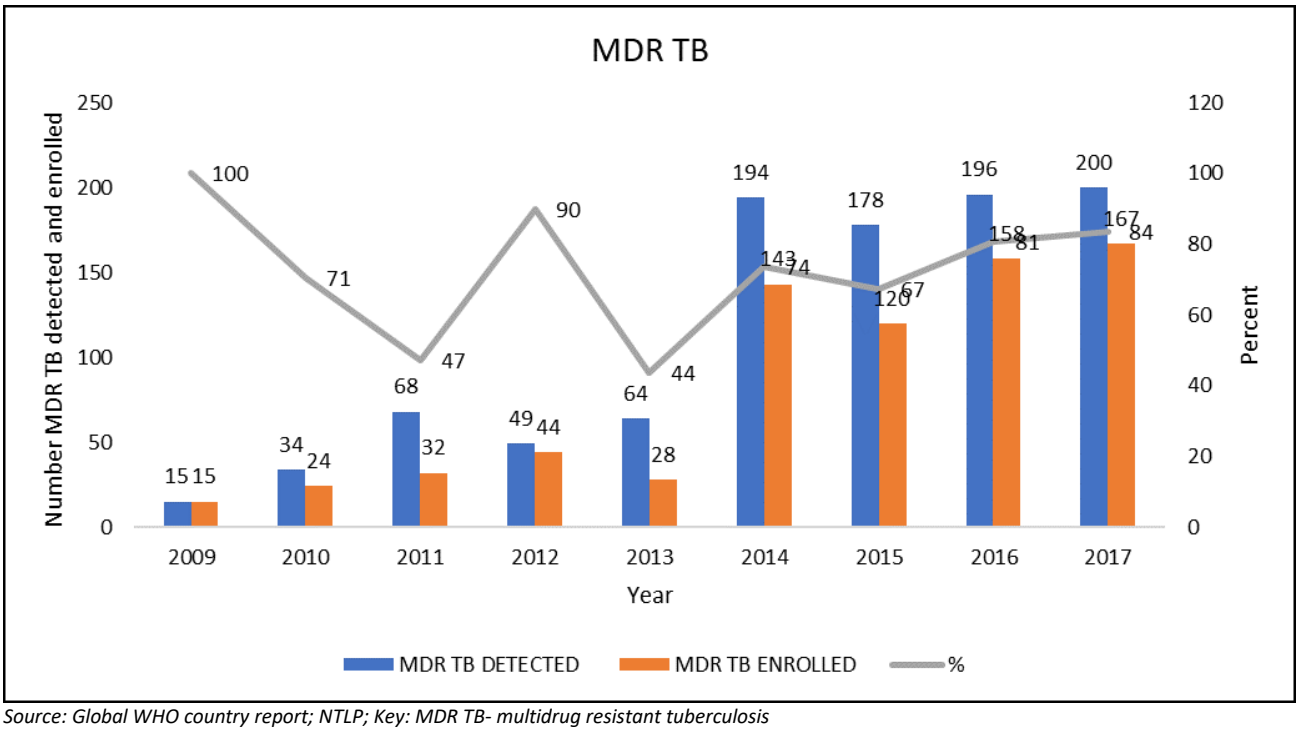


Source: NTLP; Keys: TB- tuberculosis; MDR TB- multidrug-resistant tuberculosis

MDR-TB: MDR-TB in Tanzania is characterised by low detection and poor treatment outcomes. To avoid the spread of the resistant strains, it is essential that anti-TB drug resistant levels are better understood and that there is early detection and appropriate treatment of patients with drug resistant TB (DR-TB). Prevalence studies have shown that in Africa, including Tanzania, there are significant gaps in DR-TB detection and reporting (8). Based on the 2006/2007 National DRS in Tanzania the proportion of MDR-TB among new and previously-treated TB cases is estimated to be 1.1% and 3.1% respectively in Tanzania (25).

As shown in Figure 4, based on the NTLP and global data from 2009 – 2017, detected cases of MDR-TB have risen from 15 in 2009 to 200 in 2017. This led to 15 and 167 cases respectively, being enrolled on treatment. This signifies that there is also a challenge of missing cases with DR-TB (8). This could be due to poor data recording, or delay in diagnosis, the reason behind it could not be established. More effort is needed to find the missing cases with TB and MDR-TB to prevent further transmission, enhance treatment outcomes and, ultimately to achieve the End TB 2030 targets (26).

Figure 4 MDR-TB detected and enrolled 2009-2017



Source: Global WHO country report; NTLP; Key: MDR TB- multidrug resistant tuberculosis

1.3 Background of Tanzania and National TB and Leprosy Programme

The United Republic of Tanzania is the largest country in East Africa, occupying an area of about 945,082 square kilometres (approximately 365,800 square miles) with a population of 57.3 million, according to the 2017 World Bank update.[1] Despite Tanzania being a low income country, there has been sustained, and relatively high, economic growth over the last decade, averaging 6–7% per year. The poverty rate has decreased slowly from 28.2% in 2012 to 26.9% in 2016. This decline has been accompanied by improvements in human development outcomes and living conditions. Gross Domestic Product (GDP) grew by 7.1% in 2017.

The country borders with Kenya and Uganda to the north; Rwanda, Burundi and the Democratic Republic of Congo to the west; and Zambia, Malawi and Mozambique to the south. The Indian Ocean forms the eastern border. Administratively, Tanzania has thirty-five regions, of which, thirty are in mainland Tanzania and five in Zanzibar. Dar es Salaam, with a population of 4.36 million accounts for 10% of the total Tanzania mainland population (27).

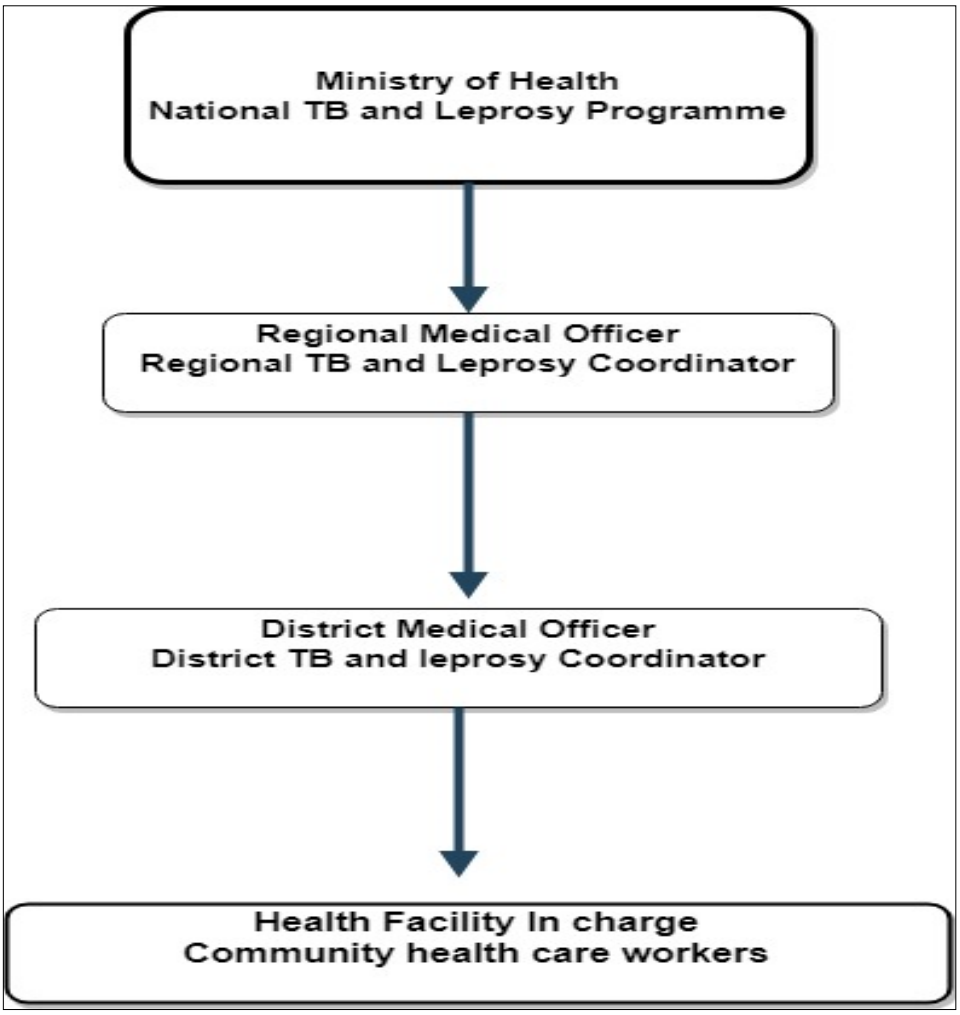
The Ministry of Health set up the TB Programme in 1977 to facilitate early diagnosis, treatment and cure of all TB and leprosy patients with the aim that the two diseases would no longer be a major public health problem in the country. The mission of the programme is to provide high quality, effective interventions for TB and leprosy care and control in Tanzania (28).

1.4 Management of TB and MDR-TB in Tanzania

At the ministerial level, National TB and Leprosy Programme (NTLP) coordinates all activities pertaining to TB and leprosy care and control in the country. It operates at the national, regional, district and community levels as shown in Figure 5.

[1] https://data.worldbank.org/indicator/SP.POP.TOTL/locations=TZ

Figure 5 National TB Programme Organisation



Key: TB-tuberculosis

Management of TB at the National level

The management at the national level is responsible for overseeing all activities at the regional, district and community levels. In addition, the national TB Programme works closely with developmental partners to implement TB and leprosy control, prevention and care measures across the country (27).

Management of TB and leprosy control activities at regional Level

The NTLP splits the Tanzania Mainland into 30 regions. The Regional Tuberculosis and Leprosy Coordinator (RTLC) manages all regional level technical issues related to TB TB/HIV and leprosy

activities and reports to the NTLP. The coordinator liaises with the local TB implementing partners to ensure that TB, TB/HIV and leprosy activities are prioritised by the communities in their respective region. He or she works closely with the Regional Health Management Team (RHMT) in planning and implementing all activities. The RTLC is administratively answerable to the Regional Medical Officer (RMO).

Management of TB and leprosy control activities at district Level

There are 165 districts across the country and the District Tuberculosis and Leprosy Coordinator (DTLC) is one of the co-opted members in the Council Health Management Team (CHMT) and collaborates with the team in addressing and implementing the NTLP agenda into a Comprehensive Council Health Plan (CCHP). Administratively, the DTLC reports to the District Medical Officer (DMO). However, for all issues pertaining to TB, TB/HIV and leprosy they report to the RTLC who as stated above then reports to the NTLP.

Management of TB and leprosy control activities at community Level

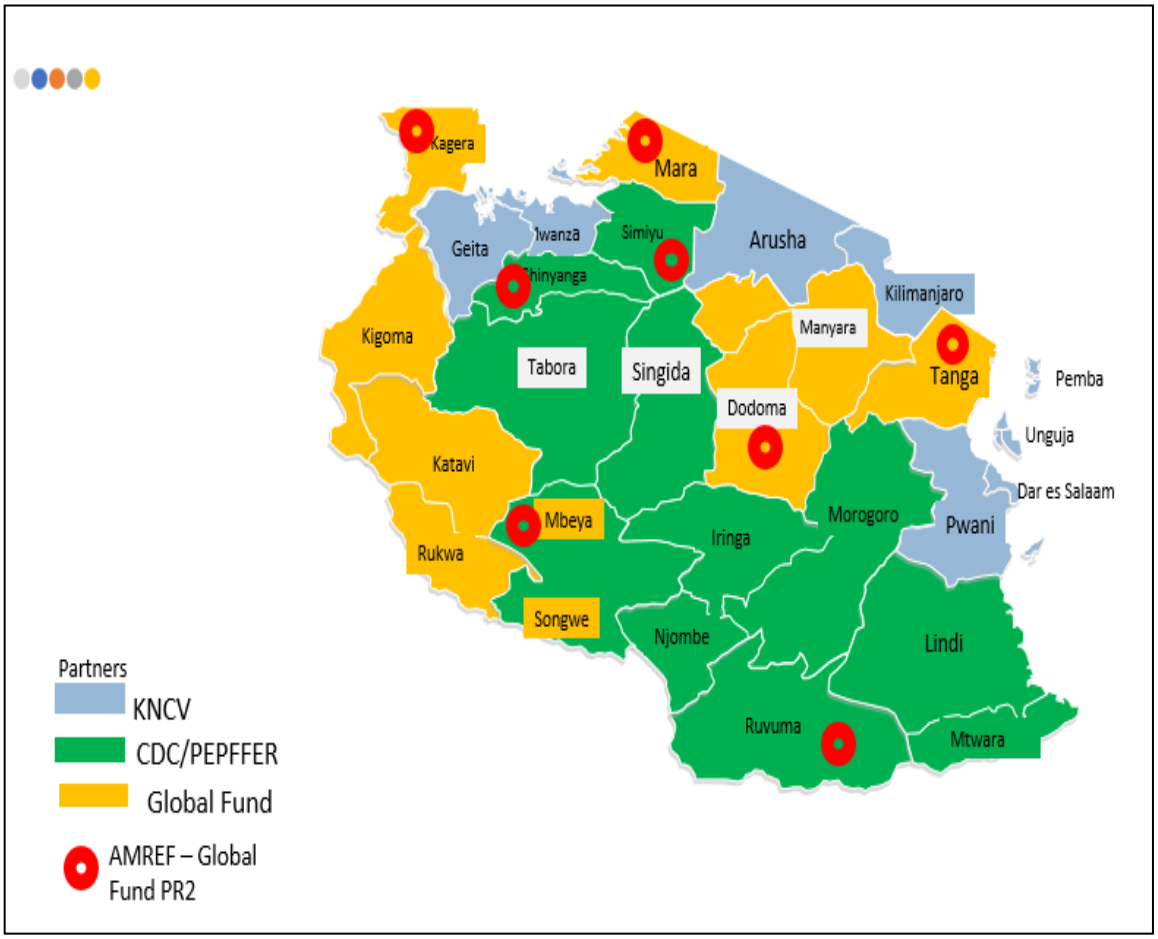
The Ministry of Health realized the importance of strengthening a linkage between health facilities and the community in the provision of health services at community level. The community is aware about TB and seek more services in TB and HIV. The NTLP adapted the ENGAGE TB approach so as to sensitize and encourage a wider range of stakeholders to involve themselves in community-based activities (29). It helped to increase case notification and reduced the workload on the health facility side (30). At the community level, TB, TB/HIV and leprosy care and control are implemented as part and parcel of routine NTLP activities to expand Directly Observed Treatment (DOT) activities beyond health facilities and to involve communities. The health care workers at the health facility level are responsible for providing and sustaining the quality of TB, TB/HIV and leprosy services. Health care workers at the facility level report to the DTLC (27).

1.4.1 Donor support

The TB Programme works closely with developmental partners to implement TB and leprosy control, prevention and care measures in the country. The NTLP receives financial support through Global Fund and other development partners (donors) to support the TB and TB/HIV component. The

majority of the key interventions promoted by the NTLP are donor-funded such as the introduction of new TB diagnostic technologies, innovative transport systems for sputum samples, and the strengthening of programme data quality - including transitioning to electronic-based platforms (31). Figure 6 shows which regions of the country are supported by which partners.

Figure 6 The TB Implementing Partners Mapping by Region



Key: KNCV-Koninklijke Nederlandse Centrale Vereniging tot bestrijding der Tuberculose (Dutch Tuberculosis Foundation). CDC- Centres for Disease Control and Prevention; GF- Global Fund; AMREF- African Medical and Research Foundation.
Note: Under NTLP region Dar es Salaam has four regions (Ilala I, Ilala II, Temeke and Kinondoni).

1.5 TB Laboratory Diagnosis in Tanzania

The Tanzanian government continues to provide both TB diagnostic services and treatment free of charge in all public and private health facilities. The core activities of the TB Programme are based on a system of passive case finding and sputum smear microscopy for suspected adult PTB cases and

delivery of effective therapy to patients. Currently there is good network coverage of laboratories, and sputum smear microscopy services are fully integrated into the general health care delivery system, including private and public health institutions. At the time of conducting this study there were 788 Acid Fast Bacilli (AFB) diagnostic centres scattered across the country. Ziehl Neelsen (ZN) method has been the traditional diagnostic tool and performed at all diagnostic centres.

In 2011 Light-Emitting Diode (LED) fluorescence microscopy was successfully piloted at two regions in Dar es Salaam. Capacity is being developed in laboratories with high workload particularly to improve the diagnostic efficiency of microscopy in TB suspects with HIV and Acquired Immunodeficiency Syndrome (AIDS) for which the sensitivity of ZN microscopy is known to be much lower, due to low bacterial load in their sputum samples (27).

Out of the 788 diagnostic centres, two act as zonal TB culture laboratories. There is also one standalone TB laboratory (Central TB Reference Laboratory – CTRL) at the national level with a capacity for DST for the whole country. In all other diagnostic centres (except at the CTRL and in a small number of new Xpert sites) AFB microscopy remains the initial test for detection of TB. For these two sputum specimens are collected. The first sample is collected on presentation of the presumptive TB case (SPOT) and the second an early morning sample the following day (MORNING). Zonal TB culture laboratories (Kibong'oto and Bugando) perform routine culture on solid LJ media. The CTRL has available both solid culture and liquid culture methods. The liquid culture approach uses the Mycobacterium Growth Indicator Tube (MGIT) method. DST is also performed at the CTRL for first- and second-line anti TB drugs.

In 2010 the molecular test using Line Probe Assay (LPA) for FLD INH and RIF was introduced at the CTRL. LPA is used to confirm MDR-TB strains found by phenotypic testing. Xpert MTB/RIF was introduced in the country in 2012 at two regional hospitals (Temeke and Iringa) for evaluation of the technique. In 2013, 4- module Xpert MTB/RIF machines were installed in 13 health facilities. These were split as follows - 4 of these were in the Dar es Salaam region, 1 in Iringa, 1 in Mwanza, 6 in Mbeya (provided by the London School of Hygiene and Tropical Medicine), plus 1 at CTRL (provided by USAID for research purposes).

The NTLP through Centres for Disease Control and Prevention (CDC) with World Bank support plan to install several more Xpert systems – this includes 4 more machines in Mwanza including one in the Bugando Zonal laboratory (more of this will be described in chapter 5). Although the Xpert machine at the CTRL was installed for research purposes, the laboratory uses it for diagnostic purposes when required by supplementing the cartridge supply (27).

In summary, the TB laboratory network in Tanzania is organised into five main levels according to the type of services provided: -

a) National: Central Tuberculosis Reference Laboratory (CTRL) (x1)

b) Intermediate: Zonal Tuberculosis Reference Laboratories (x5)

c) Regional: Referral hospital laboratories (x31)

d) District: Hospital laboratories (x169)

e) Peripheral: Health centres and dispensaries (x735)

1.5.1 Responsibilities of the TB laboratory network levels

a). National: Central Tuberculosis Reference Laboratory

The CTRL is the principal national laboratory of the TB Programme in Tanzania situated in Dar es Salaam. Although part of the laboratory network led by the Assistant Director of Diagnostic Services of the Ministry of Health, the CTRL falls directly under the authority of the NTLP Programme Manager. Its principal responsibilities include conducting TB diagnostics for the Muhimbili National Hospital, where it is housed; performing diagnostics of samples submitted for analysis by intermediate and peripheral laboratories in the country, particularly for MDR-TB as part of the Routine Surveillance System (RSS); coordinating and implementing training of TB laboratory personnel throughout the country; and conducting supportive supervision and external quality assurance (EQA) within the laboratory network. In addition, personnel at the CTRL develop policies, guidelines, and standards regarding AFB microscopy, molecular tests, culture, DST, and other novel

diagnostic technologies to advise the Programme Manager. They also ensure availability of laboratory equipment, reagents, supplies at all levels in line with the NTLP guidelines. Operational research of relevant TB and leprosy control activities is initiated and coordinated at the CTRL.

The author of this thesis is the current Head of the CTRL. The CTRL is directed by the Head of CTRL who also acts as the Laboratory Director. Head of CTRL responsibilities include professional, scientific, consultative, organizational, administrative, and educational matters relevant to the services offered by the laboratory.

The Head of CTRL also delegates some of their responsibilities to the Laboratory Manager. At the time of conducting this study the CTRL had 15 staff members, of which 2 led management activities; 9 were primarily responsible for diagnostics, supervision, training and EQA activities; 2 were laboratory attendants; and two data staff. Staff members are provided to the laboratory by a number of institutions including 3 from the Ministry of Health, 3 from partners Program for Appropriate Technology in Health (PATH), and 9 from the National Institute of Medical Research (NIMR) (28).

b). Intermediate: Zonal Tuberculosis Reference Laboratories

The Zonal TB Reference Laboratories conduct TB bacteriology testing using culture of samples referred by facilities in the relevant zone.

All positive culture slopes are sent to the CTRL for additional testing. Personnel at the zonal laboratories participate in supervision of AFB microscopy in the zone and training of laboratory workers involved in AFB microscopy, in collaboration with the RTLC. In addition, operational research of relevant TB and leprosy control activities may sometimes be initiated and coordinated from the zonal laboratory.

c). Regional: Referral Hospital Laboratories

Personnel at the regional hospital laboratories plan and supervise AFB smear microscopy and molecular testing in the region and organize training of laboratory workers involved in AFB microscopy, in collaboration with the RTLC. They ensure availability of a three-month supply of

laboratory reagents and other supplies, in collaboration with the RTLC and the regional pharmacist. They participate in EQA of AFB smear microscopy.

d). District: Hospital Laboratories

Personnel at the district hospital laboratories are responsible to supervise AFB microscopy in the district and ensure the quality is maintained by adherence to NTLP policies and guidelines. They undertake smear microscopy testing for TB and the recording of results in the NTLP laboratory request form and register. They ensure that sufficient, quality-controlled stains and reagents are supplied to health facilities. They also assist in AFB microscopy training programs and participate in the EQA of AFB smear microscopy. Sputum specimens for culture and sensitivity testing (e.g. as part of the RSS) at the reference laboratory are collected, stored, and transported from the district hospital laboratories, in collaboration with the DTLC.

e). Peripheral: Health Centres and Dispensaries

Health centres and dispensaries are responsible to facilitate proper sputum specimen collection (SPOT, MORNING) and registration. They undertake smear microscopy testing for TB and the recording of results in the NTLP laboratory request form and register. They ensure that sufficient laboratory reagents are available, in collaboration with the District Laboratory Technician (DLT) and the DTLC. They ensure the safe disposal of infected materials (e.g., sputum containers, microscopic slides) whilst retaining all examined slides for EQA in line with the NTLP guidelines. They ensure the proper care, use, and safety of the microscope. They implement recommended corrective action for improvement of services.

The levels of the network are linked through a two-way system: the lower level reports to the next higher level and higher levels supervise the lower levels, with the exception that the zonal level is not systematically involved in supervision.

1.5.2 Infrastructure of the TB laboratory network

There is a general national guidance for laboratory infrastructure within the Ministry of Health Community Development, Elderly and Children (MOHCDGEC) which guides the design and lay-out of

the laboratories in the country. The Infrastructure of TB zonal culture laboratories is of good quality, although negative air pressure is not available and is only available at the CTRL. All culture laboratories have biological safety cabinets (BSC). Infrastructure of most of the district and peripheral laboratories buildings are old and are not well maintained.

1.5.3 Maintenance and validation of TB laboratory equipment

According to the National policy on medical laboratory equipment, introduction of technologically new equipment should be approved by the Private Health Laboratory Board (PHLB) which is authorized to verify suitability of new equipment. Each laboratory is responsible for verification of any new equipment before routine use. Laboratory staff are trained in routine maintenance of equipment during technical training. The Negative pressure room and BSCs are serviced once a year by Air Filters cleaner from South Africa.

1.5.4 Management of laboratory commodities and supplies

The CTRL guides procurement of equipment based on the international standard specifications. Procurement of equipment is by two operational procurement channels: a). Procurement done by the Medical Stores Department (MSD) (supplies for microscopy), and b). Procurement done by the NTLP in collaboration with partners (supplies for culture, DST and molecular tests). The MSD procures supplies centrally and distributes to the zonal branches of the MSD. The zonal MSDs distribute supplies to the district level and large hospitals.

1.5.5 Laboratory information and data management

The laboratory information system is currently predominantly paper based using forms and registers. Electronic based systems only exist at the CTRL using Epi data.

1.6 Quality Assessment (QA)

1.6.1 Overview

Quality assurance (QA) covers processes and procedures that systematically monitor activities and processes done within the TB laboratory to ensure that testing activities generate consistently reliable results and are of the anticipated quality standard. The QA involves two major sets of activities i.e. Internal quality control (IQC) and EQA.

1.6.2 Internal Quality Control (IQC)

Internal quality control includes the means by which test procedures and instrument operations are regularly checked (32).

In Tanzania, as part of the routine IQC of AFB smear microscopy laboratories, known (1+) or scanty positive slides and known negative slides are used as controls to monitor the quality of AFB smear microscopy in the laboratory (33). For culture sterile distilled water is inoculated in both slope (pyruvate and glycerol media) as a negative control and known positive strains in used as a positive control. The IQC for DST H37RV as a positive control, this is more virulent strain for TB, with R standing for rough morphology and v standing for virulent (34). while sterile distilled water is as a negative control. The performance of internal Proficiency Testing (PT) provides an additional means to assure the quality of laboratory testing results and in addition measures personnel competency/proficiency in testing during the daily performance of the laboratory. Details of these processes are shown in section 1.6.4.

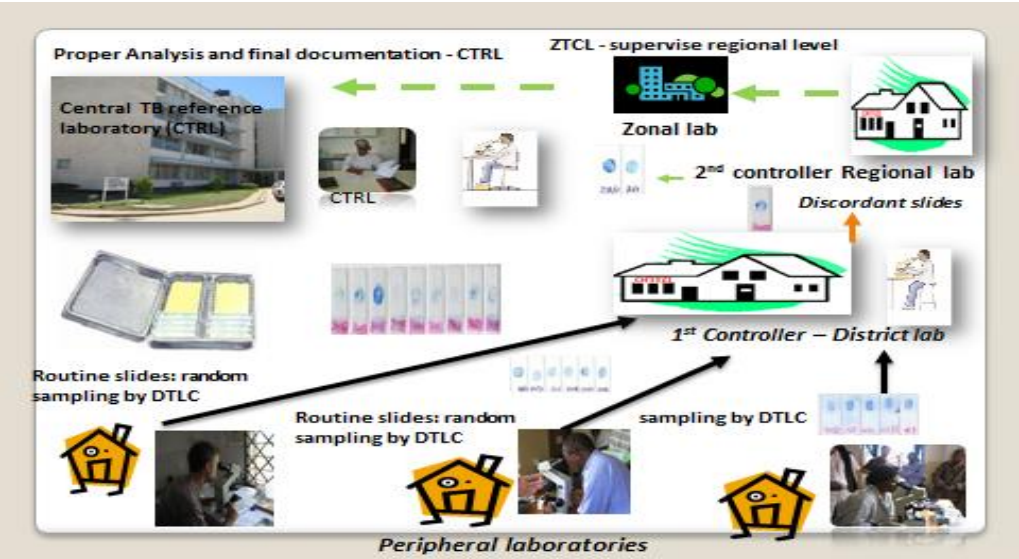
1.6.3 External Quality Assessment (EQA)

The is a system for objectively checking the laboratory's performance using an external facility. It is an indispensable part of a laboratory quality management system as it ensures that users of the laboratory can have confidence that it produces accurate and reliable results. An independent EQA of laboratory performance by a recognized scheme is the requirement of the international standard

ISO 15189: 2012[2], which states that "The laboratory shall participate in an internal laboratory comparison such as an EQA or proficiency programme appropriate to the examination and interpretations of examination results" (35). The EQA for AFB smear microscopy is a process which allows participating laboratories to access their capabilities and performances by comparing their results with those in other laboratories in the network. The EQA focuses on the identification of laboratories where there may be serious problems resulting in poor performance. The EQA for AFB smear microscopy consists of three methods (panel testing, onsite evaluation and blind rechecking) that can be combined to evaluate laboratory performance (32).

In Tanzania, EQA for sputum smear microscopy is done by using an approach known as "blind rechecking system". It was introduced in 2008 in collaboration with a technical consultant from Institute of Tropical Medicine (ITM), Antwerp, Belgium. This system covers both ZN and LED fluorescent dye techniques based on samples of smears examined in routine work. In this system, all routine slides used for TB diagnosis and follow-up are stored on a quarterly basis, ten slides are randomly sampled from each diagnostic centre and rechecked blindly by the first controller at the district level. In case of discordant results, slides are rechecked by the second controller (at the regional level), who serves as second controller (gold standard) as shown in Figure 7.

Figure 7: Organization of EQA by Blinded rechecking in Tanzania NTLP



Keys: CTRL- Central TB Reference Laboratory; ZTCL-Zonal Culture TB laboratory; lab-laboratory; DTLC- District TB and Leprosy Coordinator

[2] ISO 15189:2012, Medical laboratories – Particular requirements for quality and competence.

The rechecking data are compiled, and reports prepared and submitted to the regional and national levels. Analysis is done to identify centres performing below standard, and where corrective measures may be needed. The Zonal TB culture laboratory supervise the checking of the re-checker (second controller) at regional level (32,33).

In addition, on-site evaluation of laboratories is performed during supportive supervision. Feedback of the results to the diagnostic centres is done within a month and corrective action is taken for any problem noted. External Proficiency Testing helps identify and verify that the performance of each test in-house is comparable with peers that perform the same analysis elsewhere – see section 1.6.4.

1.6.4 Proficiency testing (PT)

The CTRL participates in PT programs as necessary covering all the types of tests done at the CTRL. This includes Smear microscopy, Culture, DST, LPA and Xpert MTB/RIF.

Smear microscopy

The CTRL receives five unstained smeared slides for AFB smear microscopy once per year from the Supranational Reference Laboratory (SRL) in Uganda for PT of sputum smear microscopy. The CTRL also completes PT from the United Kingdom National External Quality Assurance System (EQAS) (UK NEQAS) once per quarter. The EQAS results report should be submitted within one month. The threshold for quality assurance is 80% matched results.

Culture

The IQC for MTB culture by solid media LJ H37RV is used as positive control and sterile distilled water inoculated on a solid media as negative control after every 32 tests. During culture reading the controls are read to check if it has passed, if it fails specimen testing should be repeated.

The EQA procedure for culture at the CTRL involves receiving 12 lyophilised sputum for solid culture once per year, from UK NEQAS. The CTRL is required to culture and report on the presence or absence of ‘MTB’. The EQA results report should be sent back within two months. The date when a positive result is obtained should be recorded.

Drug susceptibility testing (DST)

The IQC use a standard strain of MTB with known resistance pattern to different drugs. This is used in every batch of medium as a check on drug concentration. The IQC helps to check the on procedures and the individual performance. In addition, H37RV is included as positive control whenever DST is performed.

EQA for DST: The CTRL is linked to the SRL at the ITM in Antwerp, Belgium. The SRL send 20 killed strains once per year for DST PT for FLD (INH, RIF, streptomycin (SM) and ethambutol (EMB). The CTRL is tested on the ability to detect true resistance strains (sensitivity), true susceptibility strains (specificity) and provide true results (efficiency) (resistant or susceptible). The Indication of overall laboratory efficiency in producing correct results, i.e. a combination of sensitivity and specificity should not score less than 85% score.

Line Probe Assay (LPA)

The IQC is performed using H37RV as positive control and molecular grade water as negative control whenever LPA test is done.

For EQA, the CTRL receives panel package containing 10 PT tubes each containing at least 0.1 ml of inactivated strains from SRL Uganda once per year. The PT are labelled P1 to P10. Samples are processed according to internal Standard Operating Procedures (SOP) for staining. These PT can be tested on Xpert and LPA. The pass mark of a laboratory for any tested drug is based on efficiency (accuracy of performance) which is 95% and above for INH and RIF drugs while 90% for second line drugs. Performance of less than 80% is considered a fail. Results must be submitted on forms provided by the PT provider (PT 013 F17) within one month of receiving tubes.

Xpert MTB/RIF

Xpert is a system that has some automatic internal Quality Control (QC) for each sample. During each test, the system uses one or more of the following controls:

- Sample-processing control (SPC) is included in the cartridge and ensures a sample was correctly processed.
- IQC—Verifies the performance of the Polymerase Chain Reaction (PCR) reagents and helps prevent a false negative result. The internal control PCR assay assesses if there is any inhibition, possibly by components, in the test sample. The internal control is provided in the cartridge and should be positive in a negative sample.
- Endogenous control (EC)—Normalizes targets and ensures sufficient sample is used in the test. Because of its low variability, the endogenous control can also be used to indicate sample-inhibitor contamination. The endogenous control is taken from the specimen sample.

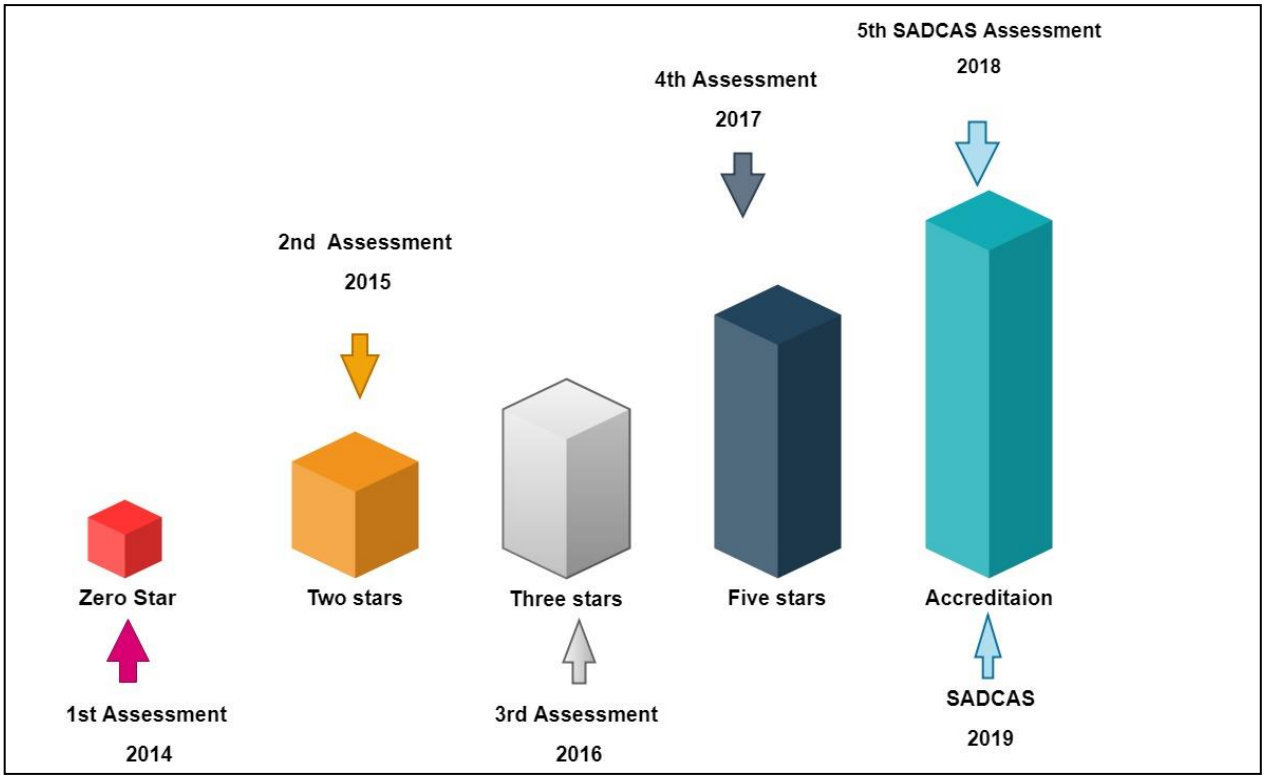
In addition to these controls, the Xpert instrument performs a probe check during the first stage of the test. A probe check verifies the presence and the integrity of the labelled probes. A probe-check status of Pass indicates that the probe check results meet the acceptance criteria (36).

1.6.5 Total Quality Management System (TQMS)

In 2014, the CTRL became involved in the East African Public Health Laboratory Networking Programme (EAPHLNP), to implement a Total Quality Management System (TQMS). The Programme anticipated that if CTRL would be engaged in the TQMS it would be able to follow Good Laboratory Practice (GLP) and adhere to the international standards. On this basis, the CTRL was evaluated against the quality assessment obtained zero star. Second assessment was carried out in 2015 and the CTRL moved from zero to two stars (Figure 8).

Additionally, in 2015 the CTRL was among the National TB Reference laboratories (NTRLs) in 18 countries (Kenya, Lesotho, Malawi, Mauritius, Seychelles, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe), to take part in a regional peer valuation on quality assessment which was supported by the East Central and Southern Africa Health Community (ECSA).

Figure 8 Road map towards routine quality improvement at the CTRL



Key: SADCAS-Southern African Development Community Accreditation Services

1.7 Drug Resistance TB Surveillance

The DR-TB Surveillance (DRS) is a systematic process of detection and monitoring the epidemiological profile of TB medicine resistance with the aim of improving its prevention and control (37). The DRS also helps determine the disease burden and monitor trends over time and plan for new treatment regimens (8). Surveillance of anti-TB drug resistant is therefore an essential tool for monitoring the effectiveness of the TB control programs and improving national and global TB control efforts (8). Initial drug resistant detected in cultures from patients who have not been treated before or have received treatment for less than one month provides an indicator of the effectiveness of diagnostics and treatment regimens. Drug resistant in patients with a history of previous treatment "acquired resistance" points to failures in the management of the disease (3,38). A robust RSS is essential to understand the scale and trends of drug resistance (3). In addition, within

the current diagnostic structure of Tanzania the RSS is a key element in the detection of drug resistant in individual patients, particularly for previously-treated TB patients.

1.8 Routine Surveillance System (RSS) in Tanzania

1.8.1 Importance of RSS

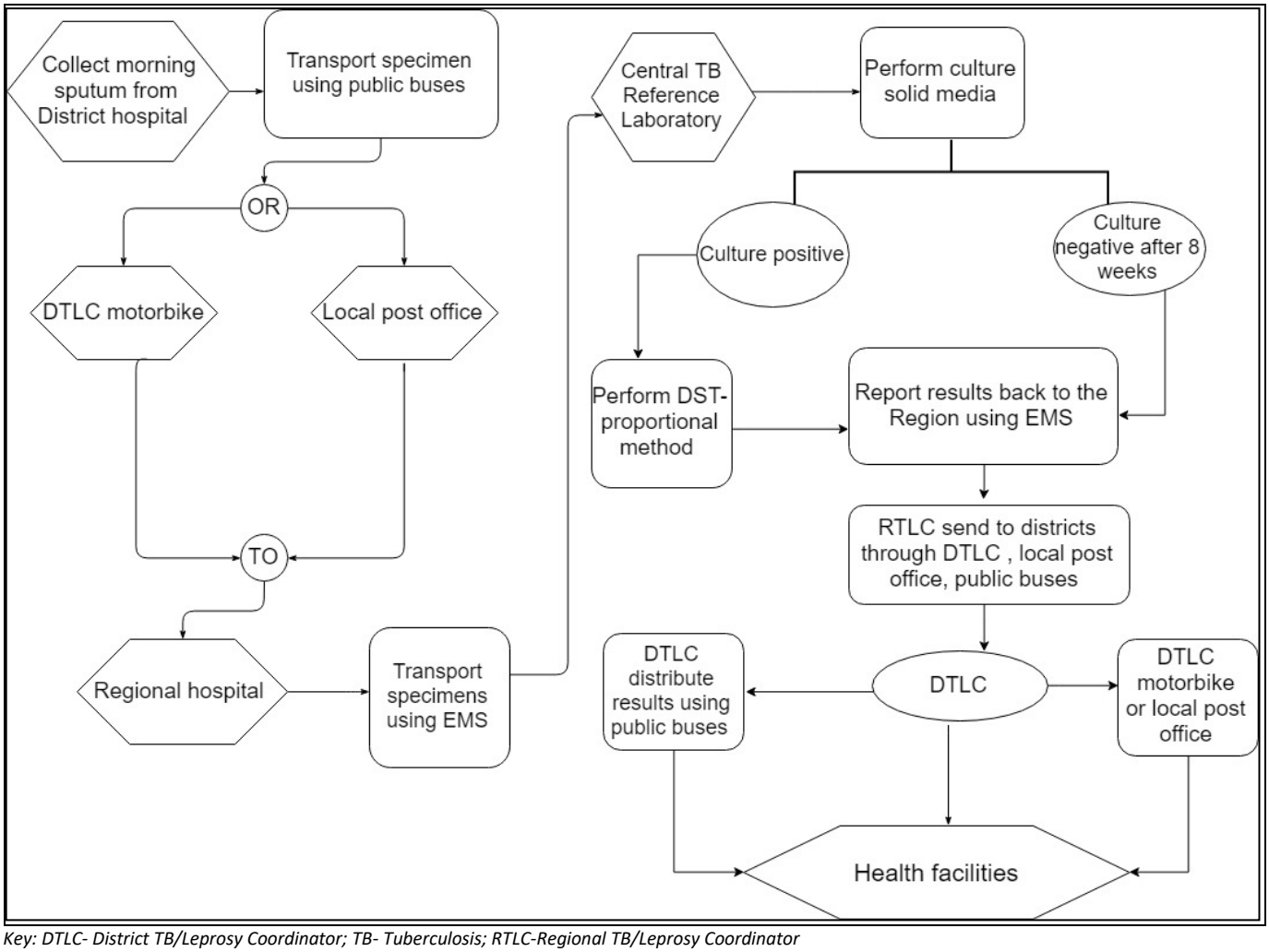
Information on TB DR prevalence is an important management tool for evaluating the performance of a National TB Programmes (NTP)(3). The RSS in Tanzania is intended to monitor treatment outcomes by assessing patient response to individual TB drugs, monitoring the trend of MDR-TB and, importantly, to identify individuals with drug resistant and inform the relevant districts so patients can start appropriate treatment as early as possible.

1.8.2 Description of the RSS

The NTLP strategy for the RSS was designed based on the limited TB culture and DST capacities in the country, the geographical distribution of TB facilities, and the DR-TB burden. The current RSS policy specifies that 25% of new and 100% of previously-treated TB cases that are smear-positive for TB should be referred to the CTRL for culture and DST. A single -morning sputum specimens should be collected from all previously-treated TB cases for culture and DST. The DST is done primarily for routine surveillance of DR-TB using the Proportion Method on solid LJ media, and the CTRL is the only standalone TB reference laboratory with a capacity to perform both FLD and second line DST (27).

The CTRL then feedbacks to the RTLC using standard expedited mail services (EMS) provided by the Tanzania Post Office after obtaining all test results. The RTLC should then distribute them to the DTLC who would communicate to the test requesters (peripheral level) see Figure 9 (27,39). The EMS system was chosen to ease specimen transportation and minimise delay in sending results back from the CTRL to the region as EMS is not available at the district and peripheral level.

Figure 9 Specimens flow for the existing Routine Surveillance System



Key: DTLC- District TB/Leprosy Coordinator; TB- Tuberculosis; RTLC-Regional TB/Leprosy Coordinator

1.8.3 Weaknesses of the existing RSS in Tanzania

There are a number of known weaknesses in the current RSS for TB in Tanzania as it is documented in the NTLP Manual (2013) (27,40).

1. The current RSS refers only to DST using solid media at the CTRL which is particularly slow in delivering diagnostic results. Recently three other technologies have been adopted by the country for TB case detection and DST (MGIT, LPA and Xpert) (27)

2. At district level Xpert is now becoming available in some centres which would allow resistance to rifampicin to be detected and an MDR-TB diagnosis to be made. The availability of Xpert is also gradually expanding across the country. The current RSS does not take account of this availability and expansion (40,41).

3. Communication and transport between the CTRL and the laboratory network area are known weakness that contribute to delays in samples being tested and results feeding back to the periphery where appropriate action can be taken. This is not uncommon in sub-Saharan Africa (42).

4. There is no National TB laboratory standard guideline for culture and DST which would provide a common understanding to laboratory staff, thus there could be a lack of consistency in approach between the CTRL and Zonal reference laboratories. In addition, guidelines for the smooth integration of new staff into their job and team and to provide existing staff with a quick reference to key policies and procedures is lacking.

5. Despite all the NTLP efforts to control the country's MDR-TB over the years, the WHO estimated number of cases is still much higher than the cases identified by the programme year after year (43). Clearly the current RSS is missing many cases and improvements could potentially help to close this gap.

6. The specimen transportation system is not reliable, leading to poor access to laboratory services at every level (44).

7. In a study conducted by a partner organization contamination levels in samples received from the periphery and tested at the CTRL were found to be high. This at best means testing is delayed and at worst means no DST is conducted at all (44).

8. Although 25% of all new cases and 100% of previously-treated cases are meant to be referred to the CTRL as part of the RSS, it is known volumes received fall well below these numbers overall (45,46).

In summary the current RSS is complex as evidenced by the schematic flow shown in Figure 9; It is slow to provide results as evidenced by the methods used; It is not meeting current volume or speed of response targets or even close to them. All these issues call into question its effectiveness. To date this has not been accurately assessed. New technologies such as Xpert MTB/RIF offer opportunities for change that also have not yet been included in the context of the RSS.

1.9 The Need for Research into the RSS

Given all the known limitations described above it is vitally important that the RSS for TB is reviewed and improved. This is particularly crucial at a time of potentially changing resistance patterns in the country. An area of major concern must be where patients have already received TB treatment that has failed or not been completed (failure, relapse, return-after-default) (43). It is therefore not surprising that the WHO advises countries to invest in an RSS for drug resistance in previously-treated cases where the majority of MDR-TB is found (50).

Many of the issues described above in section 1.8.3 are common in other countries particularly in sub-Saharan Africa (47,48). Therefore, lessons from a review in Tanzania are likely to have many implications elsewhere. In addition, failure to detect and track MDR-TB cases appropriately would probably lead to emergence of XDR-TB in the country. Understanding whether (and if not – why not?) DST took place for all previously-treated TB cases is considered critical. It would be hoped that effective specimen shipment arrangements could improve the number of viable specimens received

for DST at the CTRL and therefore improve result credibility, feedback and consequently better patient management and programme documentation.

The focus of the research should initially be on previously-treated TB cases as this is where most of the MDR-TB cases are found. The RSS for previously-treated TB cases is the most established by the NTLP in Tanzania. The NTLP target for the RSS is 100% of previously-treated cases, so there is no ambiguity about which samples should be referred. For new cases the target is 25%, primarily as there has historically been low levels of MDR-TB in new cases, and the volumes that would be required to be referred if the target were 100% is way beyond the capacity of the referral laboratories. With an initial focus on previously-treated TB cases it would still be possible to learn lessons that could also be applied to the RSS for new TB cases.

1.9.1 The Aims

This study aims to investigate the current RSS and then identify and test interventions that enhance the effectiveness of the RSS for previously-treated TB cases in Tanzania, so that more patients with DR-TB could be identified and started on appropriate treatment earlier.

1.9.2 Study specific objectives

a) To measure the under performance of the current routine surveillance system for previously-treated TB cases in Tanzania

b) To determine what factors, lead to the inadequate performance of the current routine surveillance system for previously-treated TB cases in Tanzania.

c) To design and pilot a revised routine surveillance system for previously-treated TB cases in Tanzania.

d) To evaluate the effectiveness of the revised routine surveillance system for previously- treated TB cases piloted (Comparison before and after intervention).

1.9.3 Study research questions

What is the scale of the inadequate performance of the current routine surveillance system for previously-treated TB cases in Tanzania? (Quantitative).

What is the stakeholder perception of the current RSS for previously-treated TB cases in Tanzania? (Qualitative).

What new design of routine surveillance system for previously-treated TB cases might overcome many of the weaknesses in the current system

Does the newly designed and revised RSS improve the performance of the system, in particular by reducing the time from sputum collection at the district health facility to communication of the DST result by the CTRL back to the district? (Quantitative)

Does the revised routine surveillance system reduce barriers to the effective performance of the system? (Qualitative).

1.9.4 Study hypothesis

The study hypothesizes that inadequate performance of the RSS for previously-treated TB cases is associated with poor and delayed diagnosis of MDR-TB. A revised RSS for previously-treated TB cases would identify more drug resistance cases and identify them earlier contributing to better outcomes for patients, particularly those with MDR-TB.

1.9.5 Methodologies to be used for Research

A combination of quantitative and qualitative data collection methods to determine the level of performance of the current RSS were deemed appropriate. Quantitative analysis was required to understand the level of testing taking place, the level of specimen contamination, the number of MDR-TB cases detected, and to calculate the time delays in getting results back to health facilities where appropriate treatment could be initiated. All this information is important and should be available from routine databases. Such quantitative analysis, however, would give little insight into why any delays or low volume of referrals were happening. To obtain this, qualitative analysis was

required at peripheral and central TB facilities to seek to identify the issues causing the unsatisfactory performance. In this respect it would be important to get views from many different perspectives.

Having identified the level of under-performance, and potential reasons for this, it would then be possible to redesign the RSS in a way that could address the issues found in the quantitative and qualitative data collection. This revised RSS could then be piloted, and quantitative impacts measured on things like number of specimens referred, MDR-TB volumes detected and delays in results feedback. In addition, qualitative data collective from the key stakeholders in the revised process would help identify if the issues with the previous RSS had been resolved, as well as any other measures it could be necessary to undertake.

1.10 Ethical clearance

Ethical clearance was granted by the Liverpool School of Tropical Medicine (LSTM) Research Ethical Committee in the United Kingdom and, in Tanzania, by the National Health Research Ethical Review Committee of the National Institute for Medical Research (NIMR). Application for the ethical clearance was submitted to the LSTM on 15th April 2014 and got approval on 3rd July 2014 see Appendix 1. Then a request for ethical review was sent to NIMR review committee on 2nd June 2014 and approval was granted on the 26th June 2014 in Appendix 2. During the study as details were firmed up, a further application for ethical clearance was submitted to the LSTM on 1st May 2016 and approval obtained on 20th Sept 2016 shown in Appendix 3. In addition, an application to NIMR Tanzania on 20th Oct 2015 and approval granted on the 15th Nov 2016, see Appendix 4 and Appendix 5 is the extension approval from NIMR 2017.

The Principal investigator (PI) sought permission from the NTLP and Regional Administrative Authorities to conduct the study. Permission was granted by both establishments. Each participant gave written consent prior to taking part in the study. Participants were made aware that they were

free to withdraw from the study at any time, without prejudice. Confidentiality was maintained throughout the study.

1.11 Structure of the thesis

This thesis contains seven chapters, as follows:

Chapter 1: Details the background to the research and identifies the problems in respect to TB, TB/HIV and MDR-TB globally. It also highlights TB laboratory diagnosis in Tanzania and outlines how the RSS is implemented in the country, along with an initial assessment of issues and weaknesses of that system.

