AFRICA UNIVERSITY

(A United Methodist-Related Institution)

ANALYSIS OF THE EFFECTIVENESS OF GENE XPERT TEST IN TARGETED SCREENING AND PRIMARY DIAGNOSTIC ALGORITHMS FOR MYCOBACTERIUM TUBERCULOSIS INFECTION AND RIFAMPICIN RESISTANCE IN MANICALAND, ZIMBABWE, 2017-2018

By

KATHERINE ZVINOERA

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS OF DOCTOR OF PHILOSOPHY IN PUBLIC HEALTH DEGREE IN THE COLLEGE OF HEALTH, AGRICULTURE AND NATURAL SCIENCES

2023

Abstract

Early Tuberculosis (TB) detection and early TB treatment are the backbone of breaking TB transmission cycle. Zimbabwe is a triple disease burden country with TB, HIV and multi drug resistant TB. In 2014 the World Health Organization recommended that Xpert *Mycobacterium tuberculosis*/Rifampicin (XMTB/R) be used as a primary diagnostic algorithm on all presumptive TB patients. Zimbabwe adopted XMTB/R primary diagnostic algorithm in 2016. In Manicaland the transition from XMTB/R targeted algorithm to XMTB/R primary diagnostic algorithm occurred in phases and was complete by 1st quarter 2018. However, this intervention had not been systematically evaluated in Zimbabwe. Evaluation of effectiveness of XMTB/R primary diagnostic algorithm MTB positive result pick up rate in Zimbabwe, was essential. The objective of the study was to analyse the effectiveness of Gene Xpert test in targeted screening and primary diagnostic algorithms for MTB infection and rifampicin resistance under the National TB programme in Manicaland, one of the affected provinces in Zimbabwe. This was a retrospective analysis of cohort data for National TB program presumptive TB patients' sputum results obtained 2017-2018. Categorical variables were described using frequencies, measure of association for quantitative variables using Pearson statistic and measure of agreement using cohen kappa. The level of significance was p value <0.05, at 95% confidence interval using z-score 1.96. Out of 43 809 patients' data downloaded, 36 056 had data acceptable for enrolment, while 15 719 smear microscopy patients' data were enrolled. Of the 36 056 XMTB/R patients' data, 5 769/36 056 (16.0%) were tested for TB using XMTB/R targeted screening algorithm versus 30 286/36 056 (84.0%) tested using XMTB/R primary diagnostic algorithm. The MTB positive result pick up rate for XMTB/R targeted screening algorithm and MTB positive result pick up rate for XMTB/R primary diagnostic algorithm was 430/36 056 (1.2%) and 1 791/ 36 056 (5.0%), respectively. The MTB positive result pick up rates decreased from 8.3%, in the 1st quarter of 2017 to the lowest rate of 4.8% in the 4th quarter of 2018. Rifampicin resistance detection was found in 111/2 221(5.0%), p value <0.001. Mean laboratory turnaround time improved from 1.7 ± 0.4 days in the targeted screening algorithm to 1.4 ± 0.8 days (p<0.001) in the primary diagnostic algorithm. From 1st quarter 2017 to 4th quarter 2018 the initial TB diagnosis based on MTB detected moved from 49/281 (17.4%) to 332/534 (62.2%) p value <0.001. Using GxAlert increased the capacity for geo-spatial mapping of downloaded MTB cases, with Chipinge District in Manicaland having the second highest frequency of MTB mapped [11/15 (73.3%) of its health facilities]. Buhera District had the highest proportion of 10/13 (76.9%) health facilities with rifampicin resistance mapped. In conclusion the number of TB cases detected increased and there was a statistically significant increase in detection of rifampicin resistance. Recommendation is sustained provision of the XMTB/R primary diagnostic algorithm intervention, to enable early TB detection can break the TB transmission cycle.

Keywords: Xpert *Mycobacterium tuberculosis*/Rifampicin; Targeted screening algorithm; Primary diagnostic algorithm; Tuberculosis positive pick up rate,

Declaration

I declare that this thesis is my own original work except where sources have been cited and acknowledged. The work has never been submitted, nor will it ever be submitted to another University for the award of any degree.

Katherine Zvinoera

Student's Full Name:

Student's Signature (Date 15/12/2023): 

Main Supervisor's Full Name: Professor Sungano Mharakurwa

Main Supervisor's Signature (Date 15/1/2023): 

Copyright

Acknowledgements

I wish to acknowledge the enthusiasm and support of many individuals and institutions that directly or indirectly contributed to the successful development and compilation of this project. My profound gratitude goes to the many people of different reputable background in both academic and professional circles, who have most willingly and readily availed themselves. I want to recognize and acknowledge the following persons, who supported me academically, morally, and emotionally throughout the study, without which this study would not have been completed in its present form.

The Doctoral Committee comprising: Professor Sungano Mharakurwa, Dr Junior Mutsvangwa and the late Dr Sekesai Zinyowera.

The Mentor: Professor Katharina Kranzer

The team comprising: Dr Ioana D. Olaru, Dr Munyaradzi Mukuzunga, Dr Eltony Mugomeri, Dr Palwasha Khan, Dr Claudia Denkinger, Dr John Z. Metcalfe, Mr. Hebert Mutunzi, Mr. Eliot Chikaka, Ms. Mildred Pepukai, Mr.Vincent Kampira, Mr. Menard Mutenherwa, Mrs.Wietske Mushonga and Mr. Dion Coutinho.

Funders: Trials of Excellence in Southern Africa II (TESA II grant EDCTP Reg Net 2015-1051)

Dedication

I dedicate this work to my beloved sons Mr. Munyaradzi Blessing Zvinoera and Mr. Kudzai Samson Zvinoera whose support and love kept me moving relentlessly towards the finish line. Above all, I am eternally grateful to my almighty God, without whom this doctorate would not have been possible, for in Him I move, in Him I live and in Him I have my being. Lastly but not least, to all those who gave their support but are not mentioned here, I say to you all...Thank you!

List of Acronyms

Cfu/ul Colony forming units per microliter

DNA Deoxyribonucleic acid

XMTB/R Xpert *Mycobacterium tuberculosis* with rifampicin susceptibility pattern

EPTB Extra Pulmonary Tuberculosis

HIV Human immunodeficiency virus

LTFU Loss to follow up

MDRTB Multi-drug resistant tuberculosis

MGIT Mycobacterium Growth Indicator Tube

MRCZ Medical Research Council of Zimbabwe

MSF Medicines sans Frontiers

MTB *Mycobacterium tuberculosis*

PCR Polymerase Chain Reaction

PTB Pulmonary Tuberculosis

SDG Sustainable development goals

TB Tuberculosis

TRC Treatment completed

TF Treatment failure

WHO World Health Organization

Definition of Key Terms

Algorithm- The available testing strategy options.

Diagnosis- The process of identifying a disease, condition, or injury from its signs and symptoms. A health history, physical exam, and tests, such as blood tests, imaging tests, and biopsies, may be used to help make a diagnosis.

Died- A TB patient who dies for any reason before starting or during treatment.

Treatment completed- A TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.

Cured- A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear or culture negative in the last month of treatment and on at least one previous occasion.

Treatment failure- A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.

Lost to follow up- A TB patient who did not start treatment or whose treatment was interrupted for two consecutive months or more.

Not evaluated- A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.

Treatment success- The sum of cured and treatment completed.

Xpert *Mycobacterium tuberculosis*/Rifampicin targeted screening algorithm - Selected presumptive TB sputum was analysed using Xpert *Mycobacterium tuberculosis* /Rifampicin. The legibility was reserved for those with HIV infection, diabetes, history of previous TB treatment, presumed extra pulmonary TB, MDR-TB

contacts, healthcare workers, miners, pregnant women, children aged less than 5 years and the elderly aged above 60 years. In addition patients on first-line treatment with smear-positive sputum samples at 2/3/5/6 months were offered investigations using Xpert *Mycobacterium tuberculosis* /Rifampicin.

Xpert *Mycobacterium tuberculosis*/Rifampicin primary diagnostic algorithm - Every presumptive TB sputum was analysed using Xpert *Mycobacterium tuberculosis*/Rifampicin.

Table of Contents

List of Tables

List of Figures

List of Appendices

CHAPTER 1 INTRODUCTION

1.1 Introduction

Tuberculosis despite being a preventable and curable disease remains a disease of public health concern. Tuberculosis remains the leading infectious killer globally with 1.4 million deaths in 2019 (WHO, 2020). Early TB case detection and early TB treatment commencement, are key pillars used to combat TB. The two methods of smear microscopy diagnostic tests were used for over one hundred years, until the launch of XMTB/R diagnostic test (Cepheid website). There are TB program, key performance indicators, which are tracked, as part of disease surveillance (Ministry of Health and Child Care. 2014). These indicators showed, that there were gaps in effective efficient TB diagnostic tests.

What was known about XMTB/R, was that it had diagnostic advantage over smear microscopy, the TB test it replaced. Accurate quality assured TB diagnosis was needed to help the world to identify the 3 million undiagnosed people living with TB (Ismail et al, 2023). The significance of the study, was that it showed that, introduction of any intervention, should be investigated and monitored for effectiveness. The intervention in this study was XMTB/R primary diagnostic algorithm roll out.

The Ministry of Health and Child Care (MOHCC) has a robust TB program, which is fairly quick in responding to WHO policies. In terms of TB diagnostics, once WHO gave a recommendation for XMTB/R to be used for clearly defined targeted population, the Zimbabwe TB program initiated efforts to comply, starting with Medicines Sans Frontiers procured XMTB/R placed at Murambinda mission hospital, in December 2010 (Varaine et al, 2012). The rest of the laboratories in Manicaland

followed suit at rates that were context specific, with Mutare provincial hospital having its XMTB/R installed in December 2012 (machine inventory records).

As medical science is dynamic, in 2013 the WHO encouraged countries to move to the XMTB/R primary diagnostic test, which required every presumptive TB to be investigated with WHO recommended rapid diagnostics. The laboratories in Manicaland rolled out XMTB/R primary diagnostic algorithm, at different rates according to how well prepared they were to sustain the implementation. While the changes in XMTB/R testing algorithm changed, there was little to no change in the other TB program services, such as accessibility and quality. TB screening services were available at all the 304 health facilities in Manicaland, during both eras. The TB screening tool was constantly employed in both eras.

The question then rose, to say had those recent changes in XMTB/R primary diagnostic algorithm roll out, been systematically investigated, for efficiency and effectiveness? The aim was to analyse transition from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic algorithm roll out. To investigate whether XMTB/R primary diagnostic algorithm roll out, had resulted in a positive yield on the selected TB program key performance indicators, in Manicaland, Zimbabwe. For this study, the selected TB key performance indicators were; *Mycobacterium tuberculosis* (MTB) positivity rate, rifampicin resistance, laboratory turnaround time, TB treatment outcomes and quality control. The need to analyse transition from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic test roll out, was the driving force behind this study. After going through literature search, in 2017, it was evident that no such study had been undertaken in Manicaland.

The aim of the study was to analyse transition from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic algorithm roll out in Manicaland,

Zimbabwe for 2017-2018.This study investigated if XMTB/R primary diagnostic algorithm roll out resulted in a higher numbers of people being tested using XMTB/R, as well as the MTB positivity rate. It also investigated if XMTB/R primary diagnostic algorithm roll out resulted in increased detection of rifampicin resistant TB and any evidence of overburden in the health care system. The study data collection period ended in October 2019, before the onset of severe acute respiratory syndrome coronavirus 2 (SARSCoV2) pandemic The period of 2017 and 2018 were selected as appropriate because that was the transition period from targeted XMTB/R screening algorithm to XMTB/R primary diagnostic algorithm roll out. There were no major changes in; health personnel, the number of health facilities and the TB screening tool used between 2017 and 2018. The study presented provincial level data from Manicaland in Zimbabwe for 2017 to 2018. It was for that reason that the study findings were valuable, since the main change was the transition from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic algorithm roll out.

The study population chosen was all the sixteen XMTB/R services in Manicaland. In a bid to increase the statistical power, census sampling was employed for the period 1 January 2017 to 31 December 2018. The approach that was employed was retrospective analytical observational research design. The retrospective analytical observation study design was chosen for its advantages of data mining of already existent program data, while enabling census sampling, as well as remaining economical and quick to undertake. Data extraction involved downloading excel sheets of XMTB/R results from the sixteen machines. These were then merged with data collected from facility TB registers, to capture various dependent and independent variables. Geo-spatial mapping capacity of the MTB positive results for the period was analysed. Statistical analysis was then carried out.

Literature search streamlined the study and made it relevant and context specific as the findings enabled decision making that was driven by science such as; rationale prepositioning of the limited TB resources, development of the TB high risk group identification tool (annex 18), objective selection of cadres for TB case management training, Programmatic Multi Drug Resistant Tuberculosis training, objective selection of health facilities to benefit from mentorship programs, data driven supportive supervision and awareness campaigns in targeted communities.

1.2 Background of the Study

Literature states that to end TB effectively, disease elimination campaigns need to be driven by customized responses that are informed by appropriate locally generated TB surveillance data (Theron et al, 2015) (Pooran et al, 2019). Literature also highlighted the absence of systematic analysis of such locally generated TB program data in Manicaland. The study of interest being analysis of the interventions being implemented, in the TB program. The intervention that had been implemented was XMTB/R primary diagnostic algorithm roll out.

For a customized data driven response to TB, a three step process was needed to enhance understanding of TB transmission dynamics. Two of the three strategies included; using current routinely collected programmatic TB data to direct decisions, collection of supplementary TB data such as geo-spatial mapping of MTB detected results, tracking of drug resistance TB pattern, and appreciation of TB risk factors. The third strategy was targeted collection of new data, such as TB gene sequencing data or TB surveys targeted to TB at risk populations or TB contact investigations (Theron et al, 2015). The study used two of the three strategies, meaning it used TB programmatic data and generated MTB results as XMTB/R primary diagnostic algorithm rolled out.

Generating National TB Program data for action was one of the important epidemics ending approaches to eliminate pockets or hotspots of TB disease. The recommendation of the study focused on finding ways to increase MTB positivity rate through routinely identifying the TB high risk group. Once identified, then channelling the presumptive TB patients to chest x-ray investigation, the more sensitive TB screening tool. Literature states that, screening with chest x-ray gives double the yield in picking TB presumptive patients, who can then be investigated on XMTB/R primary diagnostic algorithm.

Literature review highlighted studies that had been carried out outside Zimbabwe that investigated transition from XMTB/R targeted screening algorithm to XMTB.R primary diagnostic algorithm roll out. Some literature of studies carried out around the world, stated that there was a positive influence between XMTB/R primary diagnostic algorithm roll out with; MTB positivity rate, rifampicin positivity, laboratory turnaround time, time to treatment commencement and the improvement in TB treatment outcomes. There was also lack of geo-spatial mapping capacity of XMTB/R detected results, disaggregated by semi quantitative XMTB/R results, in Manicaland, Zimbabwe. Judging by the limited retrieved documentation, during the literature review era from 2017 to 2018, it was deemed necessary to carry out this study, to enable rationale use of the limited TB resources, in Manicaland, Zimbabwe.

1.3 Statement of the Problem

Roll out of certain specific approaches or interventions in the TB program like the use of the XMTB/R primary diagnostic algorithm for diagnosis of MTB were not supported by evidence. The lack of available literature, showed that there was no data analysis to inform program on the benefits of programmatic use of XMTB/R primary

diagnostic algorithm in Zimbabwe. At the conception of the study in 2018 to the end of the data collection period in October 2019, there was no province in Zimbabwe where the study had been conducted**.** This lack of information was the driving force for this study, to cover the gap. Analysis of transition from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic algorithm roll out and MTB detection had not been evaluated under programmatic conditions in Manicaland.

With quality provision of detection service, it was expected that there would be a change in TB related morbidity and mortality. The analysis of TB treatment outcomes and transition from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic algorithm roll out had not been systematically carried out under programmatic conditions in Manicaland. For the purposes of this study TB treatment outcomes such as the number of patients cured, treatment completed, treatment failure and died were as defined by WHO (WHO, 2013).

From the conception of this study to the end of the data collection period in October 2019, this research had not found any literature on geo-spatial mapping capacity of XMTB/R results in Zimbabwe. It was this lack of previous studies on MTB detected geo-spatial mapping capacity that explains why it was important to conduct the study and make analysis of geo-spatial mapping capacity as transition occurred from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic algorithm one of the specific objectives.

As transition occurred from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic algorithm roll out, this meant all MTB results could be remotely accessible on GxAlert/Aspect software. The GxAlert/Aspect is a systemone software that was first used for data connectivity on the multidisease platform Genexpert machine and has been extended to other machines. GxAlert/Aspect has a dashboard

that shows disease results by result types and is colour coded. Results can also be remotely exported to comma separated values file (CSV) or Excel which was then used for geo-spatial mapping, as. With GxAlert/Aspect relevant TB program managers can receive notifications via email, short message service (SMS) text. GxAlert is specifically for TB, while Aspect is for multiple diseases (Systemone, 2021). As rapid diagnosis of TB was availed, GxAlert/Aspect became an intervention for health facilities to ensure the diagnosed TB patients are linked to care and put on treatment (Mnyambwa, 2018).

The geo-spatial mapping of XMTB/R semi quantitative results was based on cycle threshold values generated by the machine. Geo-spatial mapping of facilities that had high frequencies of MTB detected results enabled decision making that was driven by science such as; ensuring MTB detected patients are linked to care, rationale prepositioning of resources, objective selection of cadres for TB case management training, Programmatic Multi Drug Resistant Tuberculosis training, evidence based supportive supervision and high yielding awareness campaigns in targeted communities.

Quality is the foundation of testing, to ensure accurate, reliable and reproducible results, quality management system requires, method verification at the end of each XMTB/R module change. This requirement was unique and new for those transitioning from smear microscopy to XMTB/R primary diagnostic algorithm roll out. In smear microscopy there are no module changes, so method verification quality sputum specimen was only required once off per laboratory. As the diagnostic test, XMTB/R primary diagnostic algorithm was rolled out, the cost of quality reference material mounted, that's where the link is, of using frozen sputum to XMTB/R primary diagnostic test roll out. There was need to establish economical quality control sputum

specimen as XMTB/R primary diagnostic algorithm rolled out. The driving force generated by transition from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic algorithm roll out, was need for cost effective methods of in country method verification of XMTB/R machine post module change, before more quality testing could be conducted. The cost effective quality reference material was use of sputum tested years prior and frozen for re use.

1.4 Research Objectives

1.4.1 Broad Objective

The aim of the study was;

To analyse effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for MTB infection and rifampicin resistance in Manicaland, Zimbabwe, 2017-2018.

1.4.2 Specific Objectives

The specific objectives of the study were to;

1.4.2.1 Evaluate effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance in Manicaland, Zimbabwe, 2017-2018, on MTB detection.

1.4.2.2 Analyse effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance in Manicaland, Zimbabwe, 2017-2018, on laboratory turnaround time.

1.4.2.3 Determine the performance of TB treatment outcomes as transition occurred from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic algorithm roll out in Manicaland, for 2017-2018.

1.4.2.4 Explore geo-spatial mapping capacity as transition occurred from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic algorithm roll out in Manicaland, for 2017-2018.

1.4.2.5 Produce frozen sputum quality control specimen as transition occurred from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic algorithm roll out.

1.4.3 Research Questions

The research questions of the study were;

1.4.3.1 What was the relationship between transition from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic algorithm roll out and MTB detection in Manicaland, for 2017-2018?

1.4.3.2 Was there a relationship between transition from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic algorithm roll out and laboratory turnaround time in Manicaland, Zimbabwe, 2017-2018?

1.4.3.3 What was performance of TB treatment outcomes as transition occurred from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic algorithm roll out in Manicaland, for 2017-2018?

1.4.3.4 Did the capacity of geo-spatial mapping vary as transition occurred from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic algorithm roll out in Manicaland, Zimbabwe, for 2017-2018?

1.4.3.5 Could a quality control specimen be made from frozen sputum as transition occurred from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic algorithm roll out?

1.5 Assumptions / Hypotheses

Null hypothesis: There was no change as transition occurred from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic algorithm roll out, in Manicaland, 2017-2018.

1.6 Significance of the Study

The findings of the study helped to inform TB program managers whether the provision of Xpert MTB/Rif primary diagnostic algorithm had helped earlier diagnosis, thus providing answers to the research questions, as well as to add to the body of knowledge. Use of locally tailored responses informed by appropriate data, enhanced the economical and effective use of limited TB resources. Systematic literature review pointed out a research gap in the Zimbabwean context.

Increased capacity in geo-spatial mapping of frequencies of XMTB/R detected results based on requesting health facilities enabled decision making that was driven by science such as; verifying linkage to care, rationale prepositioning of resources, objective selection of cadres for TB case management training, Programmatic Multi Drug Resistant Tuberculosis training, objective selection of health facilities to benefit from mentorship programs, data driven supportive supervision and awareness campaigns in targeted communities. The justification for the nested study was the need to establish economical quality control sputum specimen as XMTB/R primary diagnostic algorithm rolled out. To ascertain whether previously analysed frozen sputum could be used, for comparing with thwarted and retested results from newly availed XMTB/R tests. This reduced the cost of performing panel of XMTB/R tests each time a new XMTB/R diagnostic algorithm module was changed. The study adds

on to the body of knowledge on effect of XMTB/R primary diagnostic algorithm roll out.

1.6.1 Delimitation of the Study

Data was generated from all the sixteen Gene Xpert analysers in Manicaland, with the accompanying health facility TB registers and health facility TB laboratory registers. The data collected from the sixteen Gene Xpert analysers was only for the period 1 January 2017 to 31 December 2018. The available frozen sputum collected seven years previously in study with Medical Research Council of Zimbabwe (MRCZ) ref MRCZ A/1 552 were analysed on Xpert MTB/Rif Ultra.

1.7 Limitation of the Study

This study had several strengths and limitations. Firstly, the strength was the selection of the exact two year period of 2017 to 2018, which comprised the transition period from targeted XMTB/R screening algorithm to XMTB/R primary diagnostic algorithm roll out. The study included more than 43 809 records from routine services over a two year period by extracting aggregated data from audit reports and individual level data from Gene Xpert downloads supplemented by data from laboratory registers. This allowed investigations beyond the number of samples and the number of XMTB/R positive samples over time. Secondly, the study also investigated operational data including laboratory turnaround time, transport time and rates of unsuccessful assays, which were important to analyse after substantial changes were made within diagnostic networks. The limitations include a high proportion of missing data due to hard ware and software failures and individual level data being limited to a small set of variables reported in the laboratory register. Aggregated data from external quality assurance TB quarterly reports could not be de de-duplicated, however, this was more important

for smear microscopy samples as most patients investigated would have been asked to submit two samples.

Limitation faced with analysis of time taken to detection, was the lack of information on actual date a decision and request was made to investigate TB using XMTB/R That information was especially missed in Gene Xpert sites like Regina Coeli where 95% of the specimens processed there were requested at Regina Coeli, meaning that catchment population was practising patient referral rather than specimen referral. The challenges that came with patient referral model were delay in diagnosis as patients took time to prepare to travel to the Gene Xpert site. Prolonged diagnostic delays pose serious challenges as TB treatment may only be initiated after disease has progressed, thus potentially worsening prognosis and treatment outcomes (Takarinda et al, 2015).

Limitation faced for TB treatment outcomes specific objective was that the health facility TB register did not capture which Gene Xpert site was used in the diagnosis. The XMTB/R diagnostic algorithm had to be averaged across the province. An assumption was made on the TB treatment outcomes, that where XMTB/R was carried out and recorded, the Gene Xpert machine used was among the sixteen in Manicaland.

Limitation of the study was that it was not able to capture and control for other factors that influence TB detection like human resources at the health facility, the trainings received in TB case management and the adequacy of integrated specimen transport in place during 2017-2018. Study limitation was that, it was not able to capture other determinant of TB treatment outcomes that influence treatment outcome like presence or absence of co-morbidities, level of management of existing co-morbidities, time to taken to treatment commencement, initial method used for TB diagnosis, treatment regimen, adherence counselling and type of direct observed treatment received by the TB patients recorded in the facility TB Registers. Another limitation was that since

this study was carried out before the SARSCoV2 pandemic, its findings cannot give insight to effect of SARSCoV2 on TB.

1.8 Summary

This chapter gave an overview of the study and how it was carried out. The study was on XMTB/R primary diagnostic algorithm roll out. Concise summary of what was known about TB burden globally as well as the TB burden in Zimbabwe, was given. Details were given of strides made by the Zimbabwe National TB programme, to implement WHO recommendations on TB diagnosis. An overview of the XMTB/R diagnostic algorithm that was used upon the introduction of XMTB/R diagnostic algorithm was given, namely targeted XMTB/R diagnostic algorithm. Further explanation was given, on how the XMTB/R diagnostic algorithm evolved over the years up to the 2017-2018, the transition period, where there was roll out of the XMTB/R primary diagnostic algorithm. The chapter also explained the problems of the disease as it affected TB control efforts across the globe to enable the readers to appreciate what TB is and why it is called a disease of global public health importance. The need for in country research to enhance rationale use of limited resources by being guided by evidence based medicine was highlighted. The chapter also looked at research objectives, research questions and assumptions. At the end of the chapter, the significance of the study and the limitations of the study were outlined. The next chapter, 2 focuses on review of related literature.

CHAPTER 2 REVIEW OF RELATED LITERATURE

2.1 Introduction

Chapter 2 highlights the conceptual framework, relevance of the conceptual framework to the study. The chapter helped other researchers to appreciate what is known and what is not known on the subject of XMTB/R primary diagnostic algorithm roll out. All the areas looked at the global picture, the picture in the continent, the picture in Zimbabwe and in the context of Manicaland. Synthesis of literature was delved into on the burden of TB, history of TB disease detection up to XMTB/R testing and TB program key performance indicators. The literature search was undertaken to understand what is known about TB detection services. The chapter also helped to inspire new research ideas. The chapter established whether there was any need to refocus the study so that it would contribute to the existing body of knowledge. The chapter helped guide selection of which one of the identified gaps to address, through the undertaking of this study. As a result of the synthesis, the selected areas of focus were; MTB detection or MTB positivity rate, rifampicin resistance detected, laboratory turnaround time, TB treatment outcomes, geo-spatial mapping capacity and establishment of economical quality control sputum.

2.2 Conceptual Framework

The conceptual framework was used to show the relationships between independent variables and dependent variables and how they related to the study. The independent variables for this study were; participant number, sex, age, HIV status, requesting health facility, time taken from collection to receipt at Gene Xpert site, laboratory turnaround time defined by date received at Gene Xpert site to date of test, XMTB/R diagnostic algorithm used during the period year, quarter, Gene Xpert site and district.

The dependent variables for the study were; MTB not detected or MTB detected. Every MTB detected result then had semi quantitative result of either; MTB detected high, MTB detected medium, MTB detected low, MTB detected very low or MTB detected trace. For every MTB detected result followed rifampicin resistant result of either; rifampicin resistance not detected or rifampicin resistance detected or rifampicin resistance indeterminate. The dependant variable had a relationship with XMTB/R primary diagnostic algorithm roll out.

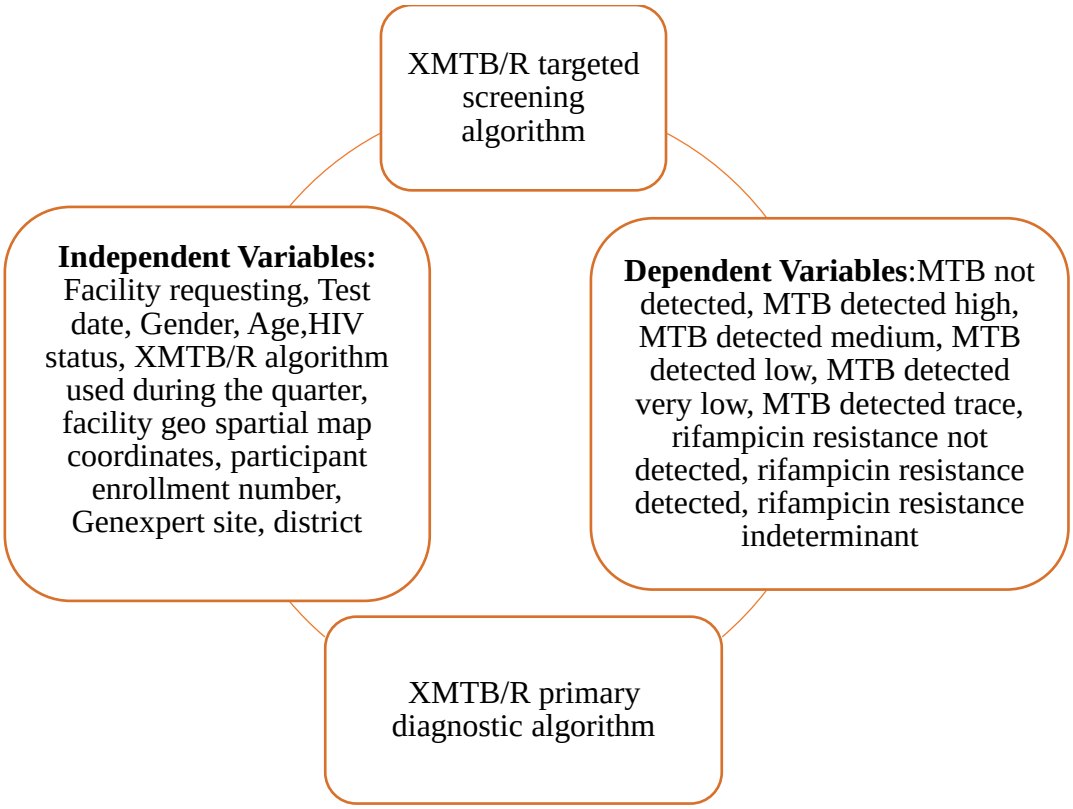


Figure1: Conceptual Framework Application

2.3 Relevance of the Conceptual Framework to the Study

The conceptual framework was built as literature search was undertaken. The conceptual framework allowed the researcher to draw conclusions, mapping out the variables used in the research and the interplay between them. The relevance of the conceptual framework to the study was that the population was presumptive TB population. The intervention was the XMTB/R machine. The comparison was the XMTB/R targeted screening algorithm or XMTB/R primary diagnostic algorithm in use. The outcome was the differences in semi quantitative MTB result in the period during targeted approach and the period after XMTB/R primary diagnostic algorithm roll out.

2.4 Review of Related Literature

In carrying out literature search, references were identified through searching in HINARI and EBSCO data bases. The search strings used in EBSCO data base was "XMTB/R roll out" or "roll out of TB diagnostic" and 800 results popped up. Out of 250 articles headings read through, 41 abstracts seemed relevant. Out of the 41, 12 failed to open. Similar search strings were used in HINARI data base and 72 results appeared. From the 72 article headings read through, 18 abstracts seemed relevant. Out of the 18 abstracts, 7 failed to open, so 11 full texts were texts were read through. When the search string was limited to "XMTB/R roll out in Zimbabwe" or " Primary TB diagnostic test in Zimbabwe" 12 articles popped up. Out of 12 results, one article was the yield, after going through 12 articles.

2.4.1 XMTB/R primary diagnostic algorithm roll out

Literature review indicated agreement that introduction of XMTB/R diagnostic algorithm, in 2010, was a game changer in the TB diagnostic landscape. If introduction of XMTB/R primary diagnostic algorithm was a game changer, then why was it that, the papers read, all unanimously agreed that tuberculosis remains the leading infectious killer globally, despite TB being a preventable and curable disease? What was the relationship between XMTB/R primary diagnostic algorithm roll out on MTB detection?

2.4.1.1 Understanding changes in MTB detection as XMTB/R primary diagnostic algorithm was rolled out

There were 1.44 million TB deaths in 2019 (WHO, 2020). The number of people newly diagnosed with TB and those reported to national governments fell from 1.44

million in 2019 to 1.41 million in 2020. There was an increase to 1.51 million in 2021(WHO, 2023). In general, ten million new cases occur annually disproportionately affecting disadvantaged populations. In 2013 the WHO declared TB a “global emergency” (WHO, 2013).

The WHO End TB Strategy describes the Sustainable Development Goals (SDG) aiming to reduce TB deaths by 95% and new cases by 90% between 2015 and 2035 (WHO, 2015). This study was anchored on two of the three pillars of the end TB strategy. Pillar one is integrated patient centered care and prevention. This has components 1A to 1D. Component 1A is early detection of TB including universal drug susceptibility testing and systematic screening of contacts and high risk groups. Universal drug susceptibility testing is another way of saying XMTB/R primary diagnostic roll out. Under pillar three is intensified research and innovation which is subdivided into component 3A and component 3B. Component 3A is discovery development and rapid uptake of new tools, interventions and strategies. This study recommended a new tool.

At the end of 2019, global statistics indicated that many high TB burden countries were not on track to reach the 2020 milestones of the End TB Strategy (WHO, 2020). While globally TB incidence rates have been falling, the decrease is unacceptably slow (Seung et al, 2019). TB is further worsened mostly in resource limited countries due to unequal and inadequate distribution of diagnostic and treatment interventions (Seung et al, 2019). The cumulative reduction from 2015 to 2019 was only 9%, which is far off the 20% reduction aimed for between 2015 and 2020. The situation is made worse by the human immunodeficiency virus (HIV) pandemic. While, the lifetime risk of developing TB disease is 10% for HIV- negative people, if a person is HIV-positive, the risk of developing TB disease is 10% per annum (Bholla et al, 2016).

According to WHO analytical factsheet 2023, Central African Republic, Democratic Republic of the Congo, Mozambique, Nigeria, United Republic of Tanzania and Zambia saw increases in notifications in 2020 and 2021. The same literature states that in the WHO African Region:

• The impact of SARSCoV2-related disruptions on the reported number of people newly diagnosed with TB was limited. There was a relatively small decrease (–2.3%) from 2019 to 2020 and an increase in 2021.

• In 2021, an estimated 2.5 million people (95% confidence interval (CI), 2.2–2.8 million) were infected with TB: 1.3 million men (aged 15 years and over), 0.8 million women (aged 15 years and over) and 0.3 million children (aged 0-14 years). • The TB incidence per 100 000 population fell by 22%, from 270 in 2015 to 212 in 2021 (target: 20% reduction by 2020).

• In 2020, the TB treatment success rate was 86% of those who started treatment. It was about 83% in 2015.

• In 2021, about 501 000 people died of TB (95% CI, 436 000–571 000), including 136 000 people with HIV.

• In 2021, the Global Plan to End TB, 2018–2022 estimated that US$ 3.9 billion would be required to achieve the targets, but only US$ 0.957 billion was mobilized for TB prevention, diagnosis and treatment.

In the WHO African region, seven countries reached the 35% reduction of TB deaths from a baseline of 2015. The countries are: Eswatini, Kenya, Mozambique, South Sudan, Togo, Uganda and Zambia.

The prevalence of TB in Zimbabwe decreased from 263 cases per 100 000, in the over fifteen year old population to 242 per 100 000 in 2017 (Chirenda et al, 2020). In 2018, the estimated incidence of TB in Zimbabwe was 210 per 100 000 population and 62%

of diagnosed TB patients were human immunodeficiency virus (HIV) co infected. Among the multi-drug resistant TB (MDRTB) patients in Zimbabwe, HIV prevalence was found to be even higher at 80% (Timire et al, 2019). Zimbabwe is among the fourteen countries with a triple burden of TB, TB/HIV and multi drug resistant TB (WHO, 2010). TB/HIV co infection was labelled as the "Perfect storm", back in 2007 and more than a decant later, the label still holds water (Wells et al, 2007).

Literature highlighted that the TB program has key performance indicators that are used to monitor TB, among which are TB prevalence surveys, TB incidence, TB positivity rate, drug resistance which includes rifampicin resistance and mortality. This study chose to analyse TB positivity rate, drug resistance, which are both components of TB detection. It also chose to analyse mortality, which is a component of TB treatment outcomes.

2.4.1.2 TB Detection as XMTB/R primary diagnostic algorithm was rolled out

A priority under TB surveillance was detection. TB diagnosis was the process of detecting TB, from its signs and symptoms. A health history, physical exam, a test such as smear microscopy or XMTB/R imaging tests and biopsies, could be used in TB diagnosis. TB diagnosis helps the world to identify the 3 million undiagnosed people living with TB (Ismail et al, 2023). The 3 million undiagnosed people living with TB were due to lack of effective diagnostic tests. This contributed to the global TB problem, as undiagnosed and untreated TB patients remained a source of infection for other members of the community. Untreated TB or delay in treatment due to delay in TB detection also resulted in considerable morbidity and death, especially in HIV co-infected individuals. There is a disagreement on the estimated figure of the undiagnosed people living with TB, as more recent literature has revised the figure

downward to just above 1 million. This may be due to the findings that national TB prevalence surveys are coming up with prevalence rates that are lower than those projected from previous surveys.

The TB detection test that was replaced by XMTB/R diagnostic algorithm was smear microscopy. Smear microscopy test involved either the Zielh-Neelson staining technique or the fluorescent microscopy technique. Zielh-Neelson is an amalgamation of the surnames of the two people who created and used the stain to identify TB from the 1870s. The full names are Friedrich Ziehl {1857- 1925} and Professor Friedrich Karl Adolph Neelsen {1854-1894} (Bishop et al, 1970). In 2009, the evidence for the efficacy of fluorescent microscopy was evaluated by the WHO. WHO recommended that fluorescent microscopy be phased in as an alternative for conventional Ziehl-Neelsen microscopy for the detection of TB. (WHO. 2011).

The company that manufactured XMTB/R was founded in 1996 and launched the first biohazard Xpert machine in 2003. In 2005 Cepheid officially launched into the clinical market, an Xpert for detecting group B Streptococcus. Literature states that XMTB/R was co-developed by: the laboratory of Professor Allan Grand, located at the University of Medicine and Dentistry of New Jersey, Cepheid Inc. and Foundation for Innovative New Diagnostics, with additional financial support from the United States National Institutes of Health (Cepheid website).

The WHO in 2009 gave a strong recommendation that XMTB/R is appropriate for drug resistant TB detection, due to its ability to give rifampicin resistance result within two hours of testing. XMTB/R purifies raw sputum, concentrates the genetic material that might be present, amplifies (by rapid, real-time polymerase chain reaction) and identifies targeted nucleic acid sequences in the TB genome, with minimal hands on technical time. XMTB/R simplifies molecular testing by fully integrating and

automating the three processes required for real time polymerase chain reaction based molecular testing. The three phases being sample preparation, amplification and detection. It uses a cartridge containing all elements necessary for the reaction, including lyophilized reagents, liquid buffers and sample wash solutions. XMTB/R actually has eleven compartments in the single cartridge, allowing for real time, target detection and characterization using a six colour laser detection device.

Besides being appropriate for drug resistant TB detection, it was already established that funds permitting the XMTB/R also had diagnostic advantages for testing of drug susceptible TB. XMTB/R tests both the presence of MTB and resistance to rifampicin in a single test. XMTB/R test allows for a rapid and accurate diagnosis which helps to ensure that patients who are detected with MTB may be commenced early on appropriate treatment. Gene Xpert machine comes with for modules, which allows 16 to 20 tests in an eight hour shift. There are bigger machines with a throughput of up to 1 000 tests per eight hour shift. It comes with a computer for result archive and requires a stable and uninterrupted electrical power supply. Each of the at least four modules requires at least one annual calibration, after which quality management systems requires, method verification.

XMTB/R has a lower limit of detection than smear microscopy as it detects 112.6 coliforms per microliter (cfu/ml) as opposed to smear microscopy which needs at least 5 000 cfu/ml for positivity (Chakravorty et al., 2017). Such a marked difference in limit of detection to both the smear microscopy test, that it was replacing, was a land mark discovery and a game changer in TB detection arena. The co-infection of HIV and TB, results in the infected person not fighting the TB pathogen that will have been introduced in the HIV infected person, due to low immunity. It was thus deemed

necessary for the population whose immune system is compromised to also have their sputum analysed using XMTB/R (Jokwiro et al, 2018).

Globally TB disease is not distributed homogenously. It is distributed heterogeneously with some countries being high TB burden countries, while others are low TB burden countries. Table 1 show the 27 priority TB countries, which are all high TB burden countries. The TB epidemiological pattern varies even within each country.

Table 1: List of 27 priority TB countries by continent in no particular order (adapted from Stop TB Partnership, 2021)

Africa	**Asia**	**South America**	**North America**	**Australia**	**Europe**
Zimbabwe	Philippines				Ukraine
South Africa	Bangladesh				
Mozambique	Pakistan				
Malawi	India				
Ethiopia	Cambodia				
Zambia	Afghanistan				
Uganda	Kazakhstan				
Ghana	Uzbekistan				
Kenya	Kyrgyzstan				
DRC	Indonesia				
Nigeria	Myanmar				
Tanzania	Tajikistan				
Cameroon	Vietnam				

Literature chronicles how Medicines Sans Frontiers (MSF) introduced the first sixteen XMTB/R testing services in routine TB program use, across the whole world as listed below;

Kirghistan (Osh) Ukraine Colombia Swaziland (Nhlangano, Hlatikulu, Mankayane, Matsapha) Kenya (Mathare, Kibera) Uganda (Arua) Kenya (Homabay) Mozambique (Moatize, Mavalane) Malawi (Chiradzulu) South Africa (Eshowe, Mbongolwane) Zimbabwe (Birchenough, Murambinda) Lesotho (Varaine et al, 2012).

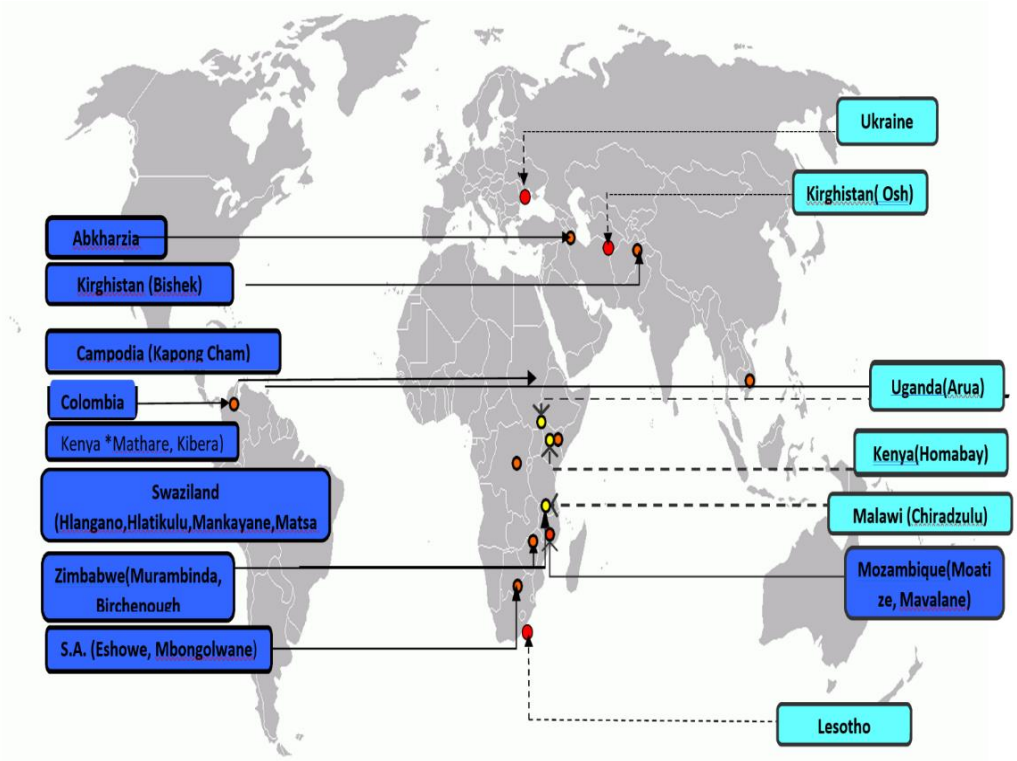


Figure 2: XMTB/R introduction around the world adapted from Varaine et al., 2012

The first MSF supported sixteen XMTB/R services globally were in 9 countries by end 2011. In the 9 countries the XMTB/R testing services were placed in sixteen MSF projects, The placement in the sixteen health facilities, by epidemiological situation was as shown in table 2

Table 2: Distribution by epidemiological situation of first sixteen XMTB/R services in routine TB programs

	High HIV Burden	Low HIV Burden	Total
High MDR	7	2	9
Low MDR	6	1	7
Total	13	3	16

The TB program key performance indicators include but were not limited to those depicted in table 3.

Table 3: TB program indicators adapted from Ministry of Health and Child Care, 2014

Indicator	Indicator definition	Tracked Key Perfomance Indicator
Case Finding Indicators	Number of presumptive TB cases per 100,000 population	Percentage of presumptive TB cases screened by smear microscopy or Xpert who had positive result
TB & HIV Indicators	% of TB cases with recorded HIV test results	% of TB cases with a recorded HIV result who are HIV-positive

TB Treatment Outcome Indicator	Cure rate	Death rate
Drug Resistant TB Indicators	Percentage of previously treated TB cases with sputum tested for XMTB/R	Drug resistant rate

The TB program indicators narrowed down on to be investigated were MTB positivity, rifampicin resistance and the presence or absence of reduction in the favourable and unfavourable TB treatment outcomes.

The stated MTB positivity rate in the sixteen health facilities were as on table 4

Table 4: XMTB/R test results from the documented first sixteen TB programmatic data

Country	**Health Facility**	**%MTB Negative**	**%MTB Detected**	**% Inconclusive Results**	**%Rif Resistance Detected**
Colombia	Buenaventura	13	83	4	15.8
Zimbabwe	Murambinda Mission Hospital	76	17	8	12.8
Zimbabwe	Birchenough Bridge Hospital	75	20	6	5.9
Kirghistan	Bishkek	50	43	7	45
Kenya	Kibera	65	31	5	3
Mozambique	Mavalane	62	30	9	8.2

Kenya	Mathare	51	26	23	2.8
Ukraine	Abkhazia	66	25	9	22.8
Swaziland	Matsapha	76	24	4	10.9
South Africa	Eshowe	75	23	2	16.4
Mozambique	Moatize	67	21	12	5.8
Swaziland	Nhlangano	75	21	4	6.7
Swaziland	Hlatikulu	75	20	6	9.6
Swaziland	Mankayane	64	18	19	11.6
Lesotho	Kampong Cham	67	15	19	5.7
South Africa	Mbongolwane	86	11	4	8.5

The first Gene Xpert machine in a public institution in Zimbabwe was in 2010, at Murambinda mission hospital, which is in Manicaland (Varaine et al, 2012) (Murambinda TB Program Registers). The TB diagnostic algorithm in use then was targeted XMTB/R screening. Targeted XMTB/R screening algorithm was used only on targeted population, while those not legible had smear microscopy examination for TB detection. Presumptive TB cases legible for targeted XMTB/R screening algorithm were those with HIV infection, diabetes, history of previous TB treatment, presumed extra pulmonary TB, multi-drug resistant TB contact, health care workers, miners, pregnant women, children less than five years of age, the elderly greater than sixty years of age, also, patients on first line treatment with direct smear microscopy positive sputum samples at 2/3/5/6 months treatment monitoring (WHO, 2011).

In 2013 WHO gave a recommendation for roll out of XMTB/R as the primary diagnostic test on all presumptive TB patients. In 2017, the Zimbabwe Tuberculosis and Leprosy Management Guidelines recommended XMTB/R primary diagnostic test roll out where XMTB/R was recommended as the primary diagnostic test for all patients presenting with signs and symptoms suggestive of TB. Roll out of the

XMTB/R primary diagnostic test was influenced by the availability of XMTB/R testing capacity; number of Gene Xpert testing sites, number of instruments and functional modules per instrument, availability of XMTB/R cartridges, Gene Xpert machine electricity back up, human resource training and sample transport systems (MOHCC, 2017).

Interpretation of the semi-quantitative XMTB/R results gives in depth insight to the TB program. Cycle thresh hold values give further insight; the geo spatial mapping data inform which requesting health facilities are surrounded by higher or lower cycle thresh hold values. The relationship of cycle thresh hold values generated and bacillary load in the semi quantitative XMTB/R result is that the lower the cycle thresh hold value the higher the bacillary load and vice versa. Cycle thresh hold values of less than 16, give a result of MTB detected high, while cycle thresh hold values of greater than 28, give result of MTB detected very low. The lower the cycle thresh hold value, the more infectious the MTB positive case (Mbelele et al, 2017). One of the indicators of how good the TB program is at a health facility is reflected by diagnosis of TB at the earliest stages of the disease when the cycle thresh hold value is still high. Knowing which health facilities have catchment population that present with MTB detected high or MTB detected trace, enables rationale use of limited resources. TB program can tailor make interventions to suit the health facility. That is the reason why geo spatial mapping of XMTB/R results per health facility was undertaken.

As XMTB/R primary diagnostic algorithm rolled out, there was need to establish economical quality control sputum specimen. Increased demand of quality machine verification reference material, arose. To answer this need, the study carried out comparative analysis of XMTB/R Version 4 and XMTB/R Ultra cartridges. XMTB/R Ultra, is a cartridge Version introduced with the advance of molecular techniques.

XMTB/R Version 4 and XMTB/R Ultra are both cartridges used to detect MTB using the same Gene Xpert machine. The same Gene Xpert machine is a multi-disease platform, which carries analysis of various diseases, by just changing the cartridge to be inserted in the Gene Xpert machine. XMTB/R is a self-contained rapid molecular test based on deoxyribonucleic acid (DNA), polymerase chain reaction. Polymerase chain reaction, is real time amplification and real time detection of DNA. With XMTB/R there is simultaneous detection of MTB and rifampicin resistant pattern and the turnaround time is two hours.

The XMTB/R Version 4 has lowest limit of detection of 112.6 colony forming units per microliter (cfu/ml). The limit of detection for XMTB/R Ultra is 15.6 cfu/ml. XMTB/R Ultra has an additional semi quantitative result of MTB detected trace. XMTB/R Version 4 sensitivity is 88% in smear positive and 22-66% sensitivity in smear negative. The XMTB/R Ultra has 5% extra increase in sensitivity across the board. The XMTB/R Version 4 specificity is 98%. The XMTB/R Ultra has decreased specificity by minus 3%. To improve on accuracy in rifampicin resistance detection, XMTB/R Ultra incorporates melting temperature based analysis. The XMTB/R version 4 uses real time analysis. The XMTB/R Ultra has more rapid thermal cycling with fully nested nucleic acid amplification. It has improved fluidics and enzymes as well as having a larger DNA reaction chamber than the XMTB/R version 4 (WHO, 2017)(Chakravorty et al, 2017)(Bisognin et al, 2018). Davis et al, 2014 noted that XMTB/R diagnostic accuracy and increased sensitivity maybe insufficient to drive adoption and that evidence on clinical and public health decision-making and outcomes may be needed.

The TB program in Zimbabwe introduced the XMTB/R Ultra into routine use in 2019. On introduction of a new TB test, performance quality verifications have to be carried

out between at least two tests using a reference specimen and one reference method. Such an exercise of new TB test method verification has cost implications. Any in country TB program has to be agile and make it feasible for new TB tests to be added for routine use.

It is a quality management system international standards organization 15 189 requirement that upon introduction of a new machine such as Gene Xpert, to a laboratory, or upon change of Gene Xpert module, an XMTB/R method verification process be undertaken before patient laboratory results can be issued in routine practice. This means all the sixteen Gene Xpert machines had to be verified at each laboratory that they were placed. There is constant requirement for reference material, to carry out method verification, of which use of pre run frozen sputum would address. To show the constant need, in 2021 alone, a total of ten Gene Xpert modules were changed in Manicaland. This meant ten post module change XMTB/R verifications were needed. Since science is dynamic, the public health laboratories had two more XMTB/R molecular testing machines which also test MTB on their multiplexed platforms. During the study period, Manicaland received four Trunat machine, four Ustar machines and two Tencolor Xpert machines. This highlighted urgent need for establishment of economical quality control sputum specimen. The cost-effective large volumes of TB sputum specimens with known values would be reference specimen, that would be analysed on the new modules or new machines during method verification to ensure quality in testing.

TB notification takes into account the catchment population as well as the country prevalence of TB. Table 5 below shows the TB notifications, the expected target per 100 000 population and the notification rate, according to the dataset from District Health Information System 2. For 2018, Buhera District, Makoni District and Mutasa

District performed above expected target. The district that performed the poorest below expected target was Nyanga District, followed by Chimanimani District. The number of notified TB cases is expressed as a notification rate per 100,000 population. The rate shows how many cases there would be in each area (e.g. clinic, district, province) if the population had been 100,000 in each of them.

Table 5: 2018 Manicaland TB target, notifications and notification rate

District	Target	Notifications	Notification rate
Buhera	405	507	125
Chimanimani	228	150	66
Chipinge Rural	550	543	99
Makoni	451	546	121
Mutare Rural	445	403	91
Mutasa	258	273	106
Nyanga	204	107	52
Mutare Urban	306	304	99

2.4.2 Evaluation of effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance, on MTB detection

In this review some pertinent issues related to XMTB/R primary diagnostic algorithm roll out and TB detection were gathered, compared and their relevance in guiding this study was shown.

2.4.2.1 Evaluation of XMTB/R primary diagnostic algorithm roll out and bacteriological confirmation

In a study carried out in Brazil one of the findings was a 59% increase in bacteriologically confirmed TB on introduction of XMTB/R testing, 95% (CI31-88%) p value 0.001 (Durovni et al., 2014). Although Brazil's northern region is high TB

and as a country is also low income, these findings could not be taken to be representative of Manicaland, Zimbabwe.

2.4.2.2 Analysis of XMTB/R primary diagnostic algorithm roll out and TB treatment commencement

In the same study TB treatment commencement, decreased from a mean of 11 days (IQR8.5-14.5) to 8 days (IQR5.4-9.3) p value 0.04.). In a study in Zimbabwe there was a no significant decrease in time to treatment commencement on multi drug resistant TB patients using centralized Gene Xpert analyser, 5 days (IQR 3-13) versus 8 days (IQR 3-23) p value 0.26 (Mupfumi et al, 2014).Analysis of XMTB/R primary diagnostic algorithm roll out on time taken to treatment commencement, could be attributed to the lower limit of detection of XMTB/R test as compared to smear microscopy. As XMTB/R primary diagnostic algorithm rolled out and was availed to all presumptive TB patients, it means patients who sought health service could be diagnosed earlier on XMTB/R, than on smear microscopy. Once MTB was detected, then it follows that the TB treatment commencement, also commenced earlier.

2.4.2.3 Evaluation of XMTB/R primary diagnostic algorithm roll out and TB notification

Overall notification rate did not increase as it remained at 15% 95% (CI -6% - 37%) (Durovni et al., 2014). In a study carried out in South Africa, the overall TB notification decreased by 12% for HIV negative and by 19% for HIV patients respectively (Hermans et al, 2017). In a study that carried in South Africa, there was a significant shortening of time to TB treatment commencement, 4 days (IQR 2-8) after roll out compared to 5 days (IQR2-14) before rolling out (Schmidt et al., 2016).

2.4.3 Evalution of XMTB/R primary diagnostic algorithm roll out and laboratory turnaround time

In a study carried out in a semi-rural area in South Africa, one of the findings was that there was a decrease in laboratory testing time less than one day, p value <0.001 (Schmidt et al, 2016). The decrease in laboratory testing time is difficult to explain, since as already stated XMTB/R eight hour shift has a throughput of twenty tests, when using a four module Gene Xpert machine. Whereas with smear microscopy one slide takes ten minutes to read and the staining can be batched to twenty slides per staining session. It can only be explained if the laboratory has one staff member, which then brings in the XMTB/R advantage of being a hands free test, while smear microscopy requires the laboratory staff member to be hands on all the time. XMTB/R is a walk away test, allowing laboratory staff member to continue with other laboratory duties, while XMTB/R testing

2.4.4 Determination of the performance of TB treatment outcomes as XMTB/R primary diagnostic algorithm rolled out

With the introduction of XMTB/R primary diagnostic test came the diagnostic advantage of low limit of detection. As already stated smear microscopy needed at least 5 000 bacilli per microliter to detect a TB positive, which XMTB/R Ultra detects MTB positive with as little as 16 bacilli per microliter. The need for early commencement to treat patients confirmed to be infected with TB comes with the necessity for early detection of TB. The roll out of, a rapid molecular diagnostic method for MTB which simultaneously detects rifampicin resistance pattern, XMTB/R changed TB landscape. It has higher sensitivity meaning TB is detected earlier than when smear microscopy diagnosis was in use.