Chapter 2: Reviews the literature relevant to the study, including articulation of the method used for searching for relevant publications, key findings of previous studies and a summary of the reviewed publications.

Chapter 3: Describes a quantitative evaluation of how the RSS is currently performing in the country, identifying both strengths and gaps.

Chapter 4: Following on from the quantitative analysis of chapter 3 this chapter explores the reason for the weaknesses in the RSS identified. It does this by exploring stakeholders' perceptions on the RSS implementation using qualitative methods and ultimately suggests possible opportunities for improvement.

Chapter 5: identifies possible interventions to fill the identified gaps in the RSS and through a pilot study of a revised RSS in Mwanza region and the CTRL in Dar es Salaam, evaluates this using a quantitative 'before and after' approach.

Chapter 6: Describes an evaluation study using qualitative methods to compare the two systems of the RSS (before and after implementation) in Mwanza and at the CTRL. This is designed to assist in determine the feasibility of implementing nationwide improvements to the RSS in Tanzania.

Chapter 7: Brings the whole thesis together with a critical discussion of the findings in the light of existing literature and in the context in which the study was undertaken. It includes a critical reflection of the study design and methods used. It also includes a reflection on what the findings might mean in the context of other LMIC and what further research might be appropriate.

Chapter 2 Literature review

2.1 Introduction

This chapter presents a review of the published literature on surveillance systems for TB diagnosis and case detection in low resource settings. The study objectives, outlined in section 1.9.2, guide the literature search, evaluation, and presentation. This chapter is divided into two main parts; part one describes the literature search process and part two presents the narrative synthesis.

2.2 The Literature Search Method

2.2.1 Overview

The search was aimed at identifying and reviewing peer-reviewed articles focusing on surveillance systems for TB; DR-TB; and diagnosis and case detection in resource-limited settings. The search period was between 2000 and 2019 in order to focus on the most recent and relevant studies. The literature review aimed to establish what peer-reviewed published literature already exists relating to the themes and research questions studied and described in this thesis. It sought to understand and explore the relevant literature in order to learn lessons that might usefully contribute to this study.

The process involved identifying search terms; choosing which search engines to use; defining inclusion and exclusion criteria; performing the search; selecting relevant articles and appraising the studies (49). Also, a summary table of reviewed articles is presented for swift referencing. It should be emphasised the literature review was not a full and exhaustive systematic review of all papers that might potentially be relevant to the key areas under consideration in this study. Although systematic reviews are often used in health-related research, they require a tightly defined intervention with outcomes reported in similar ways. Since the aim of this review was to understand a range of study outcomes on TB surveillance systems in low resource settings, the studies reviewed often could not be compared in a systematic way.

Instead as the objective of the review was to help identify new ideas and lessons learnt from previous published research that might assist in the design and execution of the data gathering and implementation of a revised routine surveillance system in Tanzania, a narrative approach was chosen.

2.2.2 Search terms

In order to establish search terms, the study objectives and research questions (see sections 1.9.2 and 1.9.3) were considered. This led to four high level search terms - Surveillance systems, Tuberculosis, Diagnosis, and Low- and Middle-Income countries (LMIC).

A list of synonyms and related terms for each search term were created and are listed below.

Group 1: Search terms related to Surveillance systems. These included: Routine surveillance, specimen transport and TB surveillance

Group 2: Search terms related to tuberculosis. The terms used included: tuberculosis, drug resistant tuberculosis, multidrug resistant tuberculosis, MDR-TB.

Group 3: Search terms related to Diagnosis. The search terms included: TB laboratory Diagnosis, Rapid Test, Xpert MTB/RIF, Line Probe Assay, drug sensitivity testing.

Group 4: Search terms related to LMIC included: Tanzania, Sub-Saharan Africa, resource limited settings and Developing countries.

The searching was performed by using some keywords to search for literature articles either as an independent group or by combining search term in group 1 AND group 2 AND group 3 AND group 4. Or by single group 1 OR group 3 etc. This was repeated until it appeared that the saturation point had been reached (in other words where new combinations of search terms did not appear to be retrieving new articles).

In addition to literature sources from scholarly theses, published journals, and conference proceeding articles, other primary literature sources were considered. These included Tanzania TB

programme documents, Ministry of Health policy documents and through government websites including Government Bureau of Statistics, Ministry and NTLP websites.

The reference lists of the selected relevant articles were also manually reviewed to see if there were any articles that may have been missed during the electronic search. This involved reading abstracts and considering what the problem was that the authors were addressing, the methods used and how the publication related to this study.

The documenting process was started by taking notes as I read through the literature and the cited sources. I made an annotated bibliography, where I compiled full reference information and wrote a paragraph of summary and analysis for each source. I kept track of the sources with references to avoid plagiarism.

2.2.3 Search engines

The following search engines were used to search for articles: The LSTM library catalogue, The Cochrane Library, Web of science, MEDLINE, Science Direct and Social Sciences Citation Index, and Google Scholar.

2.2.4 Inclusion and exclusion criteria

Inclusion criteria: The search was limited to articles published in English between January 2000 to December 2019. The cut-off years were chosen in order to ensure articles were most relevant to the current situation. Starting in 2000 and ending in 2019 ensured the articles covered a period of 10 years before, and 10 years after, the WHO's endorsement of Xpert MTB/RIF for diagnosis of TB and detection of RR as an initial diagnostic test in individuals living with HIV and/or suspected of having DR-TB.

Exclusion criteria: Any articles published in a language other than English were excluded and those older than the year 2000 were excluded.

2.2.5 Identification of applicable publications relevant to study

The search was conducted by the author using different combinations of the search terms presented above, until no new combinations of search terms appeared to be retrieving new articles. A total of 524 apparently unique peer-reviewed articles were retrieved.

Mendeley® referencing software was then used to double check no duplicates had been included. 30 duplicates saved with slightly different names were identified and these were removed leaving a total of 494 articles. 11 more key articles were added from the Ministry of Health in Tanzania making a total of 505 articles.

After performing the initial screening through titles and abstracts a total of 302 articles were removed. The main reason for exclusion was the articles were concerned with National DRS rather than RSS. This left 203 articles.

A total of 203 text articles assessed as being relevant to this study whereas 140 articles were excluded with reasons.

Therefore, full manuscripts for these were retrieved and thoroughly scrutinized, following which, a total of 62 articles applicable to this study were identified.

The search process is presented in the PRISMA diagram below in Figure 10.

Figure 10: Prisma diagram for obtaining relevant publications included in the review

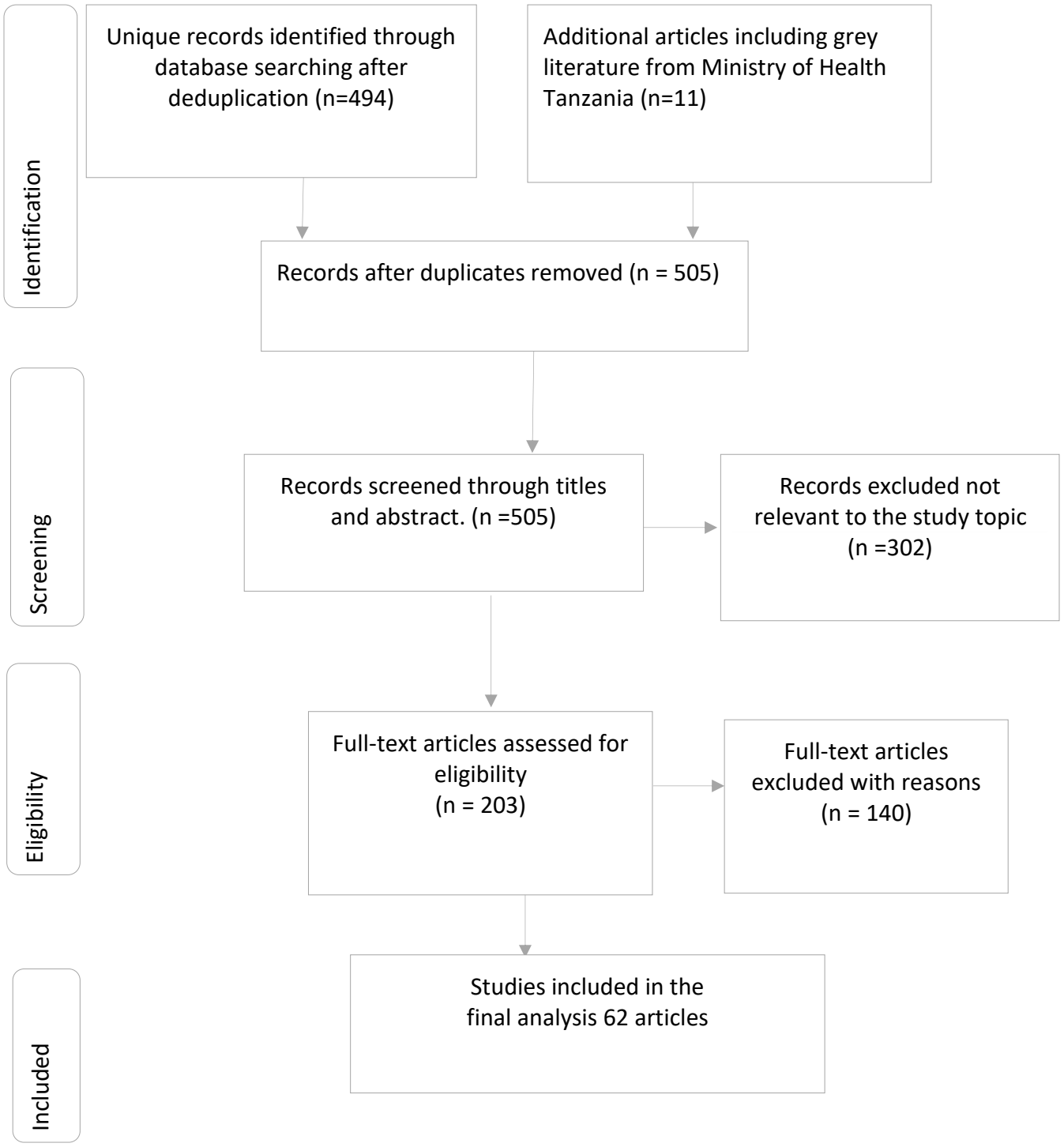


Table 1: Papers included in the final analysis

SN	First Author or Organization	Year	Setting	Title
1	WHO	2015	Global	Global Tuberculosis Report (43)
2	WHO	2016	Global	Global Tuberculosis Report (9)
3	Nkengasong JN	2009	Ethiopia	Critical role of developing national strategic plans as a guide to strengthen laboratory health systems in resource-poor settings (51)
4	Liu Z	2017	China	Feasibility of a new model for early detection of patients with multidrug-resistant tuberculosis in a developed setting of eastern China (52)
5	Hofmann-T S	2017	Germany	How should discordance between molecular and growth-based assays for rifampicin resistance be investigated? (53)
6	WHO	2017	Global	Global Tuberculosis Report (54)
7	Rabia J	2007	South Africa	Understanding the mechanisms of drug resistance in enhancing rapid molecular detection of drug resistance in Mycobacterium tuberculosis (55)
8	Acosta C	2014	Eastern Europe	Drug-resistant tuberculosis in Eastern Europe: challenges and ways forward (56)
9	Zumla A	2012	Global	Drug-Resistant tuberculosis-current dilemmas, unanswered questions, challenges, and priority needs (57)
10	Solomon SL	2009	CDC	Plan to Combat Extensively Drug-Resistant Tuberculosis (58)
11	Park P	2012	Kenya	Increasing access to the MDR-TB surveillance programme through a collaborative model in western Kenya (47)
12	Omar S	2016	Malaysia	Treatment Outcomes of Patients with Multidrug-Resistant Tuberculosis (MDR- TB) Compared (59)

13	Paul D	2012	India	Factors Associated with Delays in Treatment Initiation after Tuberculosis Diagnosis in Two Districts of India (60)
14	Sagbakken M.	2010	Global	Tuberculosis as a global challenge A qualitative study of patients' and health (61)
15	Johnson R	2010	South Africa	Drug-resistant tuberculosis epidemic in the Western Cape driven by a virulent Beijing genotype strain (62)
16	Castro K	2007	Global	Tuberculosis Surveillance: Data for Decision-Making (63)
17	Bazira J	2011	Uganda	Mycobacterium tuberculosis spoligotype and drug susceptibility pattern of isolates from tuberculosis patients in South-Western Uganda (64)
18	Hoza AS	2015	Tanzania	A cross sectional facility-base prevalence among pulmonary TB patients (65)
19	Chonde TM	2010	Tanzania	National anti-tuberculosis drug resistance study in Tanzania (25)
20	NTLP	2013	Tanzania	NTLP Manual for management of TB (28)
21	NTLP	2014	Tanzania	Report M. for new tuberculosis diagnostics: report of a consensus meeting (66)
22	García-Basteiro A	2016	Mozambique	Poor tuberculosis treatment outcomes in Southern Mozambique (2011-2012) (67)
23	Weyer K	2011	Global	Viewpoint TB diagnostics: What does the world really need? (68)
24	Kumar A	2013	State of Karnataka	Efficient, quality-assured data capture in operational research through innovative use of open-access technology (69)
25	Kilale A	2013	Tanzania	Are sputum samples of retreatment tuberculosis reaching the reference laboratories? A 9-year audit in Tanzania (46)
26	Kebede	2016	Ethiopia	Improved Specimen-Referral System and Increased Access to Quality Laboratory Services (70)

27	MOHSW	2012	Tanzania	Service Availability and Readiness Assessment (SARA) 2012 July 2013. 2013;(July) (71)
28	Olson S	2012	India	Facing the Reality of Drug- Resistant Tuberculosis in India (72)
29	Guio H	2006	Japan	Method for efficient storage and transportation of sputum specimens for molecular testing of tuberculosis (73)
30	Harries A	2004	Malawi	Using a bus service for transporting sputum specimens to the Central Reference Laboratory: effect on the routine TB culture service in Malawi (74)
31	Timire C	2018	Zimbabwe	Has TB CARE I sputum transport improved access to culture Services for retreatment tuberculosis patients in Zimbabwe? (75)
32	Bhat J	2011	Africa	Yield of culture of Mycobacterium tuberculosis complex in sputum samples transported from tribal areas (76)
33	Daum L	2015	South Africa	Yield of culture of MTB complex in sputum samples transported from tribal areas. (77)
34	UNION I	2007	Low-Income countries	Priorities for Tuberculosis Bacteriology Services in Low-Income Countries. 2007 (78)
35	Ridderhof JC	2007	Global	Roles of laboratories and laboratory systems in effective tuberculosis programmes (79)
36	Royce S	2014	Cambodia	Identification of multidrug resistance in previously treated tuberculosis patients: a mixed methods study in Cambodia (80)
37	Nagu T	2017	Tanzania	Tuberculosis associated mortality in a prospective cohort in Sub Saharan Africa: Association with HIV and antiretroviral therapy (81)
38	WHO	2010	Global	TB Diagnostics and Laboratory Services Information (82)
39	Birx D	2009	Thailand	Laboratory challenges in the scaling up of HIV, TB, and malaria programs: The interaction of

				health and laboratory systems, clinical research, and service delivery (83)
40	Cowan J	2014	Mozambique	Implementing rapid testing for tuberculosis in Mozambique (84)
41	WHO	2008	Global	Policy guidance on drug-susceptibility testing (DST) of second line antituberculosis drugs (85)
42	Agrawal M	2016	India	Comparative Study of GeneXpert with ZN Stain and Culture in Samples of Suspected Pulmonary Tuberculosis (86)
43	WHO	2017	Global	GLI Practical Guide to TB Laboratory Strengthening 2017 (87)
44	Fox GJ	2017	Australia	Preventing the spread of multidrug-resistant tuberculosis and protecting contacts of infectious cases (88)
45	Albert H	2016	South Africa	Development, roll-out and impact of Xpert MTB/RIF for tuberculosis: What lessons have we learnt and how can we do better? (89)
46	Global Fund Long R	2018	Global	Drug-resistant tuberculosis. Global Fund (90)
47	Tenover F	1993	Global	The resurgence of tuberculosis: Is your laboratory ready? (91)
48	Yon Ju Ryu	2015	Global	Diagnosis of pulmonary tuberculosis: recent advances and diagnostic algorithms (14)
49	Li Y	2013	China	Factors associated with patient, and diagnostic delays in Chinese TB patients: A systematic review and meta-analysis (92)
50	Ramsay A	2009	Global	Front-Loading Sputum Microscopy Services (93)
51	Said K	2017	Tanzania	Diagnostic delay and associated factors among patients with pulmonary tuberculosis in Dar es Salaam, Tanzania (12)
52	UNITAID	2017	Global	UNitaid. Diagnostics Technology Landscape 5th Edition, May 2017 (94)

53	Omar S	2016	South Africa	Field evaluation of a novel preservation medium to transport sputum specimens for molecular detection of Mycobacterium tuberculosis in a rural African setting (95)
54	Lienhardt C	2017	Global	Global Observatory on Health Research and Development (R & D) Background paper on Tuberculosis Specific R & D Research Priorities and Funding Gaps (96)
55	McNerney R	2011	Resource Limited Settings	Towards a point-of-care test for active tuberculosis: obstacles and opportunities (10)
56	Davis J	2011	San Francisco	The Clinical and Public Health Impact Of Automated Nucleic Acid Testing For TB Evaluation In San Francisco (97)
57	Trébucq A	2011	Low Income countries	Xpert ® MTB/RIF for national tuberculosis programmes in low-income countries: when, where and how? (98)
58	Mnyambwa PN	2017	Tanzania	Assessment of sputum smear-positive but culture-negative results among newly diagnosed pulmonary tuberculosis patients (99)
59	Hoza A	2016	Tanzania	Increased isolation of nontuberculous mycobacteria among TB suspects in North-eastern, Tanzania: public health and diagnostic implications for control programmes (100)
60	Kilale A	2016	Tanzania	Who Has Mycobacterial Disease? A Cross Sectional Study in Agropastoral Communities in Tanzania (101)
61	Shahraki A	2015	Indonesia	“Multidrug-resistant tuberculosis” may be nontuberculous mycobacteria (102)
62	Ani A	2009	Nigeria	Comparison of a DNA based PCR method with conventional methods for the detection of M. tuberculosis in Jos, Nigeria (13)

2.3 Narrative synthesis of literature

2.3.1 Introduction

The included studies were all read carefully, taking detailed notes of the design of the study, the main findings, and any interesting subjects. An annotated bibliography was produced which compiled full reference information and a paragraph of summary and analysis for each source.

A narrative approach was taken to presenting the findings of the review because the studies were too disparate to allow a meaningful systematic presentation of the results. Furthermore, a narrative review allows the researcher to reflect critically on the knowledge, which is an essential element in establishing gaps in understanding and identifying areas in which the proposed study can contribute (49). The table of the reviewed papers is described in Table 1 showing author's name, year of publication and title. Six important linked themes were identified in the reviewed literature and these are described in the following sections. The final section outlines the gaps in knowledge identified and draws conclusions.

2.3.2 Key themes from the literature review

1. The surveillance system for TB

Globally, the TB surveillance system is one of the oldest and largest surveillance systems to monitor anti-microbial resistance across the globe, reaching a milestone of 20 years of operation in 2014 (9). It commenced in the 1990s in recognition that the emergence of strains of MTB that are resistant to anti-mycobacterial agents was a worldwide problem whose global magnitude needed to be better understood (50).

In this context, it was recognised that early diagnosis, including universal access to DST, and immediate initiation of treatment are essential for an effective TB control programme (51,52), and that effective health care systems delivering accurate and

timely diagnostic tests are essential to providing critical information for the right medical decisions and management of a particular health condition. In particular, the rapid and accurate laboratory diagnosis of MDR-TB is crucial to ensure early initiation of appropriate treatment, to adequately manage the disease and to control further transmission (53). For all these reasons, a successful continuous RSS is reckoned to be the best way to detect and monitor DR-TB (9). As Rabia et al. highlighted in 2007, accurate routine surveillance is of particular importance to prevent future transmission of DR-TB (55).

Uncertainty continues to characterise the understanding of DR-TB. According to the WHO, TB transmission and the occurrence of MDR-TB has increased (9). And although the numbers of MDR-TB patients enrolled each year has also increased, MDR-TB case detection rates are still very low (9). Acosta *et al.*, provide evidence that there has been an increase in MDR-TB and XDR-TB cases in high-burden countries (56). In 2012, Zignol *et al.* revealed that the burden of DR-TB is not uniform across the globe and in many countries the prevalence is increasing (54). In the same year, the global TB report showed that strains of MTB are becoming increasingly resistant to anti-TB treatments, especially in areas where TB control programmes have been less effective (54). This was assumed to be linked to the improper use and substandard quality of anti-TB drugs in certain settings. It is agreed that this represents a major threat to TB control (54,57) and leads to emergence of XDR-TB which is much more expensive to treat (58). Park *et al.* suggested that these challenges need to be properly evaluated and addressed (47) because treating patients with MDR-TB strains is much more complex and expensive than treating patients with susceptible TB strains (59).

In this perspective, continuous surveillance of drug resistant based on the routine testing of TB patients allows for the systematic, ongoing collection of data and analysis for prompt and appropriate public health responses. In particular, there is a need to reduce TB transmission between initial diagnosis and the beginning of TB treatment (60). The TB Programmes must adopt a more holistic approach, and secure early diagnosis which may

reduce some of the physical, psychosocial and economic costs patients face while undergoing treatment (61). Routine surveillance therefore plays a number of vital roles (62). As a long-standing and large-scale multinational monitoring process it helps to improve researchers' understanding of the epidemiology and trends in MDR-TB which can assist in identifying interventions to address the needs within TB programmes. It is also central to the early diagnosis of MDR-TB and thus to the long-term goal of limiting the spread of such drug resistant forms.

The question that arises from this is, why if surveillance has been in place globally for such a long time, the prevalence of MDR-TB is still uncertain and, in so far as trends are understood, why it appears to be increasing? This would suggest that surveillance programmes have thus far not been entirely successful in the roles identified in the previous paragraph. The remaining sections of this review will therefore explore what the current knowledge has to say about the challenges in implementing an effective RSS and the potential approaches to improving such systems (9).

2. Challenges affecting the surveillance system for drug resistant TB

As discussed in the preceding section, surveillance data are crucial to measuring the burden of disease and, thus, serve as the basis for informed decisions about the planning and targeting of health care interventions (63). There is a particular need for such data in respect to TB and MDR-TB. However, the realisation of this ambition is hampered by significant practical challenges. The widespread emergence of DR-TB has complicated the management of TB disease (64), and has made the WHO's Global TB Programme's requirement for periodic DRS based on random, representative, DST among previously untreated smear-positive cases, all the more important. In resource-poor settings like Tanzania, such testing is seldom performed (65), with reliance placed mainly on phenotypic DST and with significant logistical and operational challenges (25,47). Lack of resources makes an accurate diagnosis of TB cases more difficult, and in many countries, TB control programmes rely almost exclusively on sputum microscopy for the diagnosis of TB, as part of WHO TB control strategies (9,28).

Globally, one-third of all TB cases are not notified, and many patients' samples do not undergo DST (66). In addition, there is limited data regarding the monitoring of TB treatment results and determinants of adverse outcomes under routine surveillance conditions (67). Furthermore, clinical data management is mainly paper-based which is characterized by inadequacy and insufficient quality control and surveillance (68).

3. Specimen transportation and storage

In regard to specimen transportation and storage, it has been noted that difficulties involved in the collection, transport and prompt processing of samples in clinical practice could be contributing factors for DST not being done or leading to false culture positive (69). Transport of sputum samples from peripheral facilities to central laboratories is a major bottleneck in identifying MDR-TB cases particularly among previously-treated TB patients in low resource countries, hampering efforts towards eradication of MDR-TB and XDR-TB (46). In addition, effective specimen delivery arrangements can affect specimen viability hence speed of results feedback (70), since samples that arrive at testing facilities in a poor condition cannot be properly tested, and a new sample must be obtained from the patient. This wastes time and resources, resulting in further spread of TB and MDR-TB to the community and, as a result, an increased burden on the health system and the patient (47,71). Indeed, as a study conducted in India has pointed out, longer transportation times increase the risk of contamination and false negatives (72). A study in Kenya has also pointed out the effect of unreliable means of transportation on the effectiveness of a surveillance system (47,73).

In Tanzania, a study has shown that only 10% of sputum samples from notified previously-treated TB cases received culture and were subject to DST. This study, however, could not identify the underlying causes of the shortfall in transported samples (46). Equally, a study conducted in a neighbouring country, Malawi, showed that despite implementation of a new bus transport system for specimens from previously-treated TB patients, only 40% of cases resulted in a sample being received by the central laboratory (74). Timire *et al.* evaluated a novel operational design that tries to overcome

diagnostic delivery barriers by using the existing transport system and a result tracking system. The study revealed that, a number of specimens could not undergo DST as some sputum specimens were never collected or reached the National Reference Laboratory (NRL), although they were unable to establish the reason(s) for this (75). Specimen viability can be improved by use of more reliable modes of transport and good storage conditions, especially in hard to reach areas (74,76,77).

Different approaches have been suggested, taking into consideration individual settings and the availability of resources. Findings from a study conducted in Zimbabwe in 2018 on using motorbikes to transport sputum samples (75) came to a similar conclusion as a study from Malawi which used public bus service for specimen transportation (74). Both studies point out that the new means of transportation did not lead to a higher proportion of samples reaching the lab nor did they significantly reduce the time taken for samples to be analysed. Both also concluded that there is a need for improvement in the entire system, including the increase in the number of competent and trained personnel (74,75), as well as the involvement of multiple stakeholders (47).

4. The role of the laboratory in the TB Control Programme

Another theme in the literature links shortages of staff and laboratory supplies to failures in RSS implementation and hence the identification of DR-TB. Although notable progress has been made regarding TB identification and treatment of MDR-TB cases, gaps remain in the availability and good access to effective DST, particularly at the peripheral laboratories. Adequate staffing, equipment and other provisions at all levels, including peripheral laboratories, is key to effective identification, treatment and follow-up of all categories of TB patients (78). Most peripheral laboratories in low resource settings experience serious challenges with competent staffing levels, lack of resources and lack of/or outdated standardised laboratory protocols (79). Likewise, lack of data and improper categorisation of cases led to some re-treatment patients being recorded as new patients, posing a challenge in MDR-TB case finding and monitoring for previously-treated cases (80). For example, Harries *et al.* revealed that, in Malawi, most sputum

samples were collected by general nurses who had not received any specific training on the collection of MTB specimens (74).

Another study revealed high contamination rates of 9% versus the expected maximum of 5%, which also indicates poor laboratory quality assurance mechanisms. The study suggested that on-site training and regular supportive supervision is needed if the quality of TB services at peripheral laboratories is to be optimised (74). While a study conducted in Kenya showed that lack of awareness of a TB-programme intervention by healthcare workers affected TB surveillance (47).

Royce et al. explored healthcare workers' perspectives on enablers and barriers to effective TB intervention programmes. Their study participants identified the following as enablers: (1) training on sputum sample collection; (2) streamlining sputum sample transportation; (3) prompt reporting of cases. Barriers included: (1) patient reluctance to disclose information; (2) stigma; (3) difficulty with eliciting previous treatment history, and (4) inadequate mechanisms to diagnose and report DST results. The study pointed out that correct diagnosis and classification, reviewing treatment history and making sure samples reach the central reference laboratory would increase the detection rate of MDR-TB (80).

Inefficient functioning of peripheral laboratories and an inability to perform smear microscopy can also cause a delay in both diagnosis and treatment initiation (47). According to Ridder *et al*., the laboratory plays a critical role in TB diagnosis and treatment monitoring, and the strength of the laboratory network is often a direct reflection of the success of TB Control Programmes (79). In order for peripheral laboratories to function well and contribute to enhancing the TB surveillance system, they need to be connected to central laboratories (79). Central laboratories play a key role in the quality assurance of peripheral laboratories, apart from their primary diagnostic role. Hence the robustness of the surveillance system is a reflection of the proper functioning of central laboratories (79). Park *et al.* showed that effective and integrated supervision is key to an effective surveillance system (47). Another area of

concern is that tests taking place in the private sector are not being reported centrally and a complete picture is not established (81), therefore greater engagement with the private sector is required. Overall, the WHO believes that strengthening TB laboratory services offers one of the best avenues for overall laboratory improvement as an essential health systems activity (82). Now is the time to build sustainable laboratory capacity in resource-poor settings that can be used to manage existing epidemics, fight multiple emerging and remerging diseases, and provide local facilities for scientific investigators of all levels (83).

5. Diagnostic methods for drug resistant TB

Newer molecular diagnostic methods have been developed aimed at improving case detection and identification of DR-TB (16,89,103). Case detection can be particularly challenging for TB patients who are co-infected with HIV, since smear microscopy has low sensitivity among these people (84). In 2008, several tests for rapid detection of RR were validated in laboratory-based studies and evaluated for feasibility and cost-effectiveness (85). The method has a dual advantage of detecting cases of MTB and proving the DR status for RIF in one go. Xpert has a high sensitivity of 88% for MTB and 94% for RR. This is an ideal approach for TB surveillance, however financial and logistic constraints determine its universal rollout (84).

On the other hand, in 2016, Agrawal showed that the culture method is more sensitive and specific than microscopy and Xpert and hence continues to serve as the gold standard (86). However, to perform cultures properly requires highly qualified personnel and infrastructure (87). Improved case finding is required to bridge the substantial MDR-TB case detection gap (88). Albert *et al.*, shed light on how Xpert MTB/RIF can be used as a point of care technology and can reduce the time from specimen collection to testing results, although the high costs of the Xpert machine and tests are likely to be a barrier in the developing world (89). The Xpert technology has transformed the way the world diagnoses DR-TB. It has allowed screening of thousands of TB cases around the world, quickly and efficiently (90).

The study conducted in Mozambique by Cowan J *et al.*, revealed that the cost of installing one Xpert machine and the accompanying laptop was about 17,000 USD and one cartridge, per sample, costs an additional 10 USD (84). Rolling out new diagnostic technologies is not without multiple challenges, therefore, not least high maintenance costs (91). These need to be considered when devising TB surveillance intervention programmes. Current research in the field clearly shows the need for more empirical evidence to integrate bacteriological and molecular methods of detecting TB and drug resistant that have high diagnostic accuracy (sensitivity and specificity), are cost-effective, temperature stable and simple to use. Such methods do have the potential to improve surveillance systems in resource-limited settings (84,91).

6. The need for improved RSS in Tanzania

As in many sub-Saharan Africa countries, the true burden of MDR-TB in Tanzania remains unknown due to inadequate laboratory infrastructures and lack of resources to diagnose and report MDR-TB (14). The inadequate surveillance system that is hindered by lack of resources such as staff, insufficient laboratory set-up, unreliable transport and specimen tracking methods contributes to the poor presentation of national TB programmes (14,45). The delay in the diagnosis and management of MDR-TB poses a threat to the success of the TB control programme and potentially creates an enormous financial burden and disease control issues for both individuals and the community (12,60,92). In order to minimise the economic burden and multiple patient visits to the health facilities. Andy Ramsay *et al.* suggested that, smear microscopy services should be front loaded in the interests of fairness and improved TB control. This approach could be improved if most specimens were collected the first day of consultation (93).

Despite the efforts made by the WHO on the use of rapid and sensitive diagnostic techniques that provide information on DR-TB in a timely way, such as Xpert MTB/RIF and LPA (94), researchers continue to note the poor uptake of new diagnostic tools and continued logistical delays in sub-Saharan Africa (52), which increases the threats from DR-TB (95,96). In Tanzania, there is slow uptake of the rapid technology for diagnosis of

TB (28). Like in many other LMIC, diagnosis of active TB in Tanzania is achieved by detection of bacilli through smear examination, mycobacterial culture (10) and more recently Xpert in a small number of district laboratories (97,98) as well as molecular MTBDRplus tests for DST at the CTRL (9). Smear microscopy is done in all diagnostic units while one standalone laboratory has the capacity to perform susceptibility testing for both first and second line anti-TB drugs (45). It is well-known, however, that smear microscopy suffers from low sensitivity and does not distinguish between live and nonviable organisms, or between Non-tuberculous Mycobacteria (NTM) and MTB complex (10,99). In recent years, there has been an increasing trend of NTM in Tanzania, which are easily misdiagnosed as TB (99,100), (101) and sometimes as MDR-TB (102), which may result in the unnecessary rendering of toxic second-line anti-TB drugs. Xpert has higher sensitivity than smear microscopy, however, the rollout of the assay throughout the country has been slow (61) and is characterised by an insufficient supply of cartridges (99). The culture method is more sensitive and specific than microscopy and Xpert, hence serving as the gold standard test (86). Unfortunately, most routine laboratories do not culture mycobacteria due to limited infrastructure and the slow generation time (3-8 weeks) in the LJ media (65). In addition, in a recent study conducted in Tanzania, it was reported that only one-third of MDR-TB patients diagnosed by Xpert between 2013 and 2016 were placed on MDR-TB treatment due in part to seriously inadequate data recording (61). Scaling up the coverage of rapid diagnostic techniques across the country could increase case detection, early treatment and help reduce further transmission, but this needs to be supported by accurate reporting and effective RSS (37). Strengthening decentralisation of laboratories for culture and DST with improving peripheral specimen collection as well as referral mechanisms for both specimens and patients are also recent recommendations (47).

2.3.3 Gaps in knowledge and conclusions

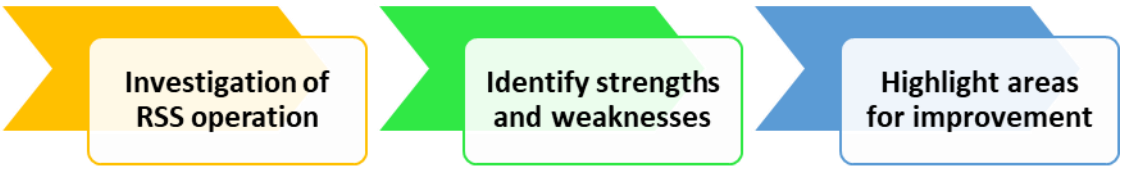
The review has revealed the importance and role of TB surveillance systems, but also identifies especially in low-resource countries such as Tanzania, there are many issues that are a barrier to efficiency and effectiveness at all levels of the surveillance cycle.

These include sample handling, accurate case and drug resistant detection, proper and timely records at the peripheral laboratories, timely diagnostic and confirmatory tests at the central laboratory, as well as the lack of a robust means of transportation that provides a reliable link between the CTRL and peripheral laboratories.

There remains a lack of clarity in the literature about how such issues may be tackled, especially in low-resource settings. Nor is it clear if all the challenges have been properly identified, evaluated, and addressed. Where solutions have been proposed, they have not necessarily been successful. For example, the use of public bus service to transport sputum samples in Malawi and use of motorbikes in Zimbabwe did not result in an increased proportion of samples from previously treated TB case patients being put forward for DST, nor was duration from sample collection to processing shortened (74,75). Furthermore, although there is increased interest in the potential of molecular diagnostic techniques, how feasible is it to fully roll these out in low resource countries is unclear.

This study takes note of these current gaps in understanding and seeks to contribute to the literature by (a) developing a fuller appreciation of the factors limiting the success of TB surveillance, and (b) proposing and piloting an integrated set of interventions in a specific low-resource country with a high burden of TB (Tanzania). This is in order to assess the feasibility of options for tackling the common challenges facing RSS in such settings.

Chapter 3 Investigating the existing Routine Surveillance System



3.1 Introduction

This chapter addresses research question (a) as referred to in the Introduction section in 1.9.3., i.e. What is the scale of the inadequate performance of the current RSS for previously-treated TB cases in Tanzania? (Quantitative). The chapter describes an investigation conducted of the existing RSS designed to understand the performance of that system and whether the NTLP policy of submitting 100% of all previously-treated TB cases to the CTRL has been fulfilled. The analysis was conducted using the previous three years' routine data held at the CTRL. It was anticipated that the study would identify strengths to be sustained, weaknesses to be rectified and importantly highlight areas for improvement.

Before this part of the study commenced there was only anecdotal evidence and a mission report carried out in 2013,[3] which suggested that the RSS was underperforming, with high levels of contaminated samples and long delays in patients being started on appropriate MDR-TB treatment.

The study used the quantitative data extracted from the routine databases to look at the efficiency of the existing system. The study focused on previously-treated TB cases only because this is where most of the MDR-TB cases are found. The RSS for previously-

[3] Tanzania Joint Mission Report conducted by Dr. Armand Van Deun and Dr. Pamela Hepple from SRL and GLI respectively; 18th – 29th March 2013

treated TB cases is the most established by the NTLP in Tanzania. The NTLP target for the RSS is 100% of previously-treated cases, so there is no ambiguity about which samples were required to be referred. For new cases the target is 25%, primarily as there has historically been low levels of MDR-TB in new cases, and the volumes that would be required to be referred if the target were 100% is way beyond the capacity of the referral laboratories. Despite only focusing on previously-treated TB cases in this study, it is believed many of the lessons learnt from this study could also be applied to the RSS for new TB cases. This chapter covers the methods used in the investigation, the findings, and a discussion of the results.

The research covered in this chapter has now been published (45).

3.2 Quantitative study

3.2.1 Study research questions

What is the scale of the inadequate performance of the current routine surveillance system for previously-treated TB cases in Tanzania? (Quantitative).

3.2.2 Study aims

This study aims to measure the effectiveness of the RSS for previously-treated TB cases in Tanzania with a view to providing evidence that will help identify interventions to improve and accelerate positive patient outcomes.

3.2.3 Study hypothesis

The study hypothesizes that the inadequate performance of routine surveillance systems for previously-treated TB cases is associated with poor TB diagnosis, particularly of MDR-TB.

3.3 Quantitative method

3.3.1 Study sites

This quantitative study reviewed the routine TB laboratory data collected electronically from TB laboratory registers at the CTRL from January 2011 to December 2013. This period was chosen in 2014 when this part of the study was conducted, as it represented the most recent 3 years where electronic data was available. The dataset contained information on all the specimens received at the CTRL from across the country (27). The information from the quantitative part of the study fed into the design of the qualitative part of the study which is covered in chapter 4.

3.3.2 Study design and population

A cross-sectional study that employed a quantitative approach was used to analysed routine data collected from January 2011 to December 2013. This included information on completion of request forms, transit times, turnaround times, culture positivity and contamination rates.

The transit time was defined as the time from specimen collection in the peripheral health facilities to the time the specimen is received at a site where DST can take place (i.e. the CTRL and/or Mwanza sites with Xpert MTB/RIF).

The turnaround time was defined as the time from specimen receipt at the CTRL to the time the DST results are sent back to the requesting clinician, as in Figure 11. Ideally it would have been preferable if the date the result was received by the peripheral facility were the end time for the turnaround time. Unfortunately, this date is not available on the electronic database and therefore the date the CTRL reported back to the region had to be used instead.

Figure 11 Specimens referral showing Transit and turnaround times from peripherals to CTRL

According to the NTLP, the anticipated transit time should be a maximum of 7 days (27). Culture at the CTRL is performed using direct sputum specimens. Culture growth can be seen from 3 weeks of incubation, but complete culture incubation is 8 weeks (56days), if there is no growth by 8 weeks it is considered culture negative. All positive isolates from zonal TB culture laboratory are sent for DST with a maximum of 6 weeks (42 days) incubation. The results are sent back after obtaining the DST results.

3.4 Sample size estimations

The study encompassed all specimen records from all previously-treated TB cases collected and processed at the CTRL for the three-year period 2011-2013.

3.4.1 Inclusion Criteria

a) Previously-treated TB case specimens.

b) Specimens collected and processed between 2011 and 2013.

c) Routine specimens for diagnosis only.

3.4.2 Exclusion Criteria

a) Specimens collected before the year 2011 or after the year 2013

b) Presumptive new case specimens.

c) Specimens collected for research purposes.

3.5 Justification of the Methodology Used

3.5.1 Quantitative Design

Quantitative studies provide answers or insights for many important questions or issues in health care and clinical research (105). In this study, quantitative data collection was selected because it provides a measurement of the scale of any performance issues in the current RSS in respect to the management of specimens associated with previously-treated TB cases. It reveals any disparity between the specimens collected at the peripheries and those processed at the CTRL. It can give a measure of the efficiency of the system by calculating the time from specimen reception to the time results are reported. It also shows the proportions of positive cultures and contamination rates for the solid medium mycobacterium cultures processed and the proportion of previously-treated TB case specimens received that had DST performed. The quantitative approach would also reveal trends related to the detection of MDR-TB.

3.5.2 Preparation and study set up

The first step was reviewing the dataset to exclude all specimens associated with studies, projects and presumptive new cases. The next step was to understand the parameters collected and their availability. The third step was data cleaning to check for missing information and rectify gaps using information from the source documents if available.

3.5.3 Data collection and analysis

Quantitative data were extracted from the routine database at the CTRL and TB laboratory registers covering the three-year period. The collected data were cleaned and analysed using Statistical Package for Social Science (SPSS) version 23. Frequency tables were generated to explore outliers and abnormal values which were then rectified using the available source documents. The transit time and the turnaround time for TB tests performed at the laboratory were calculated. The proportion of the specimens tested within the recommended time (106,107) was also calculated and coded as 1, and those outside this time coded 0. Descriptive analysis compared the proportion of specimens recorded as out of the recommended time.

3.6 Quantitative findings

a). The distribution pattern of Specimens

The study analysed routine specimens received at the CTRL during the time under review (2011-2013). There were 16,423 specimens in total including both new and previously-treated TB cases. Of these 2,750 (16.7%) were from previously-treated TB cases which were the focus of this study. The majority of these specimens (61.7%) were received in 2013 and most were from males (60.2%). A total of 1,495 (54.4%) were from the young adult population aged between 25 and 44 years. HIV status was known in 1,962 (71.4%) and of these 1,293 (65.9%) were HIV negative. A high proportion of specimens 1,118 (40.7%) were from the Eastern Zone (Mtwara, Lindi, Dar es Salaam). A total of 98 (3.6%) were recorded as contaminated (Table 2).

Table 2: Previously-treated TB cases Specimens received at the CTRL from 2011 to 2013

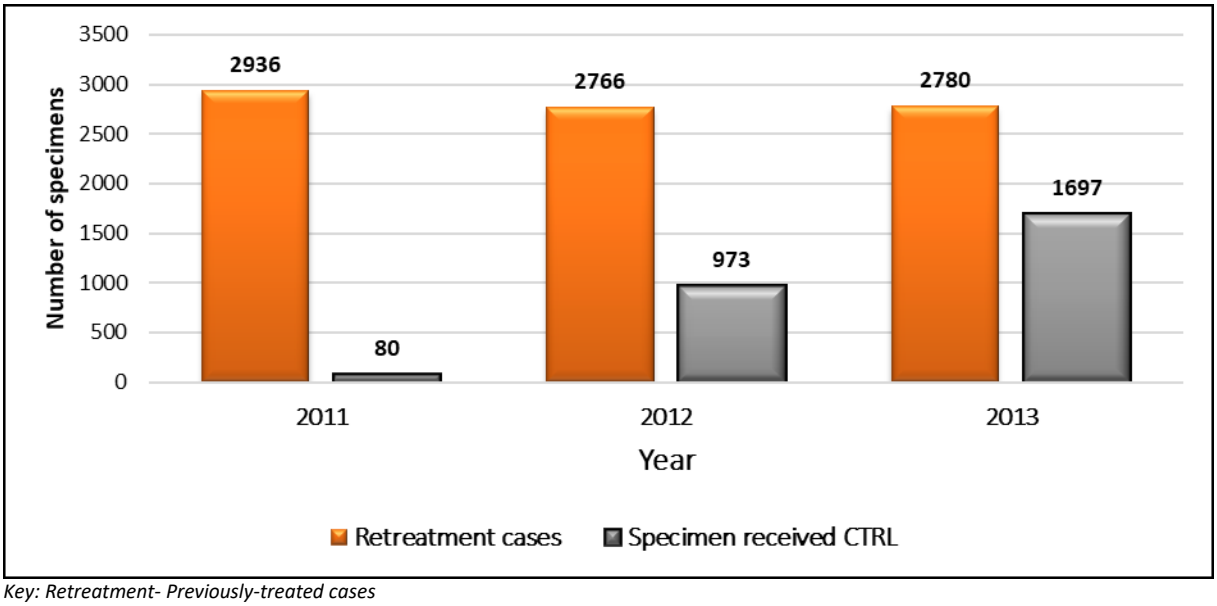
Variable	2011; N=80	%	2012; N=973	%	2013; N=1,697	%	Total	%
Zone								
Northern	37	46.3	186	19.1	630	37	853	31.0
Southern	3	3.8	115	11.8	94	5.5	212	7.7
Eastern	23	28.8	459	47.2	636	38	1,118	40.7
Lake/Central	17	21.3	210	21.6	315	19	542	19.7
Zone unknown	0	0	3	0.3	22	1.3	25	0.9
Gender								
Male	51	63.8	468	48.1	1,137	67	1,656	60.2
Female	29	36.3	319	32.8	550	32	898	32.7
Gender unknown	0	0	186	19.1	10	0.6	196	7.1
Age group								
<15	2	2.5	10	1	29	1.7	41	1.5
15-24	8	10	137	14.1	262	15	407	14.8
25-34	21	26.3	294	30.2	444	26	759	27.6
35-44	21	26.3	255	26.2	460	27	736	26.8
45-54	24	30	277	28.5	502	30	803	29.2
Age unknown	4	5	0	0	0	0	4	0.1
HIV status								
Positive	14	17.5	206	21.2	449	27	669	24.3
Negative	13	16.3	443	45.5	837	49	1,293	47.0
HIV Unknown	53	66.3	324	33.3	411	24	788	28.7
TB type								
Pulmonary -ve	0	0	4	0.4	1	0.1	5	0.2
Pulmonary +ve	67	83.8	957	98.4	1,685	99	2,709	98.5
Extra pulmonary	2	2.5	3	0.3	1	0.1	6	0.2
Not specified	11	13.8	9	0.9	10	0.6	30	1.1%
Smear result								
Positive	36	45	645	66.3	993	59	1,674	60.9
Negative	44	55	328	33.7	704	42	1,076	39.1
Culture result								
Positive	34	42.5	392	40.3	755	45	1,181	42.9
Negative	45	56.3	532	54.7	879	52	1,451	52.8
Contamination	1	1.3	44	4.5	53	3.1	98	3.6
Undocumented	0	0	5	0.5	10	0.6	20	0.7

Keys: HIV- Human Immunodeficiency Virus; N- Number; TB- Tuberculosis; Zones are Eastern (Mtwara, Lindi, Dar es Salaam); Northern (Arusha, Kilimanjaro, Tanga, Manyara); Southern (Iringa, Mbeya, Ruvuma, Katavi) Central (Dodoma, Morogoro, Singida) and Lake (Mwanza, Shinyanga, Tabora, Kagera, Kigoma, Geita)

b). The relation between cases notified versus specimens received

Analysis of the data showed that, out of 8,482 previously-treated TB cases notified across the country for the three years, only 2,750 (32.4%) were received at the CTRL. A significant variation was recorded across the years. In 2011 2,936 cases were notified and only 80 (2.7%) were received at the CTRL. The trend improved in 2013 whereby 2,780 cases were notified and 1,697 (61.0%) specimens were received at the CTRL in Figure 12.

Figure 12 Previously-treated Cases Notified Versus Specimen Received at the CTRL (2011-2013)



Key: Retreatment- Previously-treated cases

c). Transit Time (Time between sputum collection and arrival at a site where DST can take place (i.e. the CTRL and/or Mwanza sites with Xpert MTB/RIF))

The study findings showed that 2,608 (94.8%) of previously-treated TB case specimens had documented transit times. The mean and median transit time was 7.7 and 6, respectively, with a full range of 0 to 100 days. The mean and median transit time was lower 6.1 and 3 (IQR; 1-6.5) in 2011 compared to 2012 and 2013, although the difference between the years was not statistically significant (P=0.271). See Table 3.

Table 3: Transit time for previously-treated TB cases from 2011 to 2013

Year	Number	Mean transit time	Standard Deviation	Median transit time	p25	p75	F-value	p-value
2011	76	6.1	6.9	3	1	6.5	1.3	0.271
2012	911	8.4	12.2	6	4	9		
2013	1,621	8.1	11.7	5	3	9		
Total	2,608	7.7	8.4	6	3	9		

Keys: p25- is the 25th percentile (1st quartile); p75- is the 75th percentile (3rd quartile).

d). Turnaround Time (Time between specimen arrival at CTRL and results sent back)

Of the 2,750 previously-treated TB case specimens received, 1,244 were subject to microscopy, 2,703 to culture and 392 to DST. Of these, for microscopy, 1,024 (82.3%) specimens were documented and processed within the recommended turnaround time; while for culture and DST the parallel figures were 1,146 (42.4%) and 11 (2.8%), respectively Table 4). In respect to cultures performed outside the recommended time, 77.6% (1,208 out of 1557) were culture negative.

Table 4: Turnaround time for previously-treated cases from 2011 to 2013

S/N	Status	Microscopy	Culture	DST
1	Within recommended time	1,024(82.3%)	1,146(42.4%)	11(2.8%)
2	Out of recommended time	220(17.7%)	1,557(57.6%)	381(97.2%)
	Total	1,244	2,703	392

Keys: DST- drug susceptibility testing

The study findings showed specimens that took longer than the recommended turnaround time for microscopy, culture and DST by descriptive variables were not statistically significant. P values were (p=0.1, p=0.4, p=0.5, p=0.7 and p=0.8). See Table 5.