Benefits of early TB diagnosis to both patients and their families may be due to: a) decreased morbidity resulting in increased quality of life at the end of treatment; b) reduced amounts of money used during the period of seeking a confirmed diagnosis; and c) less chance of transmission. The earlier TB treatment is commenced, the less chance of a TB associated death and the higher the chance of successful TB treatment outcomes. Successful TB treatment outcomes in clinically diagnosed patients receiving TB treatment is lower compared to patients with bacteriologically confirmed TB receiving TB treatment, irrespective of HIV status and age (Abdullahi et al, 2021).

There are many determinants of TB treatment outcomes including; type of TB, method used for TB diagnosis, time taken to commencement of treatment, treatment regimen, model of treatment care and support, existing co-morbidities, level of management of co-morbidities. Tuberculosis disease is the major cause of death among adolescents co-infected with HIV (Snow et al, 2020).

A study in India did not look at many other determinants of TB treatment outcomes such as co-morbidities like diabetics where an Indian study reported 30% fewer unsuccessful treatment outcomes [aOR (0.95 CI): 0.72 (0.64−0.81)] and 2.8 times higher odds of 'no recurrence' [aOR (0.95 CI): 2.83 (2.60−2.92)] among patients with optimal glycaemic control at baseline (Shewade et al, 2017).

In a study carried out in Zambia the TB treatment outcomes established were; death 5.5 %, lost to follow-up 2.9%, and 3.2% treatment failure (Mutembo et al, 2019). In a study carried out in Ghana TB patients who were HIV positive had lower successful TB treatment outcomes than HIV negative 70% (83/107) compared to 91.2% (382/419) respectively. In the same study, 21.5% (23/107) HIV positive TB patients died compared to 5.5% (23/419) for HIV negative TB patients (Ogyiri et al, 2019). In

Cape Town, it was found that the reason for TB treatment commencement changed from a positive smear microscopy in 67% and 21% in HIV negative and HIV positive patients respectively to XMTB/R positive in 84 % and 67% in HIV negative and HIV positive patients respectively (Schmidt et al, 2017). Showing that as XMTB/R primary diagnostic algorithm rolled out the reason for commencing people on TB treatment changed from microscopy positive to XMTB/R positive.

The TB treatment outcomes findings for a study carried out in Ethiopia were as follows; cured 90/281 (32%), treatment completed 137/281 (48.8%), treatment failure 4/281 (1.4%), lost to follow up 36/281 (12.8%) and 14/281 (5%) died. The overall treatment success rate was 80.8%. (Tesema et al, 2020). Being HIV positive increased the chance of being clinically diagnosed for TB by 2.8 fold as compared to being HIV negative, adjusted OR: 2.8 (Hermans et al, 2017) (Tesema et al, 2020).

In a study carried out in Kalifi, Kenya overall unsuccessful treatment outcomes were 776 (5.3%) loss to follow up, 415 (2.8%) transferred out, 103 (0.7%) treatment failure 30 (0.2%) multidrug resistance and 1074 (7.3%) deaths. It was also established that during the last three months of treatment, being a female (aHR 0.83 (95%CI 0.70–0.97)) was negatively associated with poor treatment outcomes. While in the same last three months of treatment completion, being of an elderly age ≥50 years (aHR 1.26, a TB retreatment patient (aHR 1.57, were positively associated with poor treatment outcomes (Katana et al, 2022).

Another study in Kenya showed effect of type of TB diagnostic method used on TB treatment outcomes, meaning analysing patient clinical outcomes while comparing the method of diagnosis. The median age for the 12 856 patients enrolled was 37 [IQR 28 − 50] years. Males comprised the majority i.e. 7 639 (59%), while 11 339 (88%) were

pulmonary TB cases and HIV positivity was 3791 (29%). From the 6472 (50%) clinically diagnosed patients, 4 521/6 472 (70%) of them had a negative sputum or XMTB/R test. Comparing method of TB diagnosis namely clinically and bacteriologically diagnosed patients, there were no significant differences in defaulting or transfer out. The treatment outcome of death was significantly higher among clinically diagnosed patients: 639 (9.9%) deaths compared to 285 (4.5%) amongst the bacteriologically diagnosed patients; aHR 5.16 (Abdullahi et al, 2021).

A mathematical model evaluated potential health and economic consequences of implementing XMTB/R in five southern African countries; Botswana, Lesotho, Namibia, South Africa, and Swaziland, where drug resistance and TB/HIV co-infection are prevalent. A mathematical model comes in various forms be they physical or biological. It is a form of analysis or computation where computers are fed known variables to come up with the relationship between the variables. It may be used as a subject of operational research (Harvey et al, 2020).The mathematical model projected that implementation of XMTB/R would avert 132 000 TB cases and 182 000 (97 000–302 000) TB deaths in southern Africa over the first 10 years following introduction, and would reduce prevalence by 28% (14%–40%) by 2022, with more modest reductions in incidence (Menzies et al, 2012).

A study in Cape Town found a decrease in clinically diagnosed TB from 23% (2 445/10 643) to 11% (1 149/10 089) for HIV negative and from 42% (4 229/9 985) to 27% (2 364/8 823) for HIV positive patients. In a study carried out in South Africa the notification of clinically diagnosed TB did not increase -3%. In a study carried out in Cape Town, it was found that the reason for TB treatment commencement changed from a positive smear microscopy in 67% and 21% HIV negative and HIV positive patients respectively to MTB detected in 84 % and 67% in HIV negative and HIV

positive patients respectively (Hermans et al, 2017). Lisboa et al., (2019) in a study carried out in Beira, found that delay in detection and treatment of more than one month was associated with increased mortality(adjusted OR=12.4. In a study carried out in Zambia the TB treatment outcomes established were; death 5.5%, lost to follow up 2.9%, and 3.2% treatment failure (Mutembo et al, 2019). In a study carried out in Ghana TB patients who were HIV positive had lower successful TB treatment outcomes than HIV negative 70% (83/107) compared to 91.2% (382/419) respectively. In the same study, 21.5% (23/107) HIV positive TB patients died compared to 5.5 % (23/419) for HIV negative TB patients (Ogyiri et al, 2019).

Zimbabwe experienced 8300 deaths associated with TB. Mupfumi et al., in 2014 found a non-significant decrease in mortality on drug resistant TB patients using centralized Gene Xpert analyser, 6% and 10% respectively.

2.4.5 Exploration of geo-spatial mapping capacity as XMTB/R primary diagnostic algorithm rolled out

In a geo-spatial mapping study carried out in Si SaKet province Thailand, it was noted that populations from areas of lower altitude had more TB cases than populations from areas of higher altitude. The relationship between altitude and MTB bacilli ability to multiply is that that the biological effect of the high oxygen tension in low altitudes supports the multiplication of TB in the lungs (Hassarangsee et al, 2015). Hassarangsee et al., (2015) found that significantly high rate clusters were in Mueang Si SaKet district and Khukhan district, which are located in the North Western part of the province, while significantly low rate clusters were persistent in two districts located at the South Eastern area.

In a geo-spatial mapping study carried out in Ethiopia findings were that the most likely cluster of sputum smear TB positive were in 192 clinics in eight districts (Relative Risk of 2, p value <0.001), with 12 155 observed and 8 668 expected cases. In the same study, the space time analysis also picked the most likely cluster in 193 clinics in the same eight districts (Relative Risk of 1.9, p value <0.001), with 7 584 observed and 4 738 expected cases in 2003-2012 (Dangisso et al, 2015).

As XMTB/R primary diagnostic algorithm rolled out, the capacity to generate spatial mapping, in Manicaland, Zimbabwe, increased. GxAlert/Aspect were an added advantage to enable remote downloads. Geo-spatial mapping became critical in order to enhance rationale use of the limited TB resources and interventions. Knowledge of the geo-spatial mapping showing which health facilities had the various XMTB/R results, would provide contextual evidence, to decision makers.

2.4.6 Production of frozen sputum quality control sputum specimen as XMTB/R primary diagnostic algorithm rolled out

Chakravorty et al., (2017) reported in their findings that XMTB/R Ultra performed better than XMTB/R Version 4 on sputum spiked with known quantity of MTB strain. Bisogninet al., (2018) found that after freezing sputum for four years, some XMTB/R Version 4 negative sputum tested XMTB/R Ultra positive. This could be due to the already stated higher limit of detection of XMTB/R Version 4 over XMTB/R Ultra tests in detecting MTB. Limit of detection is 112.6 cfu/ml, and 15.6 cfu/ml, for XMTB/R Version 4 and XMTB/R Ultra respectively, plus XMTB/R Ultra has the additional semi quantitative result of MTB detected trace.

As XMTB/R primary diagnostic algorithm rolled out, another problem reared its head. The problem was that of more Gene Xpert machine module replacement and the

related quality management system requirements for post module change method verification. Literature search was undertaken to look into the possible production of what quality control sputum specimen to use as reference specimen in the carrying out of the increased number of method verifications. The question of what to do to produce a frozen sputum quality control sputum specimen as XMTB/R primary diagnostic algorithm rolled out, became pertinent. The selected way forward was analysis of concordance of same panel of frozen sputum specimen, tested using XMTB/R Version 4 and XMTB/R Ultra. The key being to use frozen sputum to save on cost of Gene Xpert post module change method verification.

2.4.7 Decisive Literature Findings

Literature review noted recommendations for future XMTB/R research were as follows; need impact studies on patients outcomes, time to treatment initiation, impact on case detection, impact on case management (Varaine et al, 2012) (Ardizzoni, et al.2015). Having gone through literature search, one of the gaps identified in 2009, which according to the literature available had not been addressed was investigating XMTB/R primary diagnostic algorithm roll out, in Manicaland Zimbabwe. This study tackled that, thus addressing two of the recommendations made after the study undertaken by MSF using Murambinda XMTB/R April 2011 to December 2012 data (Varaine et al, 2012) (Ardizzoni et al, 2015).

2.5 Summary

In the chapter conceptual framework on findings by researchers was presented including the application. Most studies reviewed also agreed on the influence of XMTB/R primary diagnostic algorithm roll out. Literature on analysis performance of

TB treatment outcomes as XMTB/R primary diagnostic algorithm rolled out, showed the many determinants of TB treatment outcomes such as; sex, age, HIV status, method used for diagnosis, time taken to TB treatment commencement, comorbidities. The studies had a general consensus on the various factors that contribute to the successful treatment outcome of cure, as well as the unsuccessful treatment outcome of death. All the studies reviewed showed that death from TB could be prevented. Prevention occurs when National TB Programs ensure patients are bacteriologically rather than clinically diagnosed. Literature established that roll out of XMTB/R as a primary diagnostic algorithm resulted in an increase in proportion of TB detection that was bacteriologically confirmed. Synthesis of literature helped to further resolve and understand the stated problem of this study, showing studies carried out outside Zimbabwe.

All the studies on geo-spatial mapping showed that the distribution of TB in any country or locality was heterogeneous, thus highlighting the need for increased capacity of local geo-spatial mapping, to enhance appropriate management interventions of high TB cluster and low TB cluster health facilities. The literature on production of quality control frozen sputum specimen as XMTB/R primary diagnostic algorithm rolled out, was lean due to the fact that, on further review the methodology used by various studies was different from that used in this study. Literature review also helped this study to use evidence generated by looking at findings from other countries, so that this study maintained relevance.

Literature on XMTB/R primary diagnostic algorithm roll out, in Manicaland, Zimbabwe was limited. It suggests that recommendations made in a XMTB/R targeted diagnostic algorithm project research in 2011, had not yet been investigated. The evidence from other researches, showed that there was a research gap in Zimbabwe

and implications for future research. However, documentation showed analysis of XMTB/R primary diagnostic algorithm roll out, in Zimbabwe was non-existent, prompting the need for this research. The next chapter, 3 focuses on the research methodology.

CHAPTER 3 METHODOLOGY

3.1 Introduction

This chapter looks at the several aspects on how the study was conducted. The chapter highlights the thought process that went into selection of the research design. There was a thought process that was taken to figure out which research design to employ. Selecting the right study design was key in making research findings more credible, valid, and coherent. The methodology had to be adequately detailed to enable reproducibility, by any researcher who might want to recreate and build on the research. Analysis of XMTB/R primary diagnostic algorithm roll out needed to be undertaken in the study setting of Manicaland. The study population, that was selected is clearly defined. The sampling technique employed to address all the chosen gaps is given in detail. The data collection instruments and data collection procedure that was employed to answer the research questions are elaborated. Ethical consideration is clearly spelt out and adhered to.

3.2 Research Design

The study employed a retrospective analytical observational study design. Research is a systematic gathering of new information and it can be likened to carrying out a scientific investigation. The driving force for a research is an identified problem or gap. A research is undertaken in order to address the identified knowledge gap. A research is guided by a research design. The research design was a strategy employed to integrate the different components of the study in a logical way. This ensured the research problem was effectively addressed. The research design constituted a clearly defined blueprint for the collection, measurement, and analysis of data.

Research designs can be broadly divided into two, that is descriptive or analytical. Analytical research was chosen because it involved evaluation of data that was already available. It started with a hypothesis on the possible relationship between variables, then the analytical research was undertaken to either confirm or dispute the hypothesis (Kothari, 2014). There are two types of analytical research designs. The first one was the one that was chosen for this study, i.e. analytical observational and the second one is analytical experimental or analytical intervention research design. Analytical study designs can be either experimental or observational. In analytical experimental studies, researchers manipulate something in the population of interest and investigate its effects. Analytical experimental research designs are used to establish a causal link between two variables. This study employed analytical observational, where researchers observed XMTB/R primary diagnostic algorithm roll out, without manipulating anything. The analytical observational research design enable the investigation of disease determinants, whether related or independent.

The advantages of retrospective study design was that since the data was already in place, the research could be performed immediately. Retrospective study was less expensive than prospective. Retrospective study design was more effective and efficient for diseases such as TB that has a long latency period. The retrospective analytical observational research design enabled analysis of XMTB/R primary diagnostic algorithm roll out intervention without manipulating anything. The disadvantage was that because the data was already in existence, there was less control of exposure factors and potential confounders.

The retrospective analytical observational study design was chosen as most appropriate to answer the research questions. It also provided opportunity for data mining of routinely collected TB program data, which was embedded in current TB

program setting. Retrospective analytical observational study design was also chosen, as economically feasible.

For the production of economical quality control sputum specimen as XMTB/R primary diagnostic algorithm rolled out, XMTB/R Version 4 and XMTB/R Ultra comparison nested study design, both retrospective analytical and prospective analytical design applied. There was the XMTB/R Version 4 tests carried out before freezing of sputum were used as retrospective analytical results. The XMTB/R Ultra test carried out in September 2018 on the frozen sputum were the prospective analytical results. These were chosen as most appropriate to answer the research question; was there any established economical quality control sputum specimen as XMTB/R primary diagnostic algorithm rolled out? In search of the economical quality control sputum specimen, there was analysis of concordance between XMTB/R Version 4 and XMTB/R Ultra plus the effect of freezing sputum on XMTB/R Ultra.

3.3 Population and Sampling

The study area was Manicaland Province (Figure 3), located on the eastern part of Zimbabwe. The province has a total area of 36 459 square kilometres. It is the second most populous province after Harare with a population total of 1.75 million (Census, 2012). It is the third most densely populated province after Harare and Bulawayo. According to the Zimbabwe District Health Information System, Manicaland province has a total of three hundred and four health facilities.

Gene Xpert sites are coloured squares; referring facilities are the coloured circles. Usually referring facilities, refer samples to the nearest Gene Xpert site with few exceptions due to administrative reasons. Administrative reasons included health facilities referring sputum to district hospital Gene Xpert sites, instead of Gene Xpert

sites in their proximity. The advantage being increased scope of services accessible to the health facility at district hospital, besides XMTB/R. The health facilities transport sputum for XMTB/R testing to the Gene Xpert sites using ministry vehicles and motor bikes. The same transport system that transports sputum for XMTB/R testing, also transports the XMTB/R results to the health facilities, thus enhancing adherence to established XMTB/R result turnaround times. Established sputum transportation schedules, ensured each health facility was visited at least once a week by transport system.

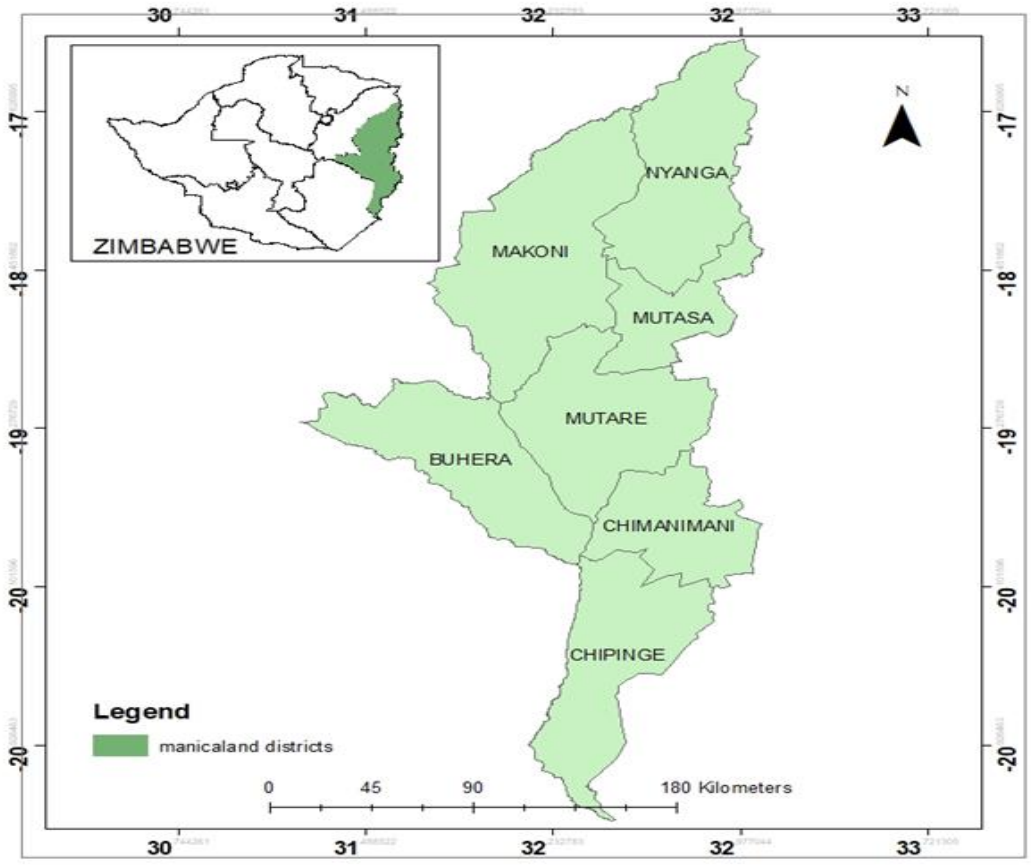


Figure 3: Map of districts in Manicaland province

The three hundred and four health facilities form clusters that were served by fifteen Gene Xpert testing sites. One of the fifteen Gene Xpert testing sites Rusape General Hospital had two Gene Xpert analyzers. That brought the total Gene Xpert machines

in Manicaland to sixteen. Mutasa district, Makoni district, Chimanimani district, Nyanga district, Buhera district, Chipinge district each has two machines and Mutare district has four machines. All Gene Xpert testing sites also offered smear microscopy. Smear microscopy was also performed at fifteen additional microscopy centres. All three hundred and four facilities despite level of operation, provided TB investigations and treatment. Any presumptive TB specimen was transported through integrated specimen transport system.

The study population was all XMTB/R results in all Gene Xpert machines, meaning total of sixteen machines, in Manicaland for the period 2017-2018. For analysis of the performance of TB treatment outcomes as XMTB/R primary diagnostic algorithm rolled out, the population was all the patients captured in the TB registers, who were commenced on TB treatment between 2017 and 2018. The participants for establishment of economical quality control sputum specimen as XMTB/R primary diagnostic algorithm rolled out study objective, belonged to the population of frozen sputum. The frozen sputum was from presumptive multi drug resistant TB patients previously analysed between 16th October 2012 and 23rd August 2013 during a study on presumptive multi drug resistant TB patients. The period stated was the data collection period of the previous study which had available frozen sputum.

3.3.1 Sample Size

Several research papers were read in an effort to decide on which proportion, in this case MTB positivity rate to use in calculation of sample size. Although Mozambique is a low income high TB burden country like Zimbabwe, the TB positivity of 30% established in its first XMTB/R test placement, was not selected for this study, as it was not generated in the similar study setting (Varaine et al, 2012). What also had to

be put in consideration was that selecting a low proportion would result in a small sample size (Shibemba et al, 2016). A small sample size has the challenge of introduction of type II error. Type II error is rejection of hypothesis when it is true. There were several similar studies in South Africa, but the proportion given could not be used, because although South Africa is a high burn country, it is not as low resourced as Zimbabwe, therefore the Namibia study was chosen, although sample size in this study was not pertinent, since there was 100% enrolment through census sampling.

The sample size was calculated using proportion, that is the established percentage of the characteristic of interest, in this case MTB positivity rate. In the Namibia study it was established that out of 1 842 presumptive TB patients who submitted sputum for XMTB/R, 594 (32.2%) were found to be positive by XMTB/R assay (Mavenyengwa et al, 2017). The Namibia study was chosen as it carried out a similar XMTB/R test in a resource limited African country near Zimbabwe. This study used a larger sample size of 36 056 instead of 683, so as to have more accurate and precise results, without any additional cost.

N=sample size

ME= $\boldsymbol{z}\sqrt{\dfrac{\boldsymbol{p}\ (\mathbf{1}-\boldsymbol{p})}{\boldsymbol{n}}}$

ME= 2, 5%

Z- Score at 95% CI is 1, 96

n=682.39

Sample size is 683 after rounding off to the nearest whole number, however this study enrolled 36 056 through census sampling.

3.3.2 Sampling Procedure

Complete enumeration or census sampling was employed to full fill all the objectives of the study, the justification for census sampling was that the population was manageable and it was cost effective. Census sampling meant enrolling all the participants that meet the inclusion criteria.

3.3.3 Data Sources

For triangulation various data sources were used to increase validity. The data sources were laboratory TB registers, Gene Xpert machine downloads, health facility TB registers and provincial TB external quality assurance reports, which were internal records of Ministry of Health and Child Care Nested study data sources were TB analysis results from MRCZ study number A/1 552 and results of XMTB/R Ultra, that were performed.

3.4 Data Collection Instruments

Paper based and electronic data capturing instruments were used. The health facility data collection form (Appendix 1) captured the data for the quarterly trend analysis of TB treatment outcomes as XMTB/R rolled out objective. This form consisted of a section that captured; health facility name, health facility longitude and latitude coordinates, year and quarter. Another section captured; enrolment number, date TB treatment commenced, sex, age, HIV status, pulmonary TB or extra pulmonary TB, village, XMTB/R result if any, smear microscopy result if any and TB treatment outcome.

Electronic data collection for analysis of XMTB/R primary diagnostic algorithm roll out and MTB detection objective (Appendix 2). The instrument was a continuation of the machine generated XMTB/R results excel. It captured; enrolment number, sex,

age, HIV status, requesting facility, date sputum collected, date sputum received in the laboratory, date and time of test, XMTB/R diagnostic algorithm used (either XMTB/R targeted algorithm or XMTB/R primary diagnostic algorithm), MTB semi quantitative result, rifampicin resistance status and if the result was unsuccessful it was recorded as either no result, invalid or error.

The data collection tool for the establishment of economical quality control sputum specimen as XMTB/R primary diagnostic algorithm rolled out objective built up on the dataset for previous study. Nested study data collection tool were TB analysis results from MRCZ study number A/1 552 and results of XMTB/R Ultra, that were performed in study A/2 385. It captured enrolment number, XMTB/R Version 4 result, XMTB/R Ultra result, smear microscopy result, Lowensten Jensen result and mycobacterium growth indicator tube result.

3.5 Pre-test of Data Collection Tools

Pre-test was conducted at Marange Rural Hospital to test the data collection tools for reliability plus validity. Marange presumptive TB register, XMTB/R results downloads, laboratory TB registers, health facility TB registers, external quality assurance TB quarterly reports were test run to enrol five participants using the data collection tools. Adjustments were made where necessary, before the study data collection commenced.

3.6 Data Collection Procedure

3.6.1 Evaluation of effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance, in Manicaland, for 2017-2018, on MTB detection

XMTB/R results for the period from 1st January 2017 to 31st December 2018 was downloaded directly from all the Gene Xpert machines, onto compact disc. Once the raw data was on compact discs, the column of the excel sheet that captured the names were deleted, as part of ethical conduct to anonymised those enrolled. There after the unique identifier used for the study was the enrolment number assigned to each test captured for the study. Additional data for each of the processed samples were extracted from the TB laboratory registers. Direct data downloads for some Gene Xpert testing sites were not available for certain time periods due to hardware problems, software failures and limited back up. For purposes of data management of XMTB/R results. Monthly maintenance as stated by Cepheid Training module of 2013, requires archive once every month to compact disc. Data were extracted from provincial TB external quality assurance reports to allow assessment of the change in i) number of tests performed by XMTB/R and smear microscopy ii) the number of TB diagnoses made iii) the number of rifampicin resistant TB diagnoses and iv) the proportion of samples with error, invalid and no results over time. The errors could be due to instrument, cartridge or handling errors, the examples include the instrument failing to reach a certain temperature, cartridges not being airtight or bubbles introduced during sample preparation. Results are categorised as invalid if the internal control failed indicating polymerase chain reaction inhibition due to blood, food participles or pus. Tests that are terminated due to interrupted power supply, software failure or manual abortion of a run are categorised as “no result”.

3.6.2 Analysis of effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance in Manicaland, Zimbabwe, 2017-2018, on laboratory turnaround time

Data collection procedure employed was downloading excel sheets of XMTB/R results, then adding on extra columns to capture date and time of sputum collection, date and time sputum specimen was received at the laboratory and date and time the XMTB/R results were issued . The date and time information, was collected from the paper based laboratory TB register.

3.6.3 Determination of performance of TB treatment outcomes as XMTB/R primary diagnostic algorithm rolled out in Manicaland, for 2017-2018

The data collection period was October to December 2019, when the principal investigator and two data collectors travelled around Manicaland health facilities. The two data collectors had previously attended a meeting where the study mentor trained them on data collection for the study. Patient demographic and clinical data were extracted from the health facility TB register, individual patient clinical notes and the district TB register. The demographic factors captured included; sex, age, HIV status. Other diagnostic factors such as; sputum smear results, pulmonary or EPTB disease, XMTB/R results as well as the XMTB/R algorithm in use, were captured as potential risk factors to TB treatment outcomes. A data collection manual was shared by the principal investigator which indicated the source of variables and explained standard procedure to be followed while each variable was captured.

3.6.4 Exploration of geo-spatial mapping capacity as XMTB/R primary diagnostic algorithm rolled out in Manicaland, for 2017-2018

Download of excel from the Gene Xpert machine was carried out and the excel data was filtered for MTB detected results. From the initial excel with 43 809 successful and unsuccessful results, there were 2 221 MTB detected results. The principal investigator collated longitude and latitude coordinates information from requesting

health facilities of the 2 221 MTB detected XMTB/R results onto electronic data collection tool. Geographic information system data of the health facilities were recorded. For the study the unit used for recording coordinates was the requesting facility. One Gene Xpert site lost its electronic records when the Gene Xpert central processing unit crushed, without having followed the good laboratory practice stated by Cepheid, of monthly archive onto compact disc. The principal investigator gave the District TB and Leprosy Coordinators opportunity to crosscheck source registers and validate ten percent of the compiled data, in their respective districts.

3.6.5 Production of frozen sputum quality control specimen as XMTB/R primary diagnostic algorithm rolled out

De-identified frozen sputum stored at Biomedical Research and Training Institute in Harare were enrolled. The storage period was seven years. The storage was in temperature monitored freezers. The de-identified frozen sputum had been collected from 16th October 2012 to 23rd August 2013 during a study on presumptive multi drug resistant TB patients. The principal investigator on 25th September 2019 analysed the specimens using XMTB/R Ultra cartridges at Mutare Provincial Hospital. The frozen sputum were first thwarted to reach room temperature, before being mixed with sample processing buffer at a ratio of one to two. After ten minutes incubation at room temperature and a second mixing step followed by a further five minute incubation, analysis on XMTB/R Ultra was performed according to manufacturer's instructions (Appendix 2).

The excel sheet with data on MGIT results, smear microscopy results and XMTB/R Version 4 results from the primary study was availed by the principal investigator of the primary study. XMTB/R Ultra result was transcribed to the excel sheet containing

XMTB/R Version 4 results data from primary study. The rationale for choosing means of collecting data was that it was most appropriate as it built on the excel sheet generated in previous study and only added the other variables from XMTB/R Ultra results. One thing that could have been done differently were it not for insufficient volumes of frozen sputum, would have been to also repeat analysis using XMTB/R Version 4, to establish what effect storage had on XMTB/R Version 4 test.