Table 5: Specimens turned around in longer than the recommended time by descriptive variable

Variable	Outside recommend-ed time Microscopy N=220	(%)	p	Outside recommend-ed time Culture N=1,557	(%)	P	Outside recommend-ed time; DST N=381	(%)	p
Zone									
Northern	48	21.8	0.5	479	30.8	0.9	91	23.9	0.5
Southern	19	8.6		119	7.6		86	22.6	
Eastern	98	44.5		633	40.7		142	37.3	
Lake/central	55	25		326	20.9		57	15.0	0.5
Unknown	0	0		0	0		5	1.3	
Gender									
Male	152	69.1	0.4	1017	65.3	0	225	59.1	0.7
Female	68	30.9		533	34.2		71	18.6	
Unknown	0	0		7	0.4		85	22.3	
Age group									
<15	2	0.9	0.4	21	1.3	0.1	4	1.1	0.8 *
15-24	35	15.9		229	14.7		41	10.8	
25-34	59	26.8		430	27.6		119	32.3	
35-44	69	31.4		397	25.5		104	27.3	
45+	55	25		480	30.8		112	29.4	
Unknown	0	0		0	0		1	0.3	
HIV status									
Positive	51	23.2	0.1	378	24.3	0.7	117	30.7	0.4
Negative	106	48.2		733	47.1		138	36.2	
Unknown	63	28.6		446	28.6		126	33.1	
Years									
2011	0	0	0.0 *	17	1.1	0	25	6.7	0.1
2012	0	0		677	43.5		155	40.6	
2013	220	100		863	55.4		201	52.8	
Test Result									
Positive	150	68.2	0.9	307	19.7	0	-		
Negative	70	31.8		1,208	77.6		-		
Culture CT	0	0		42	2.7				

*Keys: rec- recommended; DST- Drug susceptibility testing; N- Number; HIV- Human Immunodeficiency Virus; Eastern Zone (Mtwara, Lindi, Dar es Salaam); Northern (Arusha, Kilimanjaro, Tanga, Manyara); Southern (Iringa, Mbeya, Ruvuma, Katavi) Central (Dodoma, Morogoro, Singida) and Lake zone (Mwanza, Shinyanga, Tabora, Kagera, Kigoma, Geita); Culture CT- culture contaminated; * - Fisher exact*

In Table 5 we used routine data from 2011–2013 specimens showing time specimen processed to time results issued and contamination rate. These are data on what happened within the laboratory but did not include the results took to reach the clinicians, as historically the date the clinician received the result was not recorded.

Table 6: Drug Susceptibility Testing Results Profile from 2011- 2013

Year	2011	2012	2013	Total	% of Total
Positive Culture	34	392	755	1,181	100
DST not done	6	235	548	789	66.8
Total number set up for DST	28	157	207	392	33.2
Total number with DST results	28	151	194.0	373	31.6
Total number DST contaminated	0	6	13	19	1.6
DST Patterns					% of Results
Total Susceptible to all	16	123	130	269	72.1
Total MDR-TB	9	16	47	72	19.3
Total Mono resistant	3	12	12	27	7.2
Total other resistant	0	0	5	5	1.3
MDR-TB					
HRSE	5	8	18	31	8.3
HRS	4	1	14	19	5.1
HR	1	7	14	22	5.9
Mono resistant					
H	1	5	2	8	2.1
S	1	1	3	5	1.3
R	1	6	7	14	3.8
Other resistant					
HS	0	0	4	4	1.1
ES	0	0	1	1	0.3

Key: DST- drug susceptibility testing; MDR- multidrug-resistant tuberculosis; TB- tuberculosis; HRSE. H-Isoniazid; R- Rifampicin; S-Streptomycin, E-Ethambutol

The study findings showed that, from the previously-treated TB case specimens analysed (2,750), only 1,181 (42.9%) were culture positive. From the positive cultures, only 392 (33.2%) were set up for DST. This proportion fell during the 3 years from 82.4% in 2011 to 27.4% in 2013. Out of the 392 DSTs done, 373 (95.2%) obtained DST

results and 19 (4.8%) were contaminated. 269 (68.6%) of the specimen's subject to DST were susceptible to all FLD whereas 31 (8.3%) were resistant to all FLD as in Table 6.

3.7 Summary discussion

The quantitative results of this study show the target of 100% of previously-treated TB case specimens being routinely investigated for DR at the CTRL was far from being met. The proportion being sent showed a significant improvement over the 3 years, however only 61% of cases were sent for testing even in the last year (2013) of the three-year period investigated. This implies that full surveillance of the TB programme was not undertaken and thus that cases of drug resistant are likely to have been missed.

In addition, when samples were sent for surveillance the median transit time from sputum collection to arrival at the CTRL was over 7 days, which may have affected specimen culture viability, and consequently the results. The policy that all positive culture slopes should undergo DST at the CTRL was adhered to on less than 50% of occasions (falling during the 3 years from 82.4% in 2011 to 27.4% by 2013). This means drug resistant could be missed even when samples are sent for testing.

Part of the reason for the reduction in the DST% can be put down to the huge increase in volumes between 2013 and 2011 (755 vs. 34 i.e. over 20 times larger) and capacity constraints in staffing and equipment at the CTRL to process this increased volume. This is a significant weakness at the CTRL.

On the positive side culture contamination was recorded as being within the recommended level (0-5%) (108) in this study. However, a Supra-National & GLI Mission Visit Report in 2013 showed higher contamination rates (~30%).[4] The reason for this difference is unclear but may relate to how contamination rates are calculated and historically poor recording of contamination at the CTRL.

[4] *Tanzania Joint Mission Report conducted by Dr. Armand Van Deun and Dr. Pamela Hepple from SRL and GLI respectively; 18th – 29th March 2013*

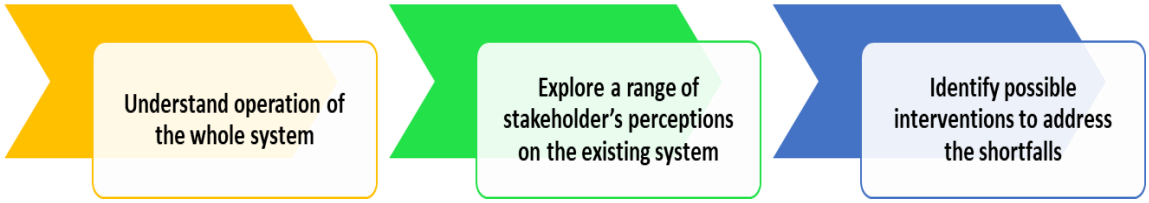
The study was not without limitations. Poor record keeping made it difficult to attain more meaningful and conclusive results on the effect of delayed submission of sputum specimens. Routine data were captured electronically, but incomplete form filling led to difficulties in analysing some information. It seems that the RSS policy was not well understood by TB health care workers as it was evident in the TB laboratory request forms that the patient's category was not usually indicated. This all made analysis difficult because of a lot of missing information.

In relation to understanding the turnaround time it would have been preferable if the date the result was received by the clinician at the peripheral facility were the end time. Unfortunately, this date was not available on the electronic database and therefore the date the CTRL reported back to the region had to be used instead. This means the true time for results to be received so they can be acted on will in reality be longer and possibly more variable than that which could be calculated.

3.8 Conclusion

The outcome from this quantitative study provides baseline data from which to focus the subsequent exploration of mechanism of transferring specimens from peripheries to the CTRL and performance within the CTRL itself. Further research to explore the reasons for this performance and stakeholder's perceptions of the RSS would potentially allow the development of measures to reduce turnaround times, increase the level of valid DSTs being completed overall, and to reduce delays in clinicians receiving results and therefore patients starting appropriate treatment. This research is described in Chapter 4.

Chapter 4 Exploring Reasons for Inefficiency in the Existing RSS



4.1 Introduction

According to Natasha Mark, qualitative approaches to operational research are targeted to generate knowledge and information that reflects the perceptions, understandings and practices of different groups (109).

This chapter addresses research question (b) as referred to in the Introduction, section 1.9.3. - What is the stakeholder perception of the current routine surveillance system for previously-treated TB cases in Tanzania? (Qualitative).

A study using a qualitative design was undertaken to understand the process and performance of the existing RSS operation. The focus was to provide explanations for the inefficiencies described by the 2011 to 2013 routine data as shown in Chapter 3. It explored the perceptions of health care workers through group discussions and in-depth interviews; seeking to understand their views, knowledge and awareness of the existing RSS policy implementation, and importantly, then to link these qualitative perceptions to the quantitative findings of chapter 3. It was anticipated that the knowledge and understanding attained would generate ideas of suitable interventions to improve performance.

The research covered in this chapter has now been published (45).

4.2 Study Overview

4.2.1 Study objectives

To determine what factors, lead to the inadequate performance of the current routine surveillance system for previously-treated TB cases in Tanzania.

4.2.2 Study research question

What is the stakeholder perception of the current routine surveillance system for previously-treated TB in Tanzania?

4.2.3 Study aim

The aim was to explore the stakeholder perception of the current routine surveillance system for previously-treated TB cases in Tanzania with a view to identifying interventions to improve and accelerate positive patient outcomes in particular with relation to DR-TB.

4.2.4 Study hypothesis

The study hypothesizes that the inadequate performance of the current RSS is associated with poor TB diagnosis for DR-TB in Tanzania.

4.2.5 Study approach

This study involved a range of different stakeholders (including health care providers and implementing partners) within the TB Programme. They were selected to investigative and understand the context and practice of the current RSS implementation from the perspective of individuals in their own place of work within the healthcare system. These observations would be based on stakeholders own reported experiences and perceptions. This qualitative research would address the policies and operation that relate to the RSS and would look at issues that patients may never see. These problems are likely to have repercussions on efficiency as well as patient outcomes. The research would seek to understand the views of the stakeholders on how the existing RSS is

carried out, what its strength and weaknesses are, and to suggest ways for improvement. This would lay the foundation for subsequent stages of the study (117).

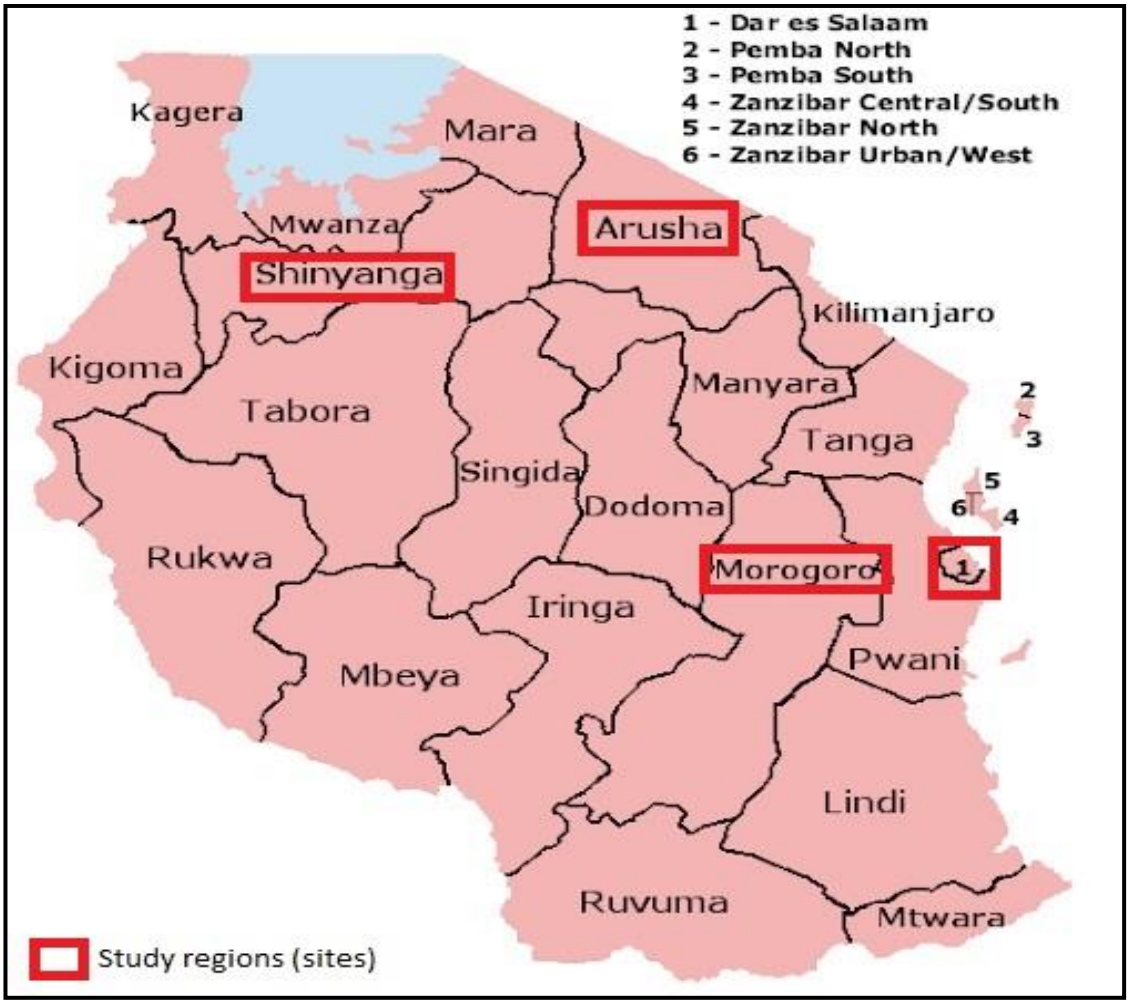
4.2.6 Study sites and population

4.2.6.1 Introduction

The study was conducted in four regions of Tanzania, representing regions with high demand for TB services and spread across the country. These four regions were among the ten regions that individually represented more than 4% of the total TB notifications in the country (110), see Figure 13. The regions were Arusha (4.9%), Dar es Salaam (21.9%), Morogoro (5.1%) and Shinyanga (6.4%). Dar es Salaam was purposefully selected as it is by far the largest region and contains the CTRL. The other 3 regions were selected using a simple random sampling technique from the remaining 9 high volume regions (111). These health regions reflected Tanzania's decentralized public health service system, in which each region is led by a Medical Officer (MO) and where all TB activities are overseen by an RTLC.

The study also involved participants from members of the health system staff at the NTLP and CTRL based in Dar es Salaam. Health care workers at TB clinics at regional and district level were also included. Also, implementing partners supporting the NTLP, Ministry of Health Officials and regional administrative authorities were included in the qualitative research.

Figure 13: Map of Tanzania showing study regions



4.2.6.2 Overview of study sites

The study was conducted in four regions in Tanzania each study site is described below. A summary of the TB characteristics of the four study sites in Tanzania is shown in Table 7.

Table 7: Summary of the study sites by 2015

Region	No. of diagnostic centers	TB Cases notified			TB/HIV	
		New cases	Previous treated TB cases	Total	Positive	Rate
Dar es Salaam	64	11,052	525	11,577	4,738	40.9%
Arusha	43	2,320	132	2,452	773	31.5%
Morogoro	34	2,668	72	2,740	995	36.3%
Mwanza	37	2,743	79	2,822	1,381	48.9%
Shinyanga	24	1,535	84	1,619	966	59.7%
Grand Total	165	20,318	892	21,210	8,853	41.7%

Keys: No- number; TB-tuberculosis; HIV-human immunodeficiency virus

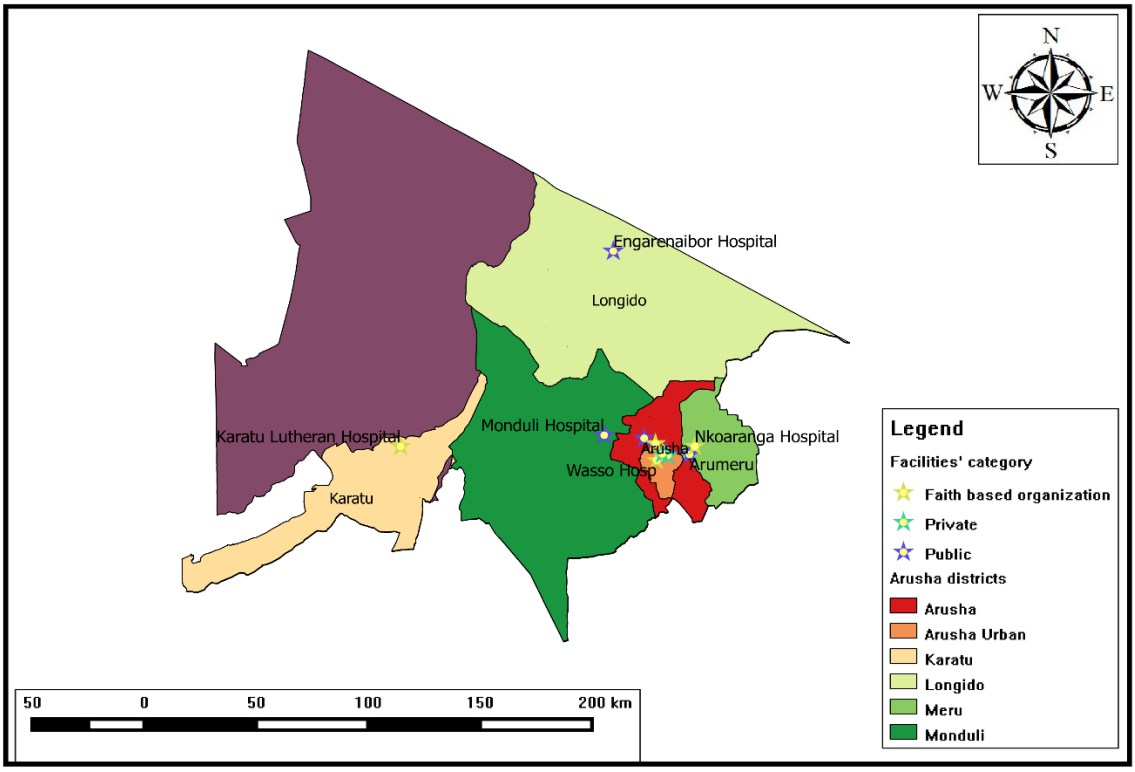
Arusha Region

Arusha is in north eastern Tanzania and is one of Tanzania's 31 administrative regions in Tanzanian Mainland. Figure 14 shows a map of the region split into districts. The city of Arusha is the capital of the Arusha region. The region has a population of 1.7 million (2012 census) (112) and a total area of 82,428 square kilometres. Around 4.3% of the region is covered by the water bodies of Lakes Eyasi, Manyara, Babati and Natron. The region has a common border with Kenya to the north, Kilimanjaro and Tanga regions to the east, it shares a border with Dodoma region to the south, and west with Singida, Shinyanga and Mara regions. The average economic growth rate for the region is relatively high, it stands at 3.8% against the national rate of 2.8%. The main economic activity of Arusha region is agriculture, tourism and mining. Arusha economically is very important to the nation, ranking second to Dar es Salaam in this respect (112). It is a multicultural city with a majority Tanzanian population of mixed backgrounds: indigenous African, Arab-Tanzanian and Indian-Tanzanian population. There is a small European and American minority population.

The main ethnic groups are Iraqw, Arusha, Maasai and Meru. Religions of the Arusha population include Christianity, Islam, Sikhism and Hinduism. Arusha city is known as a

major international diplomatic hub and hosted the East African Community from 1994 to 2015.

Figure 14: Map of Arusha Region Showing Diagnostic sites

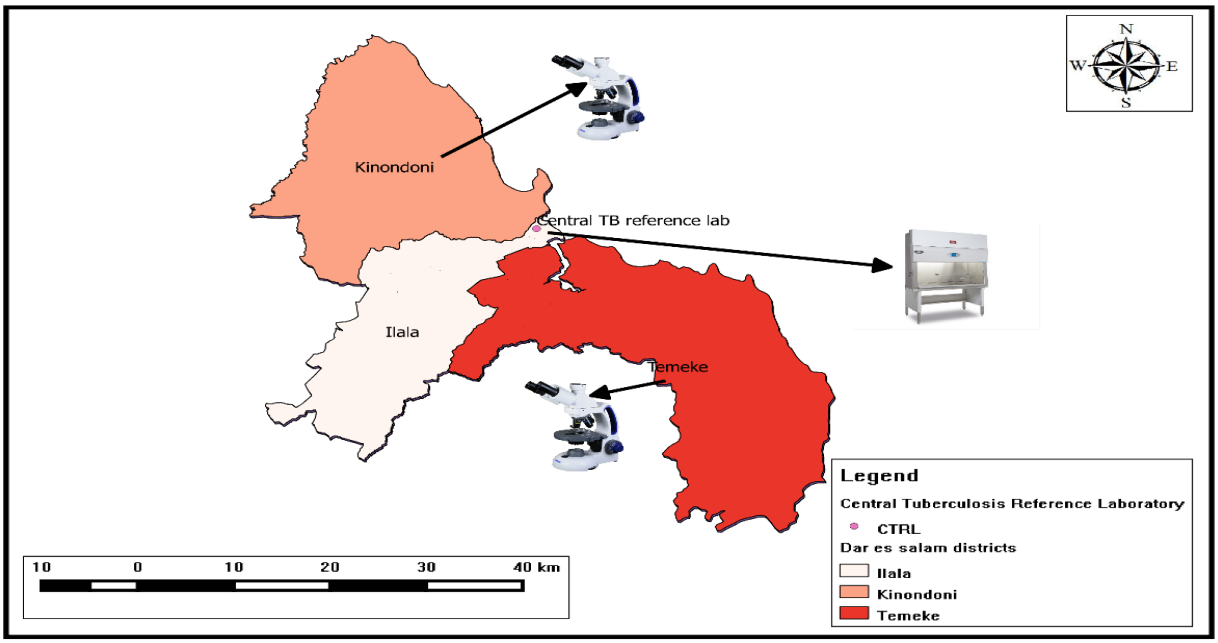


Dar es Salaam

The Dar es Salaam region is in Eastern Tanzania and is one of 31 administrative regions in Tanzanian Mainland. Figure 15 shows a map of the region split into districts.

Dar es Salaam city is the largest city in East Africa and the seventh-largest in Africa, with a population of 6.7 million (114). The city's land area is 1,393 square kilometres, making the population density 4,800 per square kilometer. The city was formerly known as Mzizima. It was the capital city until 1974, when Dodoma was named as the capital. However, today, Dar es Salaam remains the largest city in Tanzania in terms of population and is the financial and business capital of the country. Dar es Salaam is also where the NTLP head office and the CTRL are located.

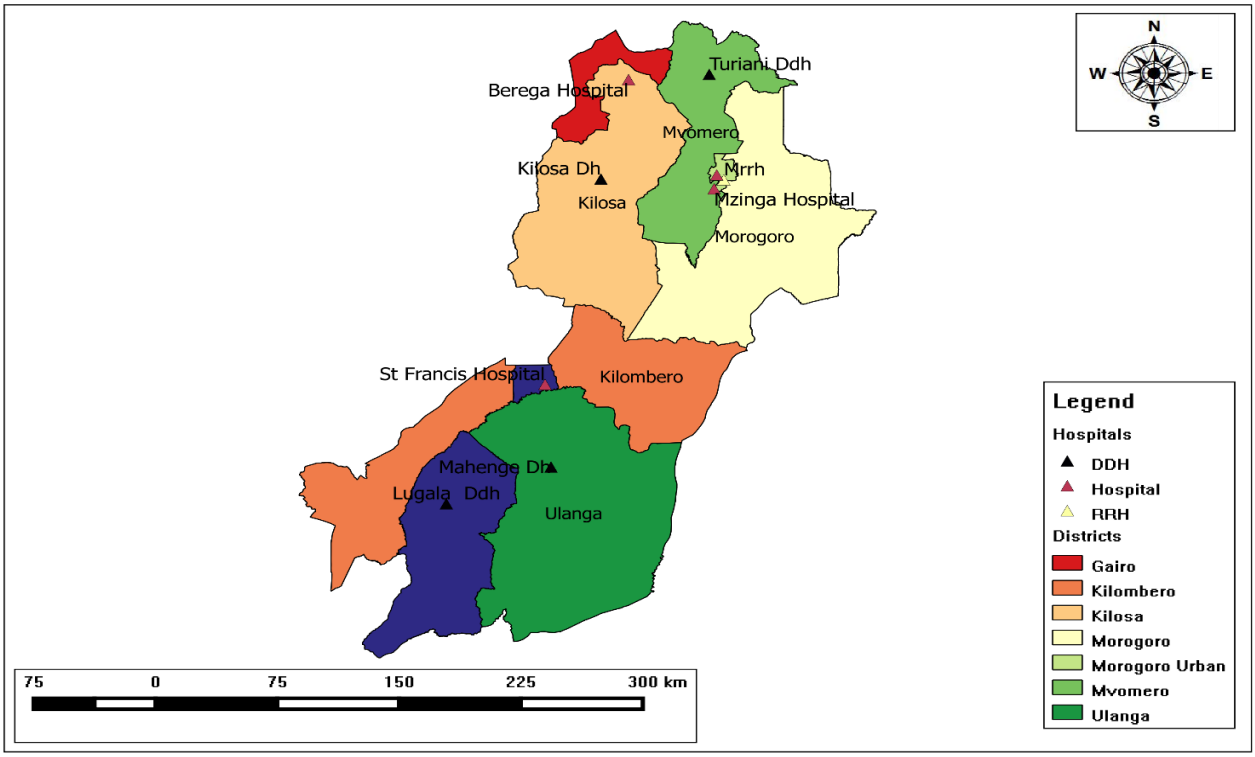
Figure 15: Map of Dar es Salaam Region showing diagnostic centers



Morogoro

Morogoro region is in the south centre of the country and is one of 31 administrative regions in Tanzanian Mainland. Figure 16 shows a map of the region split into districts. The region has a population of 1.2 million and occupies a total of 72,939 square kilometres which is approximately 8.2% of the total area of Tanzania mainland (114). It is the third largest region in the country after Arusha and Tabora regions. The region is bordered by seven other regions. Arusha and Tanga regions to the North, the Coast region to the East, Dodoma and Iringa to the West, and Ruvuma and Lindi to the South. The ethnic groups in Morogoro region are Waluguru, Wakaguru, Wandamba and Wapogoro. The economy of the region is dominated by agriculture and other allied activities. The region is almost completely covered by mountains (115).

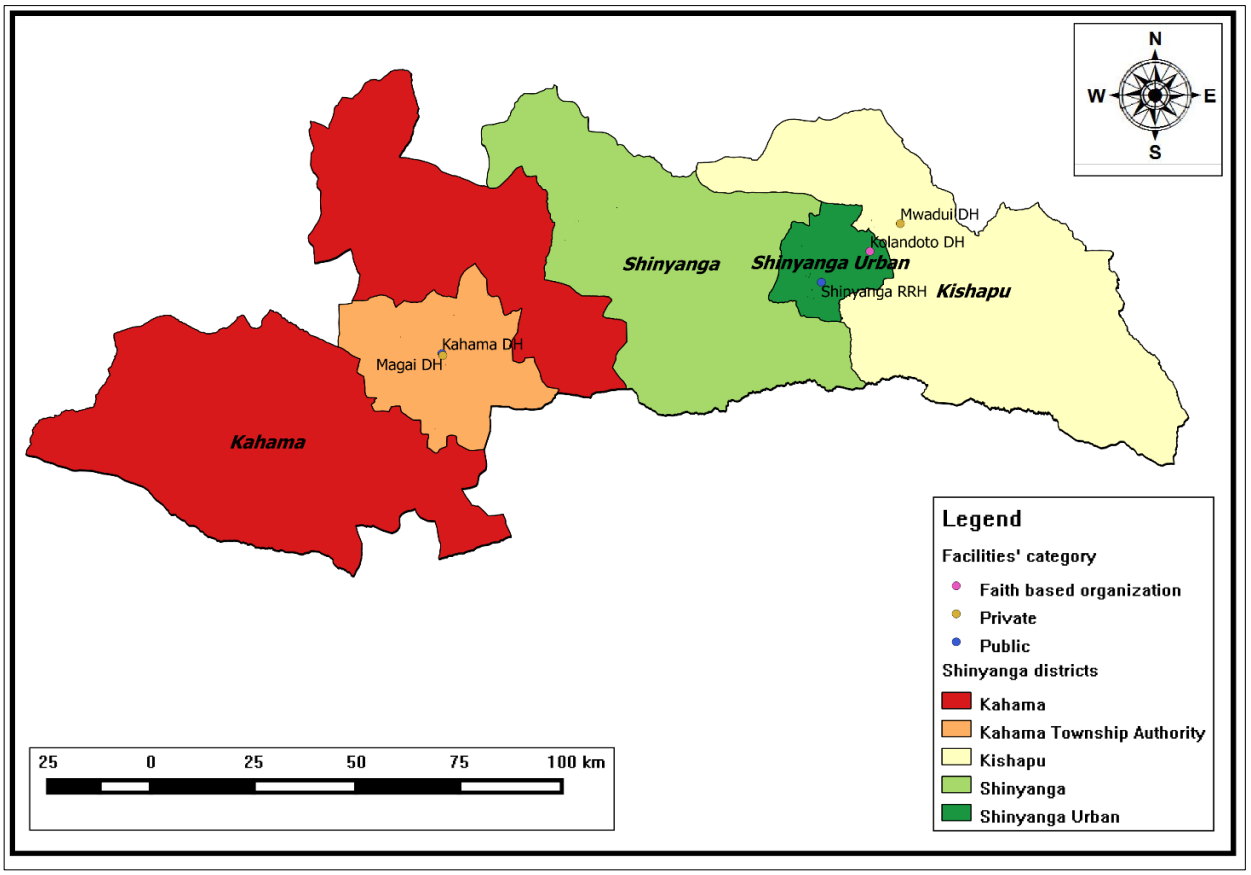
Figure 16: Map of Morogoro Region Showing Diagnostic sites



Shinyanga

Shinyanga region is in the North Western part of the country and is one of Tanzania's 31 administrative regions. The regional capital is the municipality of Shinyanga. Figure 17 shows a map of the region split into districts. It has a population of 1.5 million with a size of 50,781 square kilometres (116). The region is bordered to the north by the Mwanza, Mara, and Kagera regions and to the south by the Tabora region. Kigoma region borders to the west, and the Simiyu region to the east. The predominant tribes of the Shinyanga region are the Sukuma, Nyamwezi, and Sumbwanga tribes. The region economy depends on agricultural (116).

Figure 17: Map of Shinyanga Region Showing Diagnostic sites



4.3 Study Method

4.3.1 Methodology used and justification

A qualitative research method was selected because it is appropriate for understanding views, perceptions and to discover new thoughts that can identify problems and provide solutions to them. The method is specifically designed to uncover a target audience's thoughts and behaviour in connection to a particular topic or issue (117). A qualitative study method can obtain detailed and nuanced information. It would help in understanding fully the weaknesses in the RSS identified in the quantitative data, and to explore further the reasons for those weaknesses.

There are four main methods of collecting qualitative research data, these are: interviews, focus groups, observations and action research (118). In this study we chose to use in-depth interviews (IDIs) and focus group discussions (FGDs) with a range of health care service providers which are described in detail later in this chapter. These approaches are particularly appropriate to this study because they both allow for open-ended questions so that in-depth information can be collected (127).

IDIs involve a one-to-one session with key informants which allow an extended time to discuss topics privately and confidentially in detail with each person. Quality IDIs depend largely on the quality of interactive dialogue between the interviewer and the participant (122). They were chosen as a method appropriate for discussions with senior individuals within the health care programme and implementing partners supporting the NTLP. IDIs can be time consuming and resource intensive (128).

FGDs are a good way to gather together a group of participants from similar backgrounds to discuss a specific topic of interest. They allow participant interaction to agree and disagree thus stimulating discussion which aids in revealing respondents' real perceptions on the subject of interest (113). Gathering thoughts and traditional views on the RSS was possible through this method of data collection at both regional and national levels. The facilitators were also, where appropriate, able to use lessons and information from earlier IDIs and FGDs to improve questioning in subsequent IDIs and FGDs (118).

4.3.2 Sampling procedure for FGDs and IDIs

In this study we used both convenient and purposive sampling approaches in participant selection. The selection was done purposively targeting the RTLC and Regional Laboratory Technologist (RLT) (one per region) (117). They were chosen on the basis of their unique detailed understanding of the issues concerning the existing RSS implementation (117). Based on their experience this would enable all concerns relevant to the study to be raised (117). Health care providers at all study sites were conveniently selected (119). The health care providers working within the TB clinics and with the TB

Programme at the selected study sites (119) were selected based on availability and willingness to participate.

The CTRL had few staff, and therefore the sampling strategy of selecting study participants for a small population (i.e. less than fifty) was adopted (120). In other words, if the population is less than 50, researchers can involve the entire population in the study, and there was no need to sample. For that reason, the study targeted all 20 CTRL staff who were willing to participate in the FGDs.

Implementing Partners supporting the TB Programme, managers and administrative personnel at the regional level were all chosen for IDIs to provide information about the existing RSS. It was thought their awareness and opinions could play a large role in influencing considerations related to system improvement and policy change.

4.3.3 Sample size

The sample size for the FGD's was 45 participants (25 males and 20 females). At each selected study site, there were at least six to eight participants (mix of people) in each FGD per region as shown in (Table 2). The FGDs were guided by two trained research assistants, one leading the discussion and the other observing and writing down the main points for each theme. The total sample size for IDI's was 10 participants (6 males and 4 females). They took part in interviews as shown in (Table 3). Confidentiality was maintaining throughout the interviews. Refreshment was provided during each FGD (109).

4.3.4 Inclusion Criteria

A range of health professionals working in TB clinics, including regional administrative authority staff, TB programme staff, and laboratory staff at both the regional and national levels.

Implementing partners were included based on those present during the study period and those who agreed to participate.

4.3.5 Exclusion Criteria

a) Non-health care service staff

b) Non-TB health care professionals

4.3.6 Participants and sample size

At each selected regional study site there was a mix of people selected as shown in Table 8. Before participant recruitment, the Principal Investigator (PI) sought permission to conduct the study with all the study sites. The official request letter was signed by the NTLP Programme Manager and sent to all the study sites. All sites gave their authorisation to proceed.

The sample size for the FGD's was 45 participants (25 males and 20 females). At each selected study site, there were at least six to eight participants (mix of people) in each FGD per region as shown in Table 8. The FGDs were guided by two trained research assistants, one leading the discussion and the other observing and writing down the main points for each theme. The total sample size for IDI's was 10 participants (6 males and 4 females). They took part in interviews as shown in Table 9. Confidentiality was maintaining throughout the interviews. Refreshment was provided during each FGD (109).

Table 8: List of Participants, study sites and FGD coding

Region & study site	Participants role	No. of participants	Group	Level
Dar es Salaam, Kinondoni -Mwananyamala	RLT,DOT nurse Lab TB focal person, Courier boy, TB/HIV officer, DTLC	6 incl. 3 females 3 males	GR1	Regional
Dar es Salaam, Ilala - Amana	RLT, DOT nurse Lab TB focal person, Courier boy, TB/HIV officer, DTLC	6 incl. 4 females 2 males	GR2	Regional
Dar es Salaam, CTRL	Lab personnel, Data entry, Quality officer, Safety officer, Supplies officer, Lab in charge	6 incl. 2 females 4 males	GR3 (1)	National
Dar es Salaam, CTRL	Lab personnel (3), Data manager, Xpert focal person, Researcher	6 incl. 2 females 4 males	GR3 (2)	National
Dar es Salaam, CTRL	Courier boy, Receptionist, Attendant	3 incl. 1 female 2 males	GR3 (3)	National
Shinyanga	RLT, DOT nurse, Lab TB focal person, TB/HIV officer, DTLC, Sputum fixers	6 incl. 3 females 3 males	GR4	Regional
Morogoro	RLT, DOT nurse, Lab TB focal person, TB/HIV officer, DTLC, Sputum fixers	6 incl. 2 females 4 males	GR5	Regional
Arusha	RTLC, DOT nurse, Lab TB focal person, TB/HIV officer, DTLC, Sputum fixers	6 incl. 3 females 3 males	GR6	Regional

RLT-Regional Laboratory Technologist; DTLC-district TB/leprosy coordinator; RTLC- regional TB/leprosy coordinator

The total number of FGD participants was 45 (25 males and 20 females). The FGDs were guided by two trained research assistants (RA), one leading the discussion and the other observing and writing down the main points for each theme.

The total sample size for IDIs was 10 participants (6 males and 4 females). They took part in interviews as shown in Table 9.

Table 9: List of Participants, study sites and IDI coding

Study sites	Participant job role	Group no	Gender	Level
Morogoro	RTLC	GR7	M	Regional
Shinyanga	RTLC	GR7	M	Regional
Arusha	Ag. MO in charge	GR7	F	Regional
Kinondoni	RTLC	GR7	F	Regional
Ilala	RTLC	GR7	M	Regional
MoHSW	Ag. DPS	GR8	M	National
NTLP	PM	GR8	F	National
NTLP	MDR coordinator	GR8	M	National
Partners	MSH	GR9	M	National
Partners	PATH	GR9	F	National

Keys: *Ag. MO- acting medical officer; GR- group; MSH- management science for health; M- male; F- female; RTLC- regional TB and leprosy coordinator; NTLP – national TB and leprosy Programme; PM – Programme Manager*

Confidentiality was maintaining throughout all the FGDs and IDIs. Refreshments were provided during each FGD (109).

4.4 Study preparation

4.4.1 Pilot Study

Before the interviews, a pilot study was conducted in three regions which were not among the selected study sites: Iringa, Lindi and Manyara. The aim was to test out the qualitative research tools (topic guides). It was observed that not all the health care workers at the TB clinics had knowledge of the RSS. It was also evident that there were variations in levels of knowledge and commitment to its implementation. One region could not be interviewed as the administrative authorities refused to participate in the study. This was because of staff shortages and felt it would cause problems for their jobs. Despite providing assurance of confidentiality they were not comfortable to take part.

Due to these difficulties I engaged the NTLP Manager with study sites to emphasise the benefit of the study and provide assurance on adherence to confidentiality. They were informed that their participation would improve the outcomes of the Programme.

4.4.2 Research team responsibilities

As the head of the CTRL, the research team leader, and a laboratory scientist with several years' experience I was responsible for the overall study. In particular, I was responsible for the design of the study; support to and quality assurance of data collection; training and management of the research team; and writing up of the research in this thesis. I have experience in assisting research projects on TB under the NTLP in Tanzania, including a master's degree in Medical Microbiology and Virology. I have undergone a one-week training in conducting qualitative research as part of my PhD course. Analysis of the data collected was supported by a statistician.

The study research team consisted of a senior research assistant (social scientists) with experience of qualitative research and a research assistance (RA). Both were responsible for conducting interviews and focus group discussions. The senior research assistant ensured the careful translation of documents such as the consent sheets, topic guides and transcripts of interviews and FGDs. The second RA also undertook some transcription and translation of the recorded interviews and focus group discussions. Both the research assistants collated the data with my close supervision.

A senior laboratory person with experience of carrying out laboratory field work and some qualitative research, undertook additional qualitative research training provided by NIMR Muhimbili. He acted as my immediate assistant and was able to accompany the social scientist while conducting interviews and FGD's. In order to facilitate openness, I did not take direct part in most of the interviews and discussions. Instead, the senior laboratory person helped provide participants with an opportunity to speak out and give their ideas openly in order to accomplish the objectives of this study.

My PhD supervisors supported this research as follows: -

- PhD supervisor Professor Bertie Squire (LSTM) provided technical input and guidance on the layout of the study thesis.

- PhD supervisor Dr Ivor Langley (LSTM) has extensive experience in designing and supervising research particularly quantitative methods. He worked very closely with me and provided technical input and proof-reading support of the thesis.

- PhD supervisor Dr Eleanor MacPherson (LSTM) has extensive experience in qualitative methods. She provided technical input on qualitative design and layout. She trained me on the qualitative methods and how to conduct the qualitative study.

- PhD supervisor Dr Esther Ngadaya (NIMR) has experience doing research and supported me in Tanzania throughout the whole study as it went forward.

4.4.3 Training

The PI provided extensive training and support to the research assistants and the laboratory personnel assistant. The core skills required to establish positive interviewer and participant dynamics are rapport-building and accommodating different personalities and emotional states. Effective use of these skills affects the kinds of information that participants disclose in a research setting and depend in part on the nature and quality of the relationship participants have with the researcher (109,121).

The training provided - background to the study; how the current RSS is undertaken; selection criteria and procedures; qualitative research methods; how to ask questions; how to translate; how to record information; data analysis; ethics and confidentiality; and data collection tools with emphasis on the terms used and how to translate them. Emphasis was also given on the importance of probing; informed consent process and agreeing locations of IDIs and FGDs with health care providers. The PI together with the

RAs went through the topic guide that would be used during the interviews and FGD's, until all felt confident with it and the whole exercise of participant's confidentiality.

4.4.4 Development of tools

The data collection tools were developed using knowledge gained from the qualitative training. Alongside this, inputs were received from research supervisors, especially Dr Eleanor MacPherson of LSTM who is a Qualitative research expert. In addition, I also read about similar studies conducted in different countries in the published literature.

Topic guides were designed for FGD and IDI and are shown in tabular form in Tables 10 and 11 respectively. A topic guide is a practical framework that indicates what is to be included and reassures all involved that the researcher will cover all the important areas of the research (127). In this study it was used to guide interviewers and participants through the principal themes and issues to be covered according to the study objectives. Questions asked to participants could be modified and followed up in more detail as appropriate. In the interviews and focus groups the questions focused on specifics and getting examples of how the area under discussion supports and impacts on participants work (109).

The interview guides for FGDs and IDIs were available in Swahili and English Appendices 6 to 8). The consent form for FGDs was conducted in Swahili in Appendix 6 or in English and Appendix 7 as appropriate. The translation was done by a bilingual speaker (Ms. Marijani) at the Community department, Muhimbili University. It was then translated back to English by another bilingual speaker (Ms. Tunu) at Ifakara Health Institute (IHI) who did the verifications (Appendix 8). They were both based in Dar es Salaam, Tanzania and were not involved with other aspects of the study. The independent translations had no major differences when compared to the originals. The translators followed the principles published by Jootun, who recommend that researchers need to engage with meanings and discourses to come up with accurate and valid translations (123).

Table 10: Topic Guide for Focus Group Discussion

S/N	Tuberculosis routine surveillance system	Specimen Transportation	CTRL	Relationship to the workload	Knowledge on Tuberculosis	Concluding the discussion
1	How are TB health care workers involved in the RSS?	Does the clinic transport specimens to another laboratory?	What is the perception of the health care workers on the TB reference laboratory?	Where do your patients come from?	How do health care workers become aware of new TB diagnostic strategies?	Is there anything else you think would be useful for the programme to know?
2	Probe; what is their roles in RSS, what do they think of the current method, what is their perception on the TB Programme and the reference laboratory?).	Who does the specimen transportation? (Probe; how is it transported?)	What do they think could be done better or could be sustained?	probe ;(how many patients per day per clinic, if heavy clinic, why, issues around health education and who does the TB screening)	(Probe; from the programme, training, internet, collaboration with the TB programme, how is it disseminated)	Do you have any questions about any aspect of this interview?
3	Describe how RSS is implemented in your health facility?	Probe means of specimen transportation	(Probe: Issues around TB networking, results turnaround times and the performance).	What perceptions do the health workers have towards patient management?	What do health care workers know about TB transmission?	
4	Probe: if health care workers know about the RSS and what type of specimens need to be sent, algorithm and safety)			(Probe; compared to the number of staff, skills, motivation)	Probing on ways it is transmitted, ways it is prevented, explore questions relating to TB diagnosis)	
5	What do health care workers think are the challenges in implementing the routine surveillance system?				What knowledge do the health care workers have on RSS?	
6	Probe issues related to causes that contribute to TB diagnosis delays, is it the patients or the programme, feedback of the				Probe; how it works, collaboration with the reference lab, specimen to be transported, frequency)	

	results, specimen handling and support from the TB Programme).					
7	What could be done differently to make it better, what could be beneficial to the community?					

Key: TB- Tuberculosis; RSS – Routine surveillance system

Table 11: Topic Guide for In-depth Interview

S/N	Heath workers Views and Roles	Health workers perception	Knowledge on RSS	Perceptron on the Network	Closing
1	What are your views about the TB control Programme performance?	Ask for their perspective; is there anything, which would prevent them from changing the current services provided or the system?	What do you know about TB routine surveillance system?	Probe what is their perception of the TB networking?	Is there anything else you think would be useful for programme to know? Do you have any questions about any aspect of this interview?
2	What do you regard as the successes of routine surveillance system?	What have been some of the challenges for you as an individual?	What recommendation would you make on RSS?	Any other comments please?	
3	How do you view your own role in the TB programme? (Probe)				
4	How do you see your role in supporting TB programme policies implementation?				

Key: TB- Tuberculosis; RSS – Routine surveillance system

4.4.5 Confidentiality and Consent

The RA was trained on how to carry out the interviews and FGD's, and how to maintain confidentiality. Issues of confidentiality would also be addressed at the time of data collection. At this point, assurances of confidentiality, via consent form statements such as, "All identifying characteristics, such as occupation, city, and ethnic background, will be changed" (124). In this study codes were used in place of participant or site names to ensure anonymity and participants job security. Consent forms were provided a day before the interview to provide sufficient time for the participants to understand the information relating to the study.

The RA explained the purpose of the interviews and FGDs, confidentiality issues and the informed consent process. The RA informed potential participants both at the national and regional levels of the methods of obtaining data and the expected benefit arising from the study; this was before consent. They were then given an opportunity to go through the document before filling in the translated consent form as shown in (Appendix 6). They were also given an opportunity to ask questions and responses were provided accordingly. They were granted freedom to withdraw from the study at any point without prejudice. The RA informed them that the information collected would be treated confidentially and that the research assistant would keep the signed consent forms in a locked cabinet. The RA emphasised that no name or site name would be used throughout the study, instead codes would be used to maintain confidentiality.

4.5 IDIs and FGDs Conducted

4.5.1 Overview

There were two types of qualitative data collection used in this study. i) IDI with key informants, and ii) FGD with health care workers. Topic guides were used to guide interviews and discussions in order to ensure a structured and comprehensive approach

to the gathering of information, 6 FGDs and 10 IDIs were conducted with a total of 55 participants. The IDIs and FGDs were audio-recorded to not only capture all valuable and detailed discussions, but also to help the research team to be attentive to the conversation with study participants.

1. In-depth interviews (IDIs)

The IDIs were conducted by one of two RAs. Firstly, a senior Research Scientist from NIMR with experience in qualitative methods. She conducted interviews at health facilities in Dar es Salaam- Ilala, Kinondoni and at the CTRL in Dar es Salaam. Whilst a second RA from NIMR was hired to conduct the interviews in Arusha, Morogoro and Shinyanga. The IDIs were conducted in English on the recommendation of the participants. The IDIs involved TB programme staff, managers, policy makers at the Ministry of Health (preventive unit), regional administrative authorities and implementing partners Management Sciences for Health (MSH) and PATH who were supporting the NTLP. The venues were selected depending on the location of the participants. The sessions lasted for an hour up to 2 hours. All interviews were conducted in a quiet environment that provided privacy. The location was that preferred by the individual, but most often was their office or in the CTRL conference room. The interviews with Implementing Partners were conducted in their offices. Most of the IDI were conducted early in the morning before they started their daily routine work.

2. Focus group discussions (FGDs)

Participants for the FGDs were recruited from the selected study sites. Purposeful sampling technique was implemented at the national and regional level by intentionally selecting study participants in order to ensure that a variety of perspectives on the research topic were represented (119,127). This ensured a diverse range of views with respect to roles, seniority and experience. So as to avoid tension among participants, the higher-level staff were not included in the FGDs, instead they were recruited to the IDIs (128). This is because participants might be fearing the presence of their leaders in

answering questions. So, each FGD involved participants of similar seniority so that they would feel able to respond freely and openly to the questions (109).

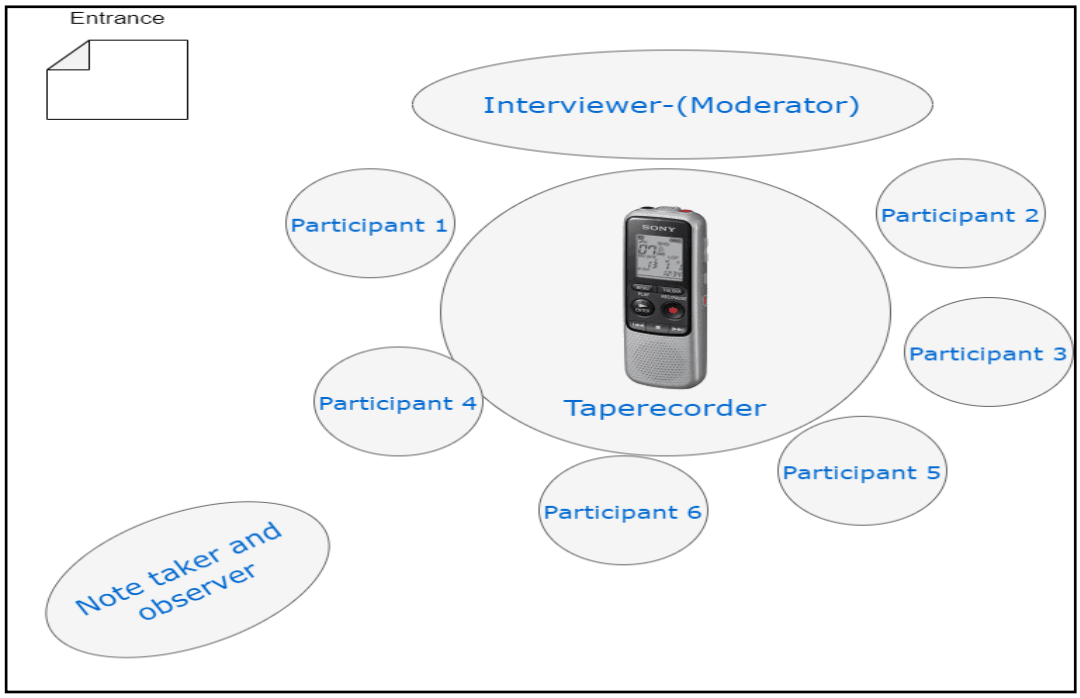
The FGDs were conducted at regional and national levels depending on the participants' availability and workplace.

3. Regional level

Six participants from each selected study site were recruited for each FGD. See participant's distribution in Table 9. In each selected region one member from DTLC, a DOT nurse, a courier person, a TB laboratory focal person and a TB/HIV coordinator were selected based on their willingness to participate in the FGD. By default the RTLC and Regional Laboratory Technologist (RLT) were purposefully selected because each region has one RTLC, while other health staff were conveniently selected (125). The district level DTLC and TB/HIV coordinators also took part in the study.

The FGDs were guided by the two RAs with the senior RA leading the discussion, and the other observing and writing down the main points for each theme. The concept of theoretical saturation was used to halt discussion when no new conceptual information was emerging from discussions (126). Data saturation was reached at six FGDs. The selection of the venue was done with the help of the RTLC. Each participant was given a consent form prior to taking part in the study. Additionally, participants were made aware that interviews were being tape recorded, and informed that the recording will be kept for up to seven years. This permitted re-analysis if need be using the tape recordings. The FGDs were conducted in Swahili and each session lasted for an hour up to 1.5 hours. Refreshments were provided during the FGD session. The FGDs conducted at the regional level used venues agreed with the participants and were undertaken late afternoon when the staff had finished attending to all patients. A typical room layout is shown in Figure 18.

Figure 18: Focus group discussion sitting positions



4. National level

FGDs were planned to be conducted involving 20 CTRL staff to explore the perception of the programme staff about RSS implementation. In the end only 15 participants took part in the FGDs at the CTRL, as some were out of the office or on annual leave. The CTRL participants for FGDs were divided into three groups; two groups each contained 6 participants and one group had three participants. The CTRL FGDs were conducted once per day for three consecutive days. The Research assistant conducted this FGD.