Inclusion criteria: All the 2017 and 2018 XMTB/R results in the sixteen Gene Xpert analysers in Manicaland were included. All the patient details recorded for the period 2017 to 2018 in facility presumptive registers, facility TB registers, facility TB laboratory registers and the external quality assurance quarterly TB reports were included. The available frozen sputum being TB positive on at least one of the previously run panel of tests in study with ref MRCZ A/1 552 were included.

3.7 Analysis and Organization of Data

A paper based as well as electronic based data collection system was used. Data capturing of the independent and dependent variables was done on a computer and access was restricted through a protected password to unauthorised users. Data were double entered, cleaned, and validated before data analysis was performed using Stata 16.0 and R v 4.0.3, that is the R Foundation for statistical computing. Data were coded as consecutive quarterly time periods, for example 1st January 2017 to 31st March 2017 was coded quarter one and 1st October 2018 to 31st December 2018 was coded as quarter eight.

The statistical comparison of the outcome of interest e.g. early detection or morbidity per quarter. While targeted XMTB/R algorithm was in use before roll out of XMTB/R primary diagnostic algorithm. Univariate analysis was used to generate frequency

tables, mean and mode. Bivariate analysis was carried out. Both simple and multiple linear regression analyses were used to assess the relationships between roll out of XMTB/R primary diagnostic algorithm and explanatory variables. Any factors associated at a p value of <0.01 were used to build multivariate logistic regression model to pick significant factors which contributed more MTB detection. Measures of association were calculated using linear regression analysis to ascertain the relationship that exist between the dependent variables and single independent variables. Factors associated with XMTB/R primary diagnostic roll out were determined and stratified for possible confounders, such as age or gender or HIV status. Proportion of bacteriologically confirmed TB were stratified by gender or HIV status.

The change in patient characteristics, MTB positivity rate and rifampicin resistance as well as percentage retention of electronic XMTB/R results were analysed by quarter. The assumption was that data lost due to hard and software failures were missing completely at random and hence proportions, medians and interquartile ranges were calculated using a complete case analysis approach. The data extracted from external quality assurance quarterly TB reports were presented as total counts stratified by quarter to investigate trends. Descriptive statistics were computed using STATA/IC version 16 to describe demographics and other independent variables. The frequencies and means for demographics were generated. P values of <0.05 were considered statistically significant at 95% confidence level, using z score of 1.96. Chi-square test was used to test for associations between variables at 5% level of significance. Chi-square test was used to compare categorical or grouped variables. That is to establish if there was association between exposure variables and the outcome variables of qualitative variables and of quantitative discreet grouped variables. For example

exposure variable was gender while outcome variable was HIV status of all presumptive TB patients. Data presentation included displaying as maps, graphs, tables and figures.

For analysis of geospatial mapping capacity, MTB data produced a categorical variable of; MTB detected high, MTB detected medium, MTB detected low MTB detected very low, MTB detected trace. Getis-Ord (Gi*) was applied on MTB detected data to detect MTB hotspots in categories across Manicaland province. The Getis-Ord (Gi*) statistic assesses the extent to which events such as MTB detected data exhibit identifiable spatial patterns in space as hotspots and cold spots (Getis et al. 1992). Hotspots occur when areas with high values are surrounded by high MTB values while cold spots are locations with typically low values surrounded by similarly low values, from a given location at spatially varying distances. The optimised hotspot analysis function in Arc Map 10.5 was used to implement the Gi* statistic. The selection of the optimised hotspot analysis was based on its ability to correct for multiple testing as well as spatial dependence (Getis et al. 1992). The z scores and p values measure statistical significance, influencing the decision whether to reject or fail to reject the null hypothesis. The Getis Ord (Gi*) has the form.

$$G_i^* = \frac{\sum_{j=1}^{n} w_{i,j}x_j - X\sum_{j=1}^{n} w_{i,j}}{s\sqrt{\frac{[n\sum_{j=1}^{n} w_{i,x}^2 - (\sum_{j=1}^{n} w_{i,j})]}{n-1}}}$$

Where $x_i$the attribute value for value j, *wij* is the spatial weight between feature*i* and *j*, *n* is the number of features.

$$X = \frac{\sum_{j=1}^{n} x_j}{n}$$

$$S = \sqrt{\frac{\sum_{j=1}^{n} x_j^2}{n} - (X)^2}$$

A high z score and small p value for a feature indicates a spatial clustering of high values. A low negative z score and small p value indicates a spatial clustering of low values. The higher (or lower) the z score, the more intense the clustering. A z score near zero indicates no apparent spatial clustering (Getis et al, 1992).

3.8 Ethical Consideration

The research was a desk review using secondary data sources, so there was no need to seek informed consent. Permission to carry out the research was sought from the Manicaland Provincial Medical Directorate of the Ministry of Health and Child Care. Ethical approval to carry out the study was sought from Africa University Research Ethics Committee (Appendix 12) and from MRCZ Ref A/2 385(Appendix 14). For Xpert MTB/Rif Ultra comparison, informed consent form used in study MRCZ A/1 552 covered the study as a sub study. Completed data instruments were kept under lock and key, separate from lists showing numbers assigned to names. Electronic data was protected by use of passwords. Disposal of paper based data when study was through was through incineration, which ensured confidentiality was adhered to.

3.9 Summary

Chapter 3 considered the research design, study setting, the population, the sampling technique employed, data collection instruments and data collection procedure. The chapter explained why a retrospective analytical observational study design was chosen as most appropriate study design. The chapter showed a map of the province where the study was undertaken. The chapter highlighted that prior to commencement of data collection, the data collection tools were pre tested in at a health facility of similar design. After pre-test exercise, the changes that were deemed necessary were made, before printing the paper based data collection tools. Similar changes were made

before adapting final version of electronic data collection tools. The chapter gave details of the data collection procedures utilised in order to meet each of the specific objectives of the study. The chapter explained how validity was upheld through triangulation of data. The chapter ended by highlighting that the study was approved by different regulatory and ethical bodies to ensure scientific and ethical integrity of data. The next chapter, 4 focuses on data presentation, analysis and interpretation.

CHAPTER 4 DATA PRESENTATION, ANALYSIS, AND INTERPRETATION

4.1 Introduction

This chapter highlights the data presentation, followed by the data analysis and interpretation. It showed the data analyses that were performed and presents the results as tables and figures in sections arranged according to the specific objectives. The sections were; evaluation of XMTB/R primary diagnostic algorithm roll out and MTB detection, analysis of XMTB/R primary diagnostic algorithm roll out and laboratory turnaround time, determination of the performance of TB treatment outcomes as XMTB/R primary diagnostic algorithm rolled out in Manicaland, for 2017-2018, exploration of geo-spatial mapping capacity as XMTB/R primary diagnostic algorithm rolled out in Manicaland, production of frozen sputum quality control specimen as XMTB/R primary diagnostic algorithm rolled out. The findings address demographic characteristics of XMTB/R results enrolled in the study during the period when targeted XMTB/R algorithm, as well as for those enrolled during the use of XMTB/R primary diagnostic algorithm roll out at each of the fifteen testing sites. The findings address the study objectives; evaluation of XMTB/R primary diagnostic algorithm roll out and MTB detection in Manicaland, analysis of XMTB/R primary diagnostic algorithm roll out and laboratory turnaround time, determination of the performance of TB treatment outcomes as XMTB/R primary diagnostic algorithm rolled out in Manicaland, exploration of geo-spatial mapping capacity as XMTB/R primary diagnostic algorithm rolled out in Manicaland, production of frozen sputum quality control specimen as XMTB/R primary diagnostic algorithm rolled out.

4.2 Data Presentation and Analysis

4.2.1 Evaluation of effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance, in Manicaland, for 2017-2018, on MTB detection

The results of the study are that, the total number of XMTB/R results, that were downloaded from Gene Xpert machines was 43 809. Out of the 43 809 XMTB/R results, 36 056/43 809 (82.3%) were successful XMTB/R results. The other 7 753/43 809 (17.7%), were unsuccessful XMTB/R results. The mean age of the patients whose XMTB/R results were enrolled, was forty two years.

Table 5 showed a positivity of 6.2% for the MTB test results generated from the sixteen Gene Xpert machines in Manicaland province, Zimbabwe. The figure of 6.2% was reached by adding all MTB positive i.e. 19+432+592+715+464, divided total of all successful XMTB/R results i.e. 36 056 multiplied by 100. The MTB semi quantitative results except MTB detected trace, all ranged between 1-2%

Table 6: Frequencies of MTB semi-quantitative results

MTB Result	Frequency	Percentage
Not Detected	33 834	93.8
High	464	1.3
Medium	715	2.0
Low	592	1.6
Very Low	432	1.2
Trace	19	0.1

Table 6 showed results of bivariate analysis. The bivariate analysis is MTB result versus HIV status and MTB result versus gender. Of those that had MTB detected, 1

070 (3.0%) of overall tests were HIV negative and 914 (2.5%) of overall tests were HIV positive. Stratification of MTB result versus HIV status showed frequencies of TB/HIV co-infection. Since the variables of HIV status and gender were collected, it meant we had controlled for them or had adjusted for the collected variables. Table 6 also show that of the 36 056, 15 826 (43.9%) were males, 19 792 (54.9%) females and 438(1.2%) had missing gender record, but of those diagnosed as having MTB detected, males were more than females, 1 127/36 056 (3.1%) and 833/36 056 (2.3%) respectively. Of those with MTB detected high, males comprised 24 0/36 056 (0.7%) versus females 217/36 056 (0.6%).

Table 7: MTB results stratified by HIV status and gender

	HIV Status (%)			**Gender (%)**		
MTB Result	**Negative**	**Positive**	**Missing**	**Male**	**Female**	**Missing**
Not Detected	17 477(48.5)	11 759(32.6)	4 598(12.8)	14 689(40.7)	18 737(52.0)	408(1.1)
High	251(0.7)	168(0.5)	45(0.1)	240(0.7)	217(0.6)	7(0.02)
Medium	353(1.0)	279(0.8)	83(0.2)	375(1.0)	329(0,9)	11(0.03)
Low	264(0.7)	272(0.8)	56(0.2)	303(0.8)	279(0.8)	10(0.0)
Very Low	191(0.5)	192(0.5)	49(0.1)	209(0.6)	222(0.6)	1(0.0)
Trace	11(0.0)	3(0.0)	5(0.0)	10(0.0)	8(0.0)	1(0.0)

Table 7 show that 5 769/36 056 (16.0 %) were analysed using XMTB/R targeted screening algorithm versus 30 286/36 056 (84.0%) analysed using XMTB/R primary diagnostic algorithm. MTB detected picked using XMTB/R targeted screening algorithm was 430/36 056 (1.2 %) versus 1 791/ 36 056 (5.0%) MTB detected using XMTB/R primary diagnostic algorithm.

Table 8: Evaluation of XMTB/R primary diagnostic algorithm roll out and MTB detection in Manicaland, for 2017-2018

	Algorithm (%)	
MTB Result	**XMTB/R targeted screening algorithm**	**XMTB/R primary diagnostic algorithm**
Not Detected	5 339(14.8)	28 495(79,0)
High	103(0.3)	361(1.0)
Medium	146(0.4)	569(1.6)
Low	104(0.4)	488(1.4)
Very Low	77(0.2)	355(1.0)
Trace	0	18(0.1)

In table 8 the total number of samples tested with XMTB/R in 2017-2018 was 43 809, of which 7 865/43 809 (18.0%) and 35 944/ 43 809 (82.0%) used the XMTB/R targeted screening algorithm and XMTB/R primary diagnostic algorithm respectively. The targeted XMTB/R screening algorithm was phased out during 2017; by fifth quarter (January-March 2018) the whole province had adopted the primary diagnostic algorithm. In addition, 15 719 samples were investigated using smear microscopy. Smear microscopy made up almost half of the investigations in first and second quarter (January-June 2017), but the number decreased as XMTB/R testing increased. Table 8 also show that all quarters over the two year period had various proportions of XMTB/R results deleted from all sixteen Gene Xpert machines, after generation of external quality assurance reports. All the sixteen Gene Xpert machines in Manicaland had retained various percentages of electronic XMTB/R results, with Marange Rural Hospital machine having retained the highest percentage of 96.9%, while Birchenough Bridge Rural Hospital machine retained 0% of the electronic XMTB/R results for the

period 2017 to 2018. The average percentage for XMTB/R results retained in the sixteen Gene Xpert machines in Manicaland for the period from 1st January 2017 to December 31st 2018 was 76.6 %.

None of the Gene Xpert sites in Manicaland could avail the monthly archived compact disc electronic XMTB/R results. The electronic XMTB/R results were all accessed on Gene Xpert machine central processing unit. The data collection period was October to December 2019, meaning for fourth quarter 2018 the Gene Xpert machine data that was missing, was deleted within nine months of generation and for the first quarter of 2017, the 33.4% data deleted occurred anywhere from month one after collection of the TB external quality assurance data to month twenty-one when the study data collection period commenced. There was 56.5 % retention of electronic XMTB/R results for fourth quarter of 2018, yet the data collection period occurred from October 2019, just nine months later.The highest retention was in quarter one 2018 with 93.9% retention. The average percentage of XMTB/R results lost in the sixteen machines in Manicaland province, for the period from 1st January 2017 to December 31st 2018 was 23.4%.

In 2017 and 2018, two hundred and sixty six of the three hundred and four health facilities in Manicaland submitted samples for XMTB/R analysis. Median number of referred samples from peripheral health facilities for XMTB/R testing in fifth quarter when all health facilities had adopted the XMTB/R primary diagnostic algorithm was 34 (interquartile range [IQR]:10-85).

Despite the fact that the number of XMTB/R tests increased over time, the number of bacteriologically confirmed TB diagnosis did not change significantly over the two years (Table 8). Overall provincial rifampicin resistant positivity was 111/2 221(5.00%). Table 8 there were fluctuations in the number of rifampicin resistance

diagnoses with the highest numbers diagnosed in the third quarter (10.5%) and eighth quarter (9.1%). XMTB/R targeted screening algorithm phased out during 2017 and by fifth quarter (January-March 2018) the whole province had adopted the XMTB/R primary diagnostic algorithm

More detailed data was available for 36 056/43 809 (82.3%) samples (Table 8).The proportion of available data, compared to data from the external quality assurance reports, ranged from 56.5% to 93.9%. The reasons for missing data were mainly due to inadvertent deletion of data before archive process, hardware failure, software failure and unavailability of external hard drives for data backup. Roll out of the XMTB/R primary diagnostic algorithm from 5% in first quarter to 100% in fifth quarter did not affect the proportion of samples sent from peripheral and central sites. In addition, age and sex distributions did not change over time. However, the proportion of samples submitted from HIV negative individuals increased from 40.3% in first quarter to 54.2% in fifth quarter.

The MTB positivity rate among samples submitted ranged from 4.8-8.3%. Higher MTB positivity rate was observed in the first four quarters compared to last four quarters. Bacterial burden as classified by the XMTB/R (high, medium, low, very low) varied over time without a clear pattern. The median days between a sample being submitted and received at the Gene Xpert sites was one day in first, third, fourth and fifth quarters while it was two days in second, sixth, seventh and eighth quarters.

Table 9a: Evaluation of XMTB/R primary diagnostic algorithm roll out and MTB detection in Manicaland, for 2017-2018

Variables	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Proportion of all tests performed based on TB EQA data	2643 (66.6 %)	2804 (61.6 %)	4032 (70.8 %)	4672 (79.1 %)	5498 (93.9 %)	6426 (86.1 %)	6019 (77.1 %)	3961 (56.5 %)
Algorithm								
XMTB/R targeted screening	95	46.1	22.7	10.2	0	0	0	0
XMTB/R primary diagnostic	5	53.9	77.3	89.8	100	100	100	100
Sex								
Male	45.4	43.9	44.4	46.8	41.4	43.4	44.8	42
Female	53.1	54.8	54.8	52.1	57.4	55.6	54	56.1
Missing	1.5	1.3	0.8	1.1	1.2	1	1.2	1.9
MTB positivity rate	8.3	7.4	6.4	7.3	6	5.7	4.8	5.3
Rifampicin Resistant MTB detected	2.7	3.9	10.5	5.5	3.6	2.5	3.8	9.1
High	28.2	16.9	26	19	20.8	23.6	14.8	17.8
Medium	31.3	41.1	27.9	32.6	30.5	28.8	32.4	37
Low	23.2	27	27.5	32.1	23	26.7	25.2	27.9
Very low	17.3	15	18.6	16.3	25.7	20.9	27.6	17.3
Transport time (days to laboratory – median (IQR))	1 (1; 3)	2 (1; 3)	1 (1; 3)	1 (1; 3)	1 (1; 2)	2 (1; 2)	2 (1; 3)	2 (1; 2)

Table 9b: Evaluation of XMTB/R primary diagnostic algorithm roll out and MTB detection in Manicaland, for 2017-2018

Variables	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Proportion of all tests performed based on TB EQA data	2643 (66.6 %)	2804 (61.6 %)	4032 (70.8 %)	4672 (79.1 %)	5498 (93.9 %)	6426 (86.1 %)	6019 (77.1 %)	3961 (56.5 %)
Algorithm								
XMTB/R targeted screening	95	46.1	22.7	10.2	0	0	0	0
XMTB/R primary diagnostic	5	53.9	77.3	89.8	100	100	100	100
Referral centre								
Peripheral	48	50.5	49.4	43.7	45.9	55.2	50.1	54.7
Central	52	49.5	50.6	50.7	54.1	44.8	49.9	45.3
HIV								
Negative	40.3	41.3	46.9	50.2	54.2	55.3	56.6	54.1
Positive	48.8	45.4	38.3	35.2	32.4	31.12	30.3	33.2
Unknown	10.9	13.3	14.8	14.6	13.4	13.54	13.1	12.7
Age								
<5	1.7	1.4	2	1.3	1.4	1.4	1.4	2.1
5-14.9	8.7	9.9	8.1	10.4	7.3	9.4	9.3	9.9
15-59.9	67.6	68.5	68	67.7	68.9	67.5	65.7	66.2
>60	22	20.2	21.9	20.6	22.4	21.7	23.6	21.8

Figure 4 below, depicts samples tested using XMTB/R primary diagnostic algorithm and those tested using XMTB/R targeted algorithm, in bar graphs positioned side by side. The number of samples tested per diagnostic algorithm showed the high portion negative MTB results. The XMTB/R primary diagnostic algorithm bar graphs have the highest number of samples. The targeted XMTB/R algorithm had the highest number of samples per quarter, the first two quarters of 2017. From the third quarter of 2017,

to the last quarter of 2018, the highest number of samples were being tested using XMTB/R primary diagnostic algorithm

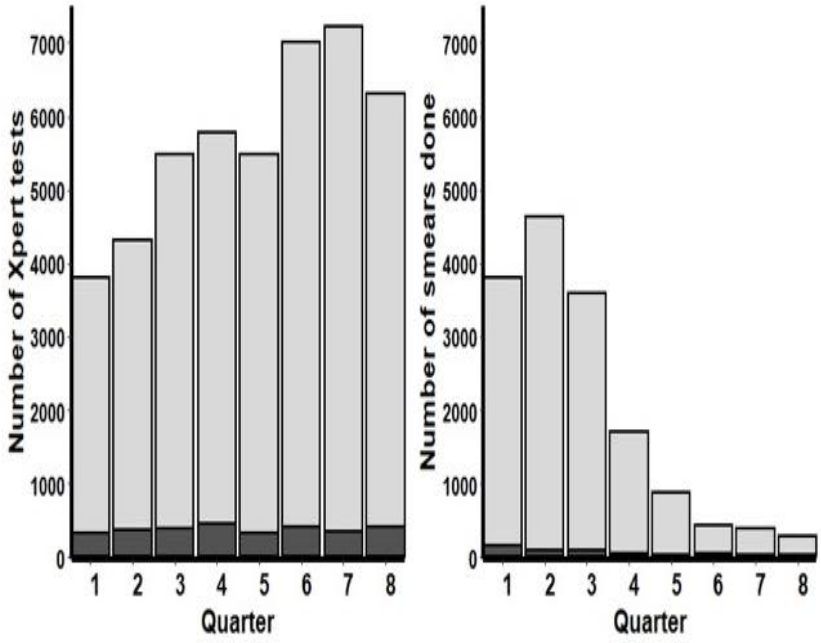


Figure 4: Number of samples tested for TB by quarter and diagnostic algorithm

Light grey: negative tests, dark grey: positive tests

Key for Quarter: 1: Quarter 1 of 2017, 2: Quarter 2 of 2017,3: Quarter 3 of 2017,4:Quarter 4 of 2017,5: Quarter 1 of 2018,6:Quarter 2 of 2018,7: Quarter 3 of 2018,8: Quarter 4 of 2018

The proportion of samples with "no result" varied greatly across Gene Xpert sites with a median of 1.5% (IQR 0.9-2.2%) (Figure 5). The proportion of samples with an invalid or error result ranged between 0.8-2.8% and 1.4-6.7%, respectively. All of the Gene Xpert machines where XMTB/R results were downloaded had some

unsuccessful results, meaning there was no Gene Xpert machine with 100% successful XMTB/R results.

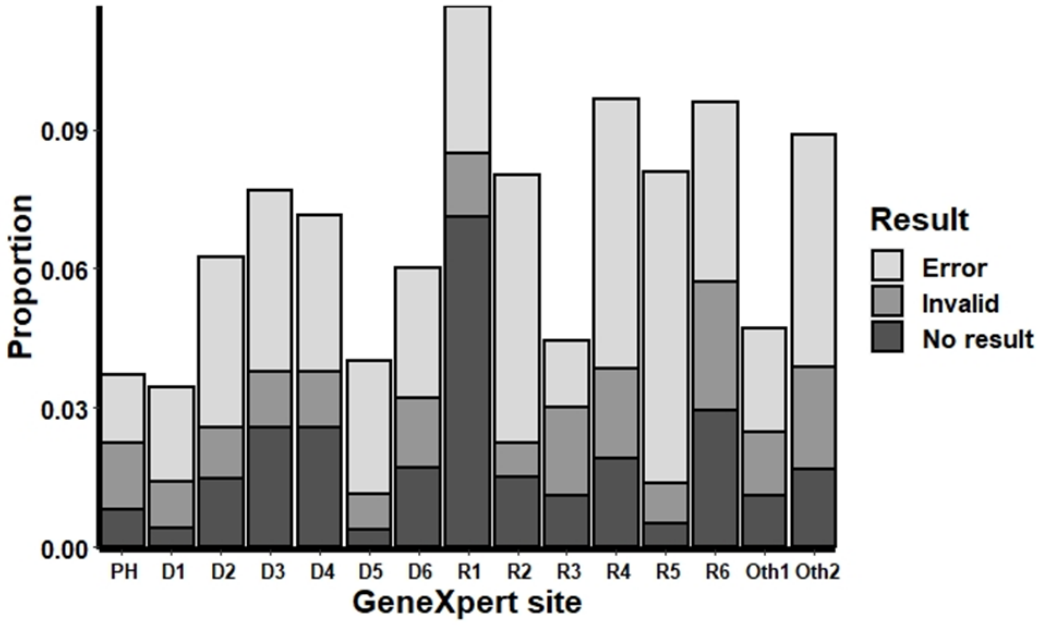


Figure 5: Proportion of samples with an invalid, error or no result by Gene Xpert site

Key: PH provincial hospital site; D1:D6 district hospital site; R1:R6 sites at rural hospitals and health centres; Oth1:Oth2 other sites (non-governmental organisation; urban council hospital).

4.2.2 Analysis of effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance in Manicaland, Zimbabwe, 2017-2018, on laboratory turnaround time

The mean number of days samples were sent to the testing facility was two days, and the mean laboratory turnaround time was 1.46 days.

a. Testing whether difference in days to laboratory was statistically significant

For targeted screening algorithm 2.5 days was the mean days taken from date specimen collected to date specimen was received at the Gene Xpert site. For XMTB/R primary diagnostic algorithm, 2.2 days was the mean days taken from date specimen collected to date specimen was received at the Gene Xpert site. For XMTB/R targeted screening algorithm and XMTB/R primary diagnostic algorithm, the standard deviation was 2.1 and 1.9 respectively. ANNOVA gave the p value of <0.001, which was way less than 0.05.

b. Testing whether difference in laboratory turnaround time was statistically significant

For XMTB/R targeted screening algorithm 1.7 days was the mean laboratory turnaround time and 1.4 days was the mean laboratory turnaround time for XMTB/R primary diagnostic algorithm. For targeted XMTB/R screening algorithm and XMTB/R primary diagnostic algorithm, the standard deviation was 0.4 and 0.8 respectively. ANNOVA gave the p value of <0.001, which was way less than 0.05.

4.2.3 Determination of the performance of TB treatment outcomes as XMTB/R primary diagnostic algorithm rolled out in Manicaland, for 2017-2018

Below are results of the evaluation of TB treatment outcomes as XMTB/R primary diagnostic algorithm rolled out in 2017 to 2018. The evaluation was per quarter, taking quarter one 2017 to quarter four 2017 as quarter 1 to quarter 4. For continuity of the quarters, the study assigned the four quarters of 2018, the numbers quarter 5 to quarter 8, starting from 2018 quarter one to 2018 quarter four.

TB treatment outcomes were one of the key performance indicators used in monitoring the TB program. The relevance of analysing TB treatment outcome for the period 2017 and 2018 was to get an overall picture of TB treatment outcomes as XMTB/R primary

diagnostic algorithm rolled out to 100%. Table 9 show the two most common TB treatment outcomes were cured 1 018/3 277 (31.1%) followed by treatment completed 1 008/3 277 (30.9%). The worst outcome which was died comprised 298/3 277(9.1%) that were captured in TB registers. There was missing outcomes data for 753/3 277(23.0%). Due to the inclusion of the proportion with missing TB treatment outcome results, the rates in table 9 were lower, than those from annual TB review report of 2017 and 2018.

Table 10: TB treatment outcomes

Outcome	Frequency	Percentage
Died	298	9.1
Treatment Failure	62	1.9
Loss to Follow Up	66	2.0
Transfer	62	1.9
Treatment completed	1 008	30.8
Cured	1 018	31.1
Not Evaluated	8	0.2
Other (e.g. stopped by doctor)	2	0.6
Missing	753	23.0

Table 10 shows the HIV status of the 3 277 patients treated for TB. 1 252/3 277(38.2%) were HIV negative. 1 676/3 277(51.1%) of the patients treated for TB were HIV positive, while 349/3 277(10.7%) had HIV status of unknown or missing field.

Table 11: Frequency of the HIV status

HIV Status	Frequency	Percentage
Negative	1 252	38.2
Positive	1 676	51.1

Unknown/Missing	349	10.7

Table 11 show method used for initial diagnosis versus the TB treatment outcome. 1 293/3 277(39.5%) field in the registers did not capture the reason for initiating TB treatment. Patients who had MTB not detected results were 286/3 277(8.7%) and these were initiated on TB treatment. Of the 8.7%, 159/286(55.56%) had outcome of treatment completed. Out of 1 509 patients who had MTB detected as the reason for starting TB treatment, 372/1 509 (24.7%), and 551/1 509 (36.5%) had treatment completed outcome and cured respectively.

Table 12: TB treatment by initial TB diagnosing method used

Outcome	MTB not detected	MTB: MTB detected	Mantoux	X-ray	MTB Gene Xpert not done	Clinically diagnosed TB	Other	Missing
Died	22	155	0	7	3	3	0	108
Treatment failure	8	21	0	0	0	0	0	33
Loss to follow up	9	22	0	1	5	1	0	28
Transfer	8	30	0	2	4	0	0	18
Treatment completed	159	372	3	26	36	20	1	391
Cured	39	551	0	17	10	3	1	397
Not evaluated	0	7	0	0	0	0	0	1
Other	0	1	0	0	0	0	0	1
Missing	41	350	5	20	11	9	1	316

Key for MTB: 0: MTB not detected, 1: MTB detected, 2: Mantoux, 3: X-ray, 4: Gene Xpert not done, 5: Clinically diagnosed TB, 6: Other, 7: Missing.

Key for Treatment Outcome: 1: Died, 2: Treatment failure, 3: Defaulted or loss to follow up, 4: Transfer, 5: Treatment completed, 6: Cured, 7:Not evaluated, 8:Other, 9: Missing

The table 12 shows that as the XMTB/R primary diagnostic algorithm rolled out from first quarter 2017 to fourth quarter 2018 the initial diagnosis based on MTB detected was increasing directly proportional to MTB from 49/281 (17.4%) to 332/534(62.2%). The proportion with reason for TB treatment as clinical diagnosis changed from first quarter 2017 to fourth quarter 2018 as follows 11/281 (3.9%) and 3/534 (0.6%). Testing for association p value of <0.001 showed there was a statistically significant association between initial TB diagnosing method used and XMTB/R primary diagnostic algorithm roll out as represented by quarters of the two years. Proportion of patients commenced on TB treatment as a result of MTB detected result increased. On the other hand the proportion of patients commenced on TB treatment despite a MTB not detected result oscillated. Pearson chi 2(49) = 376.0453 Pr = <0.00

Table 13: Initial TB diagnosing method used by quarter

	QUARTER							
MTB	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Not detected	24	20	14	26	44	67	49	42
Detected	49	84	113	131	277	291	232	332
Mantoux	0	1	1	0	4	0	1	1
Xray	4	8	9	8	19	8	10	10
Gene Xpert not done	5	7	4	4	7	19	13	13
Clinically diagnosed	11	3	3	2	8	5	1	1
Other	1	0	0	0	1	0	0	0
Missing	187	171	160	174	208	148	107	107

Key for Quarter: 1: Quarter 1 of 2017, 2: Quarter 2 of 2017, 3: Quarter 3 of 2017, 4: Quarter 4 of 2017, 5: Quarter 1 of 2018, 6: Quarter 2 of 2018, 7: Quarter 3 of 2018, 8: Quarter 4 of 2018

Table 13 shows that 224/1 676(13.4%) HIV positive had EPTB while 148/1 252(11.8%) HIV negative had EPTB, showing HIV negative were less likely to have EPTB.

Table 14: HIV status versus type of TB

	Type of TB		
HIV Status	Pulmonary TB	EPTB	Missing
Negative	1 080	148	24
Positive	1 410	224	42
Unknown/Missing	312	20	17

Table 14 show that whereas the TB treatment outcome with the highest proportion was cured 931/3 277(28.4%) for PTB. For EPTB the TB treatment outcome with the highest proportion was treatment completed 179/3 277(5.5%).

Table 15: TB treatment outcome by type of TB

	Type of TB (N=3 277)		
Outcome	**Pulmonary TB**	**EPTB**	**Missing**
Died	250 (7.6%)	42(1.3%)	6(0.2%)
Treatment failure	57(1.7%)	3(0.1%)	2(0.1%)
Loss to follow up	49(1.5%)	14(0.4%)	3(0.1%)
Transfer	56(1.7%)	6(0.2%)	0
Treatment completed	817(24.9%)	179(5.5%).	12(0.4%)
Cured	931(28.4%)	71(2.2%)	16(0.5%)
Not evaluated	6(0.2%)	2(0.1%)	0

Other	2(0.1%)	0	0
Missing	634(19.4%)	75(2.3%)	44(1.4%)

Analysis of percentage TB treatment outcome trends/quarterly

For the trend analysis we assumed the 753/3 277(23.0%) missing TB treatment outcomes were by chance and excluded them in the trend analysis. Once results with missing TB treatment outcomes were excluded the remaining 2 524 TB treatment outcome trend analysis by quarter became more comparable with the annual TB review reports.

TB treatment outcomes were further disaggregated by quarter as depicted in figure 6.The proportion of TB treatment outcome of died had a steady decrease from first quarter of 2017 30/238 (12.6%) to second quarter 2018 41/431 (9.5%). Then third quarter of 2018 the outcome died had a slight increase to just slightly above 10.0%, before going back to just below 10.0% in fourth quarter of 2018. The relevance of the eight quarters of TB treatment outlines analysed was that, those are the quarters when the XMTB/R primary diagnostic algorithm rolled out. Quarter one 2017 was the baseline, when there was 95% XMTB/R targeted test and 5% XMTB/R primary diagnostic algorithm. The XMTB/R primary diagnostic algorithm roll out occurred more and more between 2017 quarter until 2018 quarter one, which has 100% XMTB/R. The question was what was the performance of TB treatment outcomes as XMTB/R primary diagnostic algorithm rolled out in Manicaland, for 2017-2018?

The first cohort had completed treatment in six months and was included in the treatment outcome analysis of quarter three 2017 and so on and so on.

Overall this showed that as XMTB/R primary diagnostic algorithm rolled out the TB treatment outcome of died, showed a steady decrease in deaths. The proportion of cured was 2017 first quarter 90/238(37.8%) and 2018 fourth quarter 147/313 (47.0%). TB treatment outcome of treatment completed for 2017 quarter one 91/238 (38.24%)

was 2018 first quarter was 205/464(44.18%). There was no noticeable trend in the two TB treatment outcomes of cured and treatment completed.

Testing for association

Testing for association between HIV status and TB treatment outcome showed a statistically significant association with a p value of <0.001. Testing for significance of association between XMTB/R primary diagnostic algorithm roll out and TB treatment outcome showed a statistical significance with p value, <0.001. There was statistically significant association between HIV status and type of TB whether PTB or EPTB. There was statistically significant association between type of TB and TB treatment outcome, with p value <0.001.

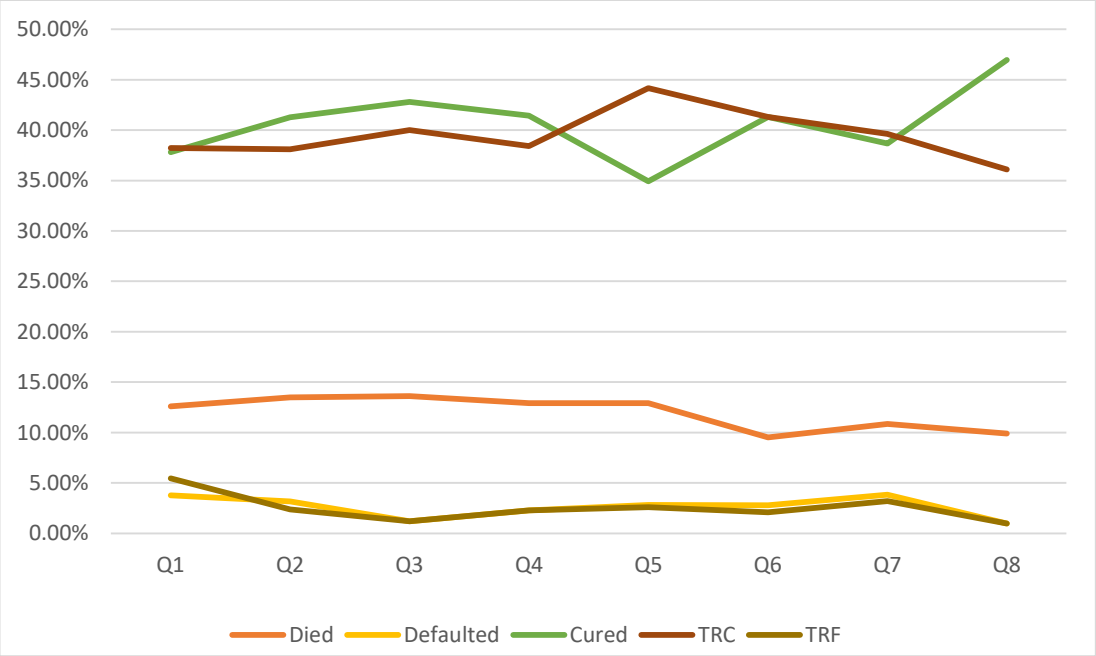


Figure 6: Determination of TB treatment outcome trends by quarter.

Key for Quarter: 1: Quarter 1 of 2017, 2: Quarter 2 of 2017, 3: Quarter 3 of 2017, 4: Quarter 4 of 2017, 5: Quarter 1 of 2018, 6: Quarter 2 of 2018, 7: Quarter 3 of 2018, 8: Quarter 4 of 2018

4.2.4 Exploration of geo-spatial mapping capacity as XMTB/R primary diagnostic algorithm rolled out in Manicaland, for 2017-2018

From the XMTB/R 36 056 patients' data, there were 2 221 MTB detected results. These were employed for analysis of geo spatial mapping capacity.

4.2.4.1 Exploration on geo-spatial mapping capacity of health facilities with high frequencies of rifampicin resistant (RR) results in Manicaland 2017-2018

Before the XMTB/R primary diagnostic algorithm roll out, rifampicin resistant result could not have been detected for all presumptive TB investigation. Figure 7 showed that rifampicin resistant was more in some requesting facilities than in others. Before XMTB/R primary diagnostic algorithm roll out, there was no capacity for geo-spatial mapping using GxAlert/Aspect that is embedded in Gene Xpert machine. Total health facilities that had high frequencies of rifampicin resistant results were; Munyanyi clinic, Rambanepasi clinic, Mombeyarara Rural Health Centre, Gombe clinic, Murambinda Mission Hospital, Nyashanu Mission Clinic, Chiwese clinic,Matotwe Rural Health Centre, Kopera Rural Health Centre, Gaza clinic seven facilities in Buhera District, two in Chipinge District and one in Makoni District. Geo-spatial mapping of Manicaland showed ten facilities that had high frequencies of rifampicin resistant results with 7/10 (70.0%) of the facilities in Buhera District.

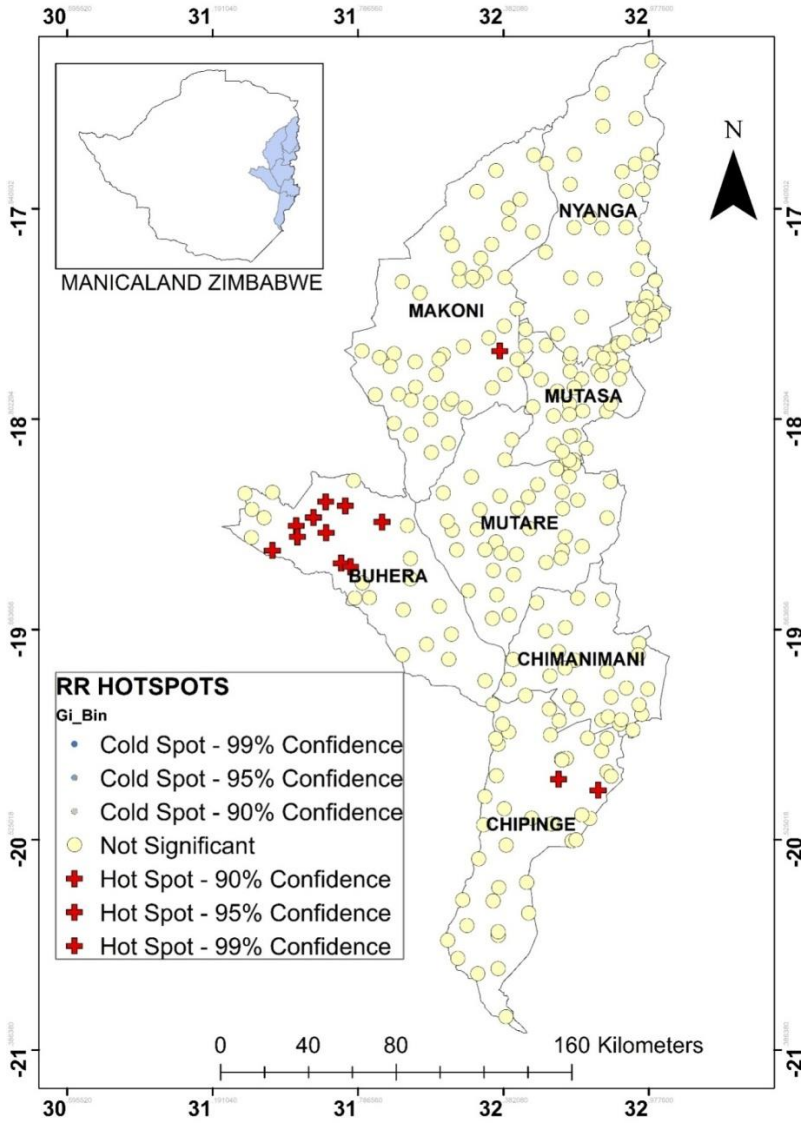


Figure 7: Health facilities with high frequencies of rifampicin resistant (RR) results

4.2.4.2 Geo-spatial mapping capacity of health facilities with high frequencies of MTB detected high results as XMTB/R rolled out

As XMTB/R primary diagnostic test rolled out, all the XMTB/R results were disaggregated into the semi quantitative MTB detected results. The relevance was that the geo-spatial mapping helped visualize the influence of XMTB/R primary diagnostic test roll out on TB detection. Figure 8 show health facilities that had high frequencies of MTB detected high results were the catchment around the following requesting facilities; Tanganda Rural Health Centre, Ngaone clinic, New Year's Gift clinic, Silver Stream clinic, Gaza clinic, Kopera Rural Health Centre, Arda Rusitu clinic. The majority was from Chipinge District. Of 304 health facilities 15 (4.9%) of them had high frequencies of MTB detected high results Chipinge District 11/15 (73.3%) Chimanimani District 3/15 (20.0%).

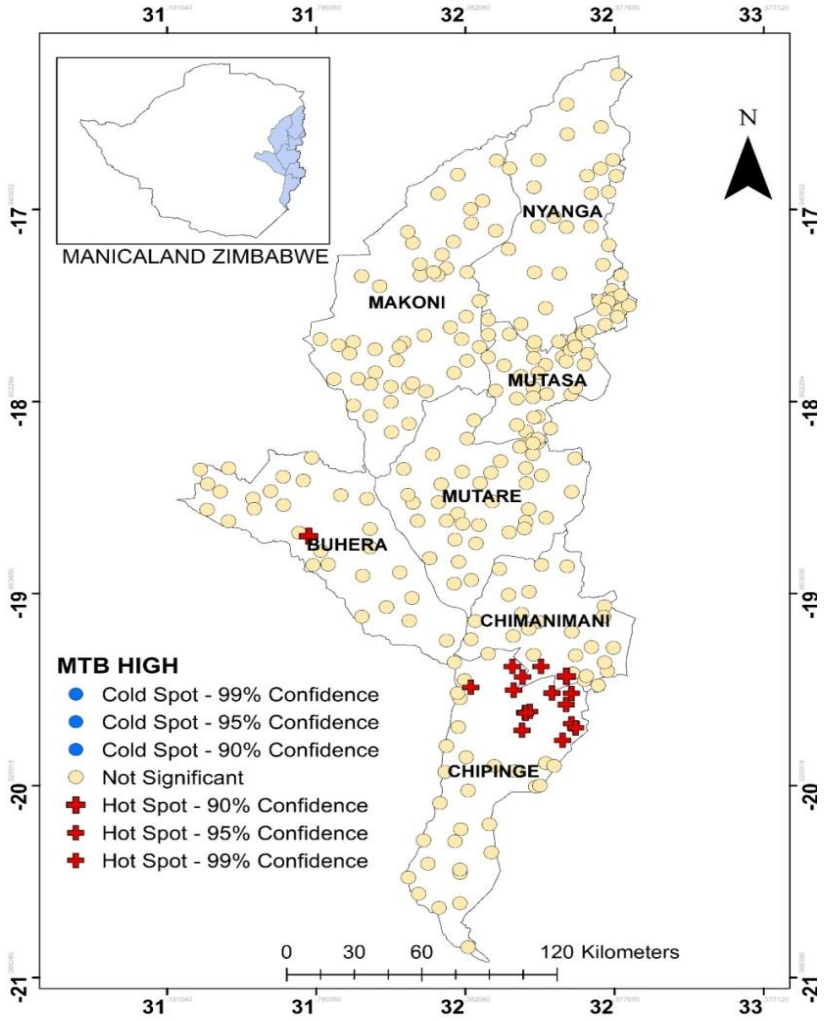


Figure 8: Health facilities with high frequencies of MTB detected high results

4.2.4.3 Geo-spatial mapping of health facilities with high frequencies of MTB detected medium results as XMTB/R rolled out

The MTB results that were analysed during XMTB/R primary diagnostic algorithm roll out period of 2017 and 2018 were depicted in geo-spatial mapping capacity. Due to inaccuracy of patient home address, the health facility longitudinal and latitudinal coordinates were measured. Figure 9 show health facilities with red crosses. The health facilities with red crosses had high frequencies of MTB detected medium results. The health facilities are; Buhera Rural Hospital, Gombe clinic, Nyashanu Mission Clinic,Murambinda Mission Hospital, Mombeyarara Rural Health Centre, Munyanyi

clinic, Mudanda clinic, Chiwese clinic, Kopera Rural Health Centre. The majority were from Buhera District, followed by Chipinge District.

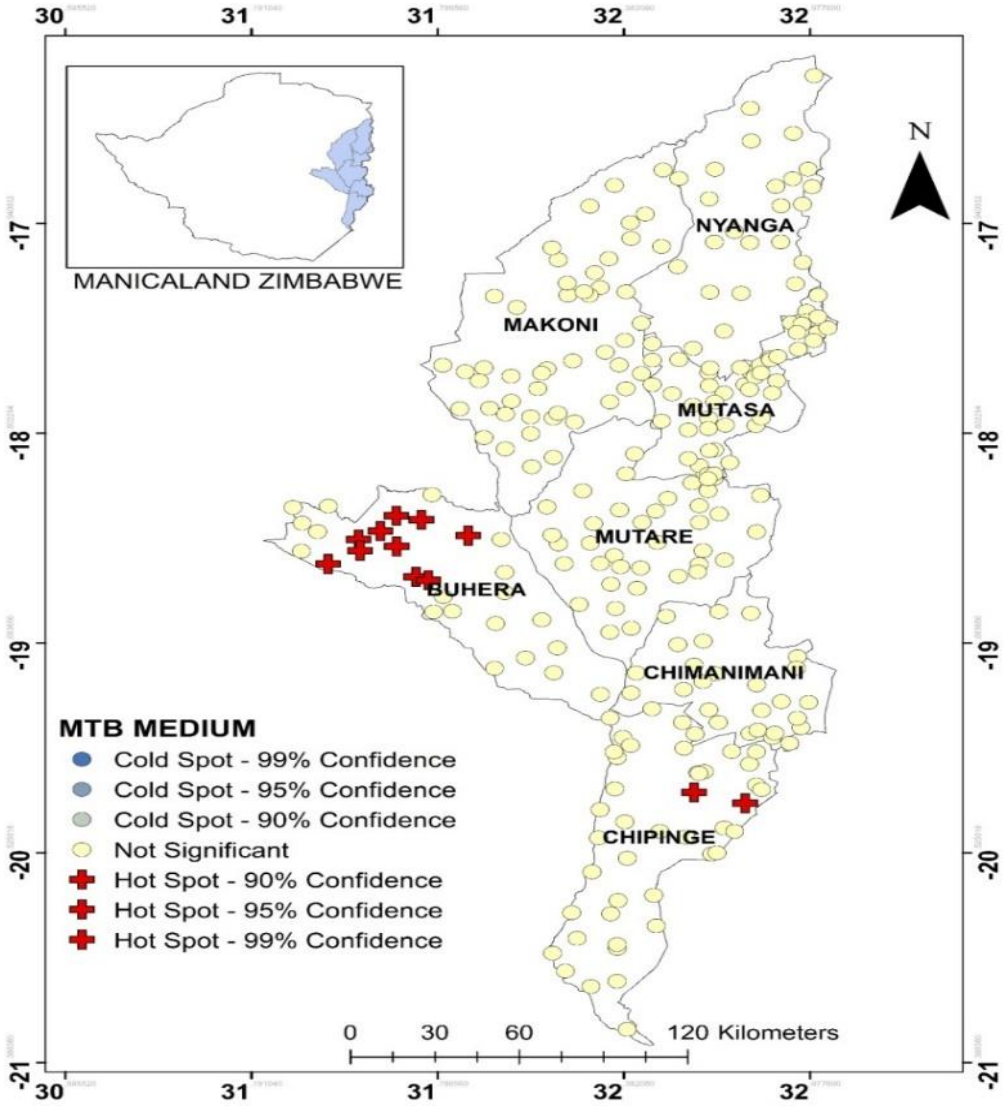


Figure 9: Health facilities with high frequencies of MTB Detected medium results

There was relevance in analysing health facility MTB result frequencies during the XMTB/R primary diagnostic algorithm roll out period of 2017 and 2018. The geo-spatial mapping capacity show the health facilities that had highest frequency of the semi quantitative MTB detected low results. As XMTB/R primary diagnostic test rolled out, 10/10 (100%) health facilities identified as having high frequencies of MTB

detected low results, were all in Buhera District. Figure 10 showed the following health facilities which had high frequencies of MTB detected low; Chapwanya clinic, Garamwera clinic, Murambinda Mission Hospital, Gombe clinic, Nyashanu Mission Clinic, Mombeyarara Rural Health Centre, Munyanyi clinic, Murambinda Mission Hospital. The majority of the referring facilities were from Buhera District.

4.2.4.4 Geo-spatial mapping capacity of health facilities with highh frequencies of MTB detected low results as XMTB/R rolled out

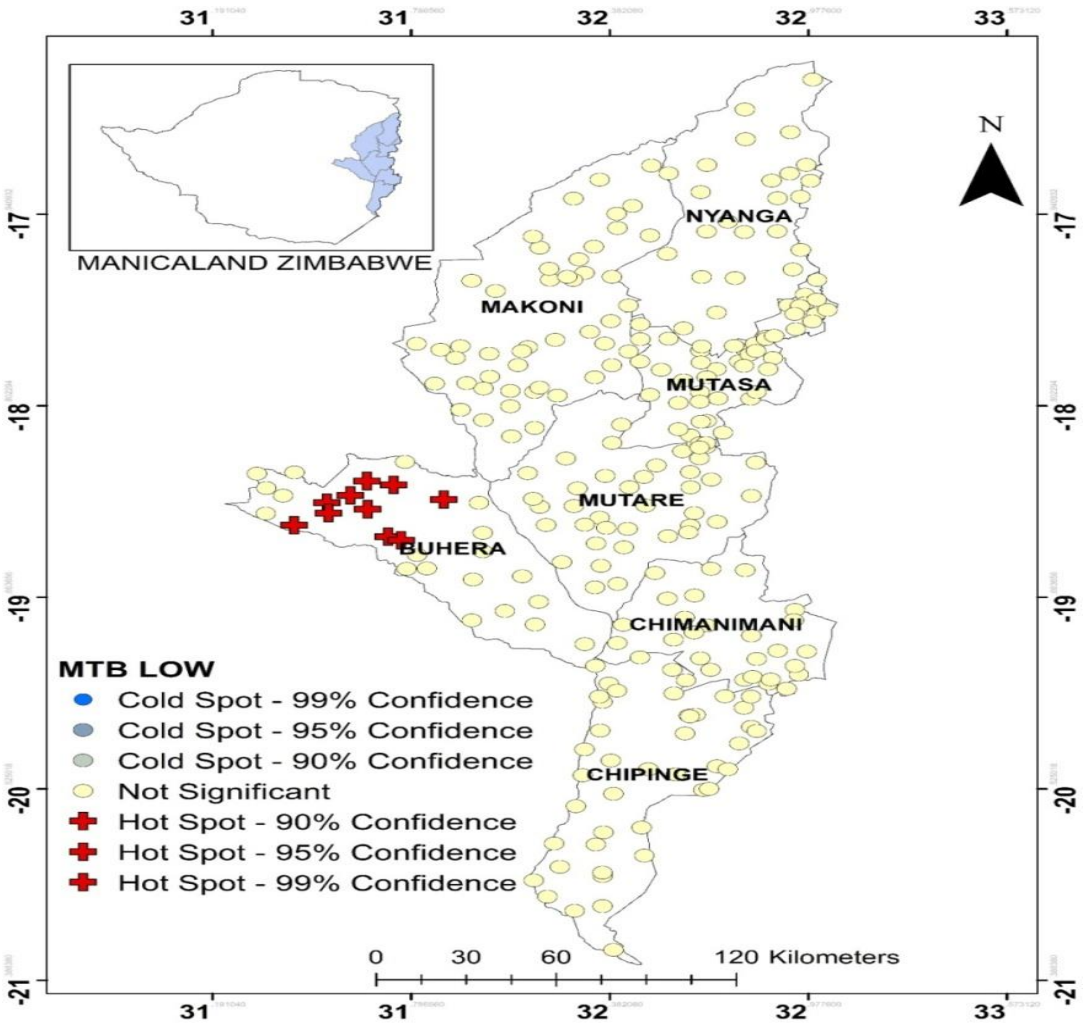


Figure 10: Health facilities with high frequencies of MTB detected low results

Figure 11 show that MTB detected very low were for results from the following requesting facilities; Tanganda Rural Health Centre, Junction Gate clinic, Kopera Rural Health Centre, Imbeza clinic, Mt Jenya, Rambanepasi clinic, Munyanyi clinic,

Mombeyarara Rural Health Centre, Chiwese clinic, Gombe clinic, Nyashanu Mission Clinic, Buhera Rural Hospital.

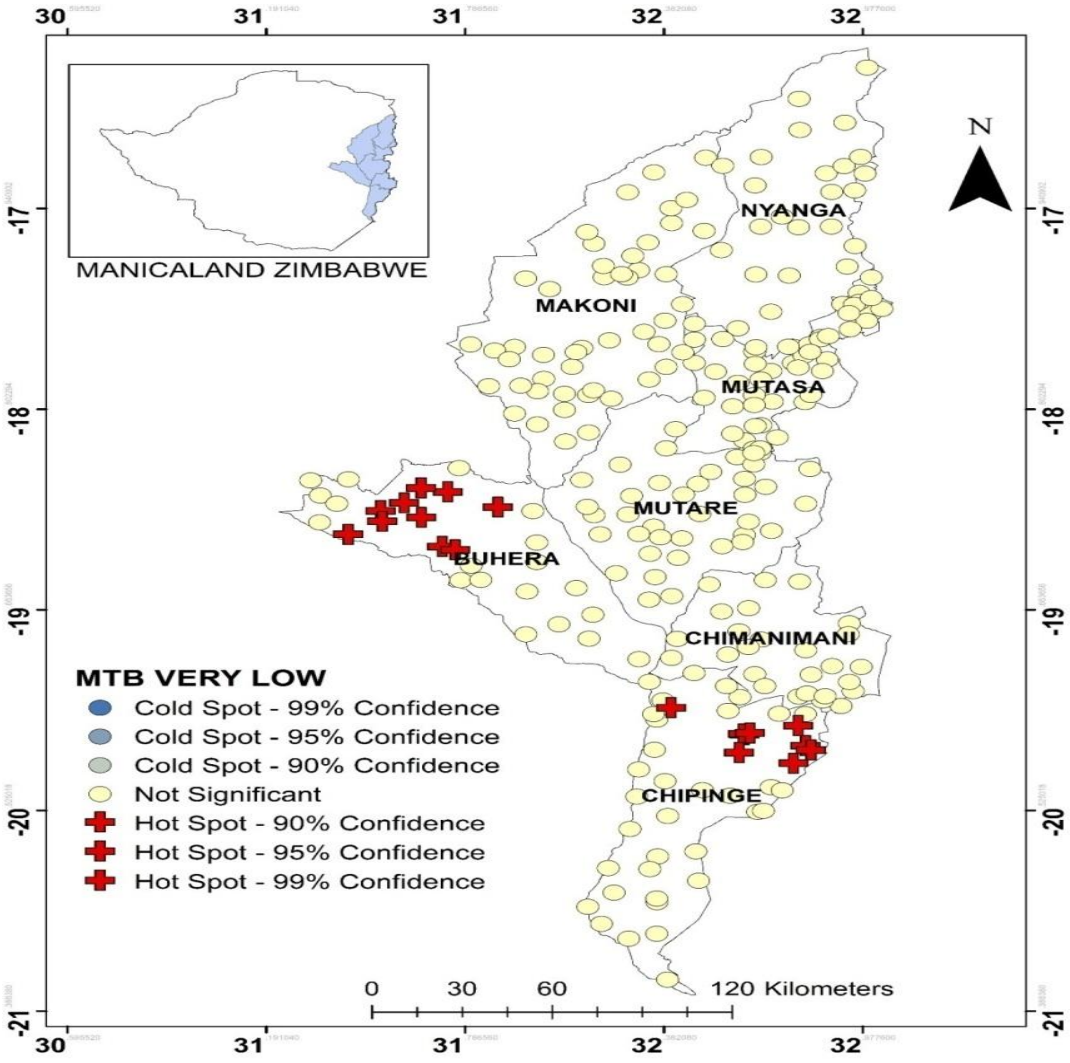


Figure 11: Health facilities with high frequencies of MTB detected very low results

4.2.5 Production of frozen sputum quality control specimen as XMTB/R primary diagnostic algorithm rolled out

Table 15 show the production of frozen sputum quality control specimen as XMTB/R primary diagnostic algorithm rolled out. There was concordance between XMTB/R

Version 4 and XMTB/R Ultra was 96/109 (88.1%). Two of the frozen sputum were frozen without XMTB/R Version 4 results.