4.5.2 Study data handling

During fieldwork, two digital audio-recorders were used to record interviews and field notes. The senior RA and the PI kept the recorders securely and the PI transferred audio files at the end of each day to their laptop which is password protected, deleting the original file from the digital device. The protected laptop was accessible only to the PI. The PI carried with her or stored it in a locked cabinet in her office at the CTRL in Dar es Salaam. A duplicate copy of electronic files was stored on a password-protected external hard drive to ensure full back-up of collected data. The hard drive, along with hard copy documents related to the study, such as handwritten field notes and signed participant consent forms, were stored in a locked cabinet at the CTRL accessible only to the PI.

Audio-recordings and corresponding transcripts and notes were marked with unique identifiers to protect participants' identities. The participants unique identifier was based on the type of data collection used (e.g. Focus Group); the group number (GR1 – GR6 depending on location); whether regional or national; gender; and participant number (between 1 and 15). For example:

1. ***FG-GR1-REG-F1***
   FG- focus group discussion
   GR1- sites name
   REG- region level
   F1- F – female 1- participants number 1

2. ***FG-GR3-NL-M15***
   FG- focus group discussion
   GR3- sites name
   NL- national level
   M1- M - male, 15- participants number 15

The participant identifiers for in depth interview participants included a group number between 7 and 9, implementing partner or national level; gender; and the participants' number. Therefore, example labelling for IDI participants:

3. ***IDI-GR9-IP-F2***
   IDI- In-depth Interview
   GR9- site name
   IP- Implementing partners
   F2- female participants number 2

4. ***IDI-GR7-RG-M7***
   IDI- In-depth Interview
   GR7- site name
   RG- regional level
   M7- Male, participants number 7

5. ***IDI-GR8-NL-M8***
   IDI- In-depth Interview
   GR8- site name
   NL- national level
   M8- Male, participants number 8

Seven years post data collection all identifying markers will be removed (de-linked) from all electronic and hard copies of transcripts and field notes. Consent forms (original and scanned versions) and digital recordings will also be destroyed.

4.5.3 Qualitative analysis

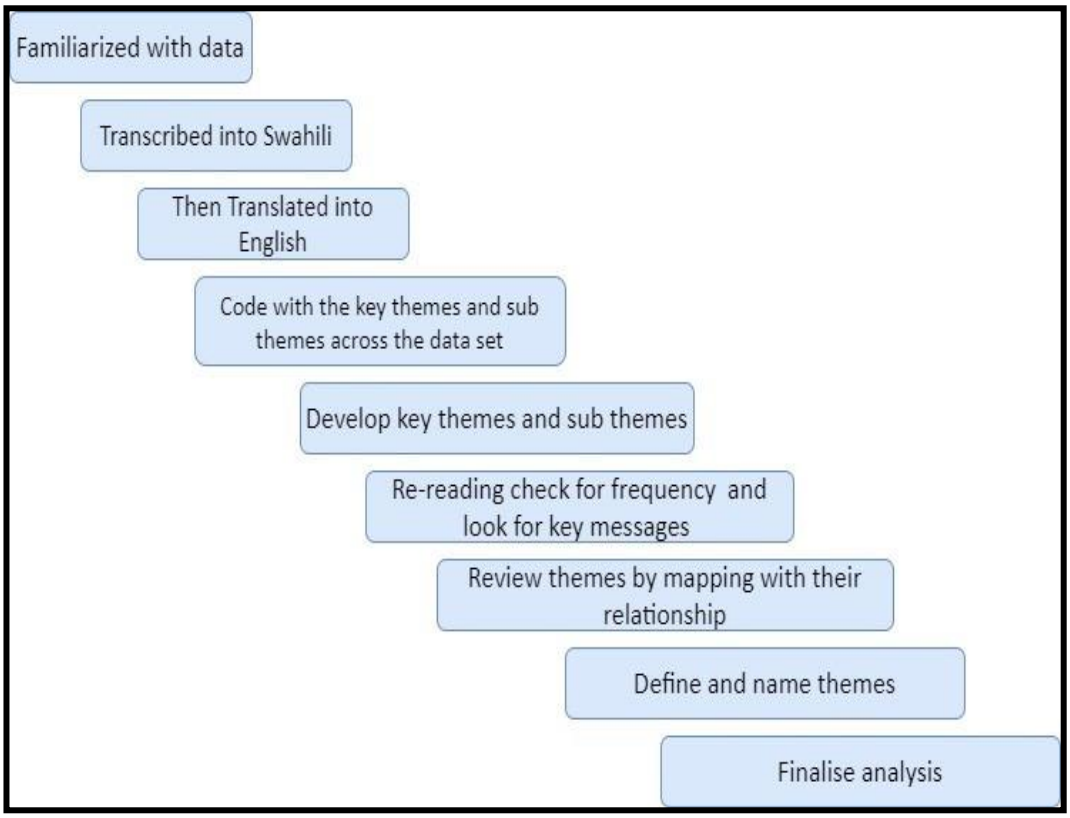
Qualitative research usually produces large amounts of textual data in the form of transcripts and field notes. The systematic and rigorous preparation and analysis of qualitative data is usually labour intensive. To lessen this burden, it is important that health researchers become aware of the possibilities of using Computer Assisted Qualitative Data Analysis Software such as ATLAS.ti, MAXqda and NVivo (129,130).

In this study the qualitative data analysis for the 10 IDIs and 6 FGDs was done using NVIVO 10™. NVivo is a qualitative data analysis computer software package. NVivo is short for Navigating Viewpoints, Images and Value Observed by informants/interviewee, FGD and observation. It has been designed for qualitative researchers working with very rich text-based and or multimedia information, where deep levels of analysis on small or

large volumes of data are required (131). The software program can also be used in a mixed-methods research such as quantitative and qualitative approach. Specifically, it is intended to help users organize and analyse non-numerical or unstructured data (132). Data analysis from the IDIs and FGDs were carried out using the framework approach which provides researchers with a systematic and flexible structure to manage and analyse data (133).

The steps taken to analyse the qualitative data is summarized in (Figure 19).

Figure 19: Steps summary to qualitative analysis



First the recorded IDIs and FGDs were transcribed in Swahili and then translated into English. Transcription and translation were conducted concurrently with data collection and continued after the interviews were completed. Manual analysis began by preparing daily summaries at the end of the interviews. For those who did not permit recording,

notes were taken and transformed into electronic format. The FGDs and IDIs were individually transcribed in its original language, Swahili. This allowed both the precise as well as the symbolic meanings of statements to be understood. The tape-recordings were transcribed verbatim in Swahili by a transcriber and then translated in English by an independent person who was not involved in this study. Each transcribed IDI and FGD was reviewed for accuracy by replaying each recorded interview whilst reading and translating the transcripts. The PI and RA had frequent meetings to evaluate transcripts and notes from the interviews and update topic guides.

Three transcripts were randomly selected and translated by a bilingual speaker who was not involved with other aspects of the study. The independent translations had no major changes when compared to the originals. NVIVO 10™ was used to facilitate the coding process, the codebook was established where key themes and sub-themes were developed from research questions and broader study objectives. The coding was used to organize data and identify different themes and the relationships between them. To refine the codebook, a few interviews were read and re-read to find out the key messages considering the frequency of responses. More frequently occurring statements were underlined, whilst keeping a record of lesser views. Quotations were used to illustrate these themes. Nodes (themes) were developed into qualitative data analysis using NVIVO 10™(131). This coding process was finalized with support from Senior RA and the PhD supervisors. The PI together with the senior RA went through the assembled table and quotes to make sure the results were grounded in the data. This was shared with the supervisors who provided advice on the quotes and assisted in drawing up a structured and simplified flow diagram of linked key themes and sub themes.

Additional emerging themes were added if their inclusion was considered important for improving the TB programme services. Common thematic explanatory categories were constructed to help shed light by identifying key bottlenecks that were limiting the usefulness of the existing RSS implementation for previously-treated TB cases. The generated key themes are described in the next section alongside quotes from

participants in the interviews and discussions. The analysis came to an end once the theoretical saturation point had been reached (127).

4.6 Qualitative findings

4.6.1 Summary of key themes

Data were coded by themes and sub-themes through content analysis. A table of matched themes with subthemes showing strengths and weakness emerging from participants comments. These are summarized in Table 12.

The three main health system areas were the District Diagnostic Centres (DDC), transportation between the DDC and the CTRL, and the CTRL itself. In each of these areas, key themes from the IDIs and FGDs were identified and then sometimes further divided into subthemes. Key themes identified at the DDC were staff demotivation, failure to follow good practice, delays sending samples, and lack of appropriate technology. In relation to transportation between the districts and the CTRL, the key themes were the lack of reliable transportation, lack of funding for transportation, and the distance between the districts and the CTRL. At the CTRL, the key themes were unreliable diagnostic technology, contaminated samples and poor communication with districts. Example quotations from the IDIs and FGDs supporting each of the key themes are provided below.

Table 12: Codebook for Qualitative Study of RSS using NVIVO 10™

Theme/Main Code	Observed weaknesses in RSS	Other observations
A. District Diagnostic Centres (DDC)		
Staff motivation	Lack of incentives Poor safety implementation Missing and poor supervision	Some feel well supported by supervisions
Follow good practice	Lack of training Poor packaging Incomplete forms Lack of lab supplies at DDC	Some feel training better in urban areas
Delays sending samples	Specimen batching	Urban sites do better
Technology	No Xpert Unreliable diagnostics No biosafety cabinets	Xpert now in place in Iringa, Temeke and being slowly rolled out.
B. Transport between DDC and CTRL		
Transportation from/to remote sites	Poor expedited mail service (EMS) No EMS available at periphery	Centres close to the CTRL have less of a problem.
Funding for transportation	Districts required to pay	
Distance between CTRL and some sites	No Zonal reference laboratory Poor communication	CTRL does receive samples from every region
C. Central Reference Laboratory (CTRL)		
Technology	Xpert technology not used Lack of guidelines for new technology incl LPA	LPA now available, but not used
Contamination	High contamination at CTRL (30%) Not all regions using recommended transport medium	The NTLP recommend use of a transport medium to avoid contamination
Communications	Lack of reliable internet and phone. Verbal messages head wrongly	Toll free number available
Delays in results	Poor communications DST just not done	Consequence of all the weaknesses

Keys: DDC- District Diagnostic Centres; CTRL- Central Tuberculosis Reference Laboratory; LPA- Line probe assay

4.6.2 IDI and FGD quotations and the key themes

4.6.2.1 District diagnostic centres

Staff Motivation

Participants considered poor staff motivation at the DDC was impacting the effectiveness of the RSS. In particular this focused on poor supervision, lack of incentives and poor health and safety. For example: -

> *"There is a need to strengthen supervision, make it more fruitful not just a vehicle visiting. It needs to be supportive, get there, stay with the staff, for them to recognise and listen to their problems, and establish the hidden problems too; then provide a solution." (IDI-GR9-IP-M1, 2015)*

> *"If the supervision is done properly it will discover many things and resolve problems." (FG-GR4-REG-M4,2014)*

> *"There is a need to strengthen supervision, make it more fruitful not just a vehicle visiting. It needs to be supportive, get there, stay with the staff, for them to recognise and listen to their problems, and establish the hidden problems too; then provide a solution." (IDI-GR9-IP-M1, 2015)*

> *"Supervision must be supportive, and we have had training often taught supportive techniques. In the district, the DLTC works in cooperation with the CHMT, goes to the facilities with help from CHMT…" (IDI-GR7-M7, 2014)*

> *"I think supervision and training is not bad but in the supervision issue it is still not done very well, mainly because there are too many sites." (IDI-GR9-IP-F2, 2015).*

> *"Supervision is done more frequent in urban areas we have seen this TB program work well because, we find that this service in the city is in frequent and even in the nearby districts. But in some remote areas is a problem because of rains and difficulties to go to there." (FGD-GR2-REG-F6,2014)*

> *"The TB program would have some incentives to employees as the CTC. The work itself is big, when specimens are brought I start to pack them well if they*

are loose, then take them to the post office are all our activities, but no one remembers you when seminars come. Seminar on sputum collection so and so will go, but they do not come to do the work that we are doing, some other things we do is by experience, not that we understand them." (FGD-GR4-REG-M3,2015)

"As my colleagues said, incentives are very helpful, giving workers heart because you look at the context of the work done is difficult, so if there is incentive at least gives one heart to work; maybe after a year you say the best worker is so and so, even if you do not give him anything only a certificate helps; even applauds someone gets motivated; it is not necessarily motivated in terms of money or anything else." (FGD-GR5-REG-F4,2015)

"Here I see no safety, for what reason, you are so close to the patient, when weighing the patient, asks you where should the sputum taken, by the window is given the first dose; that is no, now I do not know what the government is thinking about for us" (FGD-GR1-REG-M6,2015)

On the positive some feel well supported by supervisions. For example: -

"I think to be very sincere; the support they are giving us at peripheral level is tremendous. They are supportive and as far as the National TB and Leprosy Programme is concerned and very well organised when we have a problem they will sort it out." (IDI-GR7-REG-F5,2014).

Follow good practice

There were many comments which indicated a failure to follow good practice. In particular, relating to training, packaging of samples, form completion and supplies. For example: -

"Education is not only done once, but it also is a continuous process, and people need to be taught regularly, whether to provide people with new techniques or to refresh them." (IDI-GR9-IP-F2, 2015)

"As my colleagues have said, to check what is not there, what has broken down, more trainings to educate the coordinators and nurses about form completion and the rest and for us also to go to the regions." (FGD-GR3-NL-M5,2015)

"Another challenge is sometimes that there is a lack or shortage of packaging materials and supplies. We used to receive these items from the donor but their contract finished and this is now a problem. We need to know how to package specimens in layers to avoid leakages and specimen rejections at the Central TB Reference Laboratory." (IDI-GR7-M4, 2014)

"In different areas it can be difficult to get specimens to reach the central level quickly enough, and the methods used to examine the specimens, like the Lowenstein Jensen medium, take too long to get results and request forms are not filled in properly.''(FGD-GR2-REG-F6,2014)

"This is a long-standing problem – laboratory request forms are not filled in well; a lot of information is missing. We see forms coming with either one name or just initials and the rest of the information not filled in." (IDI- GR7-F5, 2015)

"Our programme is vertical, so when there is a shortage of slides we grieve. They should integrate so that some of these things could also be budgeted for by the councils at the district level." (IDI-GR7-M4, 2014)

There were some positive comments about training in urban areas and central supplies procurement: -

I think TB control program works better in urban areas, as we have said, because, firstly has invested more in urban areas such as training done for people in towns and cities, support based more in urban areas. (FGD-GR5-REG-M5, 2014).

Delays sending samples

Participants were concerned about delays in samples leaving the DDC. – E.g.: -

"In a parcel of specimens, you could find one specimen 15 days old and another 3 days old, something impossible. I think they get a specimen, but they don't send it on time. Instead, they wait for them to be many before sending." (FGD-GR3-NL-M15, 2014)

"First of all, coordinators need to know the time specimens are to be sent to Dar es Salaam for culture. The awareness of the importance of those specimens should be there so that they would have enough containers and be able to truck the specimens as they are sent by expedited mail services." (FGD-GR3-F12-NL, 2014)

Some felt things were better in Urban areas e.g.: -

A female participant felt that TB surveillance is doing well in urban areas it was also agreed with another male participant; (FGD-GR4-REG-F6, 2014).

Technology

Participants raised concerns about how well functioning the DDC network was in reality. Part of this related to equipment which as new technologies such as Xpert MTB/RIF begin to become available will need to be rolled out and included in the RSS. For example: -

"Of course we know there 900, but they might not know how many of these are functional and how many are not functioning; and for those not functioning to look at the problem/why; is this human resource, equipment or infrastructure; as i said, supervision will tell all these." (IDI- GR7-F5, 2015)

"Yes, I do but now because of HIV patients, I think a different approach should also be used to help these patients because most of them are not able to produce conducive specimen, so most of them are smear negative, nothing seen but they are ill. Therefore, because of HIV a different machine should be used like the GeneXpert that would help these people with lowered immunity and are unable to produce sputum." (IDI – GR7-M5, 2015)

"So if it would possible for the program to get some money then I am making a request even though I will be retired, when our kids come to work here should find a biosafety cabinet there, even if it is a small one; as small as it might be if they will be able to use it, it is O.K. There we have a bigger one but, because it is there and microbiology is done there too, they want us to get out, GeneXpert done there too. But if another biosafety cabinet was here then he processes his specimens then puts them in the gene Xpert and that is it. That is my biggest request." (FGD-GR6-REG-F3, 2015)

"With a new technology GeneXpert and we are trying to get to the district level, and it helps us in identifying resistance to one of the particularly important drug RF. Therefore, gene Xpert gives you two results at once. You take the specimen and start examining it, after two hours it gives you two results, you are infected with TB or not and if you are infected what type of TB, resistant to RIF or not. Therefore, straight away you know what type of TB you are dealing with, responds to the first line drugs or not. From there treatment regime may change, may be given first line drugs or second line drugs but at the same time take more specimens to check the susceptibility of the other drugs." (IDI-GR1-REG-M7, 2015)

4.6.2.2 Transport between DDC and CTRL

Transportation from/to remote sites

Transportation from and to many sites was seen as a major problem by some. E.g.: -

"Another challenge I have seen so far is that transportation is also quite a big challenge. In different areas it can be difficult to get specimens to reach the central level quickly enough,." (FGD-GR2-REG-F6,2014)

"Actually, the biggest problem is referring samples from the peripheral laboratory to district laboratory where post services are not available." (IDI-GR7-F5, 2015)

"First of all, coordinators need to know the time specimens are to be sent to Dar es Salaam for culture. The awareness of the importance of those specimens should be there so that they would have enough containers and be able to truck the specimens as they are sent by expedited mail services." (FGD-GR3-F12-NL, 2014)

Some felt there was less of a problem with centres in Dar es Salaam close to the CTRL. E.g.

"The transportation from Dar es Salaam Laboratory to the Central TB Reference Laboratory is not a problem." (FGD-GR3-F12-NL, 2014).

Funding for transportation

Finding the funds to transport samples to the CTRL was identified as a problem for some. E.g: -

> *"I said, there used to be some assistance like some amount of fuel from the district budget". (IDI-GR7-M7, 2014)*

> *"We have a challenge in how to send those specimens. Who will take the specimens to the stations and who will pick the specimens up in Dar es Salaam and who will pay the costs for sending specimens? We had a partner, but their contract ended. So, that is still hanging in the air waiting for someone else to kick in." (IDI-GR7-M4,2014).*

Distance between CTRL and some sites

Some participants saw a real difficulty with the lack of a nearer facility to do drug susceptibility testing and to take pressure off the distant CTRL. For example: -

> *"Central TB Reference Laboratory staff have been trying to perform their work, but they are overloaded with many specimens from each side of the country. One reference laboratory for culture and drug susceptibility testing in Tanzania, I would suggest that, to identify another branch to reduce congestions which causes delays in results." (IDI-GR7-F6, 2014)*

> *"In different areas it can be difficult to get specimens to reach the central level quickly enough." (FGD-GR2-REG-F6,2014)*

4.6.2.3Central TB Reference Laboratory (CTRL)

Technology

Technology at the CTRL was seen by some to be not quick enough and caused delays. E.g.: -

> *the methods used to examine the specimens, like the LJ medium, take too long to get results and request forms are not filled in properly.'' (FGD-GR2-REG-F6,2014)*

"In general, I would say, the system needs to probably encourage a lot more other techniques I would say the methods used to examine the specimens like the LJ medium method for culture and the drug susceptibility testing both take too long. I think it is a big challenge because we need to be able to get these results quicker. For instance, they could be examined by liquid culture and drug susceptibility testing is done using molecular methods these could give results quicker." (IDI-GR9-IP-F2, 2015).

Contamination

Some participants mentioned the problems associated with samples that are found to be contaminated. E.g.: -

"I think sometimes they are late. As mentioned, there are many challenges, some examinations, whose specimen has spoilt (contaminated) that needs to be re-tested and that is when they are delayed, although not intentionally." (FGD-GR3-NL, 2014)

Communications

Communications between the CTRL and the DDC can sometimes be difficult as is evidenced by theses quotes: -

"My perception is the networking is not that strong: one reference laboratory for the whole country without internet and telephone services for sharing information." (IDI-GR9-F2, 2015)

"These challenges could be solved if first communication; there should be rapid communication between the CTRL and the facilities sending specimens; as they are saying, these laboratory people who are responsible for collection at least a tiny allowance; for them it is harder than even us who only prescribe and who give medicines, the laboratory people are not remembered they are forgotten." (FGD-GR1-REG-F2,2015)

"Let me add, if communication were there, with MDR patients you would get a call a certain person with the number so and so should be prepared, we are come to pick the person up. You call the person if lives in the village and is easily picked up when the vehicle arrives. At the moment no communication, those days it was simpler." (FGD-GR4-REG-M5,2015)

"It is the turnaround time, it is supposed to be 48hrs to 72hrs, but looking at the reference laboratory, the feedback from central laboratory takes about two weeks. However, if the system is improved they can attain the period that is required about 48hrs to 72hrs. This is only in microscopy, but the culture is a bit longer but as far as results are obtained, they should not be delayed. So with time this is going to be improved because of the introduction of new laboratory information system, candidates can be instituted in central lab and communication through internet and everything." (IDI-GR7-F3, 2015)

"We would like it to be better, that everyone has a mobile phone for example, you could just send a message, and we are not at that level yet." (IDI-GR8-NL-F9, 2014)

"So, I think we have a problem, the system of feedback has to be improved in both, from central level to the peripheral level because communication has to be improved." (IDI-GR7-F3, 2015)

Some other individuals in the DDC obviously had fewer problems and welcomed toll free access: -

"With us when we have a problem, we don't keep it, we look for a way to solve it, if we fail, we communicate to the central laboratory. All the time they are supportive and communicate, tell us what to do as an alternative to the problem we have, and obviously sometime is a big problem, they usually come, they very well organized, when we have a problem they will sort it out." (FGD-GR6-REG-M3, 2014)

"With the telephone free system, the DTLCs are supposed to communicate with the CTRL without paying anything so that will improve, because the payment is not the interest anymore because has been paid by reference laboratory, the web system you can just log in the computer and get the results." (IDI-GR3-F3,2015)

Delays in results

Participants expressed concern that getting results from the CTRL took too long. For example: -

"Another challenge is the delay in results; I think the patients and the clinicians are not getting the right message. They think culture and drug susceptibility testing would only be a day's work, which is not right –culture on its own takes up to eight weeks." (FGD-GR3-NL-F9, 2014)

4.6.2.4 Some comments about the RSS overall

In addition, there were some overall comments by participants about the RSS that were worth noting. Not everything was perceived as week, but many identified improvements were needed. E.g.: -

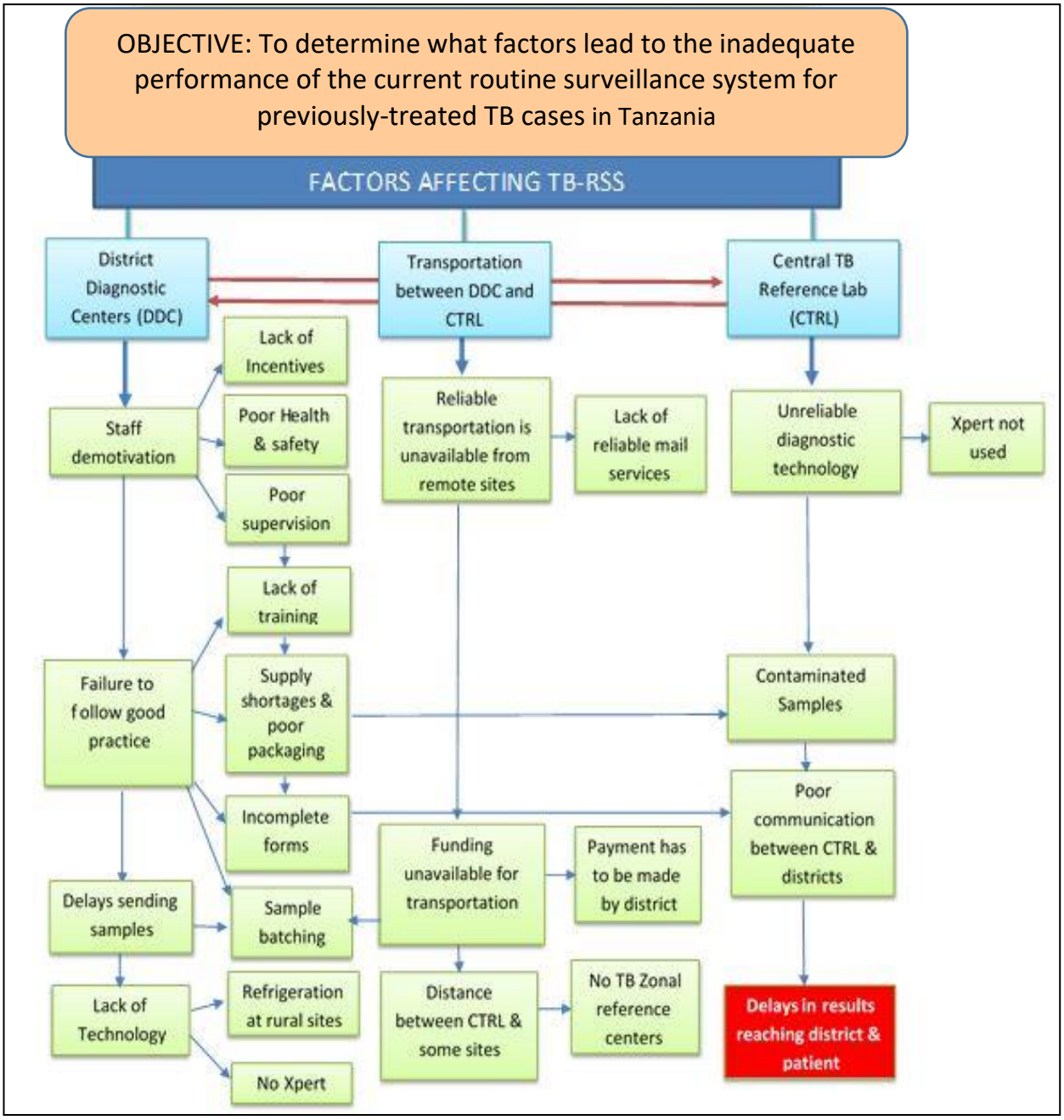
"routine surveillance system is a good programme; they also work smartly, but the programme needs some improvement…" (FGD-GR2-REG-M2,2014)

"Although Routine Surveillance is working well, the way I see it, most of its targets have not been reached. I suggest that it is better if the number of people responsible should circulate the information to all health care providers on how to do it for better understanding." (FGD-GR2-REG-M2,2014).

4.6.2.5 Summary of key themes

The results from the qualitative research were reviewed and presented according to the key themes in Table 12. These key themes and related sub-themes were simplified and links between them identified following discussions with the PhD supervisors. This resulted in the interconnected diagram of key themes and subthemes shown in Figure 20.

Figure 20: Key themes and subthemes observed from the FGDs and IDIs.



4.7 Summary discussion

This qualitative study involved using FGD's and IDI's to review every element of the routine surveillance system for previously-treated TB in Tanzania. It was designed to try and understand why some of the shortfalls in performance of the current system for previously-treated TB cases were occurring, and potentially to help identify initiatives to address these weaknesses.

The qualitative study results showed many associations between the quantitative results (Chapter 3) and qualitative findings (chapter 4). The key shortfalls identified in the quantitative study described in chapter 3 were low volumes of samples being referred for DST to the CTRL; long time delays in transit of samples when they were referred; when they did arrive at the CTRL few samples were receiving a valid DST test; and those that did had long turnaround times. The findings from this qualitative study go some way to explaining these results. For example, poor staff motivation at the DDCs resulting from poor supervision and training would probably contribute to low volumes being transferred to the CTRL. Failure to follow good practice at the DDC in areas such as sample packaging, supplies management and form completion were likely to contribute to difficulties at the CTRL when samples arrive including contamination and the ability to link the sample with a district and patient. The batching of samples and unreliability of transport between the DDC and the CTRL would contribute to long delays before and in transit. Similarly, the use of techniques such as Lowenstein Jensen for drug susceptibility testing rather than Xpert MTB/RIF and LPA would contribute to long turnaround times at the CTRL. This would be further compounded by poor communications between the CTRL and DDC's. Most of these issues including making greater use of new diagnostic techniques like Xpert MTB/RIF need to be addressed if the RSS in Tanzania is to be fit for purpose.

A potential way forward would be to redesign the RSS based on addressing many of the issues identified above. In particular, making use of new and much rapid diagnostic and DST approaches such as Xpert MTB/RIF and LPA, alongside addressing the transport and more organisational and staff related issues described above. If implemented, it would be

hoped this would also lead to an increase in the detection, and speed of detection, of MDR-TB. A way forward to test this could be by a regional pilot in the first instance

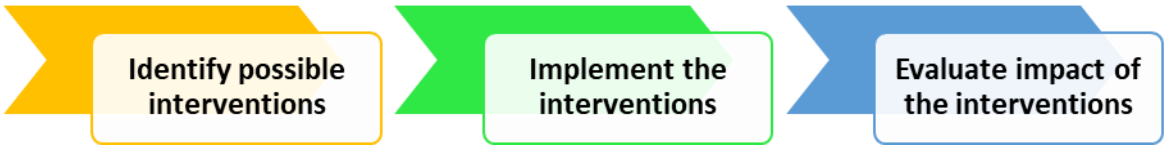
This qualitative study to gather the perceptions of stakeholders concerning the RSS was not without limitations. First, many of the experienced laboratory and districts staff were not available for IDI as a result of high staff turnover, however it was still felt a reasonable cross section of views were gathered. Secondly, it had initially been hoped that additional districts could be added to the study. Unfortunately, due to other pressures on staff time in the districts it was not possible to get a sufficiently large group together to run further FGD's.

The author of this study is unaware of any similar qualitative studies published that review this critical part of TB control in high burden TB countries. With the growth in drug resistant TB, strengthening of the RSS for TB is of particular importance. The findings and methodology used in this study would be of particular relevance for others working in similar settings.

4.8 Conclusions

The study findings provide a basis for identifying potential methods of improving the RSS and thereby providing more timely and appropriate management particularly for patients with MDR-TB. Based on these findings there is a need to address the identified shortfalls of the current system. The next step would be to design and pilot a revised a RSS that addresses some of these constraints and takes on board the use of Xpert MTB/RIF at some district diagnostic centres and LPA at the Central TB reference Laboratory with the focus on providing complete and timely information for management of previously-treated TB patients.

Chapter 5 Interventions to Address Identified Gaps in the Existing RSS



5.1 Introduction

This chapter addresses research questions c) and d) as referred to in the introduction section - 1.9.3. The chapter describes a revised TB RSS for previously-treated TB cases that seeks to address many of the issues identified in the earlier quantitative and qualitative studies described in chapters 3 and 4 respectively (45).

The revised RSS for previously-treated TB cases was designed and then piloted in Mwanza region, Tanzania. The design took into account the recent introduction of molecular diagnostic techniques (i.e. Xpert at some peripheral diagnostic laboratories and LPA at the CTRL). The analysis looked at the effects of the revised RSS on the number of specimens received and tested, the duration for specimen transportation and result feedback, and the number of MDR-TB cases detected. It was hoped the revised system would have quantitative impacts on reducing the time from specimen collection at the peripheral sites to the communication of DST results by the CTRL back to the requesters; increasing the number of specimens received and tested at the CTRL; reducing contamination rates at the CTRL; and ultimately increasing the number of cases starting appropriate MDR-TB treatment. The analysis would also enable a qualitative assessment to take place (described in chapter 6) on the benefits of the revised RSS at addressing many of the key themes and sub themes from the qualitative study described in chapter 4, Figure 20.

The research covered in this chapter has now been published (143).

5.2 Study objectives

To design and pilot a revised routine surveillance system for previously-treated TB cases in Tanzania.

5.2.1 Study research questions

This part of the overall study was designed to address research questions c) and d) as shown in section 1.9.3 and below: -

c) What new design of routine surveillance system for previously-treated TB cases might overcome many of the weaknesses in the current system?

d) Does the newly designed and revised routine surveillance system improve the performance of the system, in particular by reducing the time from sputum collection at the district health facility to communication of the drug susceptibility test result by the Central Tuberculosis Reference Laboratory back to the district? (Quantitative)

5.2.2 Study aims

Identify and pilot a revised and improved RSS in Tanzania for previously-treated TB cases that overcomes many of the barriers to performance in the current RSS.

5.2.3 Study hypothesis

A revised RSS for previous treated TB cases would accelerate and increase the number of DR-TB cases identified and provide timely information for patients, clinicians and policymakers, thus improving the control of MDR-TB in Tanzania.

5.3 Methods

5.3.1 Study site

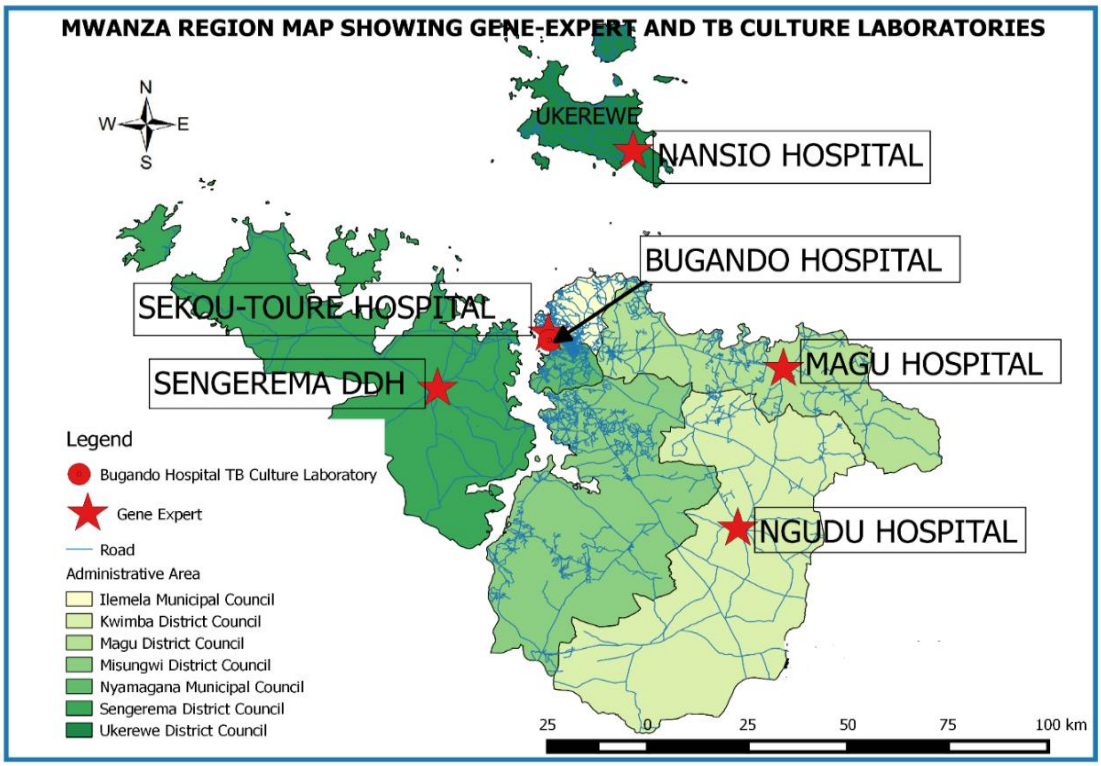
Four districts of Mwanza region (population of 2.77 million (114) were chosen for the study. Mwanza was chosen because it was not among the four regions selected in the qualitative study in chapter 4 and is a remote area with a high TB caseload and therefore an area where transportation of specimen could be particularly problematic. The region is 1,142 km by road from Dar es Salaam where the CTRL is located and where drug susceptibility testing currently takes place. There is also a high burden of HIV/AIDS in the region (23,24).

At the time this study was conducted, there were 80 smear microscopy diagnostic centres in Mwanza region, with 5 centres recently installed with Xpert MTB/RIF for routine diagnosis (4 diagnostic centres plus the Bugando Medical Centre Zonal Lab) – see Figure 21.

Mwanza is one of eight regions under the 'Challenge TB' umbrella supported through USAID. This made it easier to set specimen referral arrangements as all the components necessary to setup and run a logistics system that moves specimens from collection sites to the testing laboratories and return results were in place. In addition, this would provide facilities to monitor and track specimens; to document the level of inappropriately filled in request forms; and to improve overall communications.

Therefore, for the above reasons and due to its size and location, Mwanza was considered an effective location for evaluating the impact of a revised RSS. If a revised RSS can deliver improvements in such a region it was believed it would likely be successful elsewhere.

Figure 21: Map of Mwanza region Showing Xpert MTB/RIF and smear microscopy sites



5.3.2 Study design and population

A revised RSS was designed and a prospective pilot study of the revised RSS for previously-treated TB cases was implemented. Before and after quantitative analysis of the impact of the revised RSS was completed. Following the completion of the quantitative study a qualitative study with key stakeholders in Mwanza and the CTRL was carried out, and this is reported in chapter 6.

5.3.3 Sample Size Calculation

The primary outcomes of the study were to assess the impact of the revised RSS on specimen transit time (the time from specimen collection in the peripheral health facilities to the time the specimen is received at a site where DST can take place time) and turnaround time (the time from specimen receipt at the CTRL to the time the DST results are sent back to the requesting clinician). Outline NTLP data from 2015 were used to determine the sample size. The study sample size was powered based on the turnaround

time outcome. A total of 315 specimens were required to show a significant reduction in this time using a 95% confidence interval, 80% power, and hypothesised average difference of 10 days with a population standard deviation of 44.8[5] as shown in Tables 13 and 15.

Table 13: Population standard deviation of 44.8[4]

Turnaround time (TAT) for Mwanza Region for the year 2015					
Year	Number (TAT)	Mean (TAT)	Standard Deviation (TAT)	Minimum (TAT)	Maximum (TAT)
2015	69	88.9	44.8	12	304

Key: *N- Number; TAT- turnaround time; CTRL- Central Tuberculosis Reference Laboratory; SD- standard deviation*

Formula: $n = (Z\alpha/2+Z\beta)2 *2*\sigma2 / d2$

Where: $Z\alpha/2$ is the critical value of the Normal distribution at $\alpha/2$ (at 95% confidence levels) =1.96

a). Z_β is the critical value of the Normal distribution at β (at power 80%) =0.84

b). σ^2 is the population variance

c). d is the difference you would like to detect.

d). n is the sample size required

Table 14: Sample size titration (66)

$Z_{\alpha/2}$=1.96	Z_β=0.84	SD (σ)	d	n
1.96	0.84	44.8	5	1259
1.96	0.84	44.8	10	315
1.96	0.84	44.8	15	140
1.96	0.84	44.8	20	79

[5] https://select-statistics.co.uk/calculators/sample-size-calculator-two-means/ 15th May 2016

5.3.4 Inclusion Criteria

The study included all routine specimens tested at the study sites in Mwanza region from April 2017 to March 2018.

Specimens from previously-treated TB cases only

5.3.5 Exclusion criteria

a) Specimens from follow up cases or known MDR-TB patients who were on treatment monitoring were excluded from the study.

b) Specimens from outside Mwanza region.

c) Specimens from new cases

5.3.6 The justification for eligibility criteria

Mwanza was chosen for the reasons stated in section 5.3.1.

The study focused on previously-treated TB cases only because this is where most of the MDR-TB cases are found. The RSS for previously-treated TB cases is the most established by the NTLP in Tanzania. The NTLP target for the RSS is 100% of previously-treated cases, so there is no ambiguity about which samples were required to be referred. For new cases the target is 25%, primarily as there has historically been low levels of MDR-TB in new cases, and the volumes that would be required to be referred if the target were 100% is way beyond the capacity of the referral laboratories. Despite only focusing on previously-treated TB cases in this study, it is believed many of the lessons learnt from this study could also be applied to the RSS for new TB cases. A pilot of a revised RSS would be a great help in identifying an optimal means of specimen referral from remote areas to the CTRL, as well as provided the likely benefits of the revised RSS across the country as Xpert MTB/RIF continues to be scaled up.

5.3.7 Procedure for the pilot study

To complete the design and analysis of a revised RSS for previously-treated TB cases that has the potential to overcome many of the current barriers to its effectiveness and also takes into account Xpert MTB/RIF use routinely in some district sites, three stages were followed.

- STAGE 1 – Design of a revised RSS
- STAGE 2 – Implementation of the revised RSS in Mwanza as a pilot
- STAGE 3 – Quantitative performance evaluation of the revised RSS

(Note: A qualitative evaluation was also conducted, and this is described in Chapter 6)

Descriptions of each stage are detailed in the following sections

5.3.8 Stage 1 - Design of a revised RSS

5.3.8.1 Interventions to address key themes identified with current RSS

The key themes and sub themes from the qualitative analysis (Chapter 4) that could potentially be addressed by the revised RSS are indicated in (Figure 22). Those that could not be included in the scope of this study are indicated by the red dotted lines around the blocks. These were excluded as the PI had no direct authority to make changes to address these issues. For instance, where there were additional funding requirements with wider ramifications such as changes in the infrastructure effecting sustainability. The blocks with a solid green line around represented those that could partially or fully be addressed in this phase of the study.

Visits to study sites took place to identify possible solutions to the individual issues raised in the qualitative study described in chapter 4. Interventions were designed and are summarised in Table 15.

Figure 22: Theme and subthemes for the pilot study

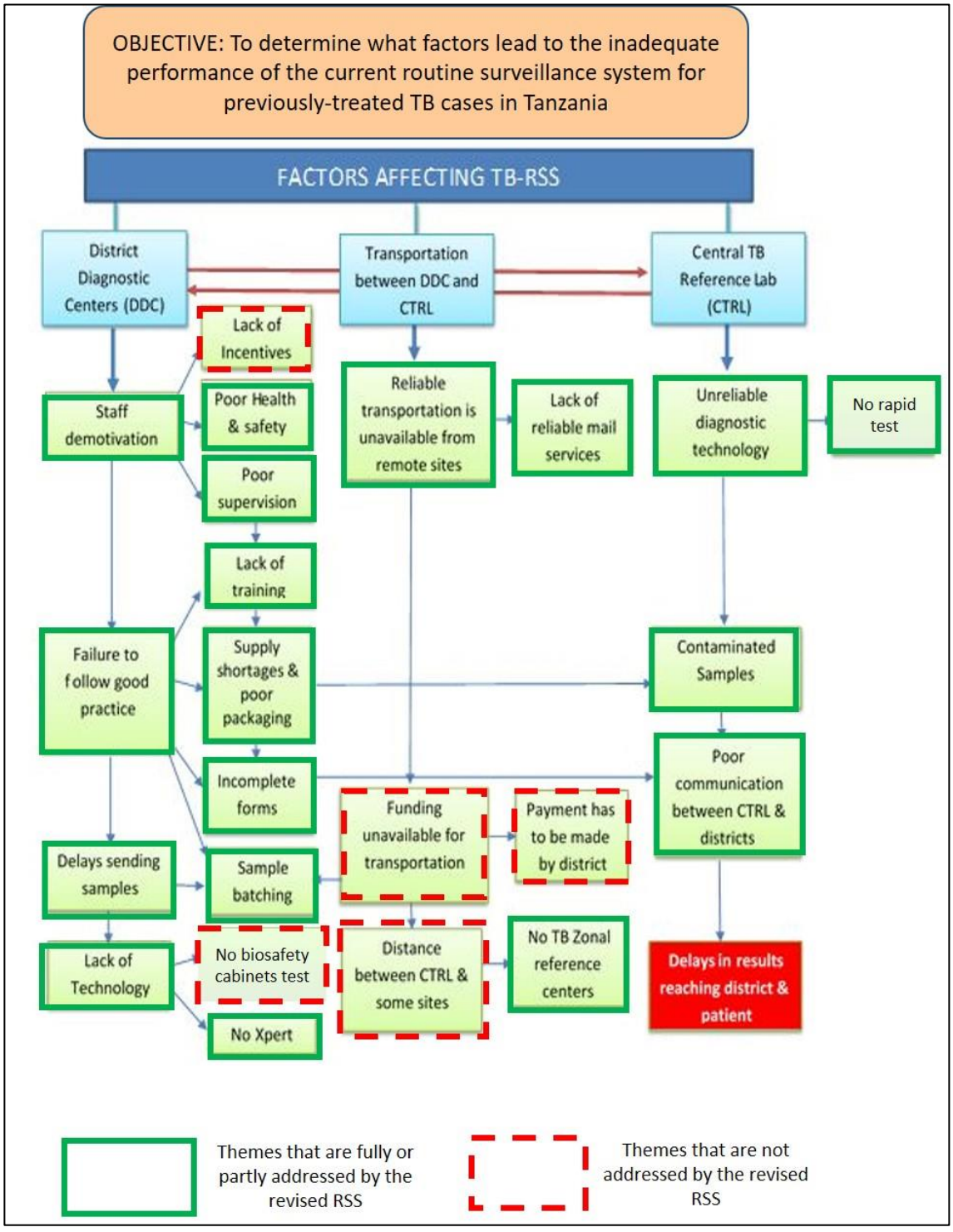


Table 15: Interventions to addresses the weaknesses observed

RSS Area	Key Theme	Weakness	Interventions
District Diagnostic Centres (DDC)	Staff Demotivation	Poor Health and safety	Introduced standard operating procedures on safe specimen packaging and transportation. Introduced 'Triple packaging' system for specimen.
		Poor supervision	Reviewed, adopted and modified supervision tools to accommodate Xpert MTB/RIF technique. Trained health care workers and trained on the use of supervisory tools. Developed new national supervisory schedules. Created standard supervision feedback tool.
	Failure to follow good practice	Lack of training	Improved and implemented new training materials for refresher and in-service training of TB lab staff. Created a training plan based on NTLP criteria.
		Supply shortages and poor packaging	Created a tool for quantification of TB laboratory supplies. Created a procurement plan based on the consumption per laboratory. Training of health care workers for the adoption of the quantification tool and procurement plan. Introduced 'Triple packaging' system for specimen. Trained study health care workers on the specimen packaging and transportation guidelines. Monitored safe specimen packaging and transportation.
		Incomplete forms	Reviewed and updated TB laboratory request forms to improve clarity and accommodate Xpert and new algorithm. Provided on the job training to health care workers on how to complete the new TB laboratory request form. Monitored daily number of incomplete forms.

RSS Area	Key Theme	Weakness	Interventions
District Diagnostic Centres (DDC) continued	Delays sending samples	Sample batching	Created standard policy guideline for specimen referral including time limits (e.g. three days' maximum). Trained health care workers on a revised specimen referral system.
	Lack of Technology	No Xpert	Introduced and promoted the use of Xpert MTB/RIF technique in Mwanza region. Mapped all diagnostic facilities with Xpert MTB/RIF. Training in the use of Xpert MTB/RIF including RR diagnosis.
Transport between DDC and CTRL	Reliable transportation is unavailable in remote sites	Lack of reliable mail services	Created service contracts for specimen transportation with local couriers – bodaboda drivers. Introduction of service levels in contracted EMS services with Tanzania Post Office. Monitoring of transit time against targets.
	Distance between CTRL & some sites	No TB Zonal reference centres	Included the Bugando Medical Centre as a Zonal laboratory for Xpert MTB/RIF and culture.
Central TB Reference Lab (CTRL)	Unreliable diagnostic technology	No rapid test	LPA technique was used to test all previously-treated TB cases received from Mwanza as part of the revised RSS at the CTRL. New monitoring approach to reduce numbers where DST not done at all.
	Contaminated samples	High contamination rate at the CTRL	Introduced culture performance guidelines including specimen to be processed as soon as it is received. Improved sterility by use of disposable pipettes or loops for culture inoculation. Processing specimen in batches of eight instead of batches of sixteen. Use of buffer instead of sterile distilled water
	Poor communication between the CTRL & districts	Poor communication between the CTRL and districts	Facilitated CTRL internet connectivity for sharing of patient results. Introduced WhatsApp groups to facilitate rapid, free and effective communication.

Keys: DDC- district diagnostic centres; NTLP-national TB and leprosy programme; CTRL- central TB reference laboratory; LPA- line probe assay

The form for specimen rejections and SOP for sputum specimen transportation that the PI introduced are available in Appendix 9 and Appendix 10 respectively. The PI also reviewed and developed a revised TB laboratory request form see Appendix 11 and modified the TB laboratory register to accommodate changes see Appendix 12.

A revised RSS included the design of a modified algorithm. Firstly, for the sites with no testing facilities, secondly sites with microscopy testing available but no Xpert, thirdly sites with Xpert technology available for previously-treated TB case specimens, and fourthly the Bugando Medical Centre Zonal laboratory – see section 5.3.8.2.

5.3.8.2 The Revised Routine Surveillance System Algorithm

The existing ('Before') RSS is described in chapter 1 Figure 9.

The revised RSS ('After') design that could be piloted, involved sputum specimens being collected from the study sites and examined using a revised algorithm is shown in Figure 25 for the detection of DR-TB. The algorithm design was in four parts, plus a new algorithm for the CTRL: -

Part A: Study sites with neither microscopy nor Xpert MTB/RIF capacity.

The design involved non-diagnostic heath facilities in remote areas transporting sputum specimen using motorbikes commonly known as *"bodabodas"* (see Figure 23) to the nearest peripheral laboratory where smear microscopy could be conducted. The *bodabodas* were identified and registered in collaboration with the Koninklijke Nederlandse Centrale Vereniging tot bestrijding der Tuberculose (KNCV).

Figure 23: Sputum specimens transportation using motorbike (bodaboda)

Part B: Study sites where only microscopy is available

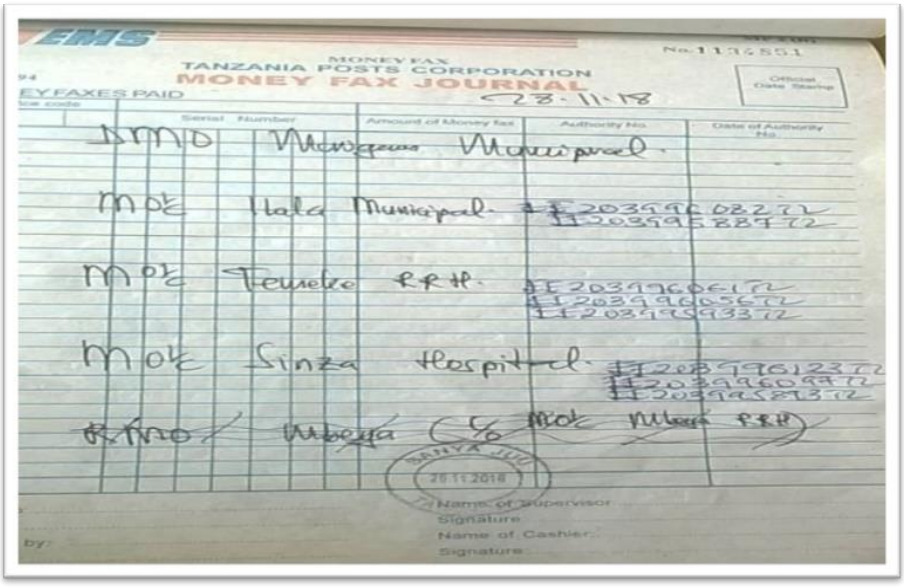
At microscopy sites where Xpert MTB/RIF for TB diagnosis is not available, samples from all previously-treated TB cases that were found to be smear positive were then referred to a local site with Xpert MTB/RIF for testing (this could be either a conventional diagnostic site with Xpert available, or the Bugando Medical Centre where Xpert MTB/RIF and culture could be performed). This would enable RIF resistance to be detected at an early stage and the patient's clinician informed. The bodaboda were used to transfer the samples and results.

Part C: Study sites where both microscopy and Xpert MTB/RIF are available

At sites where Xpert MTB/RIF was available and used as the primary diagnostic tool for TB, those with a positive MTB diagnosis wound require a sample to be sent to the CTRL through EMS (Figure 24) to be tested for first line drug susceptibility using LPA. (Figure

25). This was irrespective of whether Xpert identified RIF resistance or not. The CTRL was informed of this by means of a WhatsApp group message for easier tracking and sharing of information in case of any problems. The WhatsApp group was initiated to ease communication between the CTRL and the study sites ('Mwanza Family'). The bodaboda were available to be used to transfer the Xpert MTB/RIF result from sites with Xpert MTB/RIF, including RIF resistance status, back to patient's clinicians if required.

Figure 24: Expedited mail service (EMS) documentation



Part D: Bugando Medical Centre (Zonal TB laboratory Site)

Bugando Medical Centre is a Zonal laboratory with capacity for both Xpert MTB/RIF and TB culture (LJ media). Samples received here were first tested using Xpert MTB/RIF and any specimens with a positive MTB result (whether RIF sensitive or resistant) would then be referred for culture within the Bugando Medical Centre. The laboratory does not have the LPA technique therefore positive culture slopes were then transferred to the CTRL using EMS for DST as shown in (Figure 25). Bodaboda were available to be used to transfer the Xpert MTB/RIF result, including RIF resistance status, back to patient's clinicians if required.

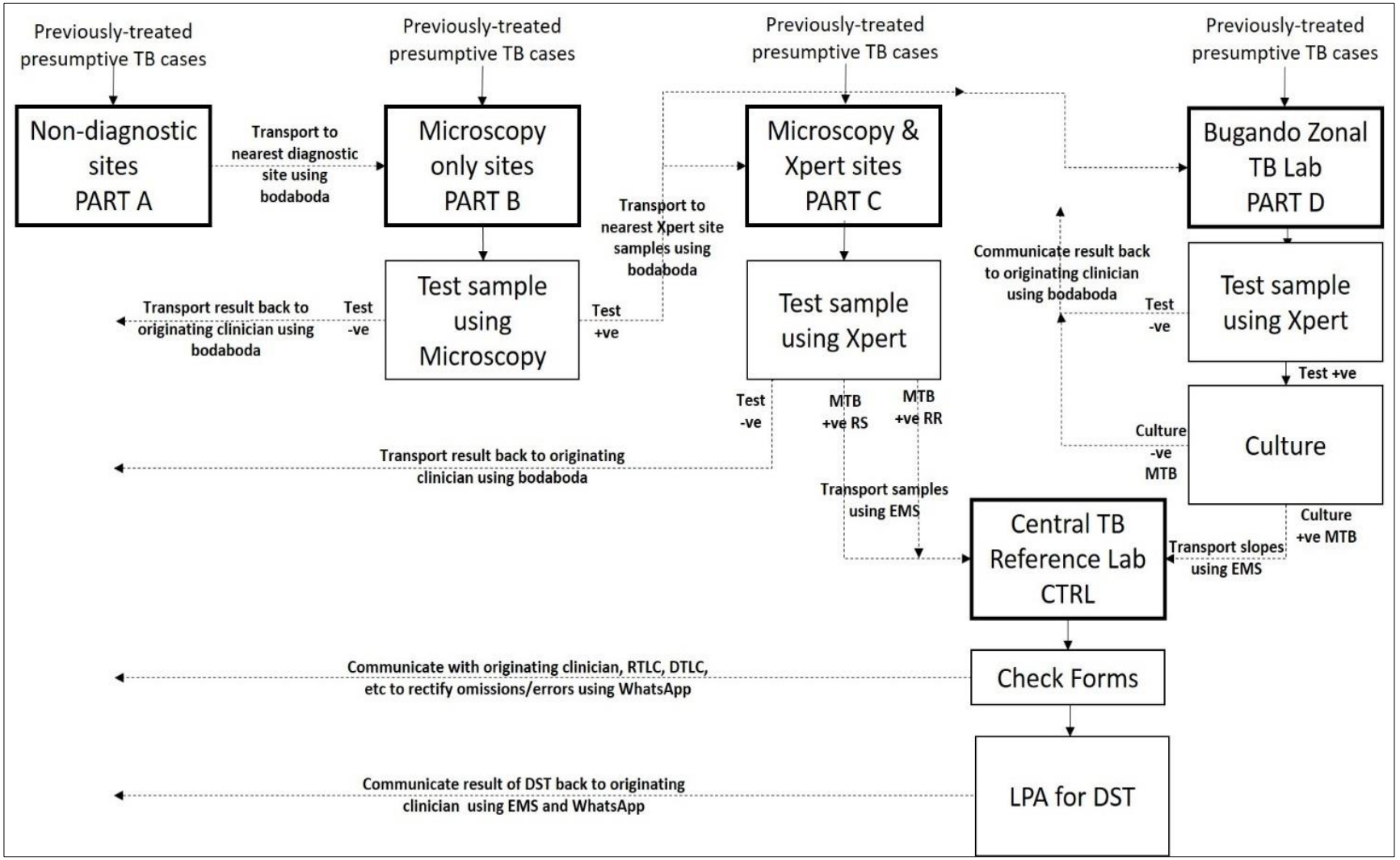
CTRL: CTRL for drug susceptibility testing

When specimens arrived at the CTRL their accompanying forms would be checked for completeness and accuracy against the specimen container. If any problems were found a message would immediately be sent through the WhatsApp groups back to the requesting clinician to rectify any problems.

Specimen preparation at the CTRL was carried out in class II biosafety cabinets and details recorded in the TB laboratory register. LPA was performed for all samples with MTB detected results. This provided evidence of DR including INH mono-resistance, RIF mono resistance, and MDR-TB (resistant to both RIF and INH). Feedback of the LPA result was to be targeted to be within 7 days from the day of collection. A unique patient identification number was generated for easy tracking and dissemination of results. No personal details about the patient were to be kept with the results other than the identification number.

Data were to be entered in an Epidata database and results put on the TB laboratory request forms, which were immediately sent back to the requesting facility through EMS and WhatsApp in case the clinician needed the results right away.

Figure 25 Revised RSS Algorithm



Key: RR- Rifampicin resistant; RS- Rifampicin sensitive; CTRL-Central TB reference laboratory; LPA-Line Probe Assay; EMS- Expedited Mail Service; +ve positive; -ve negative

5.3.9 Stage 2 – Implementation of the revised RSS in Mwanza as a pilot

5.3.9.1 Intervention summary

The redesigned RSS was implemented in Mwanza region as shown in Figure 25 alongside interventions listed in Table 15 above. A summary of the key interventions is listed below:

a) Change in the diagnostic approach to use Xpert MTB/ RIF at local sites in Mwanza and Bugando Medical Centre, and LPA at the CTRL for DST.

b) Introduction of reliable specimen and results transportation between remote sites in Mwanza and Xpert MTB/RIF sites in Mwanza using motorbike couriers (bodabodas).

c) Changes in results dissemination from CTRL to the requestor and copies to the Regional TB and Leprosy Coordinator (RTLC) using new contracted EMS and WhatsApp groups.

d) The CTRL monitored specimen transportation time against a target of a maximum of 7 days

e) The CTRL compared number of specimens received versus cases notified and communicated this to the RTLC using WhatsApp.

f) Revised TB laboratory request form and TB laboratory register were used to improve clarity and accommodate other changes.

g) A supportive supervision schedule was created and implemented with the Mwanza team.

h) Improved general communication between the CTRL and the health facilities in Mwanza region through WhatsApp groups; the Mwanza family, RTLC, DTLCs and CTRL staff was introduced.

The interventions are described in more detail in the following sections corresponding to each of the key themes and weaknesses shown in Table 15.

5.3.9.2 Staff Demotivation

Poor health and safety

Standard operating procedures on safe specimen packaging and transportation were introduced which are described in more detail in section 5.3.9.3 and in Appendix 10.

Poor supervision

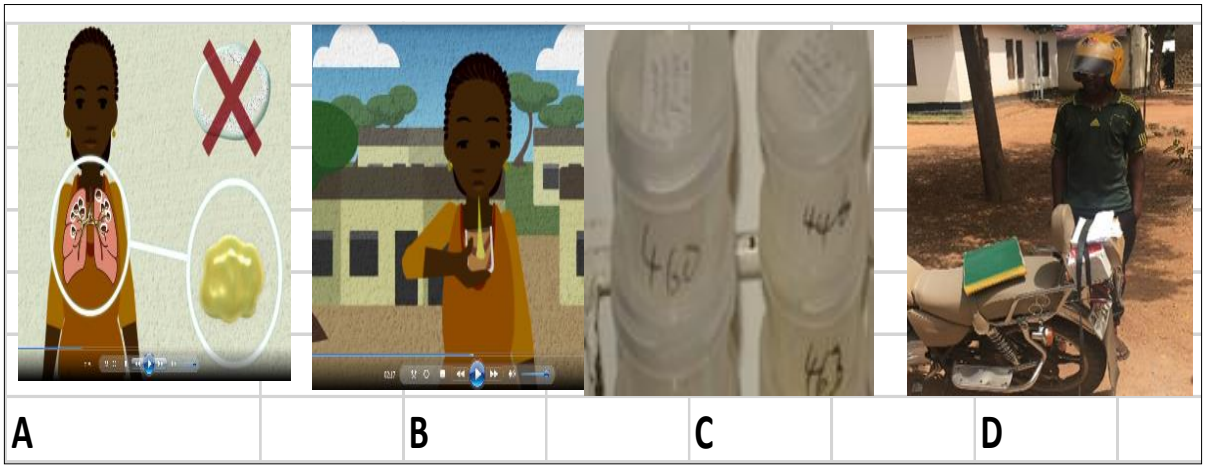
Supervision and mentorship are among the core functions of the CTRL in respect to the lower level laboratory facilities. During the study period supervision was conducted as part of continuous training and corrective action. Modified supervision tools were introduced to accommodate use of Xpert MTB/RIF. Health workers were trained on these new tools and then monitored for a trial period. In addition, new supervisory schedules were agreed and implemented. A feedback tool was introduced to allow peripheral sites to engage more closely with the CTRL as part of supervision. As normal, the CTRL itself was supervised by the Supranational Reference Laboratories (SRL) of Uganda and Antwerp Belgium.

5.3.9.3 Failure to follow good practice

Lack of training

Training was provided on the procedures for sputum specimen collection, transport, reception and accessioning to support the RSS (see Appendices 10, 13 and 14). A single morning sputum specimen should be collected from all previously-treated TB cases in all study sites using a modified algorithm depending on the test method used as shown in the revised algorithm (Figure 25). The training emphasised the importance of the 4 areas below (see Figure 26).

Figure 26: Sputum specimen collection (33)



A: The PI emphasised to the DOT nurses to use the audio-video presentation on how to produce good sputum "*Sampuli Bora ya Makohozi Kwa Kifua Kikuu*"[6] during the pilot for health education at the TB clinics. Patients were instructed on how to produce good quality sputum and not saliva for easy identification of Mycobacterium TB. Patients were informed their mouth should be free of any food substance and rinsed with water prior to sputum collection.

B: Patients were instructed to produce sputum in an open area directed by the DOT nurse.

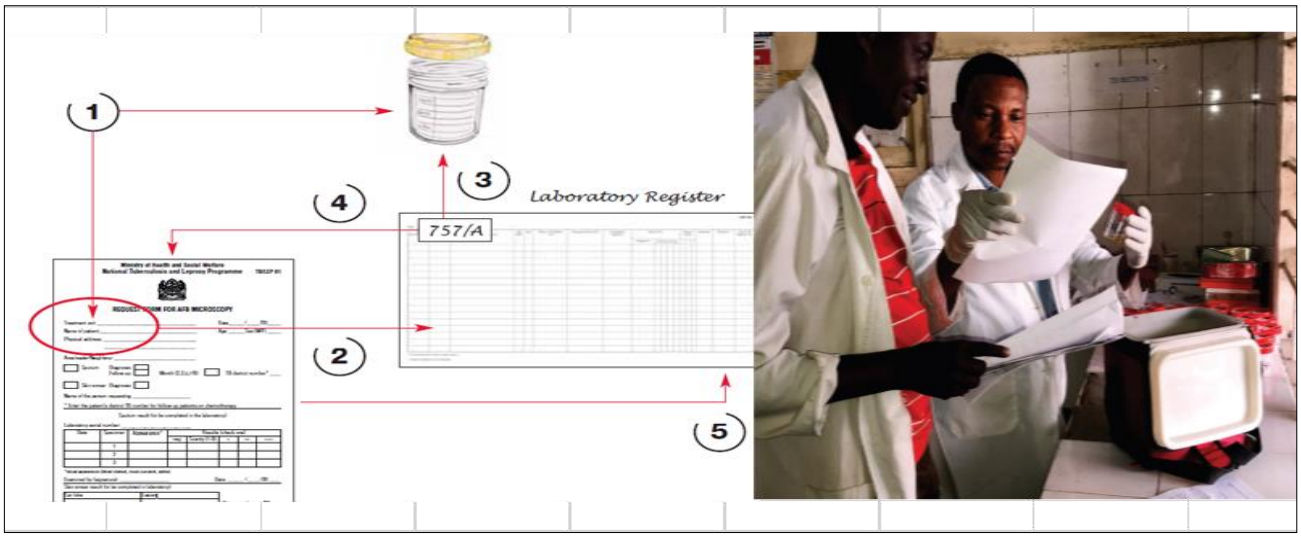
C: Sputum specimens were labelled both at the top and on the side of the container.

D: Specimens are transported to the nearby laboratory for testing using bodabodas.

Emphasis was also provided during training on proper recording of patient's information in order to avoid incomplete laboratory request forms as shown below and in Figure 27. (33).

[6] *https://www.bing.com/videos/search?q=Sampuli+Bora+ya+Makohozi+Kwa+Kifua+Kikuu*

Figure 27: Record the specimen before processing (32)



1. Label patient details on the container including: Health facility name, date, patients name, Age, gender and physical address

2. Fill in the laboratory request form, patient's details must match with those on the container.

3. Record patient details from the Laboratory Request Form to the Laboratory Register

4. Write the Laboratory Serial Number (LSN) on the side of the specimen container

5. Write the Patient study number

Training on the revised RSS using the modified TB laboratory algorithm and specimen transportation system was conducted for Mwanza TB health care workers involved in the study and at the CTRL. This included reviewing the SOPs and algorithm to maximise Xpert utilisation and smooth specimen flow and transportation within the region. In Mwanza training was organised and agreed with the RTLC and provided to the DTLC, TB/HIV

coordinator, DOT nurse, laboratory personnel working at the TB section, sputum fixers and RLT. A review of the existing system of results dissemination was also conducted. Good Laboratory Practice (GLP0 was emphasised and staff trained on how to implement the pilot study.

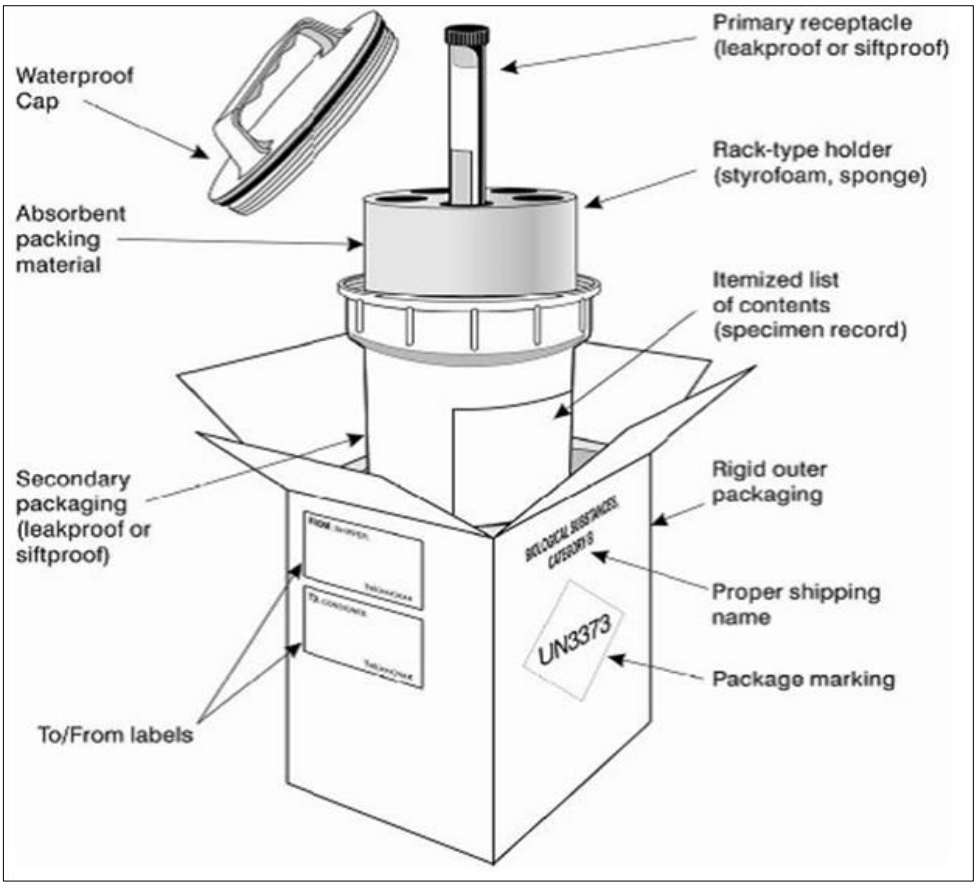
Supply shortages and poor packaging

A new tool was created for the monitoring and quantification of TB laboratory supplies. A procurement plan based on the consumption per laboratory was initiated to avoid supply shortages. Health care workers were trained in the adoption of the quantification tool and procurement plan.

For safety purposes, all specimens were securely packaged using triple pack as shown in Figure 28. A Triple pack is a system where a specimen is inserted in a clear zip bag and the zip bag is put in a small plastic container with a screw cap (known as a primary container together with absorbent material in case of leakages). Then the primary container is inserted in a plastic container (secondary container) together with the completed TB laboratory request form.

The secondary container is then put in either a metal, plastic or cardboard box. At every step, labelling is done. The laboratory personnel on duty at each site cross-check all TB laboratory request forms for completeness and appropriate packaging. Study health care workers were trained in the specimen packaging and transportation guidelines. The PI monitored safe specimen packaging and transportation as samples were received at the CTRL.

Figure 28: Triple-pack container for laboratory specimen transportation (33)



Incomplete forms

Reviewed and updated the TB laboratory request forms to improve clarity and accommodate Xpert and the new algorithm – (see Appendix 11). Daily monitoring of the number of incomplete forms took place. Incomplete forms were identified, and the respective site was immediately informed using WhatsApp's. Forms were also scanned and sent as an email attachment or through an agreed method so that the problems were quickly addressed.

5.3.9.4 Delays sending samples

Sample Batching

Specimens were transported on the day of collection whenever possible, even if it was just a single specimen. This avoided unnecessary delays which would have occurred if samples were batched with samples from previous days.

5.3.9.5 Lack of Technology at DDCs

No Xpert

Most specimens collected were analysed using either LED or ZN microscopy techniques depending on availability in the relevant laboratory (see PARTS A and B in Figure 25).

If both sputum smears were negative, the laboratory personnel sent results to the clinician for clinical management. If one or both were positive, then a morning specimen was collected and sent to the nearest Xpert MTB/RIF site for examination (this could be Bugando Medical Centre or another Mwanza site). If the Xpert test detected MTB and was RIF resistant or RIF sensitive, another specimen was collected, packaged and sent to the CTRL to be tested with LPA (see Figure 25).

All results obtained were recorded in the TB laboratory registers and on the TB laboratory request forms. Laboratory personnel submitted results to the requesting clinician who initiated treatment in accordance with the existing treatment guidelines (28).

5.3.9.6 Reliable transportation is unavailable

Lack of reliable mail services

In conjunction with study site staff, the PI developed guidelines for specimen transportation from the periphery to the Xpert MTB/RIF sites, and from these sites to the CTRL for LPA analysis using new contracted EMS with the Tanzania Post Office.

Contact details of a courier at the dispatching and destination sites were provided to the EMS or bus operators. The destination site was informed of the number of specimens

sent and the methods used. Logbooks were used to record date and time specimen received as well as the specimen's general condition (packing, documentation and problems if any). The courier at the dispatching site signed the dispatch book. Transportation by EMS was on Mondays to Thursdays. If specimens would be transported on Friday it would reach CTRL on Saturday and there would be no one in the laboratory to pick the samples, therefore there were no samples sent on a Friday. The EMS service was only available at the regional level. The peripheral laboratory was required to submit specimens to the nearest sites equipped with Xpert MTB/RIF machine by using the bodaboda.

5.3.9.7 Distance between CTRL and some sites

No TB Zonal reference centres

The Zonal reference laboratory was integrated into the revised RSS. This enabled Mwanza sites to refer specimens for Xpert MTB/RIF and culture assessment to the Zonal laboratory at the Bugando Medical Centre.

5.3.9.8 Unreliable diagnostic technology (CTRL)

No rapid test

LPA techniques at the CTRL were introduced for use with all previously-treated samples referred via the revised RSS. Using this technique, it was possible to complete drug sensitivity testing for all first line TB drugs. In addition, new daily monitoring processes of samples being received at the CTRL were introduced to increase the numbers actually receiving a DST and improve turnaround time.

5.3.9.9 Contaminated samples

High contamination rate at CTRL

CTRL staff were re-trained on routine procedures to minimise contamination and to identify factors associated with specimen contamination. The PI presented SOPs on the specimen reception and accessioning (See Appendix 13).

5.3.9.10 Poor communications between CTRL and districts

Poor communication between CTRL and districts

All results obtained at the CTRL were sent back to the requesting clinicians using the EMS service, or by secured and protected emails. During dissemination of results, patient's confidentiality was maintained throughout by using unique identifiers. Results were disseminated using sealed and stamped envelopes.

Monthly reports were generated from each laboratory, the regional coordinator compiled the regional report and sent it to the CTRL. The EQA reports were produced on a quarterly basis. The PI was responsible for developing quarterly reports and for sharing information with the regional and national levels.

WhatsApp groups such as the Mwanza Family group were created by the RTLC in Mwanza to include RTLC, DTLCs and CTRL staff. This facilitated rapid and easy communication between the CTRL and the study sites. If any problems were found, they could immediately send a message through the WhatsApp group back to the requester to rectify the problem. Also, various other WhatsApp groups were created by the NTLP Manager for lab supplies to improve communication between the NTLP and Medical Store Department for easy tracking of the laboratory commodities.

5.3.9.11 Quality control and quality assurance

Quality Control (QC) and Quality Assurance (QA) were performed in accordance with the NTLP quality assurance system (blind rechecking). This helped to detect systemic errors and improve compliance with the revised RSS design. To ensure that results of Xpert MTB/RIF and LPA were reliable and comparable, the procedure followed manufacturers' recommendations. Specifically, controls were run first to check the validity of the reagents and functionality of the equipment. Once the controls passed, tests were then performed. The quality assurance on smear microscopy was checked using blind rechecking in accordance with the NTLP guidelines.

Quarterly, ten slides from each laboratory were collected and checked for consistency and accuracy. Laboratory supplies, personnel and laboratory performances were also reviewed quarterly by the PI. The PI provided refresher training on smear microscopy EQA. Quarterly reports were generated and shared with the laboratories.

5.3.10 Stage 3 - Quantitative performance evaluation of the revised RSS

5.3.10.1 Overview

The effects of the revised RSS using a modified algorithm as outlined in Figure 25 above were assessed at the end of the pilot (after 12 months) using a before and after design. There was a quantitative assessment described in this chapter and a qualitative evaluation which is described in chapter 6.

5.3.10.2 Research Question and how it was addressed

In the evaluation of the pilot study the research questions that was addressed was research question d) from section 1.9.3, i.e.:

Does the newly designed and revised routine surveillance system improve the performance of the system, in particular by reducing the time from sputum collection at the district health facility to communication of the DST result by the CTRL back to the district? (Quantitative)

This question was further split into the following five component questions for a quantitative evaluation of the revised RSS during the pilot in Mwanza.

1) Did the revised RSS in Mwanza region increase the number of non-contaminated specimens received and tested at the CTRL?

How was this to be achieved? Reviewed TB laboratory registers to see how many specimens in total from previously-treated cases were received by the CTRL from Mwanza region in April 2017 to March 2018 compared to April 2016 to March 2017 and how many were contaminated.

Variables:

Number of previously-treated patients tested in the Mwanza region

Number of patient's specimens received at the CTRL from Mwanza region

The contamination rates for previously-treated TB case specimens calculated as the total number of contaminated slopes/samples divided by the total number of specimens received at the CTRL for each period (the 12 months before and the 12months after the intervention).

2) Does the revised RSS in Mwanza lead to better completion of TB laboratory request forms received at the CTRL?

How was this to be achieved? The proportion of forms with missing data from Mwanza was compared before and after the intervention of the new RSS.

Variables:

Proportion of forms with missing data in the following key fields – date sample collected, case number, address, ward, age and TB district number.

3) Does the revised RSS in Mwanza region reduce the time from specimen collection at peripheral health facilities to the time the specimen is received at a site where DST can take place (i.e. the CTRL and/or Mwanza sites with Xpert MTB/RIF)? (transit time).

How was this to be achieved? Routine NTLP data was analysed. The difference between the date specimens were collected in the peripheral Mwanza districts and the date specimens were received by the CTRL or the Xpert MTB/RIF site in Mwanza was calculated. This required a review both of hard copies and the CTRL electronic datasets of TB laboratory registers. Data was collected during the pilot phase April 2017 and March 2018 and compared with the previous years' data 2016/2017.

Variables:

a) Date previously-treated specimen collected at the periphery in Mwanza

b) Date and time specimen received at study site (i.e. either CTRL or Xpert MTB/RIF site in Mwanza)

c) The difference in the above dates was calculated as the transit time

4) Does the revised RSS in Mwanza region reduce the time from specimens received at the CTRL to the time results were sent back to the region? (turnaround time)

How was this to be achieved? The difference between the date results were communicated back to Mwanza region by the CTRL and the date specimens were received at the CTRL was calculated. This required a review both of hard copies and the CTRL electronic datasets of TB laboratory registers. Data was collected during the pilot phase April 2017 and March 2018 and the analysis compared with the previous years' data 2016/2017. Ideally it would have been preferable to have used the date the requesting clinician at the periphery received the result, but unfortunately this date was not available historically.

Variables:

a) Date Mwanza specimen from previously-treated cases were received at the CTRL

b) Date and time results sent back to the region

c) This was used to calculate the turnaround time from date specimen received at the CTRL to the date results were sent back to the region.

5) Did the revised RSS in Mwanza region increase the number of cases starting MDR-TB treatment?

How was this to be achieved? Reviewed TB registers to identify the number previously-treated TB cases starting MDR-TB treatment in Mwanza region in 2016/17 compared to the period of the pilot (2017/18).

Variables:

a) Number of previously-treated TB cases on MDR-TB treatment in 2016/17 and 2017/18.

b) Number of tests conducted through the RSS for previously-treated cases at the CTRL

5.3.11 Data collection and analysis

All data collected were double entered independently into the computer database in Epidata software version 3.1 by two independent data entrants located at the CTRL. Forms were sent to the CTRL throughout the data collection period. The data were validated, and consistency checks were done by a trained statistician using SPSS version 17. The statistician providing feedback queries to the data entrants for verification and rectification as required. Errors were corrected before analysis.

Data analysis used data collected from April 2017 to March 2018 in Mwanza TB centres and the CTRL. The analysis was mainly descriptive. Frequencies and proportions were used to describe characteristics of previously-treated TB cases who submitted their specimens to the respective laboratory. Transit time and turnaround time were reported although there was some missing data from 2016/2017. Results were presented in tabular format, and in graphs and charts. Bar charts were used to compare the number of MDR-TB cases between the revised and current RSS, and demographic information and Z-test data were presented in tabular format. The dataset was stored on a password protected computer accessed only by those authorised. Meanwhile, the hard copies were stored in a cabinet protected with a lock and key.

5.4 Study findings

All results below are for specimens collected as part of the RSS for previously-treated TB cases only.

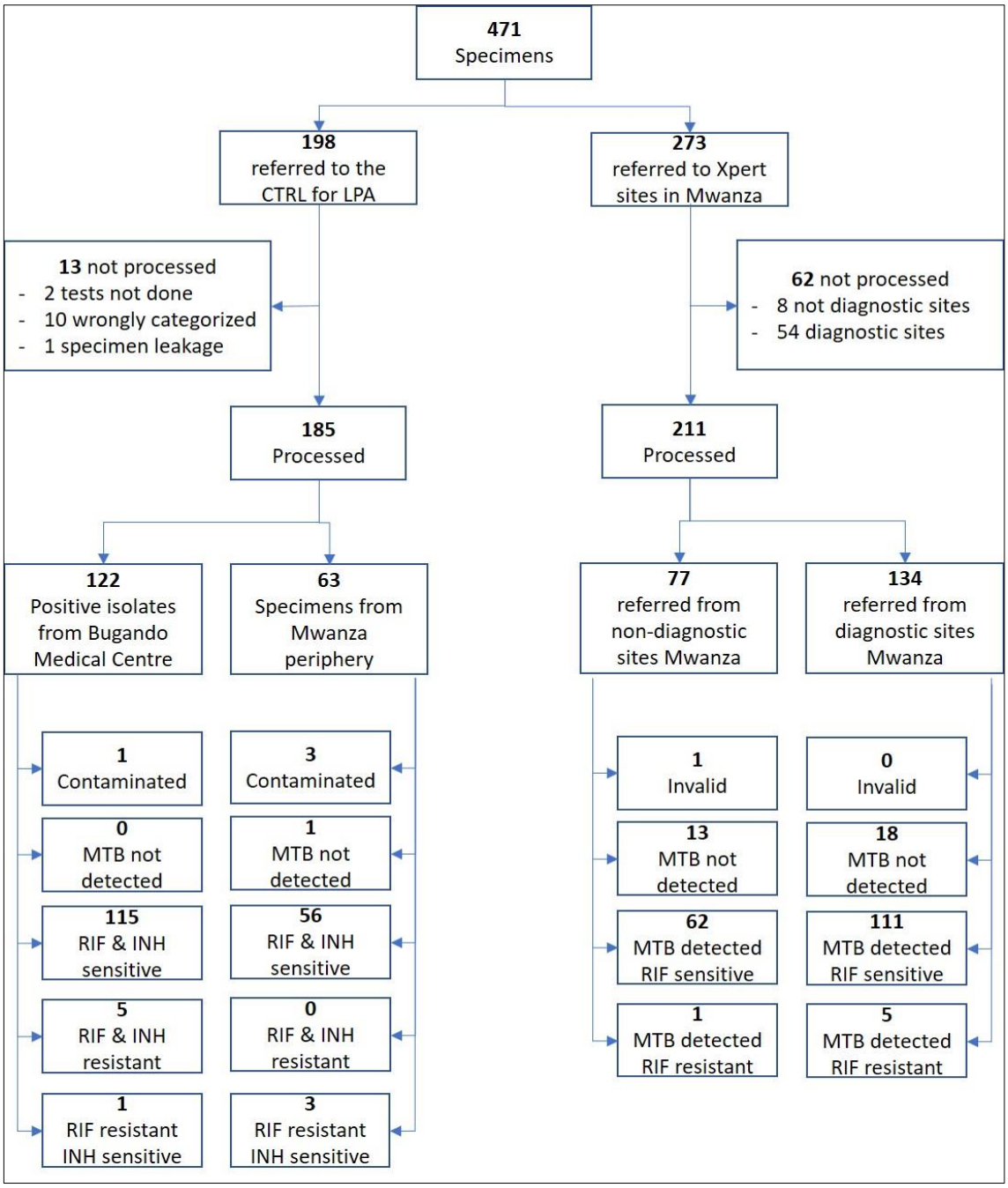
1. Number of non-contaminated specimens received and tested at the CTRL?

There were 75 Mwanza specimens sent to be processed at the CTRL from April 2016 to March 2017. Of these only 48 (64%) were processed, 27 (36%) had missing information and could not be fully analysed. Of the 75 specimens received, no contamination was found, and no positive isolate specimens were received from the Zonal TB culture laboratory in Mwanza (see Table 17).

After the intervention and during the pilot, the total specimens received and analysed both at the CTRL and Mwanza study sites are shown in Figure 29. A total of 471 specimens were collected during the study period from April 2017 to March 2018. Over half of the specimens, 273 (58.0 %) were received in the Mwanza sites and 198 (42.0 %) were received at the CTRL. 13 of the 198 (6.6%) specimens received at the CTRL were rejected (primarily due to wrong treatment category or specimen leakage). The remaining 185 (93.4 %) were sent for processing with LPA. Of these, 4 were contaminated, 1 had no MTB detected, 171 had MTB detected and were sensitive to both RIF and INH and 9 (5%) were found to be resistant to RIF or INH or both (Figure 29).

Of the 273 specimens received in Mwanza study sites; 62 (23%) were not analysed due to various reasons including shortage of reagents and equipment breakdown. The remaining 211 specimens were processed, out of which 134 (63.5%) were submitted from study sites with microscopy but no Xpert MTB/RIF capacity. 77 (36.5%) were from the study sites with no diagnostic testing available. In total out of the 211 specimens tested, 1 test was invalid, 31 had no MTB detected, 173 had MTB detected and were Rifampicin sensitive, 6 had MTB detected and were Rifampicin resistant (Figure 29).

Figure 29 Specimen analysis 2017/2018 – during the pilot study



Keys: CTRL- Central Tuberculosis Reference Laboratory; LPA- line probe assay; MTB-Mycobacterium tuberculosis; labs- laboratory; INH- Isoniazid; RIF- Rifampicin.

Table 16 shows the split of DR results at the CTRL. In particular, it shows of all samples tested and with MTB detected, 95.0% were sensitive to both INH and RIF, 2.8% resistant to both drugs and 2.2% resistant only to RIF.

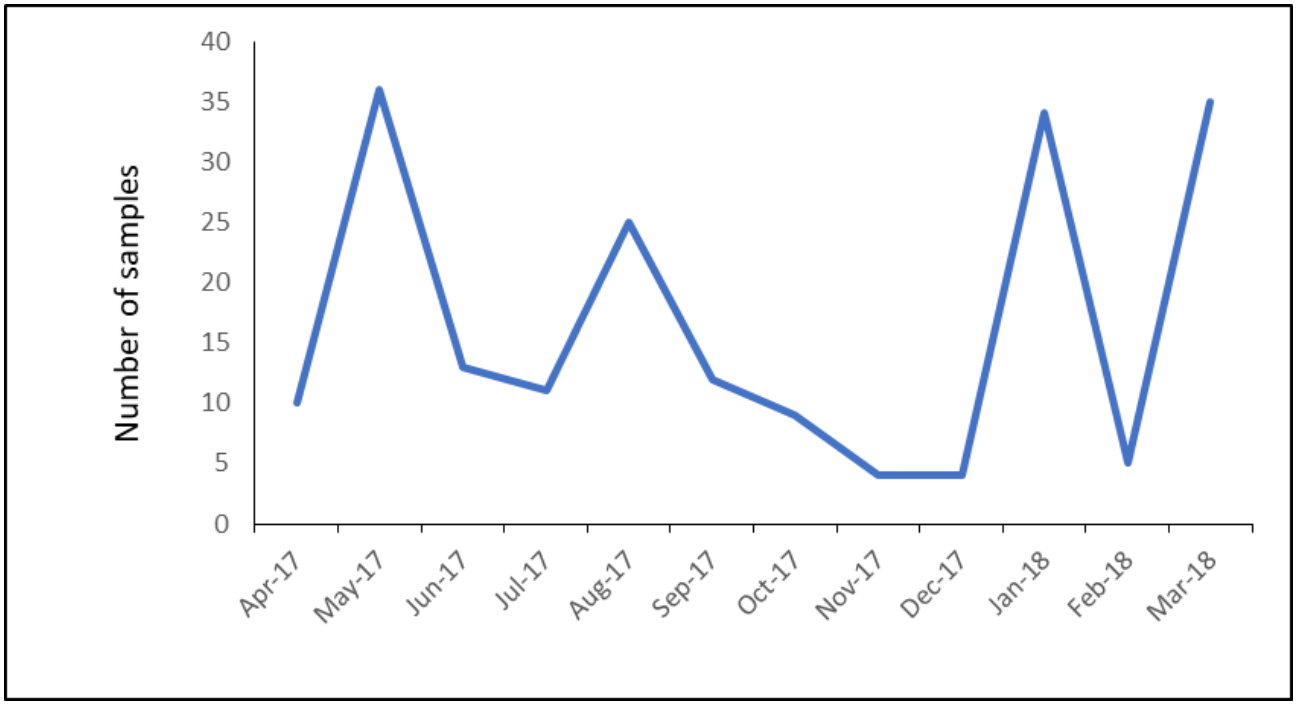
Table 16: Drug susceptibility testing results using Line Probe Assay at the CTRL in 2017/18

Line Probe Assay CTRL	Positive isolate-Zonal TB Culture laboratory	Sputum specimen Peripheral laboratory	Total	% of tests (excl. no MTB and contaminated samples
RIF (R), INH (R)	5	0	5	2.8%
RIF (R)	1	3	4	2.2%
INH (R)	0	0	0	0%
Sensitive to both RIF and INH	115	56	171	95.0%
Total	121	59	180	100.0%
MTB Not Detected	0	1	1	
Contaminated	1	3	4	

Key: CTRL- Central Tuberculosis Reference Laboratory; RIF (R) - Rifampicin resistant; INH (R) - Isoniazid resistant

Figure 30 shows the extent of the variation in the number of specimens received at the CTRL by month throughout the pilot study. This indicates the largest number of specimens were recorded in May 2017, January 2018 and March 2018. Fewer specimens were received in April and December 2018.

Figure 30 Number of previously-treated patients' specimen received at the CTRL



In 2017/2018 the total number of specimens received and examined at the CTRL was 185, of these 63 (34%) were sputum specimens from the periphery and 122 (66%) were positive TB culture isolates from Bugando Medical Centre (BMC). In comparison before the intervention from April 2016 to March 2017, of the 75 specimens received, 48 (64%) were analysed, 27 (36%) had missing information and could not be analysed. No positive isolate specimens were received. The total annual previously-treated TB cases in Tanzania were 3,072 in 2016/17 and 3,528 in 2017/18. Table 17 shows that in 2017/18 a significantly greater proportion of these came from Mwanza.

Table 17: Proportion of previously-treated specimen received from Mwanza as part of the RSS

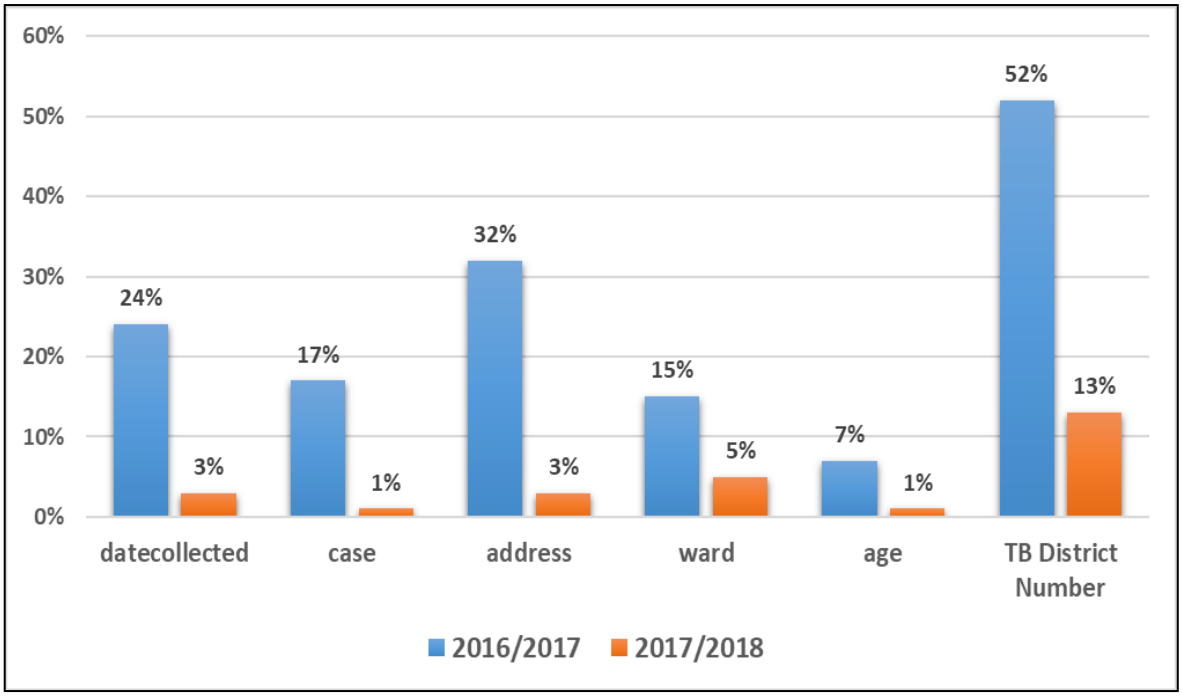
Specimens	2016/17 (Before intervention)	2017/18 (After intervention)	Difference	Difference%
Number of previously-treated TB cases in Tanzania	3072	3528	+556	+14.8%
Number referred from Mwanza to the CTRL via the RSS	75	185	+110	+146.7%
Proportion	2.44%	5.24%	+2.80% *	+114.8% *

** Statistically significant increase at 95% level*

2. Level of completion of TB laboratory request forms received at the CTRL

The completeness of TB laboratory request forms received at the CTRL before and after the intervention from Mwanza was compared for a number of key fields. In 2016/17, 32% had missing address information and 52% had missing district number. In comparison, in 2017/18, the proportion of missing address information dropped to 13% and missing district number fell to 3%. Figure 31 shows there was a significant improvement in form completion across many fields.

Figure 31 Incomplete TB Laboratory Request Forms 2016/2017 and 2017/2018



Keys: TB- tuberculosis

During the pilot, 198 samples were sent for processing at the CTRL of which 185 were processed (93%). This compares to 75 sent for processing and 48 processed the year before (64%). This improvement in proportion processed was driven by a reduction in the level of missing information on laboratory request forms.

3. The time from specimen collection at peripheral health facilities to the time the specimen is received at a site where DST can take place (transit time)

The transit time recorded in 2016/2017 for sputum showed 44 % of specimens were received after 21 days. There were no isolates sent in 2016/2017. Overall, the median and interquartile range (IQR) was 12 (51) days in 2016/2017 as shown in Table 18.

The transit time recorded in 2017/2018 for both sputum and isolates showed 21% of specimens were received after 21 days. Overall, the median and interquartile range (IQR) was 10 (9) days in 2017/2018, compared to 12 (51) days in 2016/2017 in Table 18.

Table 18: Transit time: Number (%) of the specimen received at CTRL from Mwanza site

Year	Sample	< 3 days	≥ 3 days & < 7 days	≥7 days & <21 days	≥ 21 days	Total	Median	IQR
2017/2018 After Intervention	Sputum	3 (5%)	18 (29%)	39 (62%)	3 (5%)	63	7	3
	Isolate	0 (0%)	30 (25%)	56 (46%)	36 (30%)	122	10	27
	Total	3 (2%)	48 (26%)	95 (52%)	39 (21%)	185	10	9
2016/2017 Before Intervention	Sputum	13 (27%)	4 (8%)	10 (21%)	21 (44%)	48	12	51
	Isolate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0		
	Total	13 (27%)	4 (8%)	10 (21%)	21 (44%)	48	12	51

Key: IQR – Interquartile range=Third Quartile – First Quartile

There is a significant reduction at the 95% level in the proportion taking 21 days or over between 2017/18 and 2016/17, however there is no significant difference in the proportion taking less than 7 days (the target maximum) and the number taking less than 3 days is in fact significantly lower in 2017/18 than in 2016/17 at the CTRL. However, the most notable change between the years is the big reduction in the IQR, reducing down to 9 days during the pilot compared to 51 days in the year before (i.e. transit times are much more consistent – fewer outliers). This was also associated with a slightly lower median transit time during the pilot, 10 days compared to 12 days in the year before.

Out of 273 specimens referred to the Xpert MTB/RIF study sites in Mwanza, 62 (23%) and had no recorded transit time. This maybe for a variety of reasons, e.g. the Xpert test was never performed or the dates were not recorded. Of the 211 with a recorded transit time 96% took less than 3 days (Table 19). In 2016/2017 the RSS did not have the opportunity to transfer samples to an Xpert MTB/RIF site in Mwanza as this was only introduced as part of the pilot intervention of the revised RSS. Therefore, no comparative data is available.

Table 19: Transit time from Mwanza study sites without Xpert to Mwanza sites with Xpert in 2017/2018

Year	Where sample tested	< 3 days (%)	≥ 3 & < 7 days (%)	≥ 7 & < 21 days (%)	>= 21 days (%)	Total
2017/2018	Mwanza Xpert site	128 (94.8%)	5 (3.7%)	1 (0.7%)	1 (0.7%)	135
	Bugando Medical Centre	75 (98.7%)	1 (1.3)	0 (0.0%)	0 (0.0%)	76
Total		203 (96.2%)	6 (2.8%)	1 (0.5%)	1 (0.5%)	211

4. Time from specimen receipt at the CTRL to the time the DST results are sent back to the requesting clinician (turnaround time)

Turnaround time was calculated by subtracting the date results were sent back to the requester from the date the specimen was received at the CTRL. The overall median (IQR) turnaround time was 7 (8) days for 2017/2018 and 62 (10) days for the 2016/2017 (Table 20).

Table 20: Turnaround time for specimen results at CTRL

Year	Sample	< 3 days	≥ 3 days & < 7 days	≥7 days & <21 days	≥ 21 days	Total	Median	IQR
2017/2018 After Intervention	Sputum	11 (18%)	38 (63%)	8 (13%)	3 (5%)	60	3	2
	Isolate	14(12%)	21 (17%)	55 (45%)	31 (25%)	122	7	22
	Total	25 (14%)	59 (33%)	62 (34%)	34 (19%)	182	7	8
2016/2017 Before Intervention	Sputum	0(27%)	0 (8%)	0 (21%)	8 (100%)	8	62	10
	Isolate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0		
	Total	0 (0%)	0 (0%)	0 (0%)	8 100%)	8	62	10

Key: CTRL- Central tuberculosis reference laboratory; IQR – Interquartile range
Note: 2017/2018 - 3 specimens were not processed and 2016/2017 - 67 specimens had missing date and were excluded from the analysis.

In addition to the turnaround time at the CTRL, it was possible to look at the turnaround time for Xpert MTB/RIF sites in Mwanza which had been introduced as part of the revised RSS algorithm in 2017/18. Out of 211 specimens processed, turnaround times for 59 (28%) could not be calculated due to missing dates, leaving 152 (72%). Results at the Mwanza Xpert sites (including Bugando) were sent back to the requestor in less than three days for 145 (95%). On 4 (3%) occasions the turnaround time was greater than 21 days (Table 21).

Table 21: Turnaround times for specimen results sent to an Xpert site in Mwanza from a Non Xpert sites in Mwanza Region 2017/2018

Mwanza Site	< 3 days	≥ 3 days & < 7 days	≥ 7 days & < 21 days	≥ 21 days	Total
Diagnostic Sites	75 (96%)	2 (3%)	0 (0%)	1 (1%)	78
Non-Diagnostic Sites	70 (95%)	1 (1%)	0 (0%)	3 (4%)	74
Total	145 (95%)	3 (2%)	0 (0%)	4 (3%)	152

Key: Diagnostic- sites with microscopy; Non-diagnostic- site without microscopy.

5. The number of cases starting MDR-TB treatment in Mwanza

From the findings earlier we know only 48 previously-treated cases were processed via the RSS at the CTRL in 2016/17, whereas 185 were processed in 2017/18 in Figure 29. This would on its own, be expected to lead to a rise in MDR-TB diagnosis.

In 2017/18 the proportion of samples received at the CTRL completing a valid DST was 91% (181 – excluding those not processed and contaminated samples out of 198). Unfortunately, similar data has not been recorded for 2016/17.

From the TB registers we know the number of previously-treated TB cases recorded as having started MDR-TB treatment from Mwanza in 2016/17 was 12 and in 2017/18 this rose to 20 (+67%). From Figure 29 there are 9 DR-TB cases identified in the CTRL with potentially others coming from the Xpert MTB/RIF tests performed in Mwanza sites with

Xpert MTB/RIF that were never referred to the CTRL. Unfortunately, similar breakdown of data is unavailable for 2016/17.

5.5 Summary discussion

The study involved the design and piloting of a revised RSS for previously-treated TB cases in Mwanza region. The revised RSS aimed to address many of the issues raised in the earlier quantitative (Chapter 3) and qualitative (chapter 4) studies described in this thesis (45), as well as taking into account the wider availability of molecular testing. The primary outcomes of the study were to assess the impact of the revised RSS on specimen transit time to the CTRL and the time from specimen receipt at the CTRL to when drug susceptibility results were sent back to the requesting clinician (turnaround time).

The pilot of the revised RSS showed some notable improvements compared to the current RSS. In particular, it resulted in a significant reduction in turnaround times for testing at the CTRL driven by the use of molecular techniques and closer monitoring (median of 7 days compared to 62 the year before); an increase in the number of specimens referred (198 compared to 75 the year before) and processed (185 verses 48 the year before) at the CTRL; and a reduction in incomplete forms sent with samples (e.g. only 3% of forms had missing date information when this was 24% the year before). In addition, the introduction of using Xpert MTB/RIF at the periphery in 4 Mwanza centres and at the Bugando Zonal Laboratory meant resistance to rifampicin could be reported much more rapidly than was the case with the old RSS when any resistance result had to wait until DST was completed at the CTRL. This enabled in these cases 96% of transit times to be less than 3 days and 95% of turnaround times for an Xpert MTB/RIF result, including testing for RIF resistance, in less than 3 days. The low transit time was supported by the use of motorbike couriers known as bodaboda.