Table 16: Production of frozen sputum **quality control specimen as XMTB/R primary diagnostic algorithm rolled out**

XMTB/R **ULTRA Versus** XMTB/R Version 4	**Frequency**	**Percentage**
Concordant	96	88.1%
Discordant	10	9.2%
Error XMTB/R **Ultra**	1	0.9%
No XMTB/R Version 4 result	2	1.8%

Table 16 show that of the 88 sputum that was MGIT positive, 93.2% was XMTB/R Version 4 positive, this was found by adding 78.4% and 14.8%. Out of the eleven sputum that was MGIT negative, 7/11 (63.6%) were XMTB/R Version 4 positive, this was found by adding 27.3% and 36.4%**.**

Table 17: Results of MGIT versus XMTB/R Version 4

XMTB/R **Ultra MTB Result**	**MGIT Contaminated**	**MGIT Missing**	**MGIT Negative**	**MGIT Positive**
	n=9	n=1	n=11	n=88
	n(%)	n(%)	n(%)	n(%)
XMTB/R Version 4 **Positive RR**	1 (11.1)	1 (100)	3 (27.3)	13 (14.8)
XMTB/R Version 4 **Positive RS**	8 (88.9)	0 (0.0)	4 (36.4)	69 (78.4)
Xpert Negative	0 (0.0)	0 (0.0)	4 (36.4)	4 (4.5)

XMTB/R Version 4 **Missing**		0 (0.0)	0 (0.0)	0 (0.0)	2 (2.7)

In table 17 results of MGIT versus XMTB/R Ultra, it was noted that of the 88 sputum that were MGIT positive, 85/88(96.6%) produced XMTB/R Ultra positive results and 3/88(3.4%) produced XMTB/R Ultra negative results. From table number 16 and table number 17, it was shown that sputum frozen for seven years then analysed on XMTB/R Ultra performed better than raw sputum XMTB/R Version 4 using MGIT as gold standard 96.6% and 93.2% respectively. The findings show that an economical quality control sputum specimen was established.

Table 18: Results of MGIT versus XMTB/R Ultra

XMTB/R **Ultra MTB Result**	**MGIT Contaminated**	**MGIT Missing**	**MGIT Negative**	**MGIT Positive**
	n=9	n=1	n=11	n=88
	n(%)	n(%)	n(%)	n(%)
XMTB/R **Ultra-Positive**	8 (88.9)	1 (100)	7 (63.6)	85 (96.6)
XMTB/R **Ultra-Negative**	1 (11.1)	0 (0.0.)	4 (36.4)	3 (3.4)

Table 19: Kappa measure of agreement between XMTB/R Version 4, XMTB/R Ultra and MGIT results

	Comparisons	Value	Asymp. Std. Errora	Approx. Tb	Approx. Sig
Measure of agreement Kappa N of valid cases	XMTB/R Version 4 vs. MGIT	0.186	0.104	2.883	0.004
	XMTB/R Ultra vs. MGIT	0.235	0.104	3.637	0.000
	XMTB/R Version 4 vs. XMTB/R Ultra	0.147	0.130	1.752	0.079

4. 3 Discussion and Interpretation

4.3.1 Evaluation of effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance, in Manicaland, for 2017-2018, on MTB detection

The study finding of MTB positivity of 6.2% was similar to the positivity rate of 13% and 7% (2015 and 2016 respectively) reported by Jokwiro et al., 2018, which he said was low compared to other countries which had positivity rates of 15% to 19 %. The finding in the study that 5 769/36 056 (16.0 %) were analysed using targeted screening algorithm versus 30 286(84.0%) analysed using XMTB/R primary diagnostic algorithm showed that there was increase in number of tests processed using XMTB/R primary diagnostic test. Roll out of XMTB/R primary diagnostic algorithm resulted in increase in TB detection using Xpert MTB/Rif targeted screening algorithm versus XMTB/R primary diagnostic algorithm, that is 430/36 056 (1.2%) and 1791/36 056 (5.0%) respectively. The finding in the study answers the research question, as it

showed that rolling out XMTB/R primary diagnostic algorithm had the influence of increasing MTB detection. The bivariate analysis is MTB result versus HIV status and MTB result versus gender. Females had a higher percentage of MTB not detected 18 737/ 36 056 (52.0%). Of those diagnosed as having MTB, males were more than females, 1 127/36 056 (3.1%) and 833/36 056 (2.3%) respectively. Of those with MTB detected high males comprised 240/36 056 (0.7%) versus females 217(0.6%).

4.3.2 Analysis of effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance in Manicaland, Zimbabwe, 2017-2018, on laboratory turnaround time

The finding of a decrease in the mean of laboratory turnaround time from XMTB/R targeted screening algorithm to XMTB/R primary diagnostic algorithm from 1.7 days to 1.4days agreed with the mean laboratory turnaround time for XMTB/R primary diagnostic algorithm. For XMTB/R targeted screening algorithm and access to XMTB/R primary diagnostic algorithm, the standard deviation is 0.4 and 0.9 respectively. ANNOVA gave the p value of <0.001, which is way less than 0.05.

4.3.3 Determination of the performance of TB treatment outcomes as XMTB/R primary diagnostic test rolled out

The study demonstrated that as XMTB/R primary diagnostic algorithm rolled out, the TB treatment outcome of died had a trend that was decreasing.

4.3.4 Exploration of geo-spatial mapping capacity as XMTB/R primary diagnostic algorithm rolled out in Manicaland, for 2017-2018

The study findings demonstrate that as XMTB/R primary diagnostic algorithm rolled in Manicaland, geo-spatial mapping capacity of the semi-quantitative MTB detected

result also increased, as every presumptive TB was investigated using XMTB/R test. As XMTB/R primary diagnostic test rolled, embedded in it, was GxAlert/Aspect. The study findings also showed that, there is variation in epidemiological pattern of MTB in Manicaland. The red exes were the areas of concern in figures 7 to 11. There was intra provincial epidemiological difference according to geographical setting. The study findings in figure 8 suggest that Chipinge District had 9/14(64.3%) health facilities identified as MTB detected high areas in Manicaland. The study findings in figure 10, suggest that Buhera has facilities with high frequencies of MTB detected low results.

4.3.5 Production of frozen sputum quality control specimen as XMTB/R primary diagnostic algorithm rolled out

Figures on table 17 show that there was 88% concordance between XMTB/R Version 4 results run seven years previously and XMTB/R Ultra results analysed on same sputum which had been frozen for up to seven years. This finding established an economical quality control sputum specimen, for use as XMTB/R primary diagnostic algorithm rolled out. Of the 109 sputum 10 (9.2%) were discordant between XMTB/R Version 4 and XMTB/R Ultra. Out of the ten discordant, five discordant were due to XMTB/R Version 4 result being negative where XMTB/R Ultra result was positive. Five of these XMTB/R Version 4 negative XMTB/R Ultra positive, were all culture MGIT positive. The remaining five of the ten discordant were discordant in that XMTB/R Version 4 result was positive where XMTB/R Ultra result was negative. Two of the five were MGIT negative. Three of the five were MGIT positive. 2/109 (1.8%) had no previous XMTB/R version 4 result although they were MGIT positive. 1/109(0.92%) had an XMTB/R Ultra result of error.

In table 18 the interrater reliability for the XMTB/R Version 4 code versus MGIT code was found to be Cohen's kappa coefficient of 0.186 (p value 0.004), 95% CI (0.01784, 0.38984). This measure of agreement, while statistically significant, is only a slight agreement according to kappa agreement interpretation by Landis et al., (1977). The interrater reliability for the XMTB/R Ultra code and MGIT code cross tabulation raters was found to be kappa value of 0.235 (p value <0.001), 95% CI (0.03116, 0.43884). This measure of agreement, while statistically significant, is only a fair agreement according to Kappa agreement interpretation by Landis et al., (1977).

The interrater reliability for the XMTB/R Ultra code versus XMTB/R Version 4 code raters which was found to be kappa of 0.147 (p value 0.079), 95% CI (-0.1078, 0.4018). This measure of agreement, while statistically significant, is only a slight agreement according to Kappa agreement interpretation by Landis et al, (1977). Table number 18, show that compared to XMTB/R Version 4 versus MGIT as well as XMTB/R Ultra versus MGIT and XMTB/R Version 4 versus XMTB/R Ultra, the interrater reliability were found to be all the same range of fair agreement (kappa 0.186, kappa of 0.235 and kappa 0.147).

4.4 Summary

Chapter 4 highlighted the data presentation, followed by the data analysis and interpretation. The data presentation, data analysis and interpretation were arranged into sections following the specific objectives of the study. The sections were; evaluation of XMTB/R primary diagnostic algorithm roll out and MTB detection in Manicaland, analysis of XMTB/R primary diagnostic algorithm roll out and laboratory turnaround time, determination of the performance of TB treatment outcomes as XMTB/R primary diagnostic algorithm rolled out in Manicaland, exploration of geo-

spatial mapping capacity as XMTB/R primary diagnostic algorithm rolled out in Manicaland, production of frozen sputum quality control specimen as XMTB/R primary diagnostic algorithm rolled out.

The chapter focused on tables and figures that were presented as data analysis was performed. The next chapter, 5 focuses on summary, conclusions and recommendations.

CHAPTER 5 SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

5.1 Introduction

This chapter highlights the discussion, conclusions and implications of the study findings. It also lists recommendations and suggestions for further research. For easy flow, all these are handled in sections along the lines of specific objectives of the study. These being; evaluation of XMTB/R primary diagnostic algorithm roll out and MTB detection, analysis XMTB/R primary diagnostic algorithm roll out and laboratory turnaround time, determination of the performance of TB treatment outcomes as XMTB/R primary diagnostic algorithm rolled out in Manicaland, exploration of geo-spatial mapping capacity as XMTB/R primary diagnostic algorithm rolled out in Manicaland, production of frozen sputum quality control specimen as XMTB/R primary diagnostic algorithm rolled out.

The chapter highlights the information derived from the results of the study and implications of findings. It focuses on discussion of findings and compares them to findings of other studies. The conclusion part gives a summary of the study findings and important discussion points. The recommendations point out useful evidence based actions to guide policy makers and program implementers such as context specific tool developed for routine identification of TB high risk group at health facility entry points, rationale use of resources during programmatic implementation of TB guidelines, evaluation of patient linkage to care. as well as other prevention and control interventions.

5.1.1 Evaluation of effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance, in Manicaland, for 2017-2018, on MTB detection

Findings predicted by literature were the finding that reason for commencing TB treatment based on clinical diagnosis changed from 2017 first quarter to 2018 fourth quarter as follows 11/281 (3.9%) and 3/534 (0.6%). In a study carried out in Cape Town it was also found that there was a decrease in clinically diagnosed TB from 23.0% (2 445/10 643) to 11,4% (1 149/10 089) for HIV negative and from 42,4% (4 229/9 985) to 26,8% (2 364/8 823) for HIV positive patients. The findings differ from those where clinically diagnosed TB did not increase -3%: 95% (CI: -37%-30%) (Hermans et al, 2017). This finding is a positive finding for Xpert MTB/Rif primary diagnostic test roll out, established in this study.

This study showed increase in proportion of bacteriologically confirmed diagnosis, while clinically diagnosed TB decreased, as XMTB/R primary diagnostic algorithm rolled out. The findings of this study are similar to those in Brazil which demonstrated a 59% increase in bacteriologically confirmed TB 95% (CI31-88%) p value 0.001(Durovni et al, 2014).

The study showed that there was increase in absolute numbers of XMTB/R tests, with no increase in MTB positivity. This might be due to more HIV negative individuals tested. The test XMTB/R primary diagnostic algorithm roll out resulted in a doubling of XMTB/R tests performed. Differences in patient population and their pre-test probability, for example the testing of a higher proportion of HIV negative individuals may explain the decrease in MTB positivity over time. Changes in patient population tested were a direct result of the XMTB/R primary diagnostic test roll out. Additionally, more accessible molecular diagnostics might have reduced the threshold

for TB testing resulting in patients with lower TB risk being offered testing. While lowering the threshold for TB testing may not necessarily result in increased TB diagnosis, it may lead to earlier diagnosis and reduce the period of infectiousness as well as finding those who are “hard to diagnose” (Arinaminpathy et al, 2015). This was one of the advantages of XMTB/R primary diagnostic algorithm roll out, that this study established, early MTB detection of low bacillary load.

The roll out of XMTB/R primary diagnostic algorithm, did not lead to an increase in bacteriologically confirmed TB diagnoses despite the higher sensitivity of XMTB/R compared to smear microscopy (Horne et al., 2019). However, an MTB positivity of only 6.2% among samples referred for XMTB/R testing seems particularly low compared to other studies (Creswell et al, 2014)(Ardizzoni et al, 2015). There was hence need for more detailed investigations to understand the temporal association between roll out of XMTB/R primary diagnostic algorithm and decreasing MTB positivity. A previous study on utilization rate of Gene Xpert in Manicaland comparing data from January-June 2016 and January -June 2017 reported similar results. In the same study proportion of samples testing MTB positive halved from 13.0% in 2016 to 7.0% in 2017. Over the same time period the number of TB notifications increased slightly from 967 to 1 011 and the proportion microbiologically confirmed from 48.0% to 53.0% (Jokwiro et al. 2018). The continued decrease in MTB positivity rate, despite roll out of the superior XMTB/R primary diagnostic algorithm, could be explained by the fact that, TB incidence is on a descending trajectory in Zimbabwe (Mugauri et al, 2022).

In trying to address the problem established in the findings of this study, namely decreasing MTB positivity rate, researchers identified an unmet need for optimizing TB case detection. To close the gap identified of the unmet need all TB high risk

groups could be screened using chest x-ray, instead of using the TB screening tool. Using chest x-ray to screen for presumptive TB in TB high risk groups gives double the yield (Ismail et al, 2023). In Zimbabwe the TB program had invested in TB outreach for high risk groups. There were chest x-ray and XMTB/R services during the outreach to TB high risk groups. With all that in place however, it was essential to make use of multicomponent strategies and context specific program derived solutions.

Use of program data was needed to optimize TB case detection strategies, since XMTB/R primary diagnostic algorithm roll out did not automatically lead to increased MTB positivity rate. There was need to avoid missed opportunities when HIV positive and other locally relevant TB high risk groups presented at health facilities, for non TB related services. In the care cascade, the newly developed TB screening questions to routinely identify the TB high risk groups (appendix 18) to be administered routinely at all entry points. This nouveau suggestion is not to be confused with the TB stamp strategy depicted in figure 12 below. In the TB stamp strategy the TB screening tool is routinely stamped in the patient hospital card at all points of entry. Using the TB stamp strategy all patients are routinely screened for HIV and health workers also ask questions from the stamp, looking for symptoms of TB. All presumptive TB submit specimen for XMTB/R investigation.

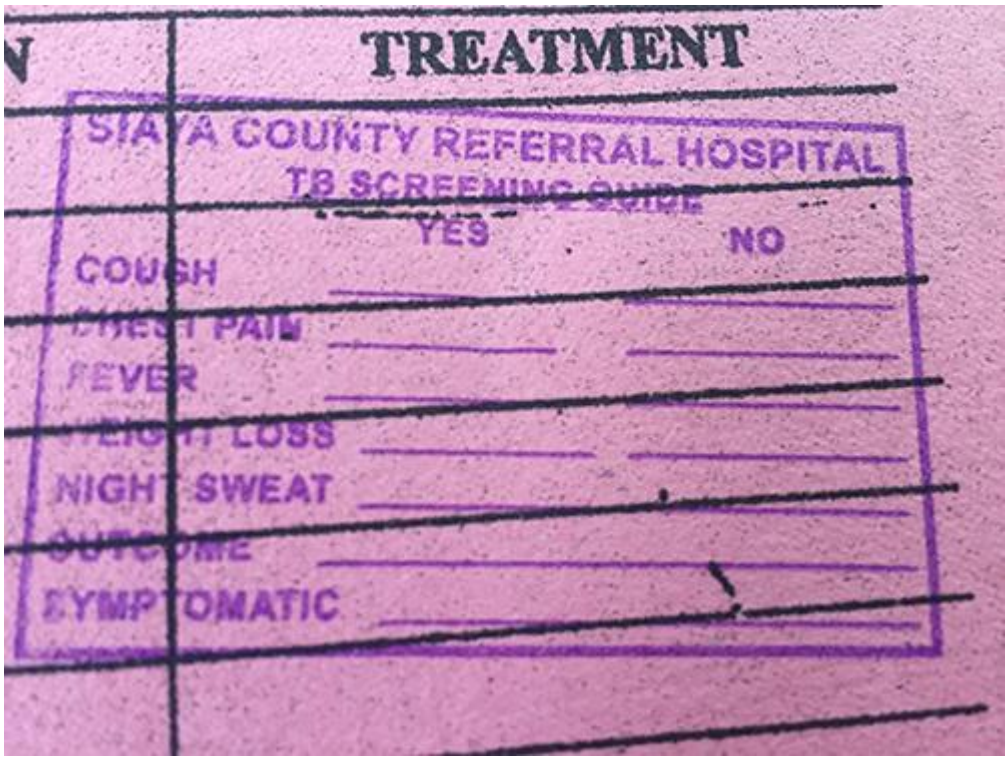


Figure 12: TB stamp strategy

This study suggested that instead of using the TB screening tool on all clients identified as TB high risk groups, use chest x-ray which gives double yield of presumptive TB clients. The routine medical history taking in health facilities might be missing an opportunity to pick potential candidates for chest x-ray screening. History taking should probe all the people who present to pick those who might have changed from TB high risk careers or once dwelt in congregated settings.

If all these are identified and have chest x-ray as the TB screening method, there may be a higher pool of presumptive TB clients. The higher pool of presumptive TB picked by the more sensitive chest x-ray screen, might yield higher MTB positivity rate. This line of thought is supported by WHO standard universal access to rapid TB diagnostics. It comprises twelve benchmarks, the eleventh benchmark, states the need to monitor MTB positivity rate, in order to continually evaluate the effect of strategies like roll out of XMTB/R primary diagnostic algorithm (Ismail et al, 2023).

Patients and their families may benefit from an earlier diagnosis brought on by XMTB/R primary diagnostic algorithm roll out in several ways: 1) decreased morbidity resulting in increased quality of life at the end of treatment; 2) reduced cost during the diagnostic period; and 3) reduced onward transmission and secondary cases. Early TB detection equally results in early commencement on treatment (Ismail et al., 2023). Within two weeks of treatment commencement, the MTB is sterilized and can no longer be transmitted. Rifampicin one of the potent first line TB medicines is known to have the sterilizing effect. Isoniazid quickly decreases the TB bacilli density through its bactericidal effect (van Ingen et al, 2011).

Evaluation of XMTB/R primary diagnostic algorithm roll out and MTB detection, showed an increase in rifampicin resistant detection. The overall rifampicin resistance detected for 2017-2018 was 5.2%. This would mean drug resistant TB patient is commenced on the drug resistant regimen earlier, rather than first being commenced on generic drug susceptible regimen, then resistance being picked up later during month two or month five or month six of treatment monitoring sputum smear microscopy, where it fails to convert. Tadokera et al., (2021) stated significant delays in accessing MDRTB care in their setting before rifampicin resistant detection was taken as a proxy for MDRTB. MDRTB is increasing in Zimbabwe, with Bulawayo and Matabeleland South provinces bearing a disproportionate overall burden (Mugauri et al, 2022).

The finding that 1293/3277(39.5%) entries in the facility TB register did not capture the reason for initiating TB treatment, points to a need in strengthening real time updating of registers, before the information is lost.

From the results it was seen that males had a poor health seeking behaviour as they present to the health facilities when the MTB bacillary load is higher. Higher MTB

bacillary load means early detection had not occurred and it also meant disease spread had occurred before disease detection. Tadokera et al., (2021) showed community delays to effective TB treatment despite the availability of molecular TB diagnostics such as XMTB/R. In a South African study delays to TB diagnosis were mainly attributed to late presentation (Boniface et al, 2012). Late presentation in male population could be due to low health seeking behaviour. Findings that are according to expectations were that males comprise bigger proportion of those with MTB detected. Findings that differ from expectations, were that females comprise the bigger proportion of those investigated for MTB.

The proportion of unsuccessful XMTB/R assays due to "no results", errors and invalid results was 6.3% overall and highly variable across sites. Unsuccessful assays are tracked as part of the XMTB/R key performance indicators by the Zimbabwe National TB Programme. For the purpose of quality management, the key performance indicators targets are set at <3% error, 1% invalid, <1% no result rates, which only two of the fifteen Gene Xpert sites achieved. Other studies investigating the operational challenges of XMTB/R roll out reported similar unsuccessful assay rates at 6.0%-10.6% (Jokwiro et al, 2018)(Creswell et al, 2014)(Ardizzoni et al, 2015). Unfortunately, none of these studies further analysed the unsuccessful assay results. A significant proportion of unsuccessful assays in this study were categorised as "no result", which is usually due to power cuts leading to interrupted analytical runs. Specifically, the Gene Xpert site with the highest "no result" rate (7.0%) had no electric back up neither generator or solar. It is known that potential power supply disruptions were high in Zimbabwe in 2017-2018.

The finding that some XMTB/R results were deleted before archive show that there is no system being followed in terms of retention of electronic XMTB/R results. The

percentage retention followed no particular trend from quarter one 2017 to fourth quarter 2018. The best practise is where purging occurs after archiving process is completed; in such a scenario the result file is archived in the Gene Xpert computer. Once a month the results should be saved on compact disc in order to avoid data loss due to computer processing unit damage or computer destruction. The once a month archive to compact disc of electronic XMTB/R results would make it possible for key performance indicator analysis in future research studies, the way Chirenda et al., used a ten year city of Harare electronic TB registry in one of his studies (Chirenda et al, 2020).

The experience on the ground however, was that the monthly archive on to compact disc was not being carried out. There was need for provision of the compact discs as well as on job training. The training would include secure compact disc storage of the compact discs on which the XMTB/R results will have been saved. The training would also include standard and unique identification of the compact discs, so that in future, quick XMTB/R result retrieval would be enhanced. The retrieved data could be restored by following Gene Xpert step by step instructions on how to restore data from a backup.

Once restored from the archive stage, the data could be analysed as disaggregated data, to track key performance indicators of XMTB/R which include among others; tracking low positivity rate, instrument error rates, user performance and machine workloads (Cepheid, 2013). The wealth of already existing electronic XMTB/R data that was being lost included; user name, machine error codes, as well as date and time test was carried out. The proceeding listed variables were not captured as a full set in paper based laboratory TB registers. By the time the scientific world would want to utilize data for research, instead of extrapolating from archived electronic XMTB /R excel

sheets, the data collectors would have to enter raw data from paper based TB register from scratch. The challenge would be that the paper based data did not capture the full range of variables that was on the extrapolated machine generated excel sheets. In the case of this study, recreating an excel data set from limited paper based variables was not necessary.

The study data benefitted from the percentage electronic XMTB/R results that were still retained on machine central processing unit. The only step that was needed in the study was to add on to the already existing XMTB/R excel. The additional columns were for capturing additional variables, which were currently not captured in the XMTB/R machine generated excel sheet, which were as follows; HIV status, age, sex, requesting facility and the date specimen was collected. The additional variables were added on to the electronic XMTB/R excel sheet from paper based laboratory TB registers.

In the case of one of the Gene Xpert sites, namely Birchenough Bridge Rural Hospital, the original Gene Xpert computer developed a fault, so in order to avoid TB diagnostic service interruption, the laboratory was loaned a central processing unit from the hospital administration department. The loaned central processing unit was used for the two year period of 2017 and 2018 to capture XMTB/R results. When the laboratory was finally provided a new Gene Xpert computer, the central processing unit from hospital administration department was removed from the laboratory, without any measures taken to retrieve XMTB/R results from the loaned central processing unit. As already stated laboratories were not in the habit of following the once a month archive on to compact disc rule from the manufacturer, so that is how the two year XMTB/R electronic results were lost at Birchenough Bridge Rural Hospital.

The added value this study brought to the world of science was bringing to the attention of TB program managers the unforeseen enemy to electronic XMTB/R results retention for future research. The in advert deletion of XMTB/R results leads to the loss of unique variables that are not captured as a full set in any other register, be it paper based or electronic. These lost variables would give rich insight if used for research in future.

In resource limited settings, operational challenges related to weak health systems were cited among the barriers to TB prevention and control activities (Cox et al, 2017). In this study electricity outage, lack of back up of appropriate Gene Xpert computer and lack of systematic XMTB/R result archiving were the challenges identified.

5.1.2 Analysis of effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance in Manicaland, Zimbabwe, 2017-2018, on laboratory turnaround time

Despite a doubling in the number of samples being referred for XMTB/R testing transport time did not change over time. Medium transport time (1 day, IQR 1-3 days) did not vary between peripheral and central sites, evidence of a fairly well organised sample transport system in Manicaland. The study finding was similar to that found in South African study, where there was a decrease in laboratory testing time less than one day, p value <0.001 (Schmidt et al, 2016).

5.1.3 Determination of the performance of TB treatment outcomes as XMTB/R primary diagnostic algorithm rolled out in Manicaland, for 2017-2018

The findings of mean age thirty eight years were similar to those established in a previous study in Kenya. Findings predicted by literature were TB treatment outcome

of cured that comprised 1 018/3 277 (31.1%) which was similar to cured 90/281(32.0%), found in a study carried out in Ethiopia. Findings that differ from expectations, were TB treatment completed 1 008/3 277 (30.8%), which differed from treatment completed of 137/281(48.8%) found in a study carried out in Ethiopia (Tesema et al. 2020). The worst TB treatment outcome which was died comprised highest of 34/250 (13.6%) to lowest 41/431(9.5 %) with overall average of 298/2 524(11.8%) that were captured in TB registers, differed from died 14/281 (5.0%) established by Tesema et al., (2020).

There was missing outcomes data for 753/3 277(22.98%). There was need to address 23.0% outcome that was still missing in facility TB registers, yet six months for fourth quarter 2018 cohort ended in June 2019 and recording period window September 2019. The transcription of laboratory results or TB treatment outcomes into the Facility TB registers be given a timeline, just like statistics is given the timeline that by the end of the next month of each quarter everything should have been compiled. This would eliminate cases where fields are left blank for long until they are just reported as not evaluated. The limitations of the study was that the study did not include evaluation of other factors besides TB detection test, that could influence TB treatment outcomes, like among others, the type of direct observed treatment model of each patient, as well as the adherence counselling sessions received by patient.

Literature states that in Zimbabwe where HIV drives TB, with high rates of co-infection (80%), TB treatment outcomes remained suboptimal due to the high mortality (Zimbabwe Ministry of Health and Child Care, 2018). Limitation was that in 2017 and 2018 the treatment outcome of defaulted, was still in use, WHO later termed it loss to follow up. Transfer was recognised as a TB treatment outcome until, WHO stated transfer was not recognised as a TB treatment outcome, since health

facilities had to request from the facilities TB patients transferred to using the referral slip and could get the concerned patients' TB treatment outcome. The TB program was dynamic in that regard. The TB registers thus were reviewed during the course of the two years, which meant that at times before distribution of current versions, previous versions of TB registers were kept in use until receipt of revised current version.

To avoid inferred influence to the variables collected namely; age, sex, HIV status, type of TB, method of diagnosis, a wider number of variables that also have an influence on the dependent variable TB treatment outcomes, needed to be collected. The wider variables are other determinant of TB treatment outcomes that influence treatment outcome like presence or absence of co morbidities, level of management of existing co morbidities, time taken to treatment commencement, initial method used for TB diagnosis, treatment regimen, adherence counselling and type of direct observed treatment received by the TB patients recorded in the facility TB registers.

5.1.4 Exploration of geo-spatial mapping capacity as XMTB/R primary diagnostic algorithm rolled out in Manicaland, for 2017-2018

As XMTB/R primary diagnostic algorithm rolled, out, universal susceptibility test results were available for all presumptive TB investigations. Geo-spatial mapping capacity showed intra provincial epidemiological difference of MTB rifampicin resistance. The heterogeneity allowed focusing of Ministry of Health and Child Care prevention and control interventions to problem areas. National TB program needs to further interrogate these findings to rule out practices leading to manmade drug resistance in the facilities that were rifampicin resistant hot spots. Other covariates have to be investigated such as facility ownership and specimen transport network at facilities.