In relation to the transit times from the Mwanza periphery to the CTRL the results are less clear, although median transit time did reduce to 10 days during the pilot from 12 days the year before. This improvement was supported by use of the contracted EMS.

However, it was noted that 27% of samples had a transit time of less than 3 days in 2016/17 whilst only 3% achieved this during the pilot. This requires further investigation, but it should be noted there was also a reduction in the proportion of samples with transit times of over 21 days to reach the CTRL from the periphery during the pilot (21% compared to 44% the year before). This reduction in outliers, led to a much narrower inter-quartile range (9 during the pilot compared to 51 the year before). This more consistent result for transit time with a slightly reduced median is encouraging.

There was no evidence of changes to the contamination rates between the new and revised RSS processes. This is a little surprising, but is mainly because from the documented evidence in 2016/17 there was nothing recorded as contaminated from Mwanza. Anecdotally, it is believed however there was contamination, and this is probably supported by the low level of samples that could be processed at the CTRL in 2016/2017 (i.e. only 48 out of 75 – 64%). Some of the loss in samples processed maybe as a result of unrecorded contamination. The contamination level in 2017/18 was 5% which was around what was expected.

The increased volume and proportion of samples being tested for drug sensitivity, and the more rapid availability of DST results, would be expected to increase the level of MDR-TB detected. MDR-TB is still at a relatively low level in Tanzania and in Mwanza, however during the pilot period, 20 new cases of MDR-TB started treatment from previously-treated TB cases, in comparison to 12 the year before. This 67% increase is an important result and suggests the revised RSS can be expected to improve detection of MDR-TB.

WhatsApp groups played an important role in this study. Various groups created by the NTLP Manager such as ‘Vitendanishi’ for lab supplies, and the ‘Mwanza family’ created by the RTLC in Mwanza, served to enhance timely communication with laboratory personnel and the DTLC group in Mwanza. These groups allowed the ground staff responsible for sending out specimens to resolve concerns in a timely manner and eased the dissemination of results which consequently probably shortening both transit and

turnaround times. Since the success of this approach in Mwanza, the WhatsApp group platform has now been replicated in other regions among DTLCs, RTLCs and laboratory teams. Use of WhatsApp groups may also be a useful approach to address other communication issues in the TB programme and beyond.

The study had some limitations due to poor record keeping, particularly in the historical data, which made some comparisons of performance difficult. For example, due to poor data recording in 2016/2017, the turnaround time is only based on eight samples where the median turnaround time was 62 days. However, to a certain degree, this poor record keeping was also symptomatic of the poorly performing RSS prior to the pilot. The revised RSS has led to improved record keeping which can hopefully be maintained. The evidence from this study shows why this improved record keeping is important as it can have a direct effect on patients getting onto appropriate treatment and in a timely manner.

There was great variability by month in the number of specimens transported for testing (Figure 30). This was due to operational reasons, for example towards the end of May 2017, there was a nationwide employees' education certificate inspection for irregularities which led to the termination of several laboratory staff and clinicians. This exercise had a negative impact on the study. In addition, in December 2017 and February 2018, fewer specimens were received which might have been due to staff shortages and some being on holiday which led to some specimen batching. This suggests that without these difficulties even better results might have been possible.

An extension to this research could include a modelling approach to provide additional insight (134).Data from this study could be used to support an operational model of alternative algorithms for a revised RSS. Such an operational model could be designed to include assessment of cost and benefits from both a patient and health system perspective.(135). A modelling approach might also help in understanding which parts of the revised RSS provide the greatest benefit overall, and which were less significant, and therefore may not be worth pursuing if they require additional resource. There was insufficient time to complete such a modelling approach in this study as it was thought

the qualitative assessment (Chapter 6), to mirror the assessment completed before the pilot (Chapter 4), was of greater priority for this research study.

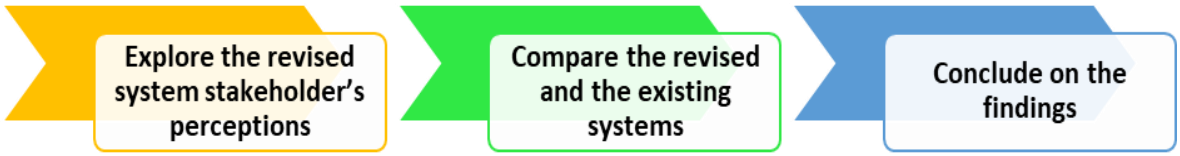
It is clear from this study there is even more to do to improve the RSS. For example, even with the focus of the revised RSS, 13% of laboratory forms had missing laboratory reference numbers and 3% missing addresses, although these were much lower than in 2016/17. Also, there were significant numbers of samples in 2017/18 that were not processed for a variety of reasons (i.e. in total 75 out of 471, 15.9% – see Figure 29). However, this again was much lower than in 2016/17. Our study focused on previously-treated cases only. All the interventions looked at could have equal value to new cases, although the level of DR would be expected to be much lower.

In the National Strategic Plan (NSP), it was estimated that the annual burden for MDR-TB was 699 and 725 for 2016 and 2017, respectively. The actual DR- TB cases notified were 197 and 200, so there is still a significant detection gap which potentially a revised RSS could help address (7,31,136).

5.6 Conclusion

The revised RSS led to an increased number of specimens received and tested at the CTRL. The use of WhatsApp within the NTLP network led to close follow-ups and timely response to concerns during the piloting. The revised system has shown the ability to reduce delays in diagnosis and in addition there has been a notable increase in numbers starting MDR-TB treatment. The shorter transit and turnaround times are important in the diagnosis of MDR-TB and TB control. These positive results suggest a larger scale study involving more regions should be considered to determine whether these benefits are robust and sustainable across similar settings.

Chapter 6 A Qualitative evaluation of the revised RSS in Mwanza

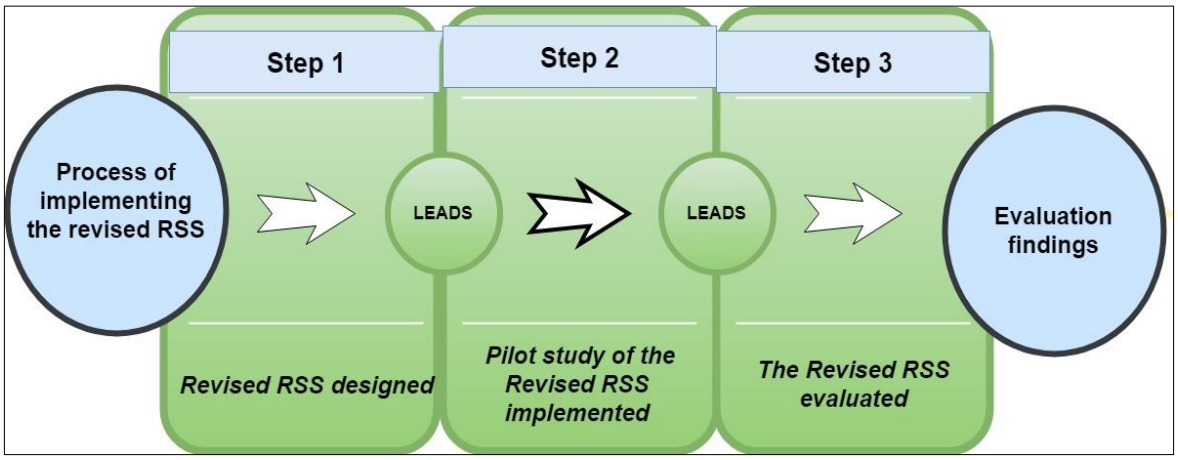


6.1 Introduction

This chapter addresses research questions (e) as referred to in the introduction section in 1.9.3. – Does the revised routine surveillance system reduce barriers to the effective performance of the system? (Qualitative).

It describes the qualitative evaluation of the revised RSS described in chapter 5 and piloted in Mwanza region after the introduction of a number of interventions. The study explored health care providers' perspectives of the revised RSS through FGDs and IDIs. The revised system was intended to address the barriers identified in the qualitative study described in chapter 4 (45). The implementation plan for the revised RSS is illustrated in Figure 32. This chapter covers the qualitative analysis of Step 3.

Figure 32 Revised RSS implementation plan



A summary of the key elements of the revised RSS intervention and how these addressed the key issues of the existing RSS are described in Chapter 5 and Table 15.

This study sought feedback from stakeholders of their perception of the revised RSS for previously-treated TB cases introduced in Mwanza, Tanzania. It also sought to facilitate comparison by stakeholders between the before and after RSS.

6.2 Study Overview

6.2.1 Objective

To evaluate the effectiveness of the revised Routine Surveillance System for previously-treated TB cases piloted in Mwanza, Tanzania from a stakeholder perspective. (Comparison before and after intervention).

6.2.2 Research Question

Does the revised routine surveillance system for previously-treated TB cases reduce barriers to the effective performance of the system? (Qualitative).

6.2.3 Study approach

A qualitative study was conducted from 1st May to 30th July 2018 after the pilot of the revised RSS had been in place for 12 months. The study involved both FGDs and IDIs as had been used in the earlier study described in chapter 4. Two trained RA conducted the FGDs and IDIs in the selected study sites. A topic guide was used to guide the FGDs and IDIs along with open ended questions. The focus was to elicit feedback from the key stakeholders in Mwanza and the CTRL on the revised RSS, especially in respect to successes and related challenges in order to facilitate comparison between the RSS in place before the intervention and the revised RSS.

6.2.4 Study sites

The study sites were in the Mwanza region where the revised RSS described in Chapter 5 was piloted. Administratively Mwanza region has 7 districts, which include Ilemela,

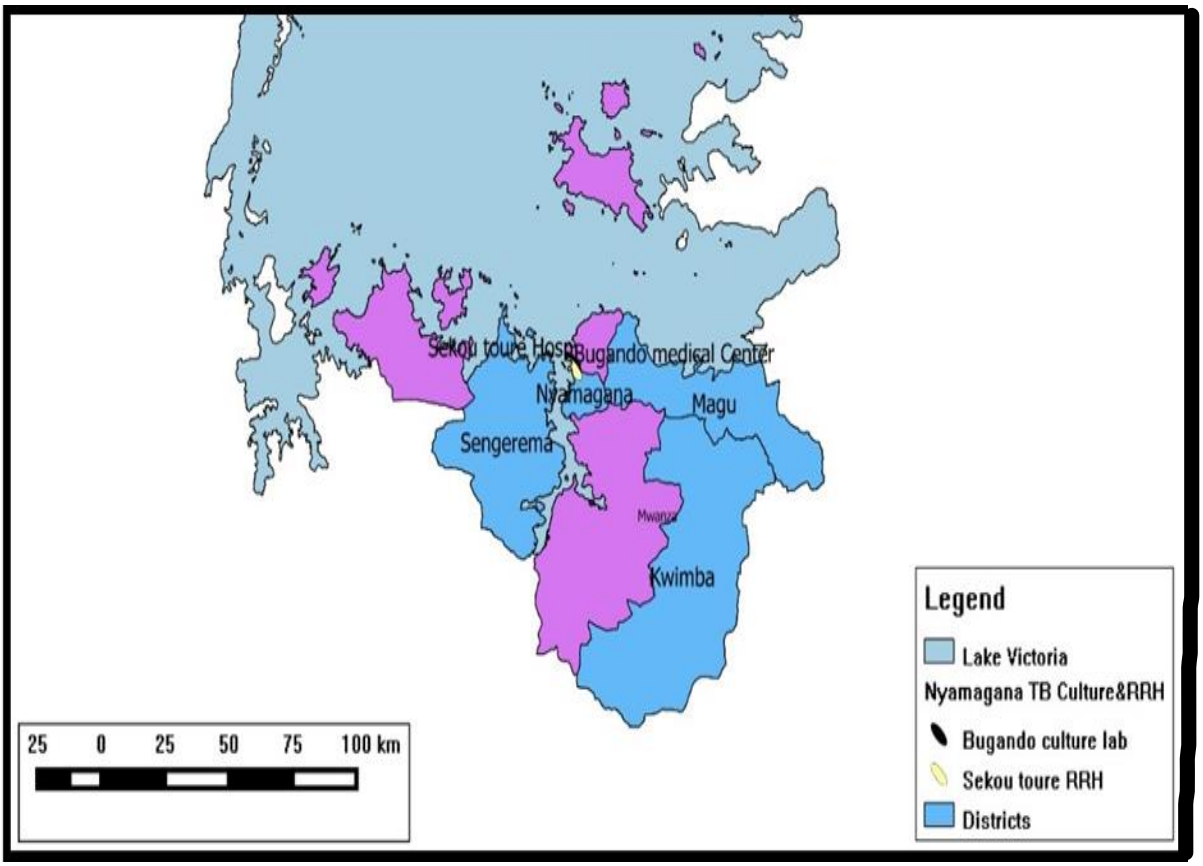
Nyamagana, Sengerema, Misungwi, Magu, Kwimba and Ukerewe. People of Mwanza mainly depend on small-scale farms, animal husbandry, fishing and to some extent mining for their livelihood.

The region has a total of 384 health facilities, of these 15 are hospitals, 44 are health centres and 325 dispensaries. At the time of conducting this study the region had 80 diagnostic facilities with 5 that had Xpert available. All facilities have been participating in quality improvement programs on AFB smear microscopy method through Proficiency Testing (PT) programme whereby random representative slides are sent by DTLC and rechecked blindly by a controller at district level. In the pilot RSS specimens from previously-treated cases were referred from peripheral sites to the nearest Xpert sites for testing as described in chapter 5, Figure 25. Positive culture slopes from Bugando zonal TB culture laboratory were also referred to the CTRL for susceptibility testing.

The region receives funds from the government and implementing partners for TB, and TB/HIV activities. The following partners are involved: Health Basket Fund, KNCV, AGPAHI and Global Fund through NTLP.

Mwanza region is too big for a researcher to assess every district and village; therefore, four districts were selected as being representative of the region. Each district is overseen by a District Medical Officer, a District Laboratory Technologist and the DTLC who are responsible for all TB activities in the district. All districts selected had access to Xpert technology. The selected districts were Kwimba, Magu, Sengerema and Nyamagana as shown in Figure 33. Health districts reflected Tanzania's decentralized public health service system.

Figure 33: Mwanza study sites



Before participant recruitment the PI sought and received permission from the TB Programme and the medical administrative authority in Mwanza to conduct the study in the sites selected. Each of the 4 health districts are described in detail below.

Kwimba district

Kwimba District has a total population of 44,964 people (By National Bureau of Statistics 2012) (114). and occupies an area of 3,903 square kilometres. It is bordered to the west by the Misungwi district and to the north by the Magu district. Most residents of Kwimba are the Sukuma tribe and are engaged in subsistence farming of rice, sweet potatoes, cassava, millet or maize. Administratively, Kwimba District is divided into five divisions, 30 wards and 119 villages. Of the 30 wards only 4 have local post office services and only 17 have access to electricity.

The district has a total of 56 health facilities - 50 government owned, 2 parastatals and 4 private sector facilities. Out of the 56, 2 are hospitals, 6 health centres and 48 dispensaries. There are 8 centres that provide TB laboratory services. The district has 1 Xpert site situated at Gundu district hospital.

According to the NTLP annual report of 2016, TB notifications were 577. This included 5 previously-treated cases. A significant challenge in this district is low TB case detection(137).

Magu district

Magu District has a total population of 299,759 people (By National Bureau of Statistics 2012),(114) with a total area of 4,795 sq. kilometres. It is bordered to the north by Lake Victoria and Busega district, to the east by Bariadi district, to the south by Itilima district, Maswa district, Kwimba district and Misungwi district, and to the west by the city of Mwanza, which consists of Nyamagana and Ilemela districts. Administratively, the district is divided into four divisions, 27 wards and 82 villages. Of the 27 wards, 12 have local post office services and 15 have access to electricity. Magu district is one of the poorest districts in Tanzania due to persistent unfavourable weather conditions. The major sources of livelihood in the district are farming and animal husbandry (accounting for over 90 percent).

The district has a total of 48 health facilities; 42 government owned, 1 parastatal, 1 faith-based organisation and 4 private facilities. Out of 48 health facilities there is 1 hospital, 5 health centres and 42 dispensaries. 11 health facilities provide TB laboratory diagnosis services. The district has 1 Xpert site situated at Magu district hospital. The district has relatively high mortality of TB, TB/HIV and MDR-TB. In 2016 TB notifications were 393, of which 9 were previously-treated TB cases (137). A big challenge in the district is the use of traditional healers.

Nyamagana district

Nyamagana district has a total population of 363,452 people (By National Bureau of Statistics 2012) (114) and covers an area of 256 square kilometres. It is bordered to the north by Ilemela district, to the east by Magu district, to the south by Misungwi district and to the west by the Mwanza Bay of Lake Victoria. Part of the region's capital, the town of Mwanza, is within Nyamagana district. The regional referral hospital and Bugando TB Zonal Culture Laboratory are in this district. The fish Industry is an important income generating activity in Mwanza City, it provides employment, food as well as income to the communities.

Administratively, Mwanza city council comprises of 18 wards and 175 streets. All wards have local post office services and access to electricity.

The district has a total of 56 health facilities; 16 government owned, 3 parastatals, 9 faith-based organisation and 28 private facilities. Out of the 56, 11 are hospitals, 13 health centres and 32 dispensaries. There are 10 TB diagnostic centres.

The district has 2 Xpert sites situated at SekouToure and Bugando Hospital. The district has relatively high mortality of TB, TB/HIV and MDR-TB. This is one of the districts where various implementing partners support different health interventions (68% are TB or HIV/AIDS related). In 2016 TB notifications were 1,036, of which 27 were previously-treated TB cases (137).

The district faces challenges as it is experiencing fast population growth by both natural increase and migration. As a result, there many different ethnic groups living in the city. HIV/AIDS is a significant social, cultural and economic problem in the district.

Sengerema district

Sengerema district has a population is 639,103 and 90% of the population live in rural areas with only 10% in the urban areas. (114). The district covers 8,817 square kilometres, of this 3,335 square kilometres is covered by dry land while the remaining

5,482 square kilometres are covered by the water of Lake Victoria. The district is bordered to the north and east by Lake Victoria, to the south by Geita region and to the southeast by the Misungwi district. The majority occupations are agriculture, livestock keeping and fishing.

Administratively the district is divided into 5 divisions, 25 Wards, 123 registered villages and 758 hamlets (Vitongoji). The district has a total of 56 health facilities; 43 government owned, 1 faith-based organisation and 2 private facilities. Out of the 46, 1 is a hospital, 4 health centres and 41 dispensaries. The district has Xpert situated at Sengerema district hospital. Out of the 56 health facilities, 15 provide TB laboratory diagnosis.

In 2016 TB notifications were 816, of these 29 were previously-treated TB cases (137). The biggest challenges of the district are transportation and electricity, almost all the diagnostic centres are using solar power.

6.3 Study Method

6.3.1 Methodology used and justification

As with the earlier qualitative study described in chapter 4, a mixed approach using FGDs and IDIs was considered the most appropriate. FGDs would be a good way to gather a group of participants from a site to discuss the implementation of the revised surveillance system in comparison to the previous system. An FGD would allow participant interaction to agree and disagree, thus stimulating discussion which would assist in revealing respondents' real perceptions. As in the earlier study, IDIs were chosen as a method appropriate for discussions with senior individuals within the health care programme and implementing partners supporting the NTLP. The perceptions of these individuals would be important to gather but being part of an FGD might restrict discussion within the group and cause confidentiality concerns.

6.3.2 Sampling procedure

The sampling approach to participant selection for both FGDs and IDIs was the same as described in detail in chapter 4 section 4.3. To facilitate this, prior information about the aim of the study and selection criteria were provided to the regional TB coordinator. The PI and the senior research assistant verified participants' eligibility. The selection of the study participants considered the health care providers working with the TB clinics, the courier persons involved with specimen transportation (who worked closely with the bodaboda riders), TB programme staff, laboratory staff at both the regional and national levels and implementing partners within the TB Programme (120).

6.3.3 Inclusion Criteria

Health professionals working in TB clinics, including regional administrative authority staff, TB programme staff, laboratory staff at both the regional (Mwanza) and national levels (CTRL). Implementing partners supporting the TB Programme.

6.3.4 Exclusion Criteria

a) Non-health care service staff

b) Non-TB health care professionals

c) Not present during the pilot study

6.3.5 Participants and sample Size

The trained RA was responsible for finalising the recruitment of the study participants and ensured that participants felt comfortable with responding to the types of questions that would be involved. Participants for the FGDs were recruited through the selected study sites. The recruitment was based on purposeful sampling where a maximum variation sample was sought (120,127). This ensured a diverse range of views with respect to their roles, seniority and experience. The research assistant informed participants about the aim of the study and the expected benefits, explained the purpose

of the interview, the importance of confidentiality and the informed consent process. Informed consent documents were translated into Kiswahili, the most used language. Participants were informed of their freedom to withdraw from the study at any time without prejudice. They were made aware that the information collected would be treated with care and participant confidentially would be maintained.

A total of 45 participants (13 females and 32 males) were selected. 35 individuals participated in the FGDs (10 females and 25 males). There were 6 FGDs and each group contained 5 or 6 participants with a mix of individual roles as shown in Table 22.

Table 22: List of participants of FGDs

Site	Participants job roles	No. of participants	Group	Level
Kwimba	DOT-nurse, DTLC, Lab technician, TB clinician, TB/HIV officer x 2	6 (3 females, 3 males)	GR1	District
Magu	Courier person, DOT-nurse, DTLC, Lab technician, Quality Officer, TB/HIV officer	6 (2 females, 4 males)	GR2	District
Sengerema	Courier person, DOT-nurse, DTLC, Lab technician, Sputum fixer, TB/HIV officer	6 (0 females, 6 males)	GR3	District
Nyamagana	DOT-nurse, DTLC, Lab technician, Quality Officer, TB clinician, TB/HIV officer	6 (4 females, 2 males)	GR4	District
CTRL 1	Data manager, Lab attendant, Lab technician x3, Quality Officer	6 (1 female, 5 males)	GR5	National
CTRL 2	Lab technician x3, Lab supervisor, Safety Officer	5 (0 females, 5 males)	GR6	National
Total		35 (10 females, 25 males)		

Keys: DTLC-district tuberculosis and leprosy coordinator; TB-tuberculosis; HIV-human immunodeficiency virus; Lab- laboratory; CTRL-Central Tuberculosis Reference Laboratory

A total of 10 participants were selected for IDIs (3 females and 7 males) – see Table 23.

Table 23: List of Participants, study sites and IDI coding

Study sites	Participant job roles	Group	Gender	Level
Nyamagana	RTLC	GR7	Male	District
Magu	DTLC	GR8	Male	District
Sengerema	DTLC	GR9	Female	District
Kwimba	TB/HIV coordinator	GR10	Male	District
MoHSW	Ag. Director diagnostic	GR11	Male	National
NTLP	Programme Manager	GR12	Female	National
	MDR-TB coordinator	GR12	Male	National
CTRL	Ass. Lab Manager	GR13	Male	National
Partners	MSH	GR14	Male	International Partner
Partners	KNCV	GR14	Female	International Partner

Keys: RTLC- regional tuberculosis and leprosy coordinator; DTLC-district tuberculosis and leprosy coordinator; TB-tuberculosis.; Ag-acting; MSH-management science for health; HIV-human immunodeficiency virus; IP-implementing partners

6.4 Study preparation

6.4.1 Research team and responsibilities

The research team was the same as described in chapter 4. I was the team leader and PI with overall responsibility for the study. In particular, I was responsible for the design of the study; support to and quality assurance of data collection; training and management of the research team; and writing up of the research in this thesis.

The study research team consisted of a senior research assistant with experience of qualitative research and a RA. Both were involved in conducting IDIs and FGDs. The senior research assistant ensured the careful translation of documents such as the consent sheets, topic guides and transcripts of IDIs and FGDs. The second RA also

undertook some transcription and translation of the recorded IDIs and FGDs. Both the research assistants collated the data with my close supervision.

A senior laboratory person was able to accompany the RA while conducting IDIs and FGDs. In order to facilitate openness, I did not take direct part in most of the interviews and discussions. Instead, the senior laboratory person helped provide participants with an opportunity to speak out and give their ideas openly in order to accomplish the objectives of the study.

My PhD supervisors supported this research as follows: -

a) Dr Ivor Langley (LSTM) provided technical input and proof-reading support of the write-up of this research.

b) Dr Eleanor MacPherson (LSTM) provided technical input on qualitative design and layout. She trained me on the qualitative methods and how to conduct the qualitative study.

c) Dr Esther Ngadaya (NIMR) supported me in Tanzania throughout the study to ensure good progress was maintained.

6.4.2 Training

As this study was similar to the one described in chapter 4 and the personnel were the same, no additional training on the approach was required. Supervision was provided throughout the study period by the PI as required.

The PI provided background to the study; how the revised RSS was undertaken; selection criteria and procedures; data analysis requirements; ethics and confidentiality; and the data collection tools to be used for this study. The PI together with the RAs went through the topic guide that would be used during the IDIs and FGDs, until all felt confident with them.

6.4.3 Development of tools

Hyman *et al.* explain that, one major caveat of using pre-existing questions is the potential result of low data quality if measures are unreliable. However, if 'recycled' questions are accurate measures of the concept of interest (and many will have been pre-tested to ensure this), the degree of validity is likely to be high, resulting ultimately in obtaining data of higher quality (139). For this reason, the study tools were based around those used in Chapter 4 which had proved to be reliable. Amendments and additions to these were made to enable capture of perceptions comparing the previous RSS with the revised RSS. The study tools were developed and finalised after receiving inputs from supervisors. The data collection tools consisted of topic guides designed for FGD and IDI as shown in Appendices 15 and 16 respectively. They were used to guide interviewers and participants through the key themes and issues to be covered according to the study objectives.

6.4.4 Confidentiality and consent

The RA was trained on how to maintain confidentiality. Issues of confidentiality were also addressed at the time of data collection. To ensure anonymity and the respondents' job security, the responses from the interviews were treated with confidentiality during the study period. No participants or site names were used; instead, special codes were used during the interviews and in documentation (124). Consent forms were provided in writing a day before the interview to give time for participants to understand the information related to the study. The consent form was the same as described in chapter 4, see Appendix 6 Swahili version and Appendix 7 in English.

6.5 IDIs and FGDs conducted

6.5.1 Overview

IDIs and FGDs took place between 1st May and 30th July 2018 in Mwanza region and at the CTRL in Dar es Salaam. The IDIs and FGDs were audio-recorded in order to capture the detailed discussions and to help the research team focus on the conversations with

study participants at the meetings. Participants were informed that the sessions would be recorded, and the recording would be kept for up to seven years. A notetaker took notes during the FGDs and IDIs and observed the participants' responses. The research assistant ensured that confidentiality was maintained throughout the study.

In-depth interview with key informants (IDIs)

The IDIs involved TB programme staff, the regional administrative authority and the implementing partners supporting the TB Programme. IDIs were conducted at a location convenient to the individual being interviewed, generally this was an office in Mwanza region or at the CTRL. For international partners this was the partners offices.

Focus group Discussion with health care providers (FGD)

FGDs were conducted in the four districts in Mwanza and the CTRL. All FGDs were conducted in health facilities with Xpert technique, with some of the participants being ferried from their health centre to the meeting. The FGDs in Mwanza region were conducted early in the morning before individuals started coming for TB services. At the CTRL the participants preferred late afternoon when they had finished dealing with specimens.

6.5.2 Data handling

At the end of each day, the RA was responsible to collate all recordings and written notes. Data was downloaded from the digital tape recorder to a password-protected laptop and then transferred to a secure external hard drive placed in a locked cabinet in the Head of the CTRL's office. The protection of participants' information through the application of appropriate ethical principles is important in all research studies (138), therefore all data were anonymized as soon as all expected interviews had been transferred and confirmed by the data manager. The Participants name or site was not used instead each participant in the FGDs was coded as group number; level in health system code; female or male; and participant number (see Table 22). Therefore, examples of participant's labelling were:

Examples

1. FG-GR1-DT-F1

FG- focus group discussion
GR1- group 1
DT- district level
F1- F – female - participant number 1

2. FG-GR5- NL –F26

FG- focus group discussion
GR5- group 5
NL- national level
F26 - F -female- participant number 26

IDI participants were similarly coded see Table 23. Examples of the participant's labelling for IDIs were as follows:

Examples

1. IDI-GR13-IP-F1

IDI- In-depth Interview
GR13- site name
IP- Implementing partners
F1 - female participants number 1

2. IDI-GR8-DT-M2

IDI- In-depth Interview
GR8- site name
DT- district
M2- male participants number 2

6.5.3 Data analysis

As with the qualitative study undertaken before the implementation of the revised RSS and described in chapter 4, NVIVO 10™ was used in the qualitative data analysis for the 10 IDIs and 6 FGDs.

The analysis included four steps. The first step involved familiarisation with the data by the PI and the research assistant who together listened to the recordings and went through all the transcripts. The second step involved data coding with key themes and subthemes across the data set. The third step involved checking for frequency of key messages. In the fourth step categories and major themes were developed and classified. NVIVO 10™ software was used for organising, coding and analysing the qualitative data.

The PI together with the senior RA went through the assembled analysis alongside quotes from participants in the FGDs and IDIs to make sure the resulting themes were grounded in the data. The key themes and observations are described in the next section alongside quotes from participants in the interviews and discussions. The data interpretation and analysis came to an end once there was no new information to be discovered (i.e. the theoretical saturation point had been reached) (127).

6.6 Study findings

This chapter presents the key themes and subthemes generated from the FGDs and IDIs conducted alongside representative quotes from the participants.

The revised RSS was piloted in the Mwanza region (described in chapter 5) where specimens were collected routinely from health facilities without an Xpert machine and transported using *bodaboda* to the Xpert site for testing. Specimens were sent to the CTRL via EMS for LPA testing.

The purpose was to identify DR-TB early and minimise delays in the dissemination of results. The findings explored how the revised RSS was understood and whether the participants observed any effect on accelerating operations; specimen transportation, availability of laboratory supplies, improvement in documentation (form filling), communication between the CTRL and the peripheral facilities and whether the revised

system had addressed the issues reported in the initial qualitative study (Chapter 4). Lastly, they explore the success and challenges observed between the two systems.

Knowledge (awareness) of the revised RSS implementation

Participants understood the NTLP policy on the submission of specimens from previously-treated cases to the CTRL. They declared that it was not clearly understood before. They gave several explanations and demonstrated how the system operates and how they were familiar with the system. The following quotes illustrate this:

> *''Yes, we have heard of RSS, through mentorship provided. It is the system to monitor drug resistance by sending all previously treated TB specimens to the CTRL for culture and drug testing." (IDI-GR7-M1-DT,2018)*

> *''Routine Surveillance is a system that is used through the TB programme and the National Laboratory to perform further tests for the whole country on culture and DST. But this procedure is being administered under the control of TB coordinators. It would be ideal to make the revised system function well for our Tanzanian patients." (FGD- GR5-F25-NL,2018)*

Barriers experienced with the revised system

Despite the successes of the revised RSS, participants identified some challenges still hindering its operation. The majority of the participants were familiar with the RSS, but a few were not familiar with the system. The following quote illustrate this:

> A male participant declared that, *"I've heard of it, but I do not know how it works and what does it target, but I heard in Mwanza, it is done at the SekouToure." (FGD_ GR2-M8-DT,2018)*

Although the revised RSS was found to be beneficial for fast-tracking results. It was reported that sometimes there is a delay in posting the specimens. The following quote illustrates this:

> *''They send samples from the peripheries to the district and the Ngudu station as a hospital takes them to the post office. Looking back at the specimen shipment procedures, the difference is on sending the specimen and receiving*

the results after several months. Here we were sent through the normal way because the EMS goes through a long channel." (FGD-GR3-M15-DT, 2018)

It was reported that sometimes the wrong container for specimen collection (15 ml instead of 50 ml) was supplied. The following quotes illustrate this:

''When we were out of stock, we ordered through the RTLC. The challenge was that the falcon tubes were not the right ones that you would give the patient to cough in and put a sample; there were 15 ml falcon tubes which were brought and if you give it to the patient, they would not be able to put the sample in there, it would spill, that is not the special one for transportation." (FGD-GR1-M6-DT,2018)

''In my day-to-day performance, I do not have the challenges I encounter at the moment I do not think there is a big challenge other than what has been said about the availability of consumables on time." (IDI-GR8-M2-DT, 2018)''

The geographical locations for some residential areas were reported to be a challenge because patients missed visits, especially during the rainy season when the roads are impassable. The following quote illustrates this:

''In our region, the majority of patients are from the neighbouring region. There is Shinyanga, at the border with Shinyanga, there is Mwamashimba facility which borders Shinyanga rural and Kahama. If you look at the distance between patients' villages and the Health Centre, they are huge, especially the Diagnostic Centres such as Mwamashimba facility." (FGD-GR1-M3-DT, 2018)

A male participant mentioned facing a challenge when it came to working with staff from other departments in hospital due to lack of collaboration. The following quote illustrates this:

''Another challenge is that the media we use for making culture is sometimes challenging. You would find that hospitals do not provide sufficient co-operation in the acquisition of items such as media making eggs. But I know the programme has a media plan, I know the programme plans to enable us to get ready-made media because when it is not accessible in time it causes

delays to prepare culture for the patients. It is not all the gears, others are always available, only a few." (IDI-GR12-M7-NL, 2018)

Perception of communication within the TB network

The majority of the respondents affirmed that the TB network has improved and simplified the communication but also enabled the facilities to get electronic results on time. They also noted that the intervention that has been made serves to reduce workload at the CTRL by increasing the number of culture zonal laboratories. The following quotes illustrate this:

''It is a good network, especially when there is active communication, extremely useful and if possible, should improve even more." (IDI-GR10-M4-DT, 2018)

''I think TB networking is getting better, especially that now there is an establishment of zonal reference laboratories across the country. It reduced the workload at the CTRL." (IDI-GR12-F6-NL, 2018)

''Zones laboratory have received some samples from their regions, so I have a good impression that the network as good if sustained." (IDI-GR12-F6-NL, 2018)

Some felt that improvement of the communication within the network helped to minimise shortages of laboratory supplies and rectify any problem that needs immediate attention. The following quotes illustrate this:

''Network is good, especially when there is active communication, especially useful and if possible, should improve even more." (FGD-GR4-F19-DT, 2018)

''My point of view is that things are going well, although we said we do not get enough number of samples but I think when it comes to the network I see that the services are improving because the CTRL itself deals with making forecasting and quantification to distribute them. I think they are doing well. (IDI-GR13-M8-NL, 20118)

''TB Networking is good where there is an availability of connection that works well. For example, just like I was telling you, we sent a sample to the reference laboratory, by sitting here I get to see the results through the system. I log into the system I get the results earlier." (IDI-GR9-F3-DT, 2018)

The improved network has facilitated better communications among facilities where sometimes if one facility runs out of medical supplies or equipment they could request from nearby facilities. The following quote illustrates this:

''TB Networking covers a lot of things; you know you can interact with a district or other regions. Suppose that the challenge was we have a deficiency of cartridges for GeneXpert, you see, when I do not have the cartridges, I could borrow from another district or other health facilities or help me transport the sample, when I suspect that my patient is an MDR, sending to Sekou Toure or Bugando." (FGD-GR2-M10-DT,2018)

Despite improvement on communication it was noted that it was still a challenge in some sites. The following quotes illustrate this:

''Communication at some point was reported to be a big challenge, few participants reported to face network issues which hinder communication as they were not able to be linked into TB network." (FGD-GR1-F5-DT, S2018)

''It was also reported that it has been difficult to communicate with the patients who do not have mobile phones and others have mobile phones but the location where they live the network is fluctuating." (FGD 2018) (FGD-GR3-M18-DT,2018)

Training, supervision and mentorship in terms of capacity building

During the FGDs, some males and two females suggested that training plays a role in the improvements offered by the revised system in many aspects. They came to understand the operation of the revised RSS after being trained and are able to explain this to their colleagues. The following quotes illustrate this:

''Yes, the RSS as I said in the beginning, is based on our patient's category especially the previously treated TB, due to the training and mentoring

provided helped us to understand the system clearly." (FGD-GR2-M7-DT, 2018)

''Some of the participants declared that training and setting standards improved the way we work and increase our knowledge about the TB programme. The programme provided various training: for example, we had training courses on culture and sensitivity, by making us create an example of sending feedback online." (FGD-GR6-M33-NL, 2018)

''We have been able to increase skills and knowledge about TB testing and through the modern methods introduced to the programme we get the opportunity to recognise them, the guideline is very useful for their daily work." (IDI-GR14-M9-IP, 2018)

''Through trainings and setting standards through National guidelines would improve the way we work and increase our knowledge about the program and TB testing." (IDI-GR11-M5-NL, 2018)

Mentorship during supervision was found to be efficient. The following quote illustrates this:

''Some female participants said that they involved us on mentorship and therefore they are mentored and through these mentorships, we are building capacity for them to be able to perform their work properly." (FGD-GR4-F20-DT, 2018).

Specimen transport mechanism

The *bodaboda* was used to transport sputum specimens between the study sites in Mwanza; from peripheral health facilities to the Xpert sites. The focus was to increase TB case detection and to detect more rifampicin-resistant (RR) cases from sites without Xpert machines and hasten the feedback of results to the requester. The study anticipated minimising hassle and cost to the patients. Specimen transportation from Mwanza to the CTRL was through EMS. The same systems were used to send back results. The specimen transport system was supported by KNCV and NTLP. This system was found

to be beneficial, as came out clearly during interviews with some participants. The following quotes illustrate this:

> *''To be honest this bodaboda issue is exceptionally good, I mean to say, we received result quicker, we know the status of the patient early; that's why I said this system is good." (FGD-GR3-M16-DT, 2018)*

> *''Yeah! RSS has reduced the waiting time, in fact, it has dramatically shortened the time. In the beginning there was the problem of delayed results, but sample shipment at present and in the past is quite different; it was taking too long to get the results." (IDI-GR10-M4-DT, 2018)*

The existence of a smooth transportation system of specimens minimised batching as the following quotes illustrate:

> *''The revised system avoids batching of specimens and was instead sent as it comes using EMS and the revised laboratory request forms are well filled." (FGD-GR5-M33-NL, 2018)*

> *''There are other groups to National level, for example, we have a group of WhatsApp that has involved the Central level and Zonal Level people." (IDI-GR13-M8-NL,2018).*

Safety and Packaging of Specimens

During the interviews, the participants reported receiving an orientation on how to prepare the sample and were also provided with the guidelines. The following quotes illustrate this:

> *''They trained us about the importance of the triple package. Any trained personnel must adhere to the rules. We displayed in the work area, it shows when the samples should be transferred and how the labelling is done before it is sent to the post office." (FGD-GR2-M12-DT,2018)*

> *''Participants acknowledged the efforts made by the CTRL team as the majority of staff working with the TB units were oriented on preventive measures, safety and packaging of the sample for transferring, staff were*

conscious about TB infection and tried to minimise the risk of contamination." (GD-GR6-M35-NL,2018)

Participants noted reduction in the rate of specimen rejection and contamination, supported by improved communication that played a part in better sharing of information. The following quotes illustrate this:

''Yes, there were samples that were rejected, because of leakages, not packaged well, but now the contamination rate has gone down. I think the RSS has managed to achieve somehow in the sense that it directs people on how to do it. Previously, the contamination rate was high and now it has decreased." (FGD-GR4-F23-DT,2018)

''Previously, some samples were rejected because of poor packaging but after staff were oriented, the rate of contamination has been reducing. I think it's because of close communication." (FGD-GR1-M2-DT,2018)

Diagnostic method and centralisation of TB laboratory services

Some of the participants said that the method used for the revised system improved the feedback of results. It hastened the process and minimised hassle for the patients. The following quotes illustrate this:

''Yes, it takes 48 hours to get the results. Previously, culture took more than two months, of course, and it is eight weeks if negative. But now if it is ''positive and has to be tested for rapid DST it means we get results within a month or two months. This is good." (FGD-GR3-M13-DT,2018)

''Actually, these are technological advances, at least there are some tests carried out with a lot more urgency than it was previously." (FGD-GR4-M21-DT,2018)

A female participant affirmed that the use of molecular techniques at CTRL minimised delay in results. The following quote illustrates this:

''This is because of the use of the rapid DST (LPA) methods for early identification of drug resistant TB technique as the point of care diagnostic

tool, reducing the specimen processing time and resulting in timely transportation." (IDI-GR14-F10-IP, 2018).

6.7 Summary discussion

A revised RSS was piloted in Mwanza region with the aim of addressing some of the weaknesses observed in the existing RSS through the quantitative and qualitative analyses described in chapters 3 and 4. The revised system sought to take care of several aspects reported as impeding smooth RSS operations and resulting in delays to DST and failure to identify some DR-TB cases. Following a successful pilot, the opinions of the revised RSS were sort from stakeholders. The general impression observed from the study participants is that the revised RSS is a big improvement over the previous RSS. In particular, in providing test results in a timely way and enabling appropriate patient management. Several features were highlighted by the participants, for example the majority of the TB programme staff were trained on the specimen packaging and were aware of the RSS and the way it operates. The specimen transportation arrangements have now been improved, enabling specimens and results tracking. The findings also show that the CTRL is now able to provide prompt feedback and clarity as necessary. Inter-facility communication has been established through social media such as WhatsApp, which has strengthened the communication in the network, punctually resolving problems such as stock-outs and queries on forms and samples received or sent. Participants added that it has become easier for them to start patient's treatment on time. The process of getting the results has improved efficiency in monitoring and controlling TB patients' conditions. Data are received on time and, through this revised system, the number of reported MDR-TB cases has been increasing because of the documentation and the reporting system improvements.

Despite all the successes of the revised RSS, the study encountered challenges. The Geographical location of patients' residence, leading to delays in specimen submission

which become more difficult during rainy season. Facility accessibility, specimen transportation and communication limitations such lack of internet connectivity are still a challenge for some facilities such as Gundu, Magu and Misungwi.

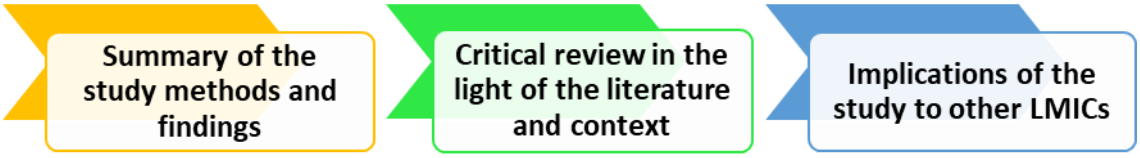
Our study indicates that the majority of hospitals and health centres were equipped for general laboratory services including TB diagnosis. However, there was evidence that many dispensaries lacked functioning microscopes and some essential equipment such as weigh scales for reagent preparations. The diagnostic centre was reduced from 80 to 72 due to lack of laboratory personnel and poor infrastructure. At some point there was a shortage of falcon tubes for specimen's transportation and at the CTRL equipment breakdown at molecular sections. Frequent power cuts also led to a number of specimens not being processes or spoiled.

There were some challenges with participation in the FGDs and IDIs especially in Mwanza region in some facilities like Misungwi where they were informed and agreed but we could not find the key people (DTLC and TB/HIV staffs to run an effective FGD). In the end we had to interview the DOT nurse using an IDI.

6.8 Conclusion

In conclusion, according to those engaged with the revised RSS in Mwanza and CTRL the revised RSS has delivered many improvements compared to the existing system. In particular, in reduced delays to getting DST results which should therefore result in increased detection of MDR-TB. This is an incredibly positive outcome and suggests the revised RSS has significant scope for roll-out across Tanzania.

Chapter 7 DISCUSSION



7.1 Introduction

This chapter presents a summary of the key study outcomes of ''Creating an effective RSS for TB in Tanzania.'' It reviews the methods and findings in the light of the literature and the context of a LMIC with a high burden of TB. It then outlines the potential implications of the study to other LMICs and what further research may be necessary.

The study aimed to answer five research questions: a). What is the scale of the inadequate performance of the current RSS for previously treated TB cases in Tanzania? b). What is the stakeholder perception of the current RSS for previously treated TB cases in Tanzania? c). What new design of RSS for previously treated TB cases might overcome many of the weaknesses in the current system. d). Does the newly designed and revised RSS improve the performance of the system, in particular by reducing the time from sputum collection at the district health facility to communication of the drug susceptibility testing results by the CTRL back to the district? e). Does the revised RSS reduce barriers to effective performance of the system?

7.2 Summary of the design and methods used for the research.

The research used a mixed method approach that included both quantitative and qualitative research methods. Firstly, quantitative data was collected and analysed for Tanzania concerning the performance of the current RSS for previously-treated TB

(described in chapter 3). Following this, qualitative data was collected from key stakeholders in a sample of regions in Tanzania. This aimed to understand their perceptions of the effectiveness of the RSS. This used FGD and IDI as appropriate (described in chapter 4). Findings from the quantitative and qualitative research were then linked and used to design a revised RSS for previously-treated TB cases to seek to address the issues identified by the research. This redesigned RSS recognised the rapid molecular technique Xpert MTB/RIF is in the process of implementation across the country in place of microscopy as the primary TB diagnostic tool. The revised RSS was then implemented as a pilot in one region (Mwanza) of Tanzania. A before and after quantitative comparison was then made of key output parameters such as the number of cases referred, transit time for samples from the periphery to the CTRL, turnaround time of DST in the CTRL, and the number of MDR-TB cases detected (described in chapter 5). Finally, a qualitative assessment using FGDs and IDIs was conducted with key stakeholders impacted by the revised RSS, to determine perceptions of whether the revised RSS had addressed the issues observed in the earlier qualitative analysis (described in chapter 6).

7.3 Key findings of the research alongside observations from the literature

Specimen referral numbers with the existing RSS

The initial quantitative study into the current RSS showed that, out of 8,482 previously treated TB cases notified across the country for the three years investigated, only 2,750 (32.4%) were received at the CTRL for DST. This implies that, the NTLP goal for the RSS of 100% of previously-treated TB cases being routinely investigated for drug resistant was far from being achieved. This infers that cases of drug resistant are likely to have been missed and surveillance by the TB programme was not fully undertaken. This finding corresponded well with the previous findings of an audit of programme data where it was shown that only 10 percent of the previously treated TB cases had their specimens

submitted to CTRL for culture and DST (46). In the follow-on qualitative study it was found that the system of TB specimen transportation in Tanzania was a major problem in remote health facilities as there were no postal services and no reliable and frequent means of transport (45).

Time taken to transport and process specimen with the existing RSS

Drug sensitivity testing is required for successful treatment of TB patients who may have drug resistance. Isolation of the mycobacteria from sputum samples within 24-48 hours is recommended (76). Studies have shown that, sputum specimens kept at room temperature beyond 3 days without preservatives, suffer a significantly low yield of isolation of *MTB* (140). In the initial quantitative study, analysis of the laboratory data collected for the three years showed significant delays in specimen transportation for culture and DST. The median transit time from sputum collection to arrival at the CTRL was over 7 days, which may have an impact on the specimen culture yield. According to the WHO, sputum specimens that are transported longer distances must be delivered as soon as possible, but no later than 48 hours from time of collection (37). However, laboratory networks in many high-TB-burden countries like Tanzania experience technical and physical resource challenges that make it impossible to comply with these WHO guidelines (141).

The turnaround time for the different tests at the CTRL only achieved the recommended time for microscopy in 82.4% of cases, 42.4% of cases for culture and just 2.8% of cases for DST. This means that more than 50% of the culture specimens and more than 95% of the DST specimens processed were unable to generate reliable results in a timely manner with consequent delays in patients commencing appropriate treatment, which in turn is likely to affect treatment outcomes. This also correlates with the follow-on qualitative study which showed result delays were one of the aspects raised in the majority of interviews with health care workers. The current RSS was seen as poor in relation to the feedback and communication of the DST results from the CTRL to the peripheries. The overall DST turnaround time is influenced by many factors including laboratory

procedures, and only one TB DST laboratory being available in Tanzania. Park *et al*. (47) comment that the centralization of drug sensitivity testing has led to overwhelming workload at the CTRL, significantly contributing to ineffectiveness of the system in the country. Our study is in line with Harries *et al.* who revealed that, problems often exist at all stages of the system from specimen transportation, processing and documentation (48). Likewise, the study findings correspond well with those reported from a study conducted by Harries *et al*. in Malawi (76). The authors emphasize an appropriate collection and transportation of sputum specimens from remote survey settings to a quality-controlled TB culture laboratory is essential to ensure accurate results that can contribute to national and global surveillance of drug resistant. The effects of delay in transporting the sputum specimen have been well discussed in previous studies.

MDR-TB detection rates with the existing RSS

In the initial quantitative study, the observed MDR-TB rate of previously-treated cases that did receive DST was surprisingly high (72 out of 373 i.e. 19.3%). WHO estimates for Tanzania in 2016 were 4.7% of previously treated cases (136). The reason for this difference is unknown, but there are three possible explanations. Firstly, that the WHO estimate is an underestimate which is possible as it was only an estimate and is not based on a recent DRS which is currently being updated. Secondly, that the observed figure in this study is an overestimate, potentially because those cases actually tested are not a random sample of all previously treated cases. They are potentially the ones that districts are most concerned about and actually have a higher probability of MDR-TB. The third possible explanation is that specimens could have been contaminated due to the short comings of the RSS. It could equally be a combination of all three reasons above.

Key stakeholder perceptions of the existing RSS

Additional observations on the existing RSS from the qualitative study with key stakeholders included comments on poor communication between the CTRL and the peripheries, weak supervision and staff shortages that contributed to low staff motivation, incomplete request forms sent with specimen transportation, lack of

availability of new diagnostic technology for DST, problems with funding and incentive payments, and a general failure to follow good practices. These and the other key themes and subthemes observed from the FGDs and IDIs have been described and linked in chapter 4, Figure 20. Some of these observations appear to be new, but others have also been observed in the literature. For example, Royce *et al.* noted that, delays due to many "handoffs" of specimens through different levels of health system and unintended consequences of health worker incentive payments, can mean even if specimens reach the laboratory they may not be of adequate quality (80). Further, Daum *et al.* observed the scaling up of the coverage of rapid diagnostic techniques (e.g. Xpert) across the country could increase case detection, early treatment and help reduce further transmission, but this needs to be supported by accurate reporting and effective routine surveillance systems (104). Shewade *et al.* in a qualitative study in India observed many similar issues related to drug sensitivity testing. For example, lack of identification of patients eligible for DST and lack of assured specimen transport after patient identification (142).