Capacity of geo-spatial mapping was further enhanced by GxAlert/Aspect software which was embedded in the Gene Xpert machine during the period XMTB/R primary diagnostic algorithm rolled out. Another advantage of XMTB/R primary diagnostic algorithm roll out, was that the semi quantitative MTB results gave further insight. The geographic information system mapping data showed which requesting health facilities were surrounded by higher or lower concentrations of TB. That's clearly building up the capacity of geo-spatial mapping of the various MTB detected results.

One of the indicators of how good the TB program was at a health facility was reflected by diagnosis of TB at the earliest stages of the disease when the semi quantitative result was still trace or low, instead of high or moderate. A health facility which diagnosed mostly MTB detected high or MTB detected medium was an indication of poor performance of the TB program at the health facility. Facilities identified as having high frequencies of MTB detected high results require interventions to break chain of transmission to be applied or invested to decrease chances of community exposure to TB. That might also have been a sign of low index of TB suspicion at facility or it might also be poor health seeking behaviour of population near MTB detected high health facilities.

These results were not comparable to any in Zimbabwe, due to lack of literature on similar studies. Chirenda et al., (2020) also carried out geo-spatial mapping, but of TB patient information archived in the Harare city TB registry. Their findings were that the home addresses of the TB patients formed hotspots in the peri-urban area where there were no amenities. The lowest unit for our study was requesting health facility. The findings showed that the hotspots were facilities that form a cluster around the Chipinge District hospital Gene Xpert site. The plausible reason could be that patients decided on their own to temporarily move to clinics served by reliable integrated

specimen transport system. That meant patients could be transient and not permanent residence of requesting facilities. That practice was called patient referral and was discouraged, while specimen referral to Gene Xpert site was encouraged, in order to avoid any patient related cost or catastrophic cost to TB detection.

Further research has to be carried out to get more insight, however these findings have allowed stream lining of prevention, control and elimination intervention efforts. The intervention efforts could be training clinicians manning the hotspots on TB case management, evaluation of patient linkage to care, mentoring via telemedicine or TB supportive visits. Hosting awareness campaigns such as the world TB day near facilities with high frequencies of MTB detected results would be another intervention strategy. These initial results help National TB program to narrow down on a few health facilities, which could be further investigated. Consolidated MTB results hot spots further investigation should establish if specimens were submitted from local population or could be people flocking from outside the district or the province. Rule out movement of people from within the district for temporary residence at convenient health facilities served by integrated specimen transport. The identified facilities with high frequencies of MTB detected results could have population at risk such as prison or artisanal miners or people dwelling in overcrowded conditions.

As XMTB/R primary diagnostic algorithm rolled out, high frequencies of MTB detected low results, may be sign of good TB program at health facility with high index of suspicion. Another plausible reason may be early health seeking behaviour of catchment population. MTB detected low incident showed that TB disease was diagnosed before the patient had a chance to infect others in the community. MTB detected low incident showed TB disease diagnosed before the patient transmitted TB in the community. The results of MTB detected very low were not conforming to the

expectations set by the other hotspot maps in this study. The plausible reason for these unexpected results, could support the fact that it was not catchment population, but transient patient who temporarily moved to near Gene Xpert sites as they sought XMTB/R testing services.

5.1.5 Production of frozen sputum quality control specimen as XMTB/R primary diagnostic algorithm rolled out

The relevance of concordance study to study aim was XMTB/R primary diagnostic algorithm roll out required reference material for ensuring quality reliable results. It was a quality management system international standards organization 15189 requirement that upon introduction of a new machine such as Gene Xpert, to a laboratory, or upon change of Gene Xpert module, an XMTB/R method verification process be undertaken before patient laboratory results could be issued in routine practice. Verification method needed reference material and investigated concordance. Hence the need to produce frozen sputum quality control specimen as XMTB/R primary diagnostic algorithm rolled out.

Results of XMTB/R Ultra on frozen sputum correlated reasonably well, therefore this study produced frozen sputum quality control specimen. The study findings showed that TB positive frozen sputum from presumptive multi drug resistant TB, run on XMTB/R Ultra after seven years freezing performed better than previously run XMTB/R Version 4 results compared to MGIT as gold standard. In light of the research findings, potential implication were that to save on cost, comparison of performance of newly diagnosed tests could be done using frozen sputum, pre run on panel of TB tests.

Chakravorty et al., (2017) reported in their findings that XMTB/R Ultra performed better than XMTB/R Version 4 on sputum spiked with known quantity of MTB strain. Bisognin et al., (2018) found that after freezing sputum for four years, some XMTB/R Version 4 negative sputum tested XMTB/R Ultra positive. The finding that was predicted by literature is XMTB/R Ultra picking positive where XMTB/R Version 4 could not pick positive, due to the explained difference in limit of detection, for the five discordant due to XMTB/R Version 4 negative (Chakravorty et al, 2017).

The current study adds to literature in that TB positive frozen sputum from presumptive multi drug resistant TB, run on XMTB/R Ultra after seven years freezing performed better than XMTB/R Version 4 compared to MGIT as gold standard.

The findings that differ from expectations were five discordant due to XMTB/R Ultra negative. Two of the five were MGIT negative. Three of the five were MGIT positive. Possible explanations could be due to additional factors that could not be conclusively resolved in this study. Literature states that Ultra ISO probe makes XMTB/R Ultra more specific for rifampicin resistance resulting in higher likelihood of picking rifampicin resistance if it's there, which was not among the findings of the study. Sputum frozen for seven years then analysed on XMTB/R Ultra performed better than raw sputum XMTB/R Version 4 using MGIT as gold standard (95.6% and 92.2% respectively). Effect of freezing sputum on XMTB/R Ultra explains the 5% increase in sensitivity not being demonstrated. The current study ascertained 88% concordance between XMTB/R Version 4 and frozen sputum analysed on XMTB/R Ultra.

There is need for TB studies to document all parameters for any TB test run, even those of no interest in current study. This will enhance frozen sputum raw data base. For an example this study could have analysed the XMTB/R Version 4 cycle thresh hold values. These would have been compared with the XMTB/R Ultra cycle thresh

holds. However, the XMTB/R version 4 documentation had not included thresh hold values.

From these findings comparison of performance of one newly diagnosed test could be done on frozen sputum, pre run on panel of TB tests. To save on cost, in country method verification of new TB diagnostic tests could be carried out on frozen sputum, pre run on panel of TB tests. Before the end of the study, as per quality management requirement, Zimbabwe has already undertaken verification exercises for more TB diagnostic tests, including TruNat and Ten Color, all due to the fast evolving TB diagnostic landscape. This ensure quality which is the foundation of testing is maintained, as XMTB/R primary diagnostic algorithm continues to be in practice.

5.2 Conclusion

5.2.1 Evalution of effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance, in Manicaland, for 2017-2018, on MTB detection

H0: There was no change as XMTB/R primary diagnostic algorithm rolled out, in Manicaland, 2017-2018.

There was sufficient evidence to support that as XMTB/R primary diagnostic algorithm rolled out there was a statistically significant change in MTB detection. The findings answered the research question which was what was the relationship between XMTB/R primary diagnostic algorithm roll out and MTB detection in Manicaland, for 2017-2018? The conclusion of the research is that provision of primary diagnostic test led to increase in rifampicin resistant detection, so it needs to be strengthened by the National TB program, as one of the strategies to end TB. There was sufficient evidence

to show that XMTB/R primary diagnostic test roll out was effective in early detection of MTB cases and rifampicin resistance as they emerge.

This study also demonstrated that roll out of more sensitive TB diagnostics did not necessarily result in increased number of bacteriologically confirmed TB diagnosis. Rolling out XMTB/R primary diagnostic algorithm did not yield additional detection of positive TB cases. Although the numbers increased, the denominator also increased as the XMTB/R primary diagnostic algorithm was rolled out. Missed opportunities may have been occurring when TB high risk clients presented at health facilities seeking services not related to TB. High level of suspicion at health facilities may yield more clients legible for the more sensitive chest x-ray TB screening. The lack of increase in MTB positivity rate could be explained by the general global decrease in TB incidence (Tadokera et al, 2021). Another conclusion is that, males delayed presenting to health facilities for TB investigation to commence. Early MTB detection which was evidenced by MTB detected low or MTB detected trace semi quantitative XMTB/R result were minimal in the male population. There was inadvert deletion of XMTB/R results, which had not been archived.

5.2.2 Analysis of effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance in Manicaland, Zimbabwe, 2017-2018, on laboratory turnaround time

In conclusion as XMTB/R primary diagnostic algorithm rolled out in Manicaland, 2017-2018, there was a statistically significant decrease in laboratory turnaround time.

5.2.3 Determination of the performance of TB treatment outcomes as XMTB/R primary diagnostic algorithm rolled out in Manicaland, for 2017-2018

In conclusion the findings answered the research question which was what was the performance of TB treatment outcomes as XMTB/R primary diagnostic algorithm rolled out in Manicaland, for 2017-2018?

The research demonstrated decrease of unfavourable TB treatment outcomes. Overall the trend of TB treatment outcome, showed a steady decrease in the TB treatment outcome died. The findings generated from this study showed that there was slow progress towards projected targets such as reduce TB deaths by 95% and new cases by 90% between 2015 and 2035 (WHO, 2015).

5.2.4 Exploration of geo-spatial mapping capacity as XMTB/R primary diagnostic algorithm rolled out in Manicaland, for 2017-2018

The research adds to literature in that the study demonstrated geo-spatial mapping capacity of frequencies of XMTB/R detected results based on requesting health facilities in Manicaland, Zimbabwe for 2017-2018. As the XMTB/R primary diagnostic algorithm rolled out, in Manicaland, GxAlert/Aspect increased capacity for geo-spatial mapping, through remote login and CVS downloads. The study identified health facilities with high frequencies of rifampicin resistant areas. This underscored the need to delineate diagnostic capacity and networks at provincial and district level to ensure high case detection rates were maintained.

5.2.5 Production of frozen sputum quality control specimen as XMTB/R primary diagnostic algorithm rolled out

The conclusion in light of the research objectives was that establishment of economical quality control sputum was achieved. There was concordance with frozen sputum. Frozen sputum could be used for economic verification as XMTB/R primary

diagnostic algorithm roll out increased demand for continuous quality verification post module change.

5.3 Implications

5.3.1 Evaluation of effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance, in Manicaland, for 2017-2018, on MTB detection

The novelty that the study brought was highlighting the need for optimization of the effective and efficient implementation of XMTB/R primary diagnostic algorithm, by systematically screening for TB high risk groups. Multi sectorial approach needed to be employed in the TB high risk screening, using the newly developed TB screening questions to routinely identify the TB high risk groups (appendix 18) at all entry points and this may improve the MTB positivity rate. This feeds into the second part of component 1A of End TB strategy pillar one, which speaks of systematic screening of contacts and systematic screening of TB high risk groups.The study established changes brought on as XMTB/R primary diagnostic algorithm rolled out on;; i) number of samples investigated for TB ii) MTB positivity rate and iii) proportion of unsuccessful results over time. Ministry of Health and Child Care needs to continue to support XMTB/R primary diagnostic algorithm testing capacity by routinely identifying TB high risk clients (using questions on appendix 18) that are legible for more sensitive chest x-ray screening

The implication of demonstrating that roll out of XMTB/R primary diagnostic test did not necessarily result in increased MTB positivity rate, was that availing of interventions, do not automatically result in increased yield, but strict adherence and monitoring of agreed upon algorithm with increased vigilance in routine TB screening

for at risk groups at health facilities. The TB high risk group identified using questions on appendix 18, are to be screened using chest x-ray which gives double yield of presumptive TB clients. A bigger presumptive TB group, identified by the more sensitive chest x-ray, may lead to increase in MTB positivity.

The implication of low health seeking behaviour of males, was that males delay diagnosis, thus increasing the chance of spreading the disease before diagnosis, while decreasing the prognosis. Implication to the findings was that campaign programs must target improvement of health seeking behaviour of males. Strengthening interventions such as active case finding, integration of private health care providers and enhanced service delivery may reduce delays in TB diagnosis of males. Awareness campaigns undertaken to focus on males may help males to present to health facilities early to enable early MTB detection which was evidenced by MTB detected low or MTB detected trace semi quantitative XMTB/R result. The implication of the research was that sustainable provision of XMTB/R diagnostic test be strengthened by the National TB program, as one of the strategies to end TB.

The implication of Gene Xpert machine data that was missing for some periods, was loss of future research source documents. To make best use of XMTB/R result downloads for surveillance, soft and hardware infrastructure needed to be strengthened. Implication of high rates of unsuccessful results was wastage of cartridges, patient time and staff time. Equally ensuring continuous electricity supply was important to reduce the rate of unsuccessful assays.

5.3.2 Analysis of effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance in Manicaland, Zimbabwe, 2017-2018, on laboratory turnaround time

The implication of XMTB/R primary diagnostic algorithm roll out and laboratory turnaround time was favourable. XMTB/R primary diagnostic algorithm roll out, had a statistically significant decrease in the time taken for patients to receive results**.**

5.3.3 Determination of the performance of TB treatment outcomes as XMTB/R primary diagnostic algorithm rolled out and in Manicaland, for 2017-2018

The implication of findings are that, if National TB program made XMTB/R the primary TB diagnostic algorithm accessible for all patients presenting with presumptive TB, TB treatment outcomes like died may continue to decrease towards the 2035 SDGs target of aiming to reduce TB deaths by 95% between 2015 and 2035.

5.3.4 Exploration of geo-spatial mapping capacity as XMTB/R primary diagnostic algorithm rolled out in Manicaland, for 2017-2018

The implication of the research was that the epidemiological distribution of TB in Manicaland was heterogeneous. As the XMTB/R primary diagnostic algorithm rolled out, it brought with it increased capacity for geo-spatial mapping. TB program managers may use geo-spatial mapping to ensure there may be MTB detected patient linkage to care at health facility level. Armed with the generated geo-spatial mapping, National TB program could resource mobilise for interventions to break the TB transmission cycle in the identified MTB hot spots as well as the identified rifampicin resistant hot spots. The package of intervention may be more streamlined to elimination intervention strategy in commensurate with identified gap namely; hotspot for rifampicin resistant or MTB detected high or MTB detected low. For the identified health facilities with high frequencies of rifampicin resistant results, National TB program may focus MDRTB prevention and control interventions like Programmatic Multi Drug Resistant Tuberculosis training, or mentoring on Short all Oral Regimen

for Rifampicin Resistant Tuberculosis. For the health facilities with high frequencies of MTB detected National TB program may focus trainings on TB case management.

5.3.5 Production of frozen sputum quality control specimen as XMTB/R primary diagnostic algorithm rolled out

The implications of findings in light of the research objectives is that frozen sputum, pre-run on panel of TB tests provides economical quality control sputum specimen as XMTB/R primary diagnostic test roll out.

5.4 Recommendations

5.4.1 Evaluation of effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance, in Manicaland, for 2017-2018, on MTB detection

Recommendations to increase MTB detection as XMTB/R primary diagnostic algorithm rolled out are listed below: Administer TB screening questions to routinely identify the TB high risk groups at all points of entry (appendix 18). Instead of using the TB screening tool on all clients identified as TB high risk groups, screen using chest x-ray which gives double yield of presumptive TB clients, this may increase MTB positivity rate.

5.4.2 Analysis of effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance in Manicaland, Zimbabwe, 2017-2018, on laboratory turnaround time

National TB program to continue provision of XMTB/R primary diagnostic algorithm, as it ensures patients get results earlier.

5.4.3 Determination of the performance of TB treatment outcomes as XMTB/R primary diagnostic algorithm rolled out in Manicaland, for 2017-2018

National TB program to continue provision of XMTB/R primary diagnostic algorithm in a bid to reduce TB deaths and increase successful TB treatment outcomes.

5.4.4 Exploration of geo-spatial mapping capacity as XMTB/R primary diagnostic algorithm rolled out in Manicaland, for 2017-2018

That National TB program may resource mobilise for interventions to break the TB transmission cycle in the identified MTB hot spots as well as the identified rifampicin resistant hotspots. TB program managers may use geo-spatial mapping capacity to verify number of MTB detected and MTB detected patients that are linked to care, per health facility. For the identified health facilities with high frequencies of rifampicin resistant results, National TB program may focus MDRTB prevention and control interventions such as; verifying linkage to care, Programmatic Multi Drug Resistant Tuberculosis training, or mentoring on Short all Oral Regimen for Rifampicin Resistant Tuberculosis.

5.4.5 Production of frozen sputum quality control specimen as XMTB/R primary diagnostic algorithm rolled out

To save on in country test verification budget of newly introduced TB tests, or continued quality XMTB/R primary diagnostic algorithm provision, consider use of the frozen sputum quality control specimen in the form of frozen sputum and ride on previous test results of reference method.

5.5 Suggestions for Further Research

Future studies are recommended to further inform the possible gaps identified in the study.

5.5.1 Evaluation of effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance, in Manicaland, for 2017-2018, on MTB detection

Suggestions for further research to evaluate the TB screening questions to routinely identify the TB high risk groups as well as to validate their usefulness and value addition to XMTB/R primary diagnostic test roll out on MTB detection

5.5.2 Analysis of effectiveness of XMTB/R test in targeted screening and primary diagnostic algorithms for *MTB* infection and rifampicin resistance in Manicaland, Zimbabwe, 2017-2018, on laboratory turnaround time

Future study to focus on time to MTB detection**.**

5.5.3 Determination of the performance of TB treatment outcomes as XMTB/R primary diagnostic algorithm rolled out in Manicaland, for 2017-2018

Future study to focus on full panel of determinants of TB treatment outcomes such as existing co-morbidities, level of management of the co-morbidities, type of TB, time taken to commencement of TB Treatment, TB regimen, and treatment model.

5.5.4 Exploration of geo-spatial mapping capacity as XMTB/R primary diagnostic algorithm rolled out in Manicaland, for 2017-2018

Suggestion for future research is to carry out a research focusing on the identified XMTB/R detected hotspots, to enable covariate analysis.

5.5.5 Production of frozen sputum quality control specimen as XMTB/R primary diagnostic algorithm rolled out

Suggestions for future research to use large volumes sputum to enable repeat of both tests on day one and year post freezing. This will address high demand for quality verification as XMTB/R primary diagnostic algorithm rolled out.

References

Abdullahi, O., Moses, N., Sanga, D., & Annie, W. (2021). The effect of empirical and laboratory-confirmed tuberculosis on treatment outcomes. *Scientific reports*, *11*(1), 14854. https://doi.org/10.1038/s41598-021-94153-0

Ardizzoni, E., Fajardo, E., Saranchuk, P., Casenghi, M., Page, A. L., Varaine, F., Kosack, C. S., & Hepple, P. (2015). Implementing the Xpert® MTB/RIF Diagnostic Test for Tuberculosis and Rifampicin Resistance: Outcomes and Lessons Learned in 18 Countries. *PloS one*, *10*(12), e0144656. https://doi.org/10.1371/journal.pone.0144656

Arinaminpathy, N., & Dowdy, D. (2015). Understanding the incremental value of novel diagnostic tests for tuberculosis. *Nature*, *528*(7580), S60–S67. https://doi.org/10.1038/nature16045

Arinaminpathy, N., & Dowdy, D. (2015). Understanding the incremental value of novel diagnostic tests for tuberculosis. *Nature*, *528*(7580), S60–S67. https://doi.org/10.1038/nature16045

Bishop, P. J., & Neumann, G. (1970). The history of the Ziehl-Neelsen stain. *Tubercle*, *51*(2), 196–206. https://doi.org/10.1016/0041-3879(70)90073-5

Bisognin, F., Lombardi, G., Lombardo, D., Re, M. C., & Dal Monte, P. (2018). Improvement of Mycobacterium tuberculosis detection by Xpert MTB/RIF Ultra: A head-to-head comparison on Xpert-negative samples. *PloS one*, *13*(8), e0201934. https://doi.org/10.1371/journal.pone.0201934

Boehme, C., (2014). FIND Because Diagnostic Tools Matter New TB Diagnostics Landscape and pipeline.

Boniface, R., Moshabela, M., Zulliger, R., Macpherson, P., & Nyasulu, P. (2012). Correlates of Delayed Diagnosis among Human Immunodeficiency Virus-Infected Pulmonary Tuberculosis Suspects in a Rural HIV Clinic, South Africa. *Tuberculosis research and treatment*, *2012*, 827148. https://doi.org/10.1155/2012/827148

Boyles, T. H., Hughes, J., Cox, V., Burton, R., Meintjes, G., & Mendelson, M. (2014). False-positive Xpert® MTB/RIF assays in previously treated patients: need for caution in interpreting results. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*, *18*(7), 876–878. https://doi.org/10.5588/ijtld.13.0853

Census Report: Zimbabwe National Statistics Agency, (2012). https://unstats.un.org/unsd/demographic-social/census/documents/

Chakravorty, S., Simmons, A. M., Rowneki, M., Parmar, H., Cao, Y., Ryan, J., Banada, P. P., Deshpande, S., Shenai, S., Gall, A., Glass, J., Krieswirth, B., Schumacher, S. G., Nabeta, P., Tukvadze, N., Rodrigues, C., Skrahina, A., Tagliani, E., Cirillo, D. M., Davidow, A., … Alland, D. (2017). The New Xpert MTB/RIF Ultra: Improving Detection of *Mycobacterium tuberculosis* and Resistance to Rifampin in an Assay Suitable for Point-of-Care Testing. *mBio*, *8*(4), e00812-17. https://doi.org/10.1128/mBio.00812-17

Chamie, G., Wandera, B., Marquez, C., Kato-Maeda, M., Kamya, M. R., Havlir, D. V., & Charlebois, E. D. (2015). Identifying locations of recent TB transmission in rural Uganda: a multidisciplinary approach. *Tropical medicine & international health : TM & IH*, *20*(4), 537–545. https://doi.org/10.1111/tmi.12459

Chirenda, J., Gwitira, I., Warren, R. M., Sampson, S. L., Murwira, A., Masimirembwa, C., Mateveke, K. M., Duri, C., Chonzi, P., Rusakaniko, S., & Streicher, E. M. (2020). Spatial distribution of Mycobacterium Tuberculosis in metropolitan Harare, Zimbabwe. *PloS one*, *15*(4), e0231637. https://doi.org/10.1371/journal.pone.0231637

Cilloni, L., Fu, H., Vesga, J. F., Dowdy, D., Pretorius, C., Ahmedov, S., Nair, S. A., Mosneaga, A., Masini, E., Sahu, S., & Arinaminpathy, N. (2020). The potential impact of the COVID-19 pandemic on the tuberculosis epidemic a modelling analysis. *EClinicalMedicine*, *28*, 100603. https://doi.org/10.1016/j.eclinm.2020.100603

Creswell, J., Codlin, A. J., Andre, E., Micek, M. A., Bedru, A., Carter, E. J., Yadav, R. P., Mosneaga, A., Rai, B., Banu, S., Brouwer, M., Blok, L., Sahu, S., & Ditiu, L. (2014). Results from early programmatic implementation of Xpert MTB/RIF testing in nine countries. *BMC infectious diseases*, *14*, 2. https://doi.org/10.1186/1471-2334-14-2

Davis, J. L., Kawamura, L. M., Chaisson, L. H., Grinsdale, J., Benhammou, J., Ho, C., Babst, A., Banouvong, H., Metcalfe, J. Z., Pandori, M., Hopewell, P. C., & Cattamanchi, A. (2014). Impact of GeneXpert MTB/RIF on patients and tuberculosis programs in a low-burden setting. a hypothetical trial. *American journal of respiratory and critical care medicine*, *189*(12), 1551–1559. https://doi.org/10.1164/rccm.201311-1974OC

Dorman, S. E., Schumacher, S. G., Alland, D., Nabeta, P., Armstrong, D. T., King, B., Hall, S. L., Chakravorty, S., Cirillo, D. M., Tukvadze, N., Bablishvili, N., Stevens, W., Scott, L., Rodrigues, C., Kazi, M. I., Joloba, M., Nakiyingi, L., Nicol, M. P., Ghebrekristos, Y., Anyango, I., … study team (2018). Xpert

MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. *The Lancet. Infectious diseases*, *18*(1), 76–84. https://doi.org/10.1016/S1473-3099(17)30691-6

Fluorescent Light-Emitting Diode (LED) Microscopy for Diagnosis of Tuberculosis: Policy Statement. (2011). World Health Organization. Haider, N., Osman, A. Y., Gadzekpo, A., Akipede, G. O., Asogun, D., Ansumana, R., Lessells, R. J., Khan, P., Hamid, M. M. A., Yeboah-Manu, D., Mboera, L., Shayo, E. H., Mmbaga, B. T., Urassa, M., Musoke, D., Kapata, N., Ferrand, R. A., Kapata, P. C., Stigler, F., Czypionka, T., … McCoy, D. (2020). Lockdown measures in response to COVID-19 in nine sub-Saharan African countries. *BMJ global health*, *5*(10), e003319. https://doi.org/10.1136/bmjgh-2020-003319

Getis, A., & Ord, J.K. (1992). The analysis of spatial association by use of distance statistics, Geographical Analysis, 24, 189-206. http://dx.doi.org/10.1111/j.1538-4632.1992.tb00261.x

Hanson, C., Osberg, M., Brown, J., Durham, G., & Chin, D. P. (2017). Finding the Missing Patients With Tuberculosis: Lessons Learned From Patient-Pathway Analyses in 5 Countries. *The Journal of infectious diseases*, *216*(suppl_7), S686–S695. https://doi.org/10.1093/infdis/jix388

Hermans, S., Caldwell, J., Kaplan, R., Cobelens, F., & Wood, R. (2017). The impact of the roll-out of rapid molecular diagnostic testing for tuberculosis on empirical treatment in Cape Town, South Africa. *Bulletin of the World Health Organization*, *95*(8), 554–563. https://doi.org/10.2471/BLT.16.185314

Hogan, A. B., Jewell, B. L., Sherrard-Smith, E., Vesga, J. F., Watson, O. J., Whittaker, C., Hamlet, A., Smith, J. A., Winskill, P., Verity, R., Baguelin, M., Lees, J. A.,

Whittles, L. K., Ainslie, K. E. C., Bhatt, S., Boonyasiri, A., Brazeau, N. F., Cattarino, L., Cooper, L. V., Coupland, H., … Hallett, T. B. (2020). Potential impact of the COVID-19 pandemic on HIV, tuberculosis, and malaria in low-income and middle-income countries: a modelling study. *The Lancet. Global health*, *8*(9), e1132–e1141. https://doi.org/10.1016/S2214-109X(20)30288-6

Horne, D. J., Kohli, M., Zifodya, J. S., Schiller, I., Dendukuri, N., Tollefson, D., Schumacher, S. G., Ochodo, E. A., Pai, M., & Steingart, K. R. (2019). Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. *The Cochrane database of systematic reviews*, *6*(6), CD009593. https://doi.org/10.1002

Ismail, N., Nathanson, C. M., Zignol, M., & Kasaeva, T. (2023). Achieving universal access to rapid tuberculosis diagnostics. *BMJ global health*, *8*(5), e012666. https://doi.org/10.1136/bmjgh-2023-012666

Jokwiro, A., Timire, C., Harries, A. D., Gwinji, P. T., Mulema, A., Takarinda, K. C., Mafaune, P. T., & Sandy, C. (2018). Has the utilisation of Xpert® MTB/RIF in Manicaland Province, Zimbabwe, improved with new guidance on whom to test?. *Public health action*, *8*(3), 124–129. https://doi.org/10.5588/pha.18.0028

Kapata, N., Chanda-Kapata, P., Ngosa, W., Metitiri, M., Klinkenberg, E., Kalisvaart, N., Sunkutu, V., Shibemba, A., Chabala, C., Chongwe, G., Tembo, M., Mulenga, L., Mbulo, G., Katemangwe, P., Sakala, S., Chizema-Kawesha, E., Masiye, F., Sinyangwe, G., Onozaki, I., Mwaba, P., … Grobusch, M. P. (2016). The Prevalence of Tuberculosis in Zambia: Results from the First National TB Prevalence Survey, 2013-2014. *PloS one*, *11*(1), e0146392. https://doi.org/10.1371/journal.pone.0146392

Katana, G. G., Ngari, M., Maina, T., Sanga, D., & Abdullahi, O. A. (2022). Tuberculosis poor treatment outcomes and its determinants in Kilifi County, Kenya: a retrospective cohort study from 2012 to 2019. *Archives of public health = Archives belges de sante publique*, *80*(1), 48. https://doi.org/10.1186/s13690-022-00807-4

Kothari, C. R. (2014). Research Methodology: Methods and Techniques. 3rd Edition.

Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. *Biometrics*, *33*(1), 159–174

Maciel, E. L., Pan, W., Dietze, R., Peres, R. L., Vinhas, S. A., Ribeiro, F. K., Palaci, M., Rodrigues, R. R., Zandonade, E., & Golub, J. E. (2010). Spatial patterns of pulmonary tuberculosis incidence and their relationship to socio-economic status in Vitoria, Brazil. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*, *14*(11), 1395–1402.

Manyame-Murwira, B., Takarinda, K. C., Thekkur, P., Payera, B., Mutunzi, H., Simbi, R., Siziba, N., Sibanda, E., Banana, C., Muleya, N., Makombe, E., Jongwe, P. L., Bhebhe, R., Mangwanya, D., Dzangare, J., Mudzengerere, F. H., Timire, C., Wekiya, E., & Sandy, C. (2020). Prevalence, risk factors and treatment outcomes of isoniazid resistant TB in Bulawayo city, Zimbabwe: A cohort study. *Journal of infection in developing countries*, *14*(8), 893–900. https://doi.org/10.3855/jidc.12319

Matambo, R., Takarinda, K. C., Thekkur, P., Sandy, C., Mharakurwa, S., Makoni, T., Ncube, R., Charambira, K., Zishiri, C., Ngwenya, M., Nyathi, S., Chiteka, A., Chikaka, E., & Mutero-Munyati, S. (2020). Treatment outcomes of multi drug resistant and rifampicin resistant Tuberculosis in Zimbabwe: A cohort analysis

of patients initiated on treatment during 2010 to 2015. *PloS one*, *15*(4), e0230848. https://doi.org/10.1371/journal.pone.0230848

Mavenyengwa, R. T., Shaduka, E., & Maposa, I. (2017). Evaluation of the Xpert® MTB/RIF assay and microscopy for the diagnosis of Mycobacterium tuberculosis in Namibia. *Infectious diseases of poverty*, *6*(1), 13. https://doi.org/10.1186/s40249-016-0213-y

Mbelele, P. M., Aboud, S., Mpagama, S. G., & Matee, M. I. (2017). Improved performance of Xpert MTB/RIF assay on sputum sediment samples obtained from presumptive pulmonary tuberculosis cases at Kibong'oto infectious diseases hospital in Tanzania. *BMC infectious diseases*, *17*(1), 808. https://doi.org/10.1186/s12879-017-2931-6

Menzies, N. A., Cohen, T., Lin, H. H., Murray, M., & Salomon, J. A. (2012). Population health impact and cost-effectiveness of tuberculosis diagnosis with Xpert MTB/RIF: a dynamic simulation and economic evaluation. *PLoS medicine*, *9*(11), e1001347. https://doi.org/10.1371/journal.pmed.1001347

Metcalfe, J. Z., Makumbirofa, S., Makamure, B., Mutetwa, R., Peñaloza, R. A., Sandy, C., Bara, W., Mungofa, S., Hopewell, P. C., & Mason, P. (2015). Suboptimal specificity of Xpert MTB/RIF among treatment-experienced patients. *The European respiratory journal*, *45*(5), 1504–1506. https://doi.org/10.1183/09031936.00214114

Metcalfe, J. Z., Makumbirofa, S., Makamure, B., Sandy, C., Bara, W., Mungofa, S., Hopewell, P. C., & Mason, P. (2014). Drug-resistant tuberculosis in high-risk groups, Zimbabwe. *Emerging infectious diseases*, *20*(1), 135–137. https://doi.org/10.3201/eid2001.130732

Metcalfe, J. Z., Makumbirofa, S., Makamure, B., Sandy, C., Bara, W., Mason, P., & Hopewell, P. C. (2016). Xpert(®) MTB/RIF detection of rifampin resistance and time to treatment initiation in Harare, Zimbabwe. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*, *20*(7), 882–889. https://doi.org/10.5588/ijtld.15.0696

Ministry of Health and Child Care, Zimbabwe. (2014). Guidelines for the Programmatic Management of Drug Resistant Tuberculosis in Zimbabwe. Harare, Zimbabwe.

Ministry of Health and Child Care, Zimbabwe. (2018). National Tuberculosis Guidelines.

Ministry of Health and Child Care, Zimbabwe. Tuberculosis National Strategic Plan (2017 to 2020)

Ministry of Health and Child Care, Zimbabwe. (2017). Zimbabwe Tuberculosis and Leprosy Guidelines for the Programmatic Management of Drug Resistant Tuberculosis in Zimbabwe. Harare, Zimbabwe.

Ministry of Health and Child Care, Zimbabwe. (2014). Making Sense of TB Data Guide for collecting analysis and making use of TB for health care workers in Zimbabwe.

Mnyambwa, N. P., Lekule, I., Ngadaya, E. S., Kimaro, G., Petrucka, P., Kim, D. J., Lymo, J., Kazwala, R., Mosha, F., & Mfinanga, S. G. (2018). Assessment of GeneXpert GxAlert platform for multi-drug resistant tuberculosis diagnosis and patients' linkage to care in Tanzania. *BMC research notes*, *11*(1), 121. https://doi.org/10.1186/s13104-018-3235-7

Mugauri Dumisani, H., Chirenda, J., Juru, T., Mugurungi, O., Shambira, G., Gombe, N., & Tshimanga, M. (2022). The epidemiology of drug-resistant tuberculosis in Bulawayo and Matabeleland South provinces, Zimbabwe 2017. *IJID regions*, *3*, 37–43. https://doi.org/10.1016/j.ijregi.2022.03.004

Mupfumi, L., Makamure, B., Chirehwa, M., Sagonda, T., Zinyowera, S., Mason, P., Metcalfe, J. Z., & Mutetwa, R. (2014). Impact of Xpert MTB/RIF on Antiretroviral Therapy-Associated Tuberculosis and Mortality: A Pragmatic Randomized Controlled Trial. *Open forum infectious diseases*, *1*(1), ofu038. https://doi.org/10.1093/ofid/ofu038

Mutembo, S., Mutanga, J. N., Musokotwane, K., Kanene, C., Dobbin, K., Yao, X., Li, C., Marconi, V. C., & Whalen, C. C. (2019). Urban-rural disparities in treatment outcomes among recurrent TB cases in Southern Province, Zambia. *BMC infectious diseases*, *19*(1), 1087. https://doi.org/10.1186/s12879-019-4709-5

O'Donnell, M. R., Larsen, M. H., Brown, T. S., Jain, P., Munsamy, V., Wolf, A., Uccellini, L., Karim, F., de Oliveira, T., Mathema, B., Jacobs, W. R., & Pym, A. (2019). Erratum for O'Donnell et al., "Early Detection of Emergent Extensively Drug-Resistant Tuberculosis by Flow Cytometry-Based Phenotyping and Whole-Genome Sequencing". *Antimicrobial agents and chemotherapy*, *63*(6), e00764-19. https://doi.org/10.1128/AAC.00764-19

Ogyiri, L., Lartey, M., Ojewale, O., Adjei, A. A., Kwara, A., Adanu, R. M., & Torpey, K. (2019). Effect of HIV infection on TB treatment outcomes and time to mortality in two urban hospitals in Ghana-a retrospective cohort study. *The Pan African medical journal*, *32*, 206. https://doi.org/10.11604/pamj.2019.32.206.18673

Policy Statement: Automated Real-Time Nucleic Acid Amplification Technology for Rapid and Simultaneous Detection of Tuberculosis and Rifampicin Resistance: Xpert MTB/RIF System. (2011). World Health Organization.

Pooran, A., Theron, G., Zijenah, L., Chanda, D., Clowes, P., Mwenge, L., Mutenherwa, F., Lecesse, P., Metcalfe, J., Sohn, H., Hoelscher, M., Pym, A., Peter, J., Dowdy, D., & Dheda, K. (2019). Point of care Xpert MTB/RIF versus smear microscopy for tuberculosis diagnosis in southern African primary care clinics: a multicentre economic evaluation. *The Lancet. Global health*, *7*(6), e798–e807. https://doi.org/10.1016/S2214-109X(19)30164-0

Programme, W. H. O. G. T. (1996). Groups at risk : WHO report on the tuberculosis epidemic 1996. Geneva: World Health Organization.

Reza, L. W., Satyanarayna, S., Enarson, D. A., Kumar, A. M., Sagili, K., Kumar, S., Prabhakar, L. A., Devendrappa, N. M., Pandey, A., Wilson, N., Chadha, S., Thapa, B., Sachdeva, K. S., & Kohli, M. P. (2013). LED-fluorescence microscopy for diagnosis of pulmonary tuberculosis under programmatic conditions in India. *PloS one*, *8*(10), e75566. https://doi.org/10.1371/journal.pone.0075566

Robsky, K. O., Kitonsa, P. J., Mukiibi, J., Nakasolya, O., Isooba, D., Nalutaaya, A., Salvatore, P. P., Kendall, E. A., Katamba, A., & Dowdy, D. (2020). Spatial distribution of people diagnosed with tuberculosis through routine and active case finding: a community-based study in Kampala, Uganda. *Infectious diseases of poverty*, *9*(1), 73. https://doi.org/10.1186/s40249-020-00687-2

Sadykova, L., Abramavičius, S., Maimakov, T., Berikova, E., Kurakbayev, K., Carr, N. T., Padaiga, Ž., Naudžiūnas, A., & Stankevičius, E. (2019). A retrospective analysis of treatment outcomes of drug-susceptible TB in Kazakhstan, 2013-

2016. *Medicine*, *98*(26), e16071. https://doi.org/10.1097/MD.0000000000016071

Schmidt, B. M., Geldenhuys, H., Tameris, M., Luabeya, A., Mulenga, H., Bunyasi, E., Scriba, T., & Hatherill, M. (2017). Impact of Xpert MTB/RIF rollout on management of tuberculosis in a South African community. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde*, *107*(12), 1078–1081. https://doi.org/10.7196

Schnippel, K., Meyer-Rath, G., Long, L., MacLeod, W., Sanne, I., Stevens, W. S., & Rosen, S. (2012). Scaling up Xpert MTB/RIF technology: the costs of laboratory- vs. clinic-based roll-out in South Africa. *Tropical medicine & international health : TM & IH*, *17*(9), 1142–1151. https://doi.org/10.1111/j.1365-3156.2012.03028.x

Seung, K. J., Omatayo, D. B., Keshavjee, S., Furin, J. J., Farmer, P. E., & Satti, H. (2009). Early outcomes of MDR-TB treatment in a high HIV-prevalence setting in Southern Africa. *PloS one*, *4*(9), e7186. https://doi.org/10.1371/journal.pone.0007186

Shewade, H. D., Jeyashree, K., Mahajan, P., Shah, A. N., Kirubakaran, R., Rao, R., & Kumar, A. M. V. (2017). Effect of glycemic control and type of diabetes treatment on unsuccessful TB treatment outcomes among people with TB-Diabetes: A systematic review. *PloS one*, *12*(10), e0186697. https://doi.org/10.1371/journal.pone.0186697

Singh, S., Singh, A., Prajapati, S., Kabra, S. K., Lodha, R., Mukherjee, A., Singh, V., Hesseling, A. C., Grewal, H. M., & Delhi Pediatric TB study group (2015). Xpert MTB/RIF assay can be used on archived gastric aspirate and induced

sputum samples for sensitive diagnosis of paediatric tuberculosis. *BMC microbiology*, *15*, 191. https://doi.org/10.1186/s12866-015-0528-z

Tadokera, R., Huo, S., Theron, G., Timire, C., Manyau-Makumbirofa, S., & Metcalfe, J. Z. (2021). Health care seeking patterns of rifampicin-resistant tuberculosis patients in Harare, Zimbabwe: A prospective cohort study. *PloS one*, *16*(7), e0254204. https://doi.org/10.1371/journal.pone.0254204

Takarinda, K. C., Harries, A. D., Nyathi, B., Ngwenya, M., Mutasa-Apollo, T., & Sandy, C. (2015). Tuberculosis treatment delays and associated factors within the Zimbabwe national tuberculosis programme. *BMC public health*, *15*, 29. https://doi.org/10.1186/s12889-015-1437-7

Theron, G., Jenkins, H. E., Cobelens, F., Abubakar, I., Khan, A. J., Cohen, T., & Dowdy, D. W. (2015). Data for action: collection and use of local data to end tuberculosis. *Lancet (London, England)*, *386*(10010), 2324–2333. https://doi.org/10.1016/S0140-6736(15)00321-9

Theron, G., Zijenah, L., Chanda, D., Clowes, P., Rachow, A., Lesosky, M., Bara, W., Mungofa, S., Pai, M., Hoelscher, M., Dowdy, D., Pym, A., Mwaba, P., Mason, P., Peter, J., Dheda, K., & TB-NEAT team (2014). Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. *Lancet (London, England)*, *383*(9915), 424–435. https://doi.org/10.1016/S0140-6736(13)62073-5

Thorson, A., Hoa, N. P., & Long, N. H. (2000). Health-seeking behaviour of individuals with a cough of more than 3 weeks. *Lancet (London, England)*, *356*(9244), 1823–1824. https://doi.org/10.1016/s0140-6736(00)03241-4

Timire, C., Sandy, C., Kumar, A. M. V., Ngwenya, M., Murwira, B., Takarinda, K. C., & Harries, A. D. (2019). Access to second-line drug susceptibility testing results among patients with Rifampicin resistant tuberculosis after introduction of the Hain® Line Probe Assay in Southern provinces, Zimbabwe. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*, *81*, 236–243. https://doi.org/10.1016/j.ijid.2019.02.007

Van Ingen, J., Aarnoutse, R. E., Donald, P. R., Diacon, A. H., Dawson, R., Plemper van Balen, G., Gillespie, S. H., & Boeree, M. J. (2011). Why Do We Use 600 mg of Rifampicin in Tuberculosis Treatment? *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, *52*(9), e194–e199. https://doi.org/10.1093/cid/cir184

Varaine, F., Ardizzoni, E., (2012). Xpert MTB/Rif Implementation in MSF Projects First Results. MSF GLI Meeting.

Vassall, A., van Kampen, S., Sohn, H., Michael, J. S., John, K. R., den Boon, S., Davis, J. L., Whitelaw, A., Nicol, M. P., Gler, M. T., Khaliqov, A., Zamudio, C., Perkins, M. D., Boehme, C. C., & Cobelens, F. (2011). Rapid diagnosis of tuberculosis with the Xpert MTB/RIF assay in high burden countries: a cost-effectiveness analysis. *PLoS medicine*, *8*(11), e1001120. https://doi.org/10.1371/journal.pmed.1001120

Wells, C. D., Cegielski, J. P., Nelson, L. J., Laserson, K. F., Holtz, T. H., Finlay, A., Castro, K. G., & Weyer, K. (2007). HIV infection and multidrug-resistant tuberculosis: the perfect storm. *The Journal of infectious diseases, 196 Suppl 1*, S86–S107. https://doi.org/10.1086/518665

World Health, O. (2010). Multidrug and extensively drug-resistant TB (M/XDR-TB) : 2010 global report on surveillance and response. Geneva: World Health Organization.

World Health, O. (2013). *Global tuberculosis report 2013*. Geneva: World Health Organization.

World Health, O. (2014). *Global tuberculosis report 2014*. Geneva: World Health Organization.

World Health, O. (2018). *Global tuberculosis report 2018*. Geneva: World Health Organization.

World Health Organization. Communicable Diseases, C. (2000). DOTS-Plus and the Green Light Committee. Geneva: World Health Organization.

World Health, O. (2010). Multidrug and extensively drug-resistant TB (M/XDR-TB) : 2010 global report on surveillance and response. Geneva: World Health Organization.

World Health, O. (2015). The End TB Strategy. Geneva, Switzerland: WHO, 2015. https://www.who.int/tb/strategy/End_TB_Strategy.

World Health, O. (2016). *Global tuberculosis report 2016*. Geneva: World Health Organization.

World Health, O. (2017). *Global tuberculosis report 2017*. Geneva: World Health Organization.

World Health, O. (2018). *Global tuberculosis report 2018*. Geneva: World Health Organization.

World Health Organization. Communicable Diseases, C. (2000). DOTS-Plus and the Green Light Committee. Geneva: World Health Organization.

World Health, O. (2019). *Global tuberculosis report 2019*. Geneva: World Health Organization.

World Health, O. (2022). *Global tuberculosis report 2022*. Geneva: World Health Organization.

APPENDICES

Appendix 1: Health facility summary data collecting tool

Health facility name…….

Health facility GPS Coordinates……Quarter…… Year….

Enrollment number	Date treatment commenced	Age	Sex	HIV Status	PTB or EPTB	Xpert MTB	RR	Smear Microscopy	Treatment Outcome

Appendix 2: Data collecting tool for TB registers and Gene Xpert machine

Allotted research number	
Age in years	
Sex	Male
	Female
HIV Status	HIV-(Code 0)
	HIV+(Code 1)
	Unknown(Code 9)
	Missing(Code 2)
Requesting Health Facility(Code 1 to 325)	
Date sputum collected	
Date sputum received by lab	
Date tested	
Test used	
Genexpert Result	MTB Not Detected
	MTB Detected
	Detected
	High
	Detected
	Medium
	Detected
	Low
	Detected
	Very Low
	Error
	Invalid
	No result

Appendix 3:Gene Xpert MTB/Rif Ultra standard operating procedure

Carefully unscrew the lid of the sputum container.

Pour two volumes of sample reagent (SR) directly into one volume of sputum in the sputum container (1ml of sputum is the minimum quantity, while 3-4ml is the optimal quantity). For larger volumes of sputum greater than 4mls, a portion of SR from a second bottle would be needed as each bottle of SR contains 8ml SR. Replace the lid and shake vigorously for 10-20 times (one back and forth movement is a single shake) or vortex.

Incubate at room temperature for 10 minutes.

After 10 minutes incubation, shake 10-20 times and incubate for an additional 5 minutes.

After additional 5 min of incubation, sample should be perfectly fluid before being tested, with no visible clumps of sputum. Sample should be perfectly fluid before testing.

If still viscous, wait 5-10 more minutes before inoculating the cartridge with 2-4 ml of the final solution and process as per analyser instructions.

Appendix 4: DHIS2 Mutasa District (43) health facilities

1	Hauna District Hospital Gene Xpert site
2	Bonda mission hospital Gene Xpert site
3	Chavhanga rural health centre
4	Chinaka health post
5	Chinamasa clinic
6	Chitombo clinic
7	Drenane clinic
8	Eastern Highlands Plantation clinic
9	Gatsi mission clinic
10	Guta clinic
11	Haparari clinic
12	Hauna clinic
13	Honde mission clinic
14	Imbeza clinic
15	Jombe clinic
16	Katiyo Tea Estate clinic
17	Mandeya II clinic
18	Mapara clinic
19	Mupotedzi clinic
20	Mt Jenya
21	Mutasa clinic
22	Mwoyoweshumba clinic
23	Ngarura clinic
24	Old Mutare mission hospital
25	Premier Central clinic
26	Redwing clinic
27	Rupinda Rural Health centre
28	Sachisuko clinic
29	Sagambe clinic
30	Sadziwa clinic
31	Sahumani clinic
32	Sakupwanya clinic
33	Samanga clinic
34	Samaringa clinic
35	Selbourne; Pine Tree
36	Sheba clinic
37	Sherukuru Rural Health centre
38	St Augustine’s clinic
39	St Barbra mission hospital
40	St Peter’s Mandeya mission hospital
41	Tsonzo Rural Hospital
42	Zindi clinic

Appendix 5:DHIS2 Mutare District health facilities

1	ZPS Mutare Remand Prison clinic
2	ArdaOdzi clinic
3	Army Dependant clinic
4	Bakorenhema clinic
5	Bezely Bridge clinic
6	Burma Valley
7	Bwizi Rural Health centre
8	Chatora clinic
9	Chiadzwa Rural Health Centre
10	Chikwariro clinic
11	Chipendeke clinic
12	Chipfatsura clinic
13	Chishingwi clinic
14	Chitaka clinic
15	Chitakatira clinic
16	Chitora clinic
17	Chiwere clinic
18	Dora clinic
19	Gutaurare clinic
20	Gwindingwi clinic
21	LeekuilTakunda clinic
22	Mambwere clinic
23	Mapofu clinic
24	Marange Rural Hospital Gene Xpert site
25	Masasi clinic
26	Mtanda clinic
27	Mavhiza clinic
28	Mkwada clinic
29	Mount Zuma clinic
30	Munyarari clinic
31	Murambi Gardens clinic
32	MuromoRural Health Centre
33	MurowaRural Health Centre
34	Mushunje clinic

Mutare District health facilities

35	Mutare Provincial Hospital Gene Xpert site
36	Mutare ZRP clinic
37	New Start Centre Gene Xpert site
38	Nyagundi Rural Health Centre
39	Nyamazura Rural Health Centre
40	Nzvenga clinic
41	Odzi clinic
42	Rowa clinic

43 Sakubva District Hospital
44 St Andrews Mission Hospital
45 St Joseph’s Mission Hospital
46 St Weirburghs clinic
47 ZPCS Farm Prison clinic
48 ZPCS Remand clinic
49 ZRP Mutare Provincial clinic
50 Zimunya clinic
51 Zimbare clinic
52 Zvipiripiri Rural Health Centre

Appendix 6:DHIS2 Mutare City health facilities

1	City clinic
2	Chikanga clinic
3	Sakubva clinic
4	Dangamvura poly clinic
5	Fern Valley clinic
6	Hobhouse clinic
7	Florida clinic
8	Mutare Infectious Disease Hospital Gene Xpert site
9	Sakubva Health Centre

Appendix 7: DHIS2 Chimanimani District health facilities

1	ArdaRusitu clinic
2	Biriri Rural Hospital
3	Bumba Rural Health Centre
4	Cashel clinic
5	Chakohwa clinic
6	Changazi Rural Health Centre
7	Charter clinic
8	Chayamiti Rural Health
9	Chikukwa Rural Health Centre
10	Chikwariro clinic
11	Chimanimani Rural Health Centre Gene Xpert site
12	Chimanimani Urban clinic
13	Chisengu clinic
14	Gudhlanga clinic
15	Gwendingwe clinic
16	Hlabiso clinic
17	Martin Forest clinic
18	Muchadziya Rural Health Centre
19	Mutambara Mission Hospital Gene Xpert site
20	Mutsvangwa clinic
21	Ngorima clinic
22	Nhedziwa clinic
23	Nyabamba clinic
24	Nyahode clinic
25	Nyanyadzi Rural Hospital
26	Roscommon clinic
27	Rusitu Mission Hospital
28	Shinja clinic
29	Tarka clinic
30	Tilbury clinic

Appendix 8:DHIS2 Chipinge District health facilities

1	ArdaChisumbanje clinic
2	Changazi clinic
3	Chibuwe clinic
4	Chichichi clinic
5	Chikore Mission Hospital
6	Chinyamukwakwa Rural Health Centre
7	Chipangayi clinic
8	Chipinge District Hospital Gene Xpert site
9	Chipinge Town clinic
10	Chipinge clinic
11	Chipinge ZRP clinic
12	Chisume clinic
13	Clearwater clinic
14	Gaza clinic
15	Gumira clinic
16	Gwenzi clinic
17	Hwakwata clinic
18	Jersey clinic
19	Junction Gate clinic
20	Kondo clinic
21	Kopera Rural Health Centre
22	Mabee Rural Health Centre
23	Madhuku clinic
24	Mahenye Rural Health Centre
25	Manzvure clinic
26	Maparadza clinic
27	Midsave clinic
28	Mount Selinda Mission Hospital
29	Musani clinic
30	Musilizwe Rural Health Centre
31	Muswera Rural clinic
32	Mutandahwe clinic
33	Mutema
34	New Start Centre
35	New Year's Gift clinic
36	Ngaone clinic
37	Nyunga clinic
38	Paidamoyo Rural Health Centre

Chipinge District health facilities

39	Ratelschoek clinic
40	Rimbi clinic
41	Silver Stream clinic
42	Southdown clinic

43	St Peters Hospital Gene Xpert site
44	Tamandayi clinic
45	Tanganda Rural Health Centre
46	Tingamira clinic
47	Tongogara Rural Health Centre
48	Tuzuka clinic
49	Veneka clinic
50	ZPCS Chipinge Prison clinic
51	Zamuchiya clinic
52	Zona clinic

Appendix 9:DHIS2 Buhera District health facilities

1 Bangura clinic
2 Berenyazvizvi clinic
3 Betera Rural Health Centre
4 Birchenough Bridge Rural Gene Xpert site Hospital
5 Buhera Rural Hospital
6 Chabata clinic
7 Chapanduka clinic
8 Chapwanya clinic
9 Chawatama Rural Health Centre
10 Chimbudzi clinic
11 Chironza clinic
12 Chiwenga clinic
13 Chiwese clinic
14 Dorowa clinic
15 Garamwera clinic
16 Gombe clinic
17 Gunura clinic
18 Madzimbashuro Rural Health Centre
19 Mombeyarara Rural Health Centre
20 Msasa Rural District Concil
21 Mudanda clinic
22 Mudawose clinic
23 Munyanyi clinic
24 Murambinda Mission Hospital Gene Xpert site
25 Murwira Rural Health Centre
26 Mutepfe clinic
27 Mutiusinazitaclinic
28 Muzokomba clinic
29 Ndyarima clinic
30 Nerutanga clinic
31 Nyashanu Mission Clinic
32 Rambanepasi clinic
33 Zangama Rural Health Centre

Appendix 10: DHIS2 Makoni District health facilities

1	Arnoldine Mission Hospital
2	Bamba Rural Health clinic
3	Chiduku clinic
4	Chikore
5	Chikodzera Rural Health
6	Chikobvore Rural Centre
7	Chinyadza clinic
8	Chinhenga
9	Chinyika I Rural Health Centre
10	Chinyika II Rural Health Centre
11	Chinyudza Rural Health Centre
12	Chitungwiza clinic
13	Dowa clinic
14	Dumbabwe clinic
15	Era Mine clinic
16	Gowakowa Rural Health Centre
17	Groobi Spring Rural Health Centre
18	Headlands clinic
19	Katsenga Rural Health Centre
20	Makoni Rural Hospital
21	Maparura Rural Health Centre
22	Masvosva Rural Health Centre
23	Matotwe Rural Health Centre
24	Matsika clinic
25	Maurice Nyagumbo clinic
26	Mavhudzi clinic
27	Mayo I Rural Health Centre
28	Mayo 2 Rural Health Centre
29	Mubvurungwa clinic
30	Mufusire clinic
31	Mukamba clinic
32	Mukuwapasi Rehab clinic
33	Name clinic
34	Nedewedzo Rural Hospital
35	Nedziwa clinic
36	Nyahowe Rural Health Centre

37	Nyahukwe Rural Health Centre
38	NyamIdzi clinic
39	Nyamukamani Rural Health Centre
40	Nyamusosa clinic
41	Nyazura clinic
42	Nyazura Mission Clinic

43 Ringanayi clinic
44 Rukweza
45 Rusape General Hospital Gene Xpert site
46 Rusape ZRP
47 Sangana clinic
48 St Michael Tanda Clinic
49 St Theresa Mission Hospital
50 Tandi clinic
51 Tariro clinic
52 Tsanzaguru Clinic
53 Tsikada Rural Hospital
54 Vengere clinic
55 Weir Rural
56 ZPCS Little Kraal
57 ZPCS Rusape Prison

Appendix11:DHIS2 Nyanga District health facilities

1	Avilla Mission Hospital
2	Bende clinic
3	Chatindo clinic
4	Chiwarira clinic
5	Claremont Estate clinic
6	Dombo Rural Health Centre
7	Elim Mission Hospital
8	ErimForest Estate clinic
9	Fombe Rural Health Centre
10	Gairezi Rural Health Centre
11	Gotekote Rural Health Centre
12	Kambudzi clinic
13	Matize clinic
14	Mt Mellery Mission Hospital
15	Nyadowa clinic
16	Nyafaru clinic
17	Nyajezi clinic
18	Nyamaropa clinic
19	Nyamombe Camp Rural Health Centre
20	Nyamombe clinic
21	Nyanga District Hospital Gene Xpert site
22	Nyanguai clinic
23	Nyangui clinic
24	Nyarumvurwe Rural Health Centre
25	Nyatate clinic
26	Nyautare Rural Health Centre
27	Regina Coeli Mission Hospital Gene Xpert site
28	Ruchera Rural Health