Design of a revised RSS for previously-treated TB cases

It has been possible to design and pilot a revised RSS for previously-treated TB cases (described in Chapter 5). The revised RSS piloted in Mwanza region, Tanzania aimed to address many of the issues raised in the earlier qualitative study, as well as taking into account availability of rapid diagnostic tools using molecular testing services such as Xpert and LPA. It is believed that this is the first time such a comprehensively revised RSS has been designed, piloted and results published (143). Previously studies have looked at individual aspects of the RSS for example transport (47), but never in such a comprehensive manor and including new diagnostic technologies such as Xpert.

Increase in the number of previously-treated TB cases receiving DST with the revised RSS

It was observed during the pilot in Mwanza of the revised RSS that the number of previously-treated patient specimens received at the CTRL more than doubled over that

which had been received under the previous RSS. Additionally, the revised RSS led to 93% of the specimens received at the CTRL being examined in comparison to just 64% in the previous year. This was probably a result of the reduction in missing information on the laboratory request forms received. However, despite improved transportation arrangements for the revised RSS, the study observed less than 50% of all culture-positive slopes for previously-treated TB cases underwent DST, meaning drug resistant cases are still probably being missed. More work is clearly still required to identify how to increase universal DST for previously-treated cases in Tanzania.

Reduction in transit and turnaround times for DST with revised RSS

The primary outcomes of the study were the impact of the revised RSS on specimen transit time and the time for DST results to reach the requesters (overall turnaround time). The revised RSS pilot has shown significant improvements compared to the existing RSS. For Mwanza sites, the transit time in 2017/2018 had a median of 10 days (IQR 6, 15) with 21% taking more than 21 days. In comparison in 2016/2017, the median was 12 days (IQR 3, 54) with 44% taking more than 21 days. Unfortunately, due to poor data recording in 2016/2017, the turnaround time was only available for 8 specimens, however for these 8 the median turnaround time at the CTRL was 62 days. The use of molecular techniques reduced the turnaround time median to 7 days during the pilot period of the revised RSS. In addition, the use of Xpert at local sites in Mwanza enabled specimen to be transported to a site within Mwanza region in less than three days in most cases, thus enabling a RIF resistant result to be available much sooner than previously. An important reason for the reductions in transit time were the use of an improved EMS system and bodaboda services. This improvement is contrary to previous studies in Zimbabwe and Malawi where no improvement was detected (42, 48).

Increase in number of MDR-TB cases identified through revised RSS

An increase from 12 to 20 in the number of MDR-TB cases diagnosed and started on treatment from previously-treated cases in Mwanza was observed. Although these numbers are small it still represents an increase of around 67% which is very

encouraging. WHO estimated in 2017 only around 22% of MDR-TB cases were successfully placed on treatment (144). Potentially the revised RSS could go some way to closing this gap.

Improved communication between the periphery and the CTRL with the revised RSS

Use of the social media tool WhatsApp played an important role in this study. Various groups were created by the NTLP Manager such as Vitendanishi for laboratory supplies and the Mwanza family created by the Mwanza's RTLC to enhance communication with laboratory personnel and the DTLCs in the region. These groups helped the ground staff responsible for sending out specimens to resolve concerns quickly and eased results dissemination, consequently shortening both transit and hence the overall turnaround times (143).

Social media use has increased over recent years, enabling millions of users to share immediate data, information and reports. (145), (146). Woods *et al.* explain how WhatsApp and its use as an alternative learning tool to improve clinicians' access to specialised management of complicated HIV/TB cases (145). The analysis found the majority of participants had gained new clinical confidence from group participation. The study findings supported the use of WhatsApp in a medical setting as an effective means of communication, long distance learning and support between peers and specialists. Our findings are also consistent with the understanding raised by Shenouda *et al*. that, smartphones are a tool appropriate for prescribing, coordinating clinical work and an alternative means of communication especially through instant messaging. (147). Lester *et al*. acknowledge that short message services is the most widespread digital communication mode, with the capacity to improve the quality of care in people with active TB and LTBI (148). The study concluded that, the increasing range of technologies available to assist treatment adherence is conducive to the goal of establishing holistic, patient centred differentiated care models for TB.

Muhjazi *et al.* showed that, compromised delivery of, and poor access to, TB diagnostic and treatment services are the main obstacles that face TB control programmes during

emergencies. A Whatsapp group was established to connect the central programme with TB workers at the governance level. This allowed workers to send patient reports including data spreadsheets from their mobile phones whenever they could get an internet connection. They also observed communications can often be severely interrupted in health centres which have no electricity or internet most of the time, an experience we also found in our study (149). Denkinger *et al*. noted that, the use of mobile phone technologies opened up opportunities for the integration of mobile phones as health intervention tools in many aspects of care for patients with TB, which will lead to improvements in health service delivery, patient care and patient satisfaction (146).

Lestari *et al.* observed that people in close contact with tuberculosis should have screening and appropriate management, as an opportunity for active case detection and prevention (150). In order to bridge the wide policy-practice gap behaviour change is needed across the three levels of the healthcare system—policymakers, healthcare providers, and patients. Use of new communication tools alongside application of continuous quality improvement cycles using routinely collected data is a way to engage clinic staff in understanding their own data to seek to motivate behaviour change (150).

Perception of stakeholders with the revised RSS compared to the previous RSS

Following a successful piloting, the opinions of the revised RSS were sought from stakeholders through IDI and FGD (described in Chapter 6). The general impression observed from the study participants is that the revised RSS is a big improvement over the existing RSS in providing test results in a timely manner and enabling appropriate patient management. It was clear the revised RSS was much appreciated by the health care workers. It was noticeable that the training provided seemed to play a major role in the progress of the revised system and this was commented on by many of the health care providers who came to understand its importance and implementation better. Stakeholders also noted that the CTRL is now able to provide prompt feedback and clarity as necessary. Inter-facility communication has been established through social media

such as WhatsApp, which has strengthened the communication in the network, punctually resolving problems such as stock-outs and sharing information about different TB programme events.

Despite the revised RSS working better in many ways, there were still systemic constraints that stakeholders considered needed consideration. Stakeholders suggested that DST services needed to be further decentralised and the mode of communication between the CTRL and peripheries could be improved further. It was felt that laboratory request forms needed to be captured electronically and checks should be established to minimise unnecessary errors. Similar issues of the effect of poor record keeping was observed in South Africa by Mngomezulu *et al.* where they identify that poor record keeping contributed to the low levels of bacteriological coverage reported (152). These shortcomings need to be addressed to improve patient care and programme management.

7.4 Reflection on the study design and methods used

The design of this study incorporated both quantitative and qualitative research methods employed before the pilot implementation of a revised RSS, and after in a matched approach. Qualitative research has been used many times before in research related to health systems including TB. For example, in identifying how to improve TB services (151), to explore the experiences and perceptions of patients and healthcare professionals in Peru (153), in the development of integrated laboratory services (154), and in identifying barriers for TB case finding in Ethiopia (155).

The mixed methods approach of using both quantitative and qualitative analysis has also been used before in research related to TB. For example, in a study focusing on identifying reasons why patients are lost to TB treatment follow-up in Japan (156), a study reviewing the performance of the TB programme in Liberia (157), a study looking at health care-seeking behaviour for those with potential TB symptoms in Tanzania (161),

and another study in Tanzania researching acceptability of community and health facility based DOT for TB (163). The approach might be considered as falling within the wider context of Implementation Research which the British Medical Journal (BMJ) defines as "the scientific inquiry into questions concerning implementation the act of carrying an intention into effect, which in health research can be policies, programmes, or individual practices (collectively called interventions)"(158). Implementation research generally uses a mixed methods approach including both quantitative and qualitative approaches and has been advocated previously by researchers working in the field of TB (159). In our study the qualitative and quantitative aspects of the research are discussed in separate chapters but cross-linking of ideas between the approaches was done. For example, incites derived from the qualitative part explained some of the quantitative findings. In addition, many of the overall study findings were consistent across the quantitative and qualitative results, for example in observing the delays to getting DST results and the resulting impact on MDR-TB diagnosis.

The qualitative research performed both before and after the intervention focused on health worker perceptions of the RSS and did not include any interviews of patients using the health system, unlike some other qualitative research discussed in the literature (153). This was primarily because we already understood the RSS was not delivering for patients in providing rapid DST. We were focused on understanding why the current RSS was not delivering on its objectives. The RSS is probably not something patients of the health system would have the detailed knowledge of to make a useful contribution to the research but are clearly impacted by its poor performance. In the future it would be interesting to conduct qualitative research with the users of the health system following the introduction of the revised RSS, to understand whether patients are experiencing the service they require, or might expect, in detection of drug resistance.

A combination of FGDs and IDIs were used as qualitative methods of data collection in this study. This is because the methods complemented one another in terms of generating ideas and understanding respondent's views and perceptions. FGDs and IDIs

provide a good social context to gain a deep understanding of a subject and enable the researcher explore the stakeholders perceptions (160). The combination of the two approaches enabled some participants to discuss their observations with their peers in the FGDs, whilst other generally more senior individuals were able to privately voice their concerns and observations with the research team. Alternative qualitative methods were considered, but it was felt they would not give the quality and breadth of data required. For example, although Surveys might have allowed more people's views to be considered, they would not have enabled a clear description of the RSS to have been provided beforehand and would not have enabled clarification via queries and questions to be provided easily. Also, in something as detailed as the RSS the concern would be response might have been low.

7.5 Operational limitations of the study

There were a number of operational limitations to this study that were observed.

First: the historical routine data captured electronically was found to be incomplete due to poor form filling that led to some difficulties in analysing information. For example, in the number of previously-treated case specimens recorded in most of the specimens received in 2011 which were not accompanied by appropriate forms or registers, and even those sent were incompletely filled. In 2012, 2013 there were improvements in the documentation, hence the increased numbers recorded compared to 2011. Even so, some information in one or more of the relevant fields (including results and personal demographic information) was missing in 2012 and 2013 data which made it exceedingly difficult to verify the data so had to be discarded. Poor record keeping sometimes made comparisons of performance difficult. However, to a certain degree, this poor record keeping was also symptomatic of the poor performing RSS. The revised RSS record keeping has improved and this is a real benefit assuming it can be sustained. The

evidence from this study shows its importance as it could have a direct effect on patients getting appropriate treatment and in a timely manner.

Second: In the qualitative studies many of the experienced laboratory staff were not available for key informant interviews as a result of high staff turnover. The initial sampling of personnel for FGDs assumed achieving appropriate number of participants. (164). In most of the selected districts the number were less than recommended resulting in exclusion of some sites. Time for the key informant interviews was also limited due to their tight schedules and therefore some interviews were unavoidably hurried. However, despite these limitations, a good range of stakeholders were still included that gave a broad range of views and perceptions.

Third: During the pilot study of the revised RSS in Mwanza there were great variations in the number of specimens received by month (Chapter 5, Figure 30). This was mainly due to operational reasons, for example towards the end of May 2017, there was a nationwide employees' education certificate inspection for irregularities which led to the termination of several laboratory staff and clinicians, which unfortunately had a negative impact on the pilot. In addition, in December 2017 and February 2018, fewer specimens were received which might have been due to staff shortages leading to specimen batching. Without, these difficulties it would be expected the pilot would have performed even better. However, such difficulties are not unusual, so potentially it is not unreasonable to expect in routine practice such problems.

Fourth: The pilot study only referred specimens tested by Xpert in Mwanza to the CTRL for confirmatory LPA testing when Rifampicin resistance was detected, so potential cases with INH resistance could have been missed as Xpert, currently only has the capacity to detect Rifampicin resistance. However, studies have shown RIF resistance is highly correlated with INH resistance, therefore the effect of this limitation is expected to be small (165).

Fifth: Despite all the successes of the revised RSS, the study encountered challenges. The geographical location of patients' residence, leading to delays in specimen submission which become more difficult during rainy season. Facility accessibility, specimen transportation and communication limitations such as lack of internet connectivity were a challenge for some facilities such as Gundu, Magu and Misungwi. In addition, at some point there was a shortage of falcon tubes for specimen transportation and at the CTRL frequent power cuts also led to a number of specimens not being processes or spoiled. However, all these are real-world routine problems that any RSS has to deal with in becoming as effective as possible.

Sixth: In the post pilot qualitative study there were some challenges with participation in the FGDs and IDIs especially in Mwanza region. In some facilities like Misungwi participants were informed and agreed to take part, but some important individuals could not be found to take part in an effective FGD. In the end additional DOT Nurses were interviewed using an IDI to ensure representation from all facilities.

Despite all the difficulties and limitations, the study produced many useful and valuable findings. It is believed these findings give a real insight into the issues surrounding the existing RSS for TB in Tanzania and highlight how a revised RSS can address many (if not all) those issues to deliver improved outcomes for patients and the health system.

7.6 Wider implications of the study

Many low- and middle- income countries (LMIC) with a high burden of TB face similar problems to Tanzania (167, 168, 169). For example, limited capacity for DST with one Central Reference Laboratory (CRL) for the whole country with inadequate access due to several barriers. These barriers include lack of programme awareness amongst physicians, limited supplies, and unreliable transport (47). Laboratories performing culture and DST are often inadequate and overloaded (48,166). Likewise, rapid transport of sputum from remote areas of the country to the reference laboratory is difficult

resulting in losses due to contamination or growth failure (166). Poor infrastructure and unsustainable logistics are also contributing factors (71,166). This study suggests that real improvement can be delivered in contexts like those in Tanzania that would increase DR-TB detection and reduce delays for patients in starting appropriate DR-TB treatment. This is the first study that the author is aware of that has taken such a comprehensive approach (including the use of quantitative and qualitative methods alongside a pilot study) to address the issues around RSS for TB in a low-income country. Lessons from this study undoubtedly have many practical applications to other similar countries with a high burden of TB.

The study focused on previously-treated TB cases only, however all the interventions could have equal value to new cases, though the level of drug resistance would be expected to be much lower.

The findings of this study could assist the NTLP in its operational plans and funding allocations. Potential interventions that could be considered are to establish national guidelines for specimen packaging and referral arrangements to counteract contamination effects; increased awareness among district coordinators on the importance of sending specimens within the recommended timeframe, decentralization of culture and DST services, and roll out of more appropriate rapid TB laboratory testing techniques such as Xpert MTB/RIF.

The design and research methods used in this study have shown appropriate data collection and analysis using both quantitative and qualitative methods, are important in contributing to knowledge, understanding, identifying solutions and piloting interventions in health care. It is a potential approach for other studies involving health delivery system improvement, especially in resource limited settings.

7.7 Reflections on the research being conducted by the Head of the CTRL

The research described and written up in this thesis was conducted by the Head of the CTRL with responsibility for all the TB laboratory functions in Tanzania (described in section 1.5.1). This has both strengths and disadvantages.

In relation to the design of the study, being the Head of the CTRL had many benefits. As the Head of the CTRL I had direct experience and understanding of the routine operation of TB control processes and strategies in Tanzania, including the RSS. In addition, I had direct experience of the outcomes of these processes, whether good or bad. For example, in my job I received frequent feedback from the regions concerning result delays from the CTRL, shortages of supplies and staff, difficulties in linking data between the CTRL and the wider TB network, equipment breakdown, and poor implementation of external quality assurance. Equally, the CTRL staff complained that the specimens received were not sent on time, were few in numbers, and often with incomplete TB laboratory request forms. This allied to the low levels of MDR-TB detection in Tanzania and the many previous unsuccessful attempts to address the issues, gave me real motivation to complete a research study into the RSS as I could see there were serious problems that needed addressing.

My role as Head of the CTRL gave me the awareness that individuals involved in the TB programme could potentially provide great insight into what was going wrong, and hopefully help identify ways to fix it. This was a major motivation behind the mixed methods design involving completing a qualitative study with key stakeholders alongside the quantitative analysis using the available data to verify the extent of the issues. In my role, as Head of the CTRL I was also well placed to identify the key individuals to include in the research and the dynamic interactions between these individuals. Potentially however, being so close to the issues could have led to concerns about highlighting my own shortcomings, or a rush to solutions without giving time for a thorough data

collection and analysis. I needed to keep reminding myself, and my colleagues, that we are doing this for the betterment of the patients and improving the programme outcomes. In addition, a rush to finding solutions was avoided by the design and structure of the qualitative research, which was completed first before the design of the pilot intervention was even considered. Close and supportive supervision and training from my academic supervisors at LSTM enabled me to use approaches to the qualitative research that I had previously had little experience of using (e.g. use of focus group discussions and in-depth interviews). There was a concern that being in a senior position over many of the individuals involved in the FGDs and IDIs could have resulted in some individuals being reluctant to speak out. This was avoided as much as possible by employing research assistants to conduct the FGDs and IDIs and ensuring the confidentiality of the whole process. This did mean that I could not take part in the interviews themselves which was a disadvantage, but through the design of clear topic guides and recording of the interviews it was still possible to be fully engaged in the data collection and subsequent analysis. The need to hire two research assistants during the study was an additional cost, but the fact that this helped to ensure unbiased data collection made the additional expense essential.

In relation to the design and execution of the pilot interventions, my role and experience helped ensure it was feasible to implement and was a great help in getting approval and buy-in from management and colleagues alike in Dar es Salaam and Mwanza. On the other hand, it is possible that more innovative and creative interventions might be identified by individuals less engrained in the current processes. To address this, external partners of the Tanzanian TB programme were included in the IDI's conducted before and after the pilot of the interventions (i.e. MSH, PATH and KNCV).

Data analysis was greatly helped by me being the Head of the CTRL as it gave me direct access to all the TB programme data systems and the resources to support the analysis. To ensure quality of the analysis my academic supervisors helped by challenging the

analysis and identifying where additional work and clarification was required. Effective interpretation of the results is key to any research. The fact I was so familiar with the existing processes and performance of the TB programme was a great help in interpreting the results. However, it was essential that there was external challenge to these interpretations to avoid misinterpretation and failure to identify new themes that may not fit with my preconceived ideas. This challenge, for example, assisted greatly in interpretation of the qualitative research described in chapter 4 and the design of the revised RSS described in chapter 5.

In conclusion, this research has benefitted from me being the Head of the CTRL. This arises from the in-depth knowledge of the current processes and people of the TB programme in Tanzania, and the authority my position gave me. However, there are some issues that this could have caused, such as an over emphasis on preconceived ideas, lack of innovation, or bias introduced in qualitative data collection from the authority of my position in the organisation. It was important to realise these dangers and put in place measures to ensure the quality of the research by, for example, engagement of hired research assistants, partners, and academic supervisors to give an external dimension. Finally, a clear benefit of my role will be in taking the results and learnings of this research forward in implementing changes to the RSS and in the further research I am now better equipped to complete. This makes me very proud that my dedication and commitment to this research has paid off.

7.8 Further Research

It is clear from this study that there is more research to do. For instance, even with the focus of the revised RSS, 13% of the laboratory request forms had missing laboratory reference numbers and 3% missing addresses, although much lower than in 2016/17. Similarly, there were significant numbers of specimens in 2017/18 that were not processed for a variety of reasons (i.e. in total 75 out of 472, 15.9%). Further research

that might identify how to close these and other gaps in performance would be worthwhile.

The WhatsApp platform used as a communication tool in the pilot study was recognised as a great success. This has begun to be replicated in other regions among DTLCs, RTLCs and laboratory teams and has proved an extremely useful means to address many communication issues in the TB programme and beyond. Potentially, there are other aspects of work in the TB programme where such an approach could benefit. Further evidence is required to evaluate the feasibility, equity and effectiveness of mobile phone interventions for TB control (170). However, one area that seems ripe for use of such technology is in reporting laboratory results and a web-link to send laboratory data to the NTLP.

The revised RSS was shown to reduce delays in diagnosis and increase the number of drug resistant cases detected. The shorter transit times and turnaround times are important in the diagnosis of MDR-TB and TB control. These positive results suggest a larger scale study involving more regions should be considered to determine whether these benefits are robust and sustainable across similar settings. Such a study could include a modelling element in order to assess the impact of a revised RSS on health system costs and to evaluate cost effectiveness.

7.9 Conclusions

The study findings provide a basis for identifying potential methods of improving the routine surveillance system and thereby providing more timely and appropriate management particularly for patients with potential MDR-TB. Based on these findings there is an urgent need to address the identified shortfalls of the existing RSS in order to provide improved feedback to peripheral centres and patients, and to increase MDR-TB detection and therefore treatment.

In conclusion, the revised RSS led to an increased number of specimens received and tested at the CTRL. The use of social media within the NTLP network led to close follow-ups and timely response to concerns during the piloting. The revised system was shown to reduce delays in diagnosis and increase the number of drug resistant cases detected. According to those engaged with the revised RSS in Mwanza, and at the CTRL, the revised RSS has delivered many improvements compared to the existing system. In particular, the shorter transit times and turnaround times are important in the diagnosis of MDR-TB and TB control. This is a very positive outcome and suggests the revised RSS has significant scope for a roll-out across Tanzania. The research should lead to further research to determine whether the benefits identified in Mwanza, Tanzania are robust and sustainable across similar settings in Tanzania and other LMIC.

References

1. Raviglione M, Sulis G. Tuberculosis 2015: Burden, challenges and strategy for control and elimination. Infectious Disease Reports. 2016;8(2):33–7.

2. AFRICAN UNION. SPECIAL SUMMIT OF AFRICAN UNION ON HIV/AIDS, TUBERCULOSIS AND MALARIA (ATM) 2006. Abuja, Nigeria; 2006.

3. Iternational Union Against Tuberculosis and Lung. Management of Tuberculosis A Guide to the Essentials of Good Practice. sixth. Sixth, editor. 2010.

4. Rieder HL. Epidemiologic basis of tuberculosis Control. Paris: International Union Against Tuberculosis and Lung Disease. 1999;73(1st Edition):17–62.

5. Segar M, Reuters /. WHO Global Tuberculosis Report Executive Summary 2018. In 2018.

6. WHO. WHO Global Tuberculosis Report 2016. WHO, editor. Vol. 39. Switzeland; 2016. 561–563 p.

7. WHO. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO. CIP data are available at http://apps.who.int/iris.; 2018.

8. World Health Organization. WHO. Global tuberculosis report. Geneva: World Health Organization; 2017.

9. World Health Organization. Global Tuberculosis Report 2016. 2016.

10. McNerney R, Daley P. Towards a point-of-care test for active tuberculosis: obstacles and opportunities. Nature Reviews Microbiology. 2011 Mar;9(3):204–13.

11. Millen SJ, Uys PW, Hargrove J, Helden PD Van, Williams BG. The Effect of Diagnostic Delays on the Drop-Out Rate and the Total Delay to Diagnosis of Tuberculosis. PloS one. 2008;3(4).

12. Said K, Hella J, Mhalu G, Chiryankubi M, Masika E, Maroa T, et al. Diagnostic delay and associated factors among patients with pulmonary tuberculosis in Dar es Salaam, Tanzania. Infectious Diseases of Poverty. 2017;6(1):1–10.

13. Ani A, Okpe S, Akambi M, Ejelionu E, Yakubu B, Owolodun O, et al. Comparison of a DNA based PCR method with conventional methods for the detection of M. tuberculosis in Jos, Nigeria. The Journal of Infection in Developing Countries. 2009 Jul;3(06):470–5.

14. Yon Ju Ryu MD. Diagnosis of pulmonary tuberculosis: Recent advances and diagnostic algorithms. Tuberculosis and Respiratory Diseases. 2015;111 (5):64–71.

15. Lambert ML, Stuyft P Van der. Editorial: Delays to tuberculosis treatment: shall we continue to blame the victim? Tropical Medicine & International Health. 2005;10(10):945–6.

16. WHO | WHO endorses new rapid tuberculosis test. In: WHO. World Health Organization; 2010.

17. Langley I, Doulla B, Lin H. Modelling the impacts of new diagnostic tools for tuberculosis in developing countries to enhance policy decisions. Health Care Mang Sci. 2012;15:239–53.

18. Kim SJ. Drug-susceptibility testing in tuberculosis: Methods and reliability of results. European Respiratory Journal. 2005;25(3):564–9.

19. Organization WH. World Health Organiztion-WHO. Global Tuberculosis Report 2018. Switzeland: CIP data are available at http://apps.who.int/iris. Sales,; 1389.

20. National Tuberculosis and Leprosy Programme. The United Republic of Tanzania Ministry of Health and Social Welfare Strategic Plan V for 2015 - 2020. Dar es Salaam; 2015.

21. PST. The First National Tuberculosis Prevalence Survey in the United Republic of Tanzania Final Report. Tanzania Health Research Bulletin. 2013.

22. Ministry of Health and Social Welfare. The United Republic of Tanzania National Tuberculosis and Leprosy Programme Annual Report 2006. 2006;

23. National Tuberculosis and Leprosy Programme. The Republic of Tanzania Ministry of Health Community Development Gender Elderly and Children Annual Report 2016. Dar es Salaam, Tanzania; 2016.

24. National Tuberculosis and leprosy Programme Annual report for 2015. The United Republic of Tanzania Ministry Of Health Community Development , Gender , Elderly and Children The. Dar es Salaam; 2015.

25. Chonde TM, Basra D, Mfinanga SGM, Range N, Lwilla F, Shirima RP, et al. National anti-tuberculosis drug resistance study in Tanzania. The International Journal of Tuberculosis and Lung Disease. 2010;14(8):967–72.

26. The Global Fund. Best Practices on TB Case Finding and Treatment. 2018. 73 p.

27. Dr. Donan W. Mmbando. United Republic of Tanzania Ministry of Health and Social Welfare Manual for the Management of Tuberculosis and Leprosy. sixth. Dar es Salaam: Colour printer, Tanzania; 2013.

28. NTLP. United Republic of Tanzania Ministry of Health and Social Welfare National Tuberculosis and Leprosy Programme Manual for the Management of Tuberculosis and Leprosy SIxth Edition. 2013;

29. World Health Organization (WHO). UNITED REPUBLIC OF TANZANIA – A harmonized system to monitor the contribution of communities to the national TB response CASE STUDY ENGAGE-TB ENGAGE-TB. WHO. 2020.

30. Tanzania Ministry of Health. UNITED REPUBLIC OF TANZANIA NATIONAL OPERATIONAL GUIDELINE FOR COMMUNITY BASED TB , TB / HIV AND DR-TB INTERVENTIONS. Dar Es Salaam, Tanzania;

31. NTLP. THE UNITED REPUBLIC OF TANZANIA MINISTRY OF HEALTH AND SOCIAL WELFARE National Strategic Plan V for Tuberculosis and Leprosy Programme. 2015.

32. John Ridderhof. External Quality Assessment for AFB smear Microscopy.

33. Lumb, Richard, Armand Van Deun, Bastian I. LABORATORY DIAGNOSIS OF TUBERCULOSIS BY SPUTUM MICROSCOPY. Mark Fitz-Gerald Technical, editor. SA Pathology trading as IMVS; 2009.

34. Chakravorty S, Mahmud H, Tyagi J. Lysis of tubercle bacilli in fresh and stored sputum specimens: Implications for diagnosing tuberculosis in stored and paucibacillary specimens by PCR. 2007;

35. WHO. Quality Assurance of Sputum Microscopy in DOTS Programmes Countries in the Western Pacific Quality Assurance of Sputum Microscopy in DOTS Programmes.

36. Cepheid. GeneXpert Dx System Operating Manual. © Cepheid 2012. France; 2013.

37. Anna Dean and Matteo Zignol. WHO Guidelines for surveillance of drug resistance in tuberculosis. 5th ed. Vol. 5th editio. © World Health Organization 2015; 2015. 2011 p.

38. Van Deun A, Salim AH, Rigouts L, Rahman M, Fissette K, Portaels F. Evaluation of tuberculosis control by periodic or routine susceptibility testing in previously treated cases. International Journal of Tuberculosis and Lung Disease. 2001;5(4):329–38.

39. Annabel Baddeley et al. WHO Global Tuberculosis Report 2014. Vol. 11. Geneva, Switzerland: WHO Library Cataloguing-in-Publication Data; 2014. 564–570 p.

40. Nunn PT leader. Report of the United Republic of Tanzania National Tuberculosis and Leprosy Programme External Review. 2014.

41. NTLP and FIND. Xpert ® MTB / RIF test Rollout and Implementation Plan United Republic of Tanzania. First. South Africa; 2015.

42. Timire C, Takarinda KC, Sandy C, Zishiri C, Kumar AM V., Harries AD. Has TB CARE I sputum transport improved access to culture services for retreatment

tuberculosis patients in Zimbabwe? Public Health Action. 2019;8(2):66–71.

43. WHO. Global tuberculosis report 2015. 2015.

44. Dr. Armand Van Deun. Mission Report -Tanzania. SRLN. Dar es Salaam; 2013.

45. Doulla BE, Squire SB, MacPherson E, Ngadaya ES, Mutayoba BK, Langley I. Routine surveillance for the identification of drug resistant Tuberculosis in Tanzania: A cross-sectional study of stakeholders' perceptions. Plos One. 2019;14(2):e0212421.

46. Kilale AM, Ngowi BJ, Mfinanga GS, Egwaga S, Doulla B, Kumar AM V., et al. Are sputum samples of retreatment tuberculosis reaching the reference laboratories? A 9-year audit in Tanzania. Public Health Action. 2013;3(2):156–9.

47. Park PH, Magut C, Gardner A, O'yiengo DO, Kamle L, Langat BK, et al. Increasing access to the MDR-TB surveillance programme through a collaborative model in western Kenya. Tropical Medicine and International Health. 2012;17(3):374–9.

48. Harries AD, Michongwe J, Nyirenda TE, Kemp JR, Squire SB, Ramsay AR, et al. Using a bus service for transporting sputum specimens to the Central Reference Laboratory: Effect on the routine TB culture service in Malawi. International Journal of Tuberculosis and Lung Disease. 8(2):204–10.

49. Denney AS, Tewksbury R. How to Write a Literature Review. Journal of Criminal Justice Education. 2013;24(2):218-234.2.

50. David L. Cohn FB, Raviglione and MC. Drug-Resistant Tuberculosis: Review of the Worldwide Situation and the WHO/IUATLD Global Surveillance Project David. Clinical Infectious Diseases. 1997;24(Suppl 1):19–45.

51. Nkengasong JN, Mesele T, Orloff S, Kebede Y, Fonjungo PN, Timperi R, et al. Critical role of developing national strategic plans as a guide to strengthen laboratory health systems in resource-poor settings. American Journal of Clinical Pathology. 2009;131(6):852–7.

52. Liu Z, Pan A, Wu B, Zhou L, He H, Meng Q, et al. Feasibility of a new model for early detection of patients with multidrug-resistant tuberculosis in a developed setting of eastern China. Tropical Medicine & International Health. 2017 Oct;22(10):1328–33.

53. Hofmann-Thiel S, Hoffmann H, Hillemann D, Rigouts L, Van Deun A, Kranzer K. How should discordance between molecular and growth-based assays for rifampicin resistance be investigated? The International Journal of Tuberculosis and Lung Disease. 2017;21(7):721–6.

54. WHO. Global WHO Tuberculosis report 2017. France: World Health Organization; 2017.

55. Rabia Jhonson. Understanding the mechanisms of drug resistance in enhancing rapid molecular detection of drug resistance in Mycobacterium tuberculosis Rabia Johnson. 2007.

56. Acosta C. Drug-resistant tuberculosis in Eastern Europe: challenges and ways forward. Public Health Action. 2014;I(1):26–31.

57. Zumla A, Abubakar I, Raviglione M, Hoelscher M, Ditiu L, McHugh TD, et al. Drug-Resistant tuberculosis-current dilemmas, unanswered questions, challenges, and priority needs. Journal of Infectious Diseases. 2012;205(SUPPL. 2):1–13.

58. Solomon SL, Rutledge TF, Boyd MF. Plan to combat extensively drug-resistant tuberculosis: recommendations of the Federal Tuberculosis Task Force. Vol. 58, MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports / Centers for Disease Control. 2009. 1–43 p.

59. Omar Salad et al. Treatment Outcomes of Patients with Multidrug-Resistant Tuberculosis (MDR- TB) Compared with Non-MDR-TB Infections in Peninsular Malaysia. Original Article. 2016;23(1):17–25.

60. Paul D, Busireddy A, Nagaraja SB, Satyanarayana S, Dewan PK, Nair SA, et al. Factors Associated with Delays in Treatment Initiation after Tuberculosis Diagnosis in Two Districts of India. Pai M, editor. PLoS ONE. 2012 Jul;7(7):e39040.

61. Sagbakken M. Tuberculosis as a global challenge A qualitative study of patients ' and health. 2010.

62. Johnson R, M Warren R, van der Spuy G, Gey van Pittius N, Theron D, Streicher E, et al. Drug-resistant tuberculosis epidemic in the Western Cape driven by a virulent Beijing genotype strain. Vol. 14, The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2010. 119–121 p.

63. Castro KG. Tuberculosis Surveillance: Data for Decision-Making. Clinical Infectious Diseases. 2007;44(10):1268–70.

64. Bazira J, Asiimwe BB, Joloba ML, Bwanga F, Matee MI. Mycobacterium tuberculosis spoligotypes and drug susceptibility pattern of isolates from tuberculosis patients in South-Western Uganda. BMC Infectious Diseases. 2011;11:1–8.

65. Hoza AS, Mfinanga SGM, König B. Anti-TB drug resistance in Tanga, Tanzania: A cross sectional facility-base prevalence among pulmonary TB patients. Asian Pacific Journal. 2015;8(11):907–13.

66. Report M. for new tuberculosis diagnostics : report of a consensus meeting. 2014.

67. García-Basteiro AL, Respeito D, Augusto OJ, López-Varela E, Sacoor C, Sequera VG,

et al. Poor tuberculosis treatment outcomes in Southern Mozambique (2011-2012). BMC Infectious Diseases. 2016;16(1):1–9.

68. Weyer K, Carai S, Nunn P. Viewpoint TB diagnostics: What does the world really need? Journal of Infectious Diseases. 2011;204(SUPPL. 4).

69. Kumar AM V., Naik B, Guddemane DK, Bhat P, Wilson N, Sreenivas AN, et al. Efficient, quality-assured data capture in operational research through innovative use of open-access technology [Short communication]. Public Health Action. 2013;3(1):60–2.

70. Kebede Y, Fonjungo PN, Tibesso G, Shrivastava R, Nkengasong JN, Kenyon T, et al. Improved Specimen-Referral System and Increased Access to Quality Laboratory Services in Ethiopia: The Role of the Public-Private Partnership. Journal of Infectious Diseases. 2016;213(CDC):S59–64.

71. MOHSW. Tanzania Service Availability and Readiness Assessment (SARA) 2012 July 2013. 2013;(July).

72. Olson S, English R a, Guenther RS, Claiborne AB. Facing the Reality of Drug-Resistant Tuberculosis in India. Washington; 2012. 2–22 p.

73. Guio H, Okayama H, Ashino Y, Saitoh H, Xiao P, Miki M, et al. Method for efficient storage and transportation of sputum specimens for molecular testing of tuberculosis. International Journal of Tuberculosis and Lung Disease. 2006;10(8):906–10.

74. Harries AD, Michongwe J, Nyirenda TE, Kemp JR, Squire SB, Ramsay AR, et al. Using a bus service for transporting sputum specimens to the Central Reference Laboratory: Effect on the routine TB culture service in Malawi. International Journal of Tuberculosis and Lung Disease. 2004;8(2):204–10.

75. C. Timire. Has TB CARE I sputum transport improved access to culture services for retreatment tuberculosis patients in Zimbabwe. Public Health Action. 2018;I(November 2013):14–8.

76. Bhat J, Selvakumar N, Rao VG, Gopi PG, Yadav R, Wares DF. Yield of culture of *Mycobacterium tuberculosis* complex in sputum samples transported from tribal areas. The International Journal of Tuberculosis and Lung Disease. 2011 Apr;15(4):478–82.

77. Daum LT, Peters RPH, Fourie PB, Jonkman K, Worthy SA, Rodriguez JD, et al. Yield of culture of Mycobacterium tuberculosis complex in sputum samples transported from tribal areas. The International Journal of Tuberculosis and Lung Disease. 2015 May;19(5):552–7.

78. Union I, Tuberculosis A, Disease L. Priorities for Tuberculosis Bacteriology Services

in Low-Income Countries. 2007.

79. Ridderhof JC, Van Deun A, Kai MK, Narayanan PR, Aziz MA. Roles of laboratories and laboratory systems in effective tuberculosis programmes. Bulletin of the World Health Organization. 2007;85(5):354–9.

80. Royce S, Khann S, Yadav RP, Mao ET, Cattamanchi A, Sam S, et al. Identifying multidrug resistance in previously treated tuberculosis patients: A mixed-methods study in Cambodia. International Journal of Tuberculosis and Lung Disease. 2014;18(11):1299–306.

81. Nagu TJ, Aboud S, Mwiru R, Matee MI, Rao M, Fawzi WW, et al. Tuberculosis associated mortality in a prospective cohort in Sub Saharan Africa: Association with HIV and antiretroviral therapy. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2017 Mar;56:39–44.

82. WHO. TB Diagnostics and Laboratory Services Information Note. In 2010. p. 1–7.

83. Birx D, De Souza M, Nkengasong JN. Laboratory challenges in the scaling up of HIV, TB, and malaria programs: The interaction of health and laboratory systems, clinical research, and service delivery. American Journal of Clinical Pathology. 2009;131(6):849–51.

84. Cowan J, Michel C, Manhiça I, Monivo C, Saize D, Creswell J, et al. Implementing rapid testing for tuberculosis in Mozambique. Bulletin of the World Health Organization. 2015;93(2):125–30.

85. World Health Organization. 2008. Policy guidance on drug-susceptibility testing (DST) of second-line antituberculosis drugs World Health Organization. World Health. GENEVA; 2008.

86. Agrawal M, Bajaj A, Bhatia V, Dutt S. Comparative Study of GeneXpert with ZN Stain and Culture in Samples of Suspected Pulmonary Tuberculosis. Journal of clinical and diagnostic research : JCDR. 2016 May;10(5):DC09-12.

87. World Health Organization. GLI Practical Guide to TB Laboratory Strengthening. 2017. 130 p.

88. Fox GJ, Schaaf HS, Mandalakas A, Chiappini E, Zumla A, Marais BJ. Preventing the spread of multidrug-resistant tuberculosis and protecting contacts of infectious cases. Clinical Microbiology and Infection. 2017;23(3):147–53.

89. Albert H, Nathavitharana RR, Isaacs C, Pai M, Denkinger CM, Boehme CC. Development, roll-out and impact of Xpert MTB/RIF for tuberculosis: What lessons have we learnt and how can we do better? European Respiratory Journal. 2016;48(2):516–25.

90. Global Fund Long R. Drug-resistant tuberculosis Global Fund. Vol. 163, Cmaj. 2018.

91. Tenover FC, Crawford JT, Huebner RE, Geiter LJ, Horsburgh CR, Good RC. The resurgence of tuberculosis: Is your laboratory ready? Journal of Clinical Microbiology. 1993;31(4):767–70.

92. Li Y, Ehiri J, Tang S, Li D, Bian Y, Lin H, et al. Factors associated with patient, and diagnostic delays in Chinese TB patients: A systematic review and meta-analysis. BMC Medicine. 2013;11(1):1.

93. Ramsay A, Yassin MA, Cambanis A, Hirao S, Almotawa A, Gammo M, et al. Front-Loading Sputum Microscopy Services : An Opportunity to Optimise Smear-Based Case Detection of Tuberculosis in High Prevalence Countries. 2009;2009.

94. UNitaid. Diagnostics Technology Landscape 5th Edition, May 2017. 2017.

95. Omar S V, Peters RPH, Ismail NA, Jonkman K, Dreyer AW. Field evaluation of a novel preservation medium to transport sputum specimens for molecular detection of Mycobacterium tuberculosis in a rural African setting. 00(00):1–7.

96. Lienhardt C, Gebreselassie N, Raviglione M. Global Observatory on Health Research and Development (R & D) Background paper on Tuberculosis Specific R & D Research Priorities and Funding Gaps.

97. Davis JL, Ho C, Cattamanchi A, Grinsdale J, Metcalfe JZ, Pandori M, et al. The Clinical And Public Health Impact Of Automated Nucleic Acid Testing For TB Evaluation In San Francisco. In: C94 DETECTING AND PREVENTING TUBERCULOSIS AND DRUG-RESISTANT TUBERCULOSIS: REAL PROGRESS. American Thoracic Society; 2011. p. A5314–A5314.

98. Trébucq A, Enarson DA, Chiang CY, Deun A Van, Harries AD, Boillot F, et al. Xpert ® MTB/RIF for national tuberculosis programmes in low-income countries: when, where and how? INT J TUBERC LUNG DIS. 2011;15(12):1567–71.

99. Mnyambwa PN, Kim D-J, Ngadaya ES, Kazwala R, Petrucka P, Mfinanga SG. Assessment of sputum smear-positive but culture-negative results among newly diagnosed pulmonary tuberculosis patients in Tanzania. 2017;199–205.

100. Hoza AS, Mfinanga SGM, Rodloff AC, Moser I, König B. Increased isolation of nontuberculous mycobacteria among TB suspects in Northeastern, Tanzania: public health and diagnostic implications for control programmes. BMC Research Notes. 2016 Dec;9(1):109.

101. Kilale AM, Ngadaya E, Muhumuza J, Kagaruki GB, Lema YL, Ngowi BJ, et al. Who Has Mycobacterial Disease? A Cross Sectional Study in Agropastoral Communities in Tanzania. Cardona P-J, editor. PLOS ONE. 2016 May;11(5):e0153711.

102. Shahraki AH, Heidarieh P, Bostanabad SZ, Khosravi AD, Hashemzadeh M, Khandan

S, et al. “Multidrug-resistant tuberculosis” may be nontuberculous mycobacteria. European Journal of Internal Medicine. 2015;26(4):279–84.

103. Mnyambwa NP, Lekule I, Ngadaya ES, Kimaro G, Petrucka P, Kim D-J, et al. Assessment of GeneXpert GxAlert platform for multi-drug resistant tuberculosis diagnosis and patients’ linkage to care in Tanzania. BMC Research Notes. 2018 Dec;11(1):121.

104. Daum LT, Peters RPH, Fourie PB, Jonkman K, Worthy SA, Rodriguez JD, et al. Molecular detection of Mycobacterium tuberculosis from sputum transported in PrimeStore® from rural settings. International Journal of Tuberculosis and Lung Disease. 2015;19(5):552–7.

105. McKibbon KA, Gadd CS. A quantitative analysis of qualitative studies in clinical journals for the 2000 publishing year. BMC Medical Informatics and Decision Making. 2004;4:1–8.

106. MoHSW. Tanzania National Guidelines for the Management of Tuberculosis in children. 2012.

107. Ministry of health and Social welfare. Manual for the Management of Tuberculosis and Leprosy. 2013;1–215.

108. ISABEL NARVAIZ DE KANTOR SANG JAE KIM, FRIEDEN T, LUELMO ALF, RIEDER P-YNH, KARINWEYER P, On. Service in Tuberculosis Control Culture. Part III C. WHO Library Cataloguing-in-Publication; 1998. 97 p.

109. Mark N. Qualitaive Research Method, A data collectors field guide. USAIDS, editor. North Carolina: publications@fhi.org; 2011.

110. Ministry of health and Social welfare. The United Republic Of Tanzania National Tuberculosis And Leprosy Programme Annual Report 2011. 2012.

111. Bernard H, Marshal D. Qualitative Research Methods Overview [Internet]. Vol. 2005, Qualitative Research Methods A Data Collectors Field Guide. 2011. 1–12 p. Available from: http://www.fhi360.org/NR/rdonlyres/etl7vogszehu5s4stpzb3tyqlpp7rojv4waq37elpbyei3tgmc4ty6dunbccfzxtaj2rvbaubzmz4f/overview1.pdf

112. National Bureau of Statistics Ministry of Finance Dar es Salaam. 2012 POPULATION AND HOUSING CENSUS Population Distribution by. 2013;

113. Masadeh M a. Focus Group : Reviews and Practices. Int J Appl Sci Technol [Internet]. 2012;2(10):63–8. Available from: http://www.ijastnet.com/journals/Vol_2_No_10_December_2012/9.pdf

114. NBST. Tanzania population and housing census. National Bureau of Statistics

Ministry of Finance Dar es Salaam. 2012. 244 p.

115. Commission THEP, Salaam DARES, Office RCS. THE UNITED REPUBLIC OF TANZANIA MOROGORO REGION SOCIO-ECONOMIC PROFILE.

116. Chief Government Statistician. Shinyanga Basic Demographic and Socio-Economic Profile. Dar es Salaam: Ministry of Finance; 2016.

117. Snape D, Spencer L. The Foundations of Qualitative Research. Qualitative research practice: A guide for social science students and researchers. 2003. 2–10 p.

118. Barrett D, Twycross A. Data collection in qualitative research. Evidence-based nursing. 2018;21(3):63–4.

119. Taherdoost H. Sampling Methods in Research Methodology; How to Choose a Sampling Technique for Research. SSRN Electronic Journal. 2016;(September).

120. Israel GD. Sampling the Evidence of Extension Program Impact 1. IFAS Extension. 2015;1–9.

121. Anyan F. The Influence of Power Shifts in Data Collection and Analysis Stages : A Focus on Qualitative Research Interview The Influence of Power Shifts in Data Collection and Analysis Stages : A. 2013;18(18):1–9.

122. Jacobvitz D, Curran M, Moller N. Measurement of adult attachment: The place of self-report and interview methodologies. Attach Hum Dev. 2002;4(2):207–15.

123. Mr Dev Jootu. Reflexivity-in qualitative. In Scotland; p. 1–12.

124. Kaiser K. Protecting respondent confidentiality in qualitative research. Qualitative Health Research. 2009;19(11):1632–41.

125. Zikmund athomas@eit.ac.nz. What a difference a term makes. Journal of Population Economics. 2014;

126. Baker SE, Edwards R. How many qualitative interviews is enough ? National Centre for Research Methods Review Paper. 2012. 1–42 p.

127. Lewis RJ. Qualitative research practice: A guide for social science students and researchers. Sage Publications. 2003.

128. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K, et al. "Dentists face added drug regulation. Dental survey. 1968;44(12):73.

129. Zamawe FC. The implication of using NVivo software in qualitative data analysis: Evidence-based reflections. Malawi Medical Journal. 2015;27(1):13–5.

130. Spurlock GH, Spurlock SL. Projectile dart foreign body in a horse. Journal of the American Veterinary Medical Association. 1988;193(5):565.

131. Oldfield S. Introduction to Nvivo Centre for Staff & Educational Development. 1.0. Anglia U of E, editor. Anglai; 2014. 68 p.

132. Czerkawski B. Using NVivo to Analyze Qualitative Classroom Data on Constructivist Learning Environments. 2016;(May).

133. Hackett A, Strickland K. Using the framework approach to analyse qualitative data: a worked example. Nurse researcher. 2019;26(2):8–13.

134. Dowdy DW, Houben R, Cohen T, Pai M, Cobelens F, Vassall A, et al. Impact and cost-effectiveness of current and future tuberculosis diagnostics: The contribution of modelling. International Journal of Tuberculosis and Lung Disease. 2014;18(9):1012–8.

135. Langley I, Lin HH, Egwaga S, Doulla B, Ku CC, Murray M, 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 [Internet]. 2014;2(10):e581–91. Available from: http://dx.doi.org/10.1016/S2214-109X(14)70291-8

136. WHO. Global WHO Tuberculosis Report 2016. 13th ed. Switzerland: WHO Library Cataloguing-in-Publication Data; 2016.

137. NTLP. The United Republic of Tanzania Ministry Of Health Community Development , Gender , Elderly and Children The National Tuberculosis and leprosy Programme Annual report for 2016. Dar es Salaam; 2016.

138. Roshaidai S, Arifin M. Ethical Considerations in Qualitative Study. 2018;(October).

139. Hyman L, Lamb J, Bulmer M. The Use of Pre-Existing Survey Questions : Implications for Data Quality. Eur Conf Qual Surv Stat. 2006;3.

140. Das D, Dwibedi B, Kar SK. Transportation of sputum samples in cetylpyridinium chloride for drug resistance studies from remote areas of Odisha, India. Journal of Infection in Developing Countries. 2014;8(8):1059–62.

141. Heifets L. Mycobacteriology laboratory. Clinics in Chest Medicine. 1997;18(1):35–53.

142. Shewade HD, Kokane AM, Singh AR, Parmar M, Verma M, Desikan P, et al. Provider reported barriers and solutions to improve testing among tuberculosis patients 'eligible for drug susceptibility test': A qualitative study from programmatic setting in India. PLoS ONE. 2018;13(4):1–18.

143. Doulla BE, Squire SB, MacPherson E, Ngadaya ES, Mutayoba BK, Langley I. Reducing delays to multidrug-resistant tuberculosis case detection through a revised routine surveillance system. BMC Infectious Diseases. 2020;20(1):1–11.

144. World Health Organization (WHO). WHO Global TB Report 2018. Geneva; 2010.

145. Woods J, Moorhouse M, Knight L. A descriptive analysis of the role of a WhatsApp clinical discussion group as a forum for continuing medical education in the management of complicated HIV and TB clinical cases in a group of doctors in the Eastern Cape, South Africa. Southern African Journal of HIV Medicine. 2019;20(1):1–9.

146. Denkinger CM, Grenier J, Stratis AK, Akkihal A, Pant-Pai N, Pai M. Mobile health to improve tuberculosis care and control: A call worth making. International Journal of Tuberculosis and Lung Disease. 2013;17(6):719–27.

147. Shenouda JEA, Davies BS, Haq I. The role of the smartphone in the transition from medical student to foundation trainee: A qualitative interview and focus group study. BMC Medical Education. 2018;18(1):1–10.

148. Lester R, Park JJ, Bolten LM, Enjetti A, Johnston JC, Schwartzman K, et al. Mobile phone short message service for adherence support and care of patients with tuberculosis infection: Evidence and opportunity. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2019;16:100108.

149. Muhjazi G, Baghdadi S, Dye C, Qusaibaty M. Sustaining a national tuberculosis control programme during civil crisis: 6 years of experience in Syria. The Lancet Respiratory Medicine [Internet]. 2018;6(4):255–6. Available from: http://dx.doi.org/10.1016/S2213-2600(18)30114-0

150. Lestari T, Graham S, Van den Boogard C, Triasih R, Poespoprodjo JR, Ubra RR, et al. Bridging the knowledge-practice gap in tuberculosis contact management in a high-burden setting: a mixed-methods protocol for a multicenter health system strengthening study. Implementation Science. 2019;14(1):1–15.

151. Noyes J, Popay J. Directly observed therapy and tuberculosis: How can a systematic review of qualitative research contribute to improving services? A qualitative meta-synthesis. Journal of Advanced Nursing. 2007.

152. Mngomezulu N, Cameron D, Olorunju S, Luthuli T, Dunbar R, Naidoo P. Reasons for the low bacteriological coverage of tuberculosis reported in Mpumalanga Province, South Africa. Public Health Action. 2015;5(2):122–6.

153. McNally TW, De Wildt G, Meza G, Wiskin CMD. Improving outcomes for multi-drug-resistant tuberculosis in the Peruvian Amazon - A qualitative study exploring the experiences and perceptions of patients and healthcare professionals. BMC Health Services Research. 2019;19(1):1–17.

154. Technical Brief. Strategic Support for Integrated Laboratory Services. In Geneva; 2016. p. 1–15.

155. Ereso BM, Yimer SA, Gradmann C, Sagbakken M. Barriers for tuberculosis case finding in Southwest Ethiopia: A qualitative study. PLoS ONE. 2020;15(1):1–20.

156. Kawatsu L, Uchimura K, Ohkado A, Kato S. A combination of quantitative and qualitative methods in investigating risk factors for lost to follow-up for tuberculosis treatment in Japan – Are physicians and nurses at a particular risk? PLoS ONE. 2018;13(6):1–13.

157. Tekie Desta K, Masango TE, Nkosi ZZ. Performance of the national tuberculosis control program in the post conflict Liberia. PLoS ONE. 2018;13(6):1–22.

158. Peters DH, Adam T, Alonge O, Agyepong IA, Tran N. Republished research: Implementation research: What it is and how to do it. British Journal of Sports Medicine. 2014;

159. Squire SB, Ramsay ARC, Van Den Hof S, Millington KA, Langley I, Bello G, et al. Making innovations accessible to the poor through implementation research. International Journal of Tuberculosis and Lung Disease. 2011;15(7):862–70.

160. Jordan J, Lynch U, Moutray M, O'Hagan M-T, Orr J, Peake S, et al. Using Focus Groups to Research Sensitive Issues: Insights from Group Interviews on Nursing in the Northern Ireland "Troubles." International Journal of Qualitative Methods. 2007;6(4):1–19.

161. Senkoro M, Hinderaker SG, Mfinanga SG, Range N, Kamara D V., Egwaga S, et al. Health care-seeking behaviour among people with cough in Tanzania: Findings from a tuberculosis prevalence survey. International Journal of Tuberculosis and Lung Disease. 2015;19(6):640–6.

162. WHO. World Health Organisation Global Tuberculosis Report. Tuberculosis. Geneva; 2009. 17 p.

163. Wandwalo E, Makundi E, Hasler T, Morkve O. Acceptability of community and health facility-based directly observed treatment of tuberculosis in Tanzanian urban setting. Health Policy. 2006;

164. Ritchie J, J. L. Qualitative Research Practice: A Guide for Social Science Students and Researchers . Sage Publications, London (336 pages). Reviewed by: In: QUALITAIVE. 2003. p. 76–9.

165. Bisimwa BC, Nachega JB, Warren RM, Theron G, Metcalfe JZ, Shah M, et al. Xpert Mycobacterium tuberculosis/Rifampicin–Detected Rifampicin Resistance is a Suboptimal Surrogate for Multidrug-resistant Tuberculosis in Eastern Democratic Republic of the Congo: Diagnostic and Clinical Implications. Clinical Infectious Diseases. 2020;(June).

166. Hoza AS. Asian Paci fi c Journal of Tropical Medicine pulmonary TB patients.

2015;8(11):907–13.

167. CDC C for disease control and prevention. TB Elimination (Multidrug-Resistant Tuberculosis (MDR TB)). Cdc. 2012. p. 1–2.

168. Maitre T, Aubry A, Jarlier V, Robert J, Veziris N, Bernard C, et al. Multidrug and extensively drug-resistant tuberculosis. Médecine et Maladies Infectieuses. 2017;47(1):3–10.

169. Rifat M, Hall J, Oldmeadow C, Husain A, Hinderaker SG, Milton AH. Factors related to previous tuberculosis treatment of patients with multidrugresistant tuberculosis in Bangladesh. BMJ Open. 2015;5(9):1–9.

170. Saunders MJ, Wingfield T, Tovar MA, Herlihy N, Rocha C, Zevallos K, et al. Mobile phone interventions for tuberculosis should ensure access to mobile phones to enhance equity – A prospective, observational cohort study in peruvian shantytowns. Tropical Medicine and International Health. 2018;23(8):850–9.

Appendixes

Appendix 1: Certificate of Approval from LSTM 14.023 (2014)

LSTM
LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Pembroke Place,
Liverpool, L3 5QA, UK
Tel: +44 (0)151 705 3100
Fax: +44 (0)151 705 3370
www.liv.ac.uk/lstm

Basra Esmail Doulla
Liverpool School of Tropical Medicine
Pembroke Place
Liverpool
L3 5QA

Thursday, 03 July 2014

Dear Mrs Doulla,

Re. Research Protocol (14.023) The Impact of Introducing an Effective Routine Surveillance System for Drug Resistant Tuberculosis in Tanzania

Thank you for your letter of 27/05/2014 responding to the action points set by the committee and for subsequently providing the necessary in-country ethical approval requirements for this study. The committee is satisfied with your response and the protocol now has formal ethical approval from the LSTM Research Ethics Committee.

The approval is for a fixed period of three years and will therefore expire on 02/07/2017. The committee may suspend or withdraw ethical approval at any time if appropriate.
Approval is conditional upon:

- Continued adherence to all in-country ethical requirements.
- Notification of all amendments to the protocol for approval before implementation.
- Notification of when the project actually starts.
- Provision of an annual update to the Committee. Failure to do so could result in suspension of the study without further notice.
- Reporting of new information relevant to patient safety to the Committee
- Provision of Data Monitoring Committee reports (if applicable) to the Committee

Failure to comply with these requirements is a breach of the LSTM Research Code of Conduct and will result in withdrawal of approval and may lead to disciplinary action. The Committee would also like to receive copies of the final report once the study is completed. Please quote your Ethics Reference number with all correspondence.

Yours sincerely

Dr Angela Obasi,
Chair, LSTM Research Ethics Committee

Appendix 2: Certificate of Approval from NIMR (2014

THE UNITED REPUBLIC OF
TANZANIA

National Institute for Medical Research
P.O. Box 9653
Dar es Salaam
Tel: 255 22 2121400/390
Fax: 255 22 2121380/2121360
E-mail: headquarters@nimr.or.tz
NIMR/HQ/R.8a/Vol. IX/1753

Ministry of Health and Social Welfare
P.O. Box 9083
Dar es Salaam
Tel: 255 22 2120262-7
Fax: 255 22 2110986

26th June 2014

Ms Basra E Doulla
National Tuberculosis and Leprosy Programme
Ministry of Health and Social Welfare
P O Box 9083, DAR ES SALAAM

CLEARANCE CERTIFICATE FOR CONDUCTING MEDICAL RESEARCH IN TANZANIA

This is to certify that the research entitled: The impacts of introducing an Effective Surveillance system for Drug-Resistant Tuberculosis (TB) in Tanzania, (Doulla B E *et al*), has been granted ethical clearance to be conducted in Tanzania.

The Principal Investigator of the study must ensure that the following conditions are fulfilled:

1. Progress report is submitted to the Ministry of Health and the National Institute for Medical Research, Regional and District Medical Officers after every six months.
2. Permission to publish the results is obtained from National Institute for Medical Research.
3. Copies of final publications are made available to the Ministry of Health & Social Welfare and the National Institute for Medical Research.
4. Any researcher, who contravenes or fails to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine. NIMR Act No. 23 of 1979, PART III Section 10(2).
5. Sites: Shinyanga, Morogoro, Dar es Salaam, Mwanza, Arusha, and Kilimanjaro regions.

Approval is for one year: 26th June 2014 to 25th June 2015.

Name: Dr Mwelecele N Malecela

Signature
CHAIRPERSON
MEDICAL RESEARCH
COORDINATING COMMITTEE

Name: Dr Donan Mmbando

Signature
CHIEF MEDICAL OFFICER
MINISTRY OF HEALTH, SOCIAL WELFARE

CC: **RMO**
DED
DMO

Appendix 3: Certificate of Approval from LSTM 16-041 (2016)

LSTM
LIVERPOOL SCHOOL OF TROPICAL MEDICINE
Pembroke Place,
Liverpool, L3 5QA, UK
Tel: +44(0)151 705 3100
Fax: +44(0)151 705 3370
www.lstmed.ac.uk

Basra Doualla
P.O.BOX 56324
Dar Es Salaam
Tanzania

Tuesday, 20 September 2016

Dear Mrs Doualla,

Re. Research Protocol (16-041) 'The Impact of Introducing An Effective Routine Surveillance System for Drug Resistance Tuberculosis In Tanzania'

Thank you for your letter of 13 September 2016 responding to the action points requested by the Research Ethics Committee. The protocol now has in principle ethical approval from the Chair of LSTM Research Ethics Committee.

Full approval will only be issued once the necessary in-country ethical approval documents have been submitted to the Research Office. Please send the documents to the LSTM Ethics Secretariat via lstmrec@lstmed.ac.uk.

Failure to provide these documents will result in withdrawal of in principle approval. This will constitute a breach of the LSTM Research Code of Conduct and may result in disciplinary proceedings. Please note that no research activities can be carried out for this project until full ethical approval has been given.

Please remember to quote your ethics reference number with all related correspondence.

Yours sincerely

Angela Obasi

Dr Angela Obasi
Chair
LSTM Research Ethics Committee

Researching and educating to save lives
A Company Limited by Guarantee. Registered Number 83405, England and Wales. Registered Charity Number 222655.
Athena SWAN Bronze Award
INVESTORS IN PEOPLE

Appendix 4: Certificate of Approval from NIMR (2016)

THE UNITED REPUBLIC OF TANZANIA

National Institute for Medical Research
3 Barack Obama Drive
P.O. Box 9653
11101 Dar es Salaam
Tel: 255 22 2121400
Fax: 255 22 2121360
E-mail: headquarters@nimr.or.tz

Ministry of Health, Community
Development Gender, Elderly & Children
6 Samora Machel Avenue
P.O. Box 9083
11478 Dar es Salaam
Tel: 255 22 2120262-7
Fax: 255 22 2110986

NIMR/HQ/R.8a/Vol. IX/2347

15th November 2016

Mrs Basra Esmail Doulla
Ministry of Health Community Development,
Gender Elderly and Children
National Tuberculosis Reference Laboratory
P O box 9083, 11478 DAR ES SALAAM

CLEARANCE CERTIFICATE FOR CONDUCTING MEDICAL RESEARCH IN TANZANIA

This is to certify that the research entitled: The Impact of Introducing An Effective Routine Surveillance System for Drug Resistance Tuberculosis in Tanzania (Doulla B E *et al)*, has been granted ethical clearance to be conducted in Tanzania.

The Principal Investigator of the study must ensure that the following conditions are fulfilled:

1. Progress report is submitted to the Ministry of Health, Community Development, Gender, Elderly & Children and the National Institute for Medical Research, Regional and District Medical Officers after every six months.
2. Permission to publish the results is obtained from National Institute for Medical Research.
3. Copies of final publications are made available to the Ministry of Health, Community Development, Gender, Elderly & Children and the National Institute for Medical Research.
4. Any researcher, who contravenes or fails to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine. NIMR Act No. 23 of 1979, PART III Section 10(2).
5. Site: Mwanza Region

Approval is for one year: 15th November 2016 to 14th November 2017.

Name: Dr Mwelecele N Malecela

Signature
CHAIRPERSON
MEDICAL RESEARCH
COORDINATING COMMITTEE

Name: Prof. Muhammad Bakari Kambi

Signature
CHIEF MEDICAL OFFICER
MINISTRY OF HEALTH, COMMUNITY
DEVELOPMENT, GENDER, ELDERLY
&CHILDREN

CC: RMO Mwanza,
DED Mwanza
DMO

Appendix 5: Certificate of Extension Approval from NIMR 2017

THE UNITED REPUBLIC OF TANZANIA

National Institute for Medical Research
3 Barack Obama Drive
P.O. Box 9653
11101 Dar es Salaam
Tel: 255 22 2121400
Fax: 255 22 2121360
E-mail: ethics@nimr.or.tz

Ministry of Health, Community Development, Gender, Elderly & Children
University of Dodoma, Faculty of Arts and Social Sciences
Building No 11
P.O. Box 743
40478 Dodoma

NIMR/HQ/R.8c/Vol. II /897

21st November 2017

Basra Esmail Doulla
Ministry of Health, Community Development,
Gender, Elderly and Children
National Tuberculosis Reference Laboratory
P.O. Box 9083
Dar es Salaam

RE: APPROVAL FOR EXTENSION OF ETHICAL CLEARANCE

This letter is to confirm that your application for extension on the already approved proposal: The impact of introducing an effective routine surveillance system for drug resistance tuberculosis in Tanzania (Doulla B.E. *et al*) has been approved.

The extension approval is based on the progress report dated 15th November 2017 on the project with Ref. NIMR/HQ/R.8a/Vol. IX/2347 dated 15th November 2015. Extension approval is valid until 14th November 2018.

The Principal Investigator must ensure that other conditions of approval remain as per ethical clearance letter. The PI should ensure that progress and final reports are submitted in a timely manner.

Name: Prof. Yunus Daud Mgaya

Signature
CHAIRPERSON
MEDICAL RESEARCH
COORDINATING COMMITTEE

Name: Prof. Muhammad Bakari Kambi

Signature
CHIEF MEDICAL OFFICER
MINISTRY OF HEALTH, COMMUNITY DEVELOPMENT, GENDER, ELDERLY & CHILDREN

Appendix 6: Informed Consent Form for Focus Group Discussion -Swahili Version

A: Form ya ridha

Jina la mchunguzi: Basra Esmail Doulla Jina la Taasis: National Tuberculosis/Leprosy Programme and Liverpool University Jina la Ugunduzi: Unchunguzi wa Mfumo wa Kuchunguza sampuli za wagonjwa wa kifua Kikuu Tarehe ya kupitishwa: PIN ya Mshiriki:

Ridhaa ya kushiriki katika Uchunguzi wa mfumo wa kuchunguza Mpango wa kifua kikuu

Utangulizi

Fomu ya idhini katika uzuria Kikao cha majadiliano (FGD) na mchakato wa mahojiano kuhusu mfumo wa kuchunguza kifua kikuu. Fomu hii itatumika katika sehemu mbili za mahojiano kati ta mahojiano ya mtu Mmoja nay a makundi kwa wafanyakazi wa sekta ya Afya.

Unaruhusiwa kuchagua sehemu ambayo ungependa mahojiano haya yafanyike, na mahojiana yatachukuwa muda usiozidi saa moja. Upo huru kuuliza swali lolote na utajibiwa. Pia upo huru kujitoa katika mahojiana wakati wowote bila kuathiriwa. Taarifa utakazotowa hapa zitahifaziwa kwa siri na zitatumika kwa lengo husika tu. Usitoe taarifazozote zile zitakazo kutambulisha wewe, jibu maswali yanayo husiana na utafiti huu tu. Takwimu utaazo toa zitarekodiwa, tutawapa hapa namba, hatutatumia jina la mtu, pia unaruhusiwa kujitoa katika mahojiano wakati woowte ule bila kutoa sababu yeyote ile. Takwimu utakazotoa zita haribiwa baada ya miaka mitano. Tunaomba mzingatie usiri wa mahojiano. Pia tutawapa vinywaji na chakula pia. Mahojiano hayatafanyika mpaka msaidizi wa uchunguzi atakapo waelezea dhumuni la mahojiano na

mfumo wa uchunguzi kwa kina. Pia atawapatia fomu ya ridhaa ya kushiriki katika mahojiano. Mnaruhusiwa kuuliza swali lolote lile, na utapewa ufafanuzi wa kina.

Angalizo:

Wakati wa mahojiano na washiriki twakimu zenu itasikilizwa na mjumbe wmingine ambaye pia ni mtafiti kwa ajili ya kuhakiki.

Fomu ya Ridhaa ya Mahojiano ina sehemu mbili:

Sehemu A: Inaelezea maelezo muhimu na madhumuni ya uchunguzi.

Sehemu B: Kibali cha maadili kwa washiriki na ridhaa ya kushiriki katika utafiti

Sehemu A: Yatakayokuwa anaelezwa Mshirika

Jina langu ni ---------- nafanya kazi katika Wizara ya Afya na Ustawi wa Jamii (MoHSW) kupitia NTLP tungependa kukukaribisha kushiriki katika kuratibu mfumo wa kuchunguza kifua kikuu (TB) ujulikanao kama Routine Surveylance System (RSS) katika mitandao ya maabara hapa nchini.

Tunania ya kuelewa vitu vinavyochangia kudorora kwa mfumo huu wa kuchunguza kifua kikuu hapa nchini, sababu za specimen kutofika au kuchelewa kufika katika maabara kuu pamoja na kubaini matatiza yanayo ambatana na kutofika au kuchelewa kwa sampuli kufika katika maabara kuu ikiwa ni pamoja na madhara yanayoweza kutokea. Pia tungependa kusikia uzoefu wa waratibu wa kifua kikuu na ukoma katika mikoa husika kabla sampuli hazijatumwa Maabara kuu ya kifua kikuu Tanzania kwaajili ya uchunguzi. Pamoja na hayo tunge penda kupata maelezo ya viashiria vilivyokua vinafuatilia utendaji wa mfumo huu wa kuchunguza kifua kikuu siku za nyuma. Mshiriki Msaidizi ataongoza majadiliano baada ya makubaliano na kutia saini ya ridhaa ya mahjiano.

Faida za Utafiti huu?

Tungependa kujua maoni yako kama mhudumu wa afya kuhusu mpango wa kudhibiti kufua kikuu (KKK),pia tungependa kujua uzoefu wako,vikwazo na changamoto kaika utekelezaji wa shuguli za mfumo wa kuchunguza kiffua kikuu.

Hatuna mpango wa kuzungumza na wafanyakazi wote katika kitengo cha kupambana na kifua kikuu katika kituohiki cha afya. Wewe ni mmoja wa walio chaguliwa kutowa maoni yao katika utafiti huu kama upo tayari. Ushiriki wako unaweza kuwakilisha wafanyakazi wote katika kituo hiki cha afya. Majibu tutakayo pata kutoka kwako yatachambuliwa kupata majibu ya ujumla kuhusiana na uelewa wa wafanyakazi wa afya katika mpango wa kupambana na kifua kikuu, changamoto na vikwazo vinavyo sababisha kudorora kwa mfumo wa kawaida wa ugunduzi wa kifua kikuu pia vitafahamika. Tunaamini kuwa kama tutapata ufafanuzi juu ya Routine Surveylance System (RSS) katika mitandao ya maabara hapa nchini.?

Kwanini Nimealikwa Katika Majadiliano?

Umealikwa katika mahijiano kwa sababu unafanya kazi katika kitengo cha KKK. Unamuhudumia mgonjwa na unachukuwa sampuli zake kwa uchunguzi Zaidi katika kiliniki za kKK(TB). Mahojiano haya ytatoa ufafanuzi muafaka. Jisikie huru na toa maoni yako kwa uhuru. Kama hutotaka kushiriki katika mahojiano haya ni sawa pia. Unaweza kutuuliza maswali yoyote uliyonayo wakati wowote. Pia tunakuhakikishia usiri wa majibu utakayo tupa wakati wote.

Utafiti unahusika na nini?

Kwa kushiriki katika utafiti huu tutapenda ushiriki kwa hiari katika mahijiano mojawapo na utachukuwa tariban lsaa moja mpaka mawili. utapata faida ya moja kwa moja kwa kupata fursa ya kuimarisha mfumo wa kuchunguza kifua kikuu na kuboresha uangalizi wa

wagonjwa hapa nchini. Pia tutaomba ridhaa yako ya hiari kwa kususainia kibali hiki cha kushiriki.

Haki zako kama mshiriki katika Utafiti huu?

Ushiriki wako katika utafiti huu ni wa hiari kabisa na unaweza kukataa kushiriki au kusimamisha ushiriki wakati wowote bila kutowa sababu yoyote. Kuondoka kwako hakuta hathiri utafiti huu. Hivyo upo huru kutoa taarifa zako au kukataa kutoa.

Utachukuwa Muda gani?

Utachukuwa takriba miezi miwili hivi pia titakutumi barua ya mwaliko wa kushiriki

Kuna hasara gani kwa kushirik?

Hatutegemei kuwa na hasara kwa kushiriki kwako katika utafiti huu. Aidha unaweza kuogopa kwa ajili ya ajira yako, lakini hatutatumia jina lolote la mshiriki, ila tutatumia namba ya uchunguzi (study number). Kila mahijiano yatakuwa ya usiri kabisa na msaidizi wa uchunguzi atakuwa anakumbushia usiri wakati wote.

Faida Za Kushiriki katika utafiti ni nini?

Ushiriki wako unaweza kuwakilisha wafanyakazi wote katika kituo hiki cha afya. Majibu tutakayo pata kutoka kwako yatachambuliwa kupata majibu ya ujumla kuhusiana na uelewa wa wafanyakazi wa afya katika mpango wa kupambana na kifua kikuu, changamoto na vikwazo vinavyo sababisha kudorora kwa mfumo wa kawaida wa ugunduzi wa kifua kikuu pia vitafahamika. Tunaamini kuwa kama tutapata ufafanuzi juu ya Routine Surveylance System (RSS) katika mitandao ya maabara hapa nchini.

Je Kuna Malipo?

Hautopata malipoyoyote ya fedha kwa kushiriki katika utafiti huu.

usiri

Timu ya utafiti itahakikisha kwamba, taarifa zote na matokeo ya uchambuzi vitahifaziwa kwa usiri mkubwa. Taarifa zako zitakuwa zinatambuliwa kwa number tu. Na hakutakuwa na uhusiano wowote kutoka kwenye namba ya dodoso na fomu ya ridhaa jina lako halitahitajika kujaza fomu hii. Taarifa zitakazo andikwa katika majarida ya kisayansi hayata jumuisha taarifa zitakazo kutambua wewe kwa jina l au nafasi yako. Taarifa zako zitapitiwa na timu inayofanya utafiti huu tu, hakuna mtu mwengine yeyote atakaye ruhusiwa kupitia taarifa zako.

Katika kutoa ridhaa ya kushiriki katika utafiti huu pia unatoa idhini ya kukubaliana na yaliyo ainishwa hapo juu.

KushirikianaTakwimu

Hakuna kitu kitakacho kuhusisha wewe na takwimu zitakazo patikana. Takwimu zitapelekwa kwa Mpango wa KKK, na Viongozi wa Wilaya na kujadiliwa kabla ya kusambazwa kote(publish)

Uhalali wa Kujitoa

Unaruhuiswa kujitoa katika mahoiano wakati woowte bila kutoa sababu zozote zile. Na wala haitadhuru kazi yako. Wala ushirikiano wako na Mpango wa KKK. Maelezo yako bado yatakuwa ni ya usiri kabisa.

Kibali cha Mahadili

Utafiti huu umewasilishwa katika Chuo Kikuu cha Liverpool School of Tropical Medicine na Medical Research Coordination Commettee (MRCC) yaani Kamati ya utafiti wa magonjwa katika wizara ya afya na maendeleo ya jamii. Barua ya Idhini ya kufanya utafiti huu imetolewa kwa NTLP.

Sehemu B: Kibali cha Ridhaa

Nimeelezwa kuhusu dhumuni la utafiti na faida itakayopatika na utafiti huu. Nimeelewa na hiari yangu nakubali kushiriki katika mahojiano ya hiari. Fomu ya idhini katika uzuria Kikao cha majadiliano (FGD) na mchakato wa mahojiano kuhusu mfumo wa kuchunguza kifua kikuu. Na kwamba ninaweza kuacha kushiriki wakti wowote ule.

Mshiriki

Mshiriki: Natoa ridha ya kushiriki katika mahojiano. Mshiriki Nemekubali/ sijakubali (weka alama panapostahili)	**ndiyo**	**hapana**

Saini ya Mshiriki	**Tarehe na wakati wa ridha**:
Jina la Mtafiti Msaidizi	**Tarehe**

Naelewa kuwa sual hili ni muhimu kwa mtafiti msaidizi kurikodi majadialiano kwa kutumia chombo cha kurikodia.

Mtafiti Msaidizi	Tarehe na wakati wa ridha:

Ambaye atajibu maswali kuhusiana na Utafiti huu.

Kama unahitaji maelezo yoyote ya ziada, kuhusiana na utafiti huu, tafadhali jisikie huru kuwasiliana na kiongozi wa utafiti huu aliye ainishwa hapo chini:

Bi. Basra Doulla Mtafiti Mkuu SLP: 65324 Dar es Salaam **Simu:** 0773 230 778	

Kwa maswali yoyote kuhusu haki zako kama mshiriki:

Kama kuna maswali yoyote kuhusu haki zako kama wa utafiti huu, na kama ungependa kuwasiliana na mtu mwingine zaidi ya timu inayo endesha utafiti huu wasiliana na watu walio ainishwa hapo chini., Kama unataka kutoa malalamiko yako kuhusu utafiki huu unaweza pia kuwasiliana na watu walio ainishwa hapo chini.

Ethical committee at Institute for Medical Research Tel: 222121400

Appendix 7: Informed Consent Form for Focus Group Discussion -English Version

A: Informed Consent Form

Investigator's name: Basra Esmail Doulla Name of Organization: National Tuberculosis/Leprosy Programme and Liverpool University Title: Impact of Introducing an Effective Routine Surveillance System for Drug Resistance Tuberculosis in Tanzania Date: Study Number:

Introduction

This Consent form will cater for both interviews with the participants from the Focus Group Discussion (FGD) and in-depth interview with the IDI process. However, each interview will be conducted separately. Before the interviews engaged, courtesy call will be undertaken both at the national and regional administrative and health authorities. The principal investigator (PI) or trained research assistance (RA) will explain the aim, study objectives and expected benefits of the study to the authorities in detailed. The same information will be presented to participants in Kiswahili, the National language. In order to ensure respondent's job security, no name or any identification of the participants will be required; instead study number will be used. In addition, the RA will undertake the consent process, since participants are literate; the consent will be given in writing one day before the interview to provide room for the participants to understand the information relating to the study. The RA will ensure confidentiality and emphasis that, none of the responses will impact on the employment of the participants given participant will be discussing their work practices.[7,8]

[7] *Qualitative Method For Health Research; Judith Green and Nicki Thorogood (2005)*

[8] *Guidance note: Detailed WHO guidelines on the design of consent forms are available on the following website: http://www.who.int/rpc/research_ethics/guidelines/en/index.html*

The study RA will separately administer and conduct the interview after obtaining consent both oral and written from the participants. RA will inform the participant that, the interview will be tape recorded. Refreshment will be provided in the middle of the interview.

Note:

During FGD the focus group discussions the participant's responses will be heard by other researchers.

This informed consent form has two sections:

Section A: Information sheet explaining the information of the study to be undertaken

Section B: Certificate of Consent for the participant to sign if you agree to take part in this study

Section A: Information Sheet

My name is ----------, working with the Ministry of Health and Social Welfare (MoHSW) through the National Tuberculosis/Leprosy Programme (NTLP) would like to invite you to participate in an interview on routine surveillance system (RSS) on TB laboratory networking. You do not have to agree now, please take your time to read the consent form for better understanding. Before you make your choice, you can discuss among yourselves and feel calm with about the research. You can also ask any question for clarification or if you need more details do not hesitate to do so. I would also like to introduce the study research assistant (RA) who will undertake this interview.

What is the Aim of the Study?

The main purpose of the RSS in Tanzania is to monitor the program performance at district, regional and national level. This includes monitoring treatment outcomes by

assessing patient response to individual TB drugs, monitoring the trend of multidrug resistance tuberculosis (MDR TB) in the country, and identifying individuals with drug resistance and informing the districts so they can start patients on appropriate treatment as early as possible. We are interested in understanding the factors contributing to lower performance of RSS, reasons for specimen does not reach or delay to reach to the central laboratory together with associated risk factors. Also, we would like to hear experiences with the implementation of RSS from regional and district TB health workers. We believe this will give a better understanding to know the description of available historic indicators that monitor the performance of the RSS?

Why have I been invited to participate in the study?

You have been invited to take part in this study because you are working under TB clinic/ department; you are dealing with the TB patients and sputum specimen for diagnosis processes in one way or the other. By interviewing health workers working at the TB department/clinic, we anticipated to know your views on the TB programme as health workers' knowledge, attitudes, practices, barriers and challenges in implementing its activities.

What will the study involve?

This study will involve your participation in a FGD. We will ask you to take part in one of the session of the FGD as one of the health worker working under TB department. We would also require you to consent to your participation in the study.

What will be done during the study?

If you agree to take part, you will be requested to participate in FGD which will last about 50 to one hour. The discussion will be led by the RA. During the discussion you and other participants will be asked to discuss about your daily practice as TB staff, will include questions around your perception towards TB program's performance, knowledge of TB and how is TB networking relates to the routine surveillance. We would like to record this discussion. This tape will be kept confidentially and will be used for writing reports.

For how long will this study last?

This study will take two – three months. During that time, we will invite you to participate in one of the FGD.

Are there any risks of taking part in the study?

We do not anticipate having major risks. However, the participants might be scared and find uncomfortable on their responses might have impacted on their employment. In order to ensure respondent's job security, we will ensure that, no name or any identification of the participants will be taken; ***instead study number will be used***. It is important that, whatever is discussed during FGD will be kept confidential, participant will be advised not to discuss with anyone who was not taking part in the FGD. However, ensuring confidentiality during FGD will be difficult, but RA will always remind the participants the significance of sustaining confidentiality.

What are the benefits to taking part in the study?

There will be no direct benefit to you of participating in this study. However, by participating in the FGD you will have a direct benefit by getting an opportunity to strengthen routine surveillance system in Tanzania. In addition, the study findings will

help in the future planning and implementation strategies for better patient's management.

Reimbursements

You will not receive any financial or incentive in taking part in this study. However, refreshment will be provided (snacks and drinks) at the middle of the discussion.

Confidentiality

The researcher team will ensure that, all information and the results of the analysis will be kept confidential. Your information will be identified by a study number only. Data that maybe reported in scientific journals will not include any information that identifies you by name or working position. This information may be reviewed by authorized representatives of the study only. In giving consent to participate in this survey you are also agreeing to the above conditions.

Sharing the results

Noting you tell us today will be shared with anyone outside the research team; nothing will be attributed to you by name. There will be a debriefing with TB staff at your region to discuss study results, this will be announced. Following the debriefing we will publish the results so that other interested people in the regions will learn from the research findings.

Right to refuse or withdraw

Your participation in this focus group/interview is entirely voluntary and you can refuse to participate or stop at any time without stating any reason. Your withdrawal will not affect the collaboration with the programme. You are willing to agree your information to be used in the report without bridge confidentiality.

Ethical Approval

This focus group/interview has been submitted to the University of Liverpool School of Tropical Medicine and Medical Research Coordination Committee (MRCC) of the MoHSW and an approval letter has been granted by the NTLP to conduct this study.

Section B: Certificate of Consent

I have been informed about the aim of the study and expected benefit and I fully understand these. I deliberate agree to take part in the study. I also understand that my participation does not have any monetary or incentive reward and that I have the right to withdraw from the study at any point of time without notice and my identity will not be disclosed.

Respondent (Participants):

Respondents: Do you agree to participate in this survey? (Tick response)	**YES**	**NO**

Participant's signature	**Date of signature**
Interviewer's signature	**Date of signature**

I understand that it is particularly useful for the researcher to record the discussion with a tape recorder

Participant's signature	Date of signature

Who can answer your questions about the study?

If you require more information, related to the study, please feel free to contact the investigator details listed below:

Ms. Basra Doulla

Principal Investigator

P O Box 65324

Dar es Salaam

Telephone: 255773 230 778

Email: Basra.Doulla@liverpool.ac.uk / bedoulla@gmail.com

For any concern about your rights as participant in the study, contact:

If you wish to ask questions about your rights as a study participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the FGD,

please contact: Ethical committee at Institute for Medical Research Tel**:** 222121400.

Appendix 8: Translation Verifications

IFAKARA HEALTH INSTITUTE
research | training | services

Bagamoyo Research and Training Centre

TRANSLATION VERIFICATION FORM

Protocol ID/Number:	Sponsor:

Please tick one of the blocks below to indicate which of the following are being verified.

[X] Translation

[ ] Back Translation

	Complete Name of document (including Language) / Author / Translator/Version/Date
1st Language Document	**Language:** English **Document Title:** The Impact of Introducing an Effective routine surveillance System for Drug resistance Tuberculosis in Tanzania **Version: 1.0 Dated 13/03/2014**
2nd Language Document	**Language: Swahili** **Document Title:** Utafiti juu Ya kuanzishwa kwa Ufuatiliaji wa Mara kwa Mara wa Kifua kikuu sugu Tanzania **Translator:** Halima Marijani **Translation Version: 1.0 Dated 17/03/2014**

Review verification

I confirm that this translation is accurate and complete.

Printed Name	QA Officer BRTC Functional Role
Signature	20/03/2014 Date

Appendix 9: Specimens Rejection Form

SAMPLE REJECTION FORM

Patient Name/ Sample ID _____ **Date collected** _____

Date and Time sample Received at CTRL _____

The above sample has not met the criteria of a good specimen for the tests requested and processing this sample will give unreliable results. Therefore, we cannot submit the specimen for further analysis.

You are advised to collect another specimen from the patient if possible.

REASON FOR SAMPLE REJECTION

	Criteria for Sample Reception*	
Criteria for Sample Reception	**Met**	**Not Met :**(reason for rejection)
Sample collected in proper container		
Sample properly sealed/not leaking		
Sample properly labelled at least with name/patient ID and Date of collection		
Nature of the sample delivered is appropriate for tests requested		
Volume of samples requiring culture must be at least 1.5ml and above (ideal volume is 5ml)		
Sample was delivered with a request form		
At least patient name on both request form and sample container should be in agreement		

* For each of the criterion, tick the appropriate column if it has been met or not met

We apologize for any inconvenience this has caused.

CTRL Tech. Name/Sign _____ Date: _____

NB: Photocopy this form and the Laboratory Request form, staple the copies and keep in CTRL file while the originals are sent back to the clinic/person that sent the sample.

Appendix 10: Standard Operating Procedure for Sputum Specimens Transportation

SOP Approval

	Name	**Signature**	**Date**
Prepared by	Basra Doulla		
Reviewed by	E. Shogolo S. Mfaume		
Authorized by	Dr Mutayoba		
Date withdrawn:			
Approved changes			
Change approved by	**Brief description of the change**		
Annual Changes and Reviews			
Name of reviser	**Changes compared to previous version**		

ACKNOWLEDGEMENT OF READING AND UNDERSTANDING THIS SOP

Name	**Signature**	**Date**

1. Title

Standard operating procedure for specimen's transportation of sputum from regions to the central tuberculosis reference laboratory

2. Objective and Scope

3. Purpose

Sputum specimen's collection, package, and transportation procedure to the CTRL

4.Abbreviations

5. Task and Responsibility

Responsibility:

Laboratory Technician from the respective regions

he/ she can delegate to laboratory personnel handling samples; will be responsible for following the shipment procedure

Safety and Environment

All samples should be well labelled

The box should have the mark of potential hazards

6. Procedure

1. Sputum specimens for eligible subjects is collected in a sterile universal container or 50 ml wide-mouth polypropylene falcon tube, 30 x 115 mm with screw cape.
2. information of specimen is recorded in special dispatched book
3. Sputum specimens will be labelled and packed into transport boxes or in boxes containing materials that can absorb leakage during transportation.
4. The specimens will be accompanied with the well filled TB lab request forms with patient's details
5. A person at CTRL is informed immediately by message (sms), WhatsApp/email during specimen's shipment
6. Transportation is either by courier EMS, private bus, or courier boy
7. specimens are delivered to the CTRL

Appendix 11: Reviewed Tuberculosis Laboratory Request Form

Ministry of Health and Social Welfare
National Tuberculosis and Leprosy Programme

Request and Reporting form for Xpert, LPA, TB Culture and Drug Susceptibility Test (DST)

Patient TB District number _____ Patient identification study number _____

Surname and first name of patient: _____ Age: _____ Sex: _____

Ward / Department: _____ Address: _____

*HIV-status: Pos / Neg / Unknown _____

Region: _____

TB Disease type and treatment history

Site: □ Pulmonary
□ Extra pulmonary (specify):_____

History: □ New (never treated before for ≥1 month)
□ Relapse
□ Failure

Previous treatment: □ Cat.1
□ Cat.2
□ Cat.4 (second-line drugs)
□ Other _____

□ Return after default
□ Chronic excretor
□ MDR contact
□ Uncertain

Origin of request: **Region ID**: _____ District ID: _____Local laboratory name: _____

Date of specimen collection ____/____/20____ Date of specimen processed ____/____/20____Lab serial number _____

Local laboratory Results: Smear result: 1st ____ 2nd ____ specimen

Microscopy technique used: □ Ziehl-Neelsen
□ Fluorescence

Xpert MTB _____
Rifampicin_____

Request for testing at the Reference laboratory:

Reason: □ Diagnosis
□ Follow-up at ____ months **DURING** treatment
□ Follow-up at ____ months **AFTER** treatment

Specimen: □ Sputum
□ Sputum in preservative, type CPC
□ other specify: _____

Requested tests: □ Microscopy □ Culture □ DST □ LPA □ MGIT □ GeneXpert

Person requesting examination: Name: _____ Position: _____

* Information that can be disclosed optionally ID = identification number or code

---

Reference laboratory results:

Date received at Reference Laboratory ____/____/20____ Date of specimen processed ____/____/20____

Reference Laboratory serial number: _____

Microscopic examination:

Neg	1-9	1+	2+	3+

□ Ziehl-Neelsen
□ Fluorescence

LPA Results:

	R	S
INH		
Rif		

Date Test results____/_____/20_____

Xpert Results:	N	T	RR	Ti	I	Date result
Xpert MTB/Rif						

MGIT Results:	Pos	Neg	Contaminated	Date results
MGIT				

□ **Date Culture result inoculated ____/____/20____; Time_____**

Contaminated	Neg	*Mycobacterium tuberculosis* complex				Non-TB *mycobacteria* (species)	Date contaminated	Date results
		1-9 colonies actual count	10 – 100 col 1+	>100 - 200 col 2+	>200 col 3+			

DST Results: □ will follow
□ Phenotypic method used _____ DST Batch: _____
□ Genetic method used _____

			Legend: S = Susceptible; R = Resistant; ND = Not done					
	INH	Rifampicin	Streptomycin	Ethambutol	Ofloxacin	Kanamycin	Date processed	Date contaminated

Appendix 12: Reviewed Tuberculosis Laboratory Register - Mwanza

S/N	Local lab #	TB district #	Local site Name	date collected	Date specimens transported-microscopy sites	Date specimens received microscopy sites	Smear result reported	Date specimens transported-Xpert sites	Date specimens received - Xpert sites	Date Xpert results reported	Date specimens transported-CTRL

Appendix 13: Standard Operating Procedure for Specimen Reception and Accessioning

SOP Approval

	Name	Signature	Date
Prepared by	Basra Doulla		
Reviewed by	E. Shogolo S. Mfaume		
Authorized by	Dr. Mutayoba		
Date withdrawn:			

Approved changes

Change approved by	Brief description of the change

Annual Changes and Reviews

Name of reviser	Changes compared to previous version

ACKNOWLEDGEMENT OF READING AND UNDERSTANDING THIS SOP

NAME	SIGNATURE	DATE

1. Title

Specimens reception and accessioning

2. OBJECTIVE AND SCOPE

This SOP will describe the reception and the allocation of the accession number of specimens in CTRL. This will help maintaining patient confidentiality, preventing specimens mix up, ensuring specimens integrity, and overall quality handling of specimens. It is imperative that

all personnel in the CTRL follow this SOP appropriately. This procedure is the first step in preparing patient specimens for processing, storing, and transferring to appropriate department of the CTRL for testing.

3.ABBREVIATIONS

NTLP	National Tuberculosis and Leprosy Programme
CTRL	National Tuberculosis Reference Laboratory
LRFR	Laboratory Request Form Reconciliation form
SOP	Standard Operating Procedure

4. Tasks, responsibilities and accountabilities

Tasks	Responsible	Accountability
Specimens collection	Authorized laboratory staff	Head CTRL
Specimens registration	Authorized laboratory staff	Head CTRL

5. Safety and environment

1. Wear gloves when handling specimen, and treat all the specimens as infectious material
2. Label all specimens with laboratory serial number corresponding to the lab request from container as well as reception register. For study specimens label with a study identification number.
3. Try to complete reception of specimens while the person who delivered them is still present so that he can carry back some information if available.
4. Documentation of any corrections made should be noted on the laboratory request form and the reception TB register.

6. PROCEDURE

Material required.

1. Laboratory register
2. Pens; blue or black and red and Fine Tip Markers
3. Gloves
4. Laboratory Coat
5. Specimens racks
6. Laboratory Request Form file

Step procedure.

1. Biological specimens such as sputum and aspirates are collected via standard techniques

and are delivered to the laboratory.

2. The specimens must be shipped to the laboratory under conditions that are appropriate for subsequent processing, culture and testing.
3. Each specimen MUST be accompanied by a TB lab request form or its equivalent for research specimens.
4. Unpack the patient specimens and the TB lab request form. Match each specimen with the corresponding request form and make sure that the identifiers on the specimen's containers match those on the request form.
5. Check the criteria for acceptation of a specimens (see SOPs P001_v1.0 Specimens Rejection criteria). In case of rejection, follow the procedures mentioned in P001_v1.0 Specimens Rejection criteria
6. If the specimens are acceptable, the date and time that the specimens were received at CTRL and the initials of the personnel handling the specimens, specimen's appearance and volume are noted down on the lab request form.
7. Transfer all the information in the reception TB laboratory register
8. Record the Laboratory serial number with four digits eg 0001 and the numbers must be serial disregard of the origin of the specimens, from the request form, TB lab reception register, and on all specimen containers/ slides.
9. Record the specimens' laboratory number and the patient's information in the Primary Culture Laboratory register in which subsequent monitoring will be done.
10. Put all received specimens on a suitable rack and send the specimens to the Tb lab 3rd floor
11. If specimens have been received later in the evening, store appropriately in a fridge at 2 - 8°C or cooler place till the next morning.
12. Dispose packing waste (cotton wool, gauze etc) in the biohazard bag/container under the specimen's reception table.

7. Related documents

Authorization list

Safety manual

8. Related forms

CTRL lab request form

9. References

ISO 15189 Guidelines for clinical laboratories

10. Attachments / Annexes

NA

Appendix 14: Standard Operating Procedure for Sputum Specimen Collections

SOP Approval

	Name	**Signature**	**Date**
Prepared by	Basra Doulla		
Reviewed by	E. Shogolo S.Mfaume		
Authorized by			
Date withdrawn:			
Approved changes			
Change approved by	**Brief description of the change**		
Annual Changes and Reviews			
Name of reviser	**Changes compared to previous version**		

ACKNOWLEDGEMENT OF READING AND UNDERSTANDING THIS SOP

NAME	SIGNATURE	DATE

1. Title

Standard Operating Procedures for sputum specimen's collection in the tuberculosis laboratories

2. Objective and Scope

This SOP describes the correct method of obtaining a good quality sputum specimen from a TB suspects for the diagnosis of TB disease. The method is only applicable to adults only

Purpose

This procedure provides instructions for the collection sputum.

3. Abbreviations and definition

AFB Acid Fast Bacilli

TB Tuberculosis

SOP Standard Operating Procedure

4. Task responsibility and accountability

Task	**Responsibility**	**Accountability**
Collection instructions	Lab staff at reception desk	Lab supervisor
Container provision	Lab staff at reception desk	Lab supervisor
Container labeling and registrations	Lab staff at reception desk	Lab supervisor
Specimens acceptance/rejection	Lab staff at reception desk	Lab supervisor
Specimens provision	TB suspect	Lab staff at reception desk
Specimens processing	All Lab staff	Lab supervisor

5.0 Safety and environment

Instruct the patient with the following recommendations:

- Collection must be done in open area away from other people
- Use of handkerchief while coughing, sneezing, talking, to avoid aerosol formation
- Avoid spiting outside the container
- Gloves and laboratory coat must be worn when performing this procedure.

All specimens must be regarded as potentially infectious

Refer to Health Laboratory Safety and Waste Management Manual for safety considerations

6. Procedure

Materials

Reagents	Supplies	Equipment
Not applicable.	• Screw-capped sputum containers • Disposable Gloves • Laboratory coat • Soap • Permanent marking pens	• Specimen transport box

Collection, Labeling and Registration

1.1 Have all the needed specimen collection tools on hand Refer to specimen test catalog.
1.2 Wear gloves and laboratory coat.
1.3 Label patient details on the container including: Health facility name, date, patients name, Age, gender and physical address
1.4 Fill in the laboratory request form, patient's details must match with those on the container.
1.5 Explain the specimen collection procedure to the patient
1.6 Provide patient with the screw-capped container
1.7 Instruct patient to cough deeply and spit up sputum (phlegm) into the screw-capped sputum container.
1.8 Instruct patient to seal the specimen container tightly.
1.9 Ensure the sputum in the container is sent to the laboratory.
1.10 Label each specimen immediately with identifying information – patient identificationnumber, date and time of collection.
1.11 Fill out lab request/report form for each specimen with date, time and initials of collector.
1.12 Check that lab serial number on the specimen container matches with that on the lab request form.

NOTE: This labeling and matching is the primary responsibility of the collector and must be done carefully and precisely.

1.13 Place collected specimens in a transport container at an appropriate temperature, awaiting transport to the laboratory.
1.10 Dispose of gloves and wash hands after each specimen collection/handling.

1.11 Enter specimen information into clinic/phlebotomy specimen register book

1.12 Send specimen to the laboratory.

7. Related Documents

8. Related Forms

9. References

10. Attachments/Annexes

Appendix 15: Topic Guide for Focus Group Discussion

Target: Focus Group Discussion (FGD) for (Health workers working at the TB clinics, departments at the regional level, TB Programme staff and the Central tuberculosis reference laboratory staff).

Before commencing the Focus Group Discussion (FGD), you will seek permission to conduct this study at the selected study sites and capture key demographic data on each of the participants this includes: sign written consent form.

Focus Group Discussion ……. …. ……. Designation……

Organization ……..

Interviewer…….

Date……..

Topic 1: Objectives

To understand what factors leads to inadequate performance of the routine surveillance system (RSS) in Tanzania for previously treated TB cases before and after intervention of the pilot study in Mwanza region.

What is the scale of the inadequate performance of the current RSS? Probe if there was any difference before and after intervention?

What factors do stakeholders in the process believe are affecting performance of RSS?

Topic 2: Introduction to the discussion

Introduce the study objectives and explain the aim of the FGD- will be discussion on the factors leads to inadequate performance of the RSS in Tanzania for previously treated cases and perception of the TB health workers and other stakeholders in relation to the RSS and the pilot study conducted in Mwanza region

Emphasise the importance of confidentiality and ensure respondent's job security, no name or any identification of the participants will be required during FGD. (all matters that will be discussed in this private room will be held in confidence)

Remind participants of the need to keep responses made confidential

Explain that there are no wrong answers or right answers

Ask each participant to introduce themselves.

All discussion will be tape recorded

Participant will have allowed withdrawing from the study at any given time without notice.

Topic 3: Tuberculosis routine surveillance system

How do TB health workers involve in the RSS? (Probe; what is the role of the health workers in RSS, what do they think of the current method and the pilot study? what is their perception on the TB Programme and the reference laboratory?)

Describe how RSS is implemented in your health facility? (Probe; if health workers know about the RSS, and what type of specimen needs to be send, algorithm and safety) if it in Mwanza region probe if they know the revised RSS. Probe if revised RSS would be continuing?

What do health workers think are challenges in implementing the routine surveillance system? How about the revised RSS? (Probe issues related to: related causes that contribute to TB diagnosis is it patients or programme, feedback of the results, specimen handling and support from TB Programme).

What could be done differently to make it better, what could be of beneficial to the community? (Probe for both systems current and revised RSS)

Does the clinic transport specimen to another laboratory? Who does the specimen transportation? (Probe; how is it transported?)

What perception of the health workers toward TB reference laboratory? What do they think it could be done better or sustain? (Probe; Issues around TB networking, results turnaround time and the performance).

Topic 4: Relationship the workload

Where does your patients come from probe;(how many patients per day per clinic, if heavy clinic, why, issues around health education and who does the TB screening)

What perceptions do the health workers feel towards patient management? (probe; compared to the number of staff, skills, motivation)

Topic 5: Knowledge on Tuberculosis

How do health workers become aware of new TB diagnostic strategies? (Probe; from the programme, training, internet, collaboration with the TB programme, how is it disseminated).

What do health workers know about TB transmission? (probing on ways it is transmitted, ways it is prevented, explore questions relating to TB diagnosis)

What knowledge do the health workers have on RSS? (probe; after intervention, do they still feel the same? how it works, collaboration with the reference lab, specimen to be transported, frequency).

Topic 6: Ending the discussion

Before we break up, is there anything else you think would be useful for programme to know?

Do you have any questions about any aspect of this interview?

OK, thank you very much for your help and active participation.

Try to leave the discussion in a positive way thanking everyone for her participation. Make sure you stay behind in case any one wishes to speak further. Make sure you are assured them nothing will jeopardize their *professions.*[9]

Note:

When introducing this topic, it is important to be very sensitive as we are talking on people's careers. No participant should be forced to respond to these questions. Again reassure participants that there are no wrong answers to these questions. If people do not want to disclose anything concerning the TB programme it is very important not to force the discussion.[10]

[9] Qualitative Research Methods: A Data Collector's Field Guide (NATASHA MACK et al) July 2011

[10] Qualitative Research Methods: A Data Collector's Field Guide (NATASHA MACK et al) July 2011

Appendix 16: In depth Interviews Discussion Guides for Evaluation study

1. **Target:** Participants (members of the National Tuberculosis/Leprosy Programme (NTLP), Programme Manager, Programme staff, Donor Representative Agencies (DRA) supporting tuberculosis (TB) interventions in the country. The Ministry of Health and Social Welfare at the Department of Preventive Services where TB programme is under the directorate.

2. Objectives

To determine what factors leads to inadequate performance of the routine surveillance system (RSS) in Tanzania for previously treated cases after intervention. (Probe if there is any difference before and after pilot study conducted in Mwanza region), explore area which shows or not show any changes?

- What is the scale of the inadequate performance of the current RSS before and after intervention? Probe what do they prefer, is there any changes for the better?
- What factors do stakeholders in the process believe are affecting performance of RSS?
    - To explore stakeholders' perceptions of the successes and challenges in the TB Control Programme in Tanzania
- What evidence exists in support of the factors above?
    - To identify stakeholders‟ own roles and contributions to the TB Control program in Tanzania

Participants ……. …. …….. Designation……

Organization …….

Interviewer…….

Date…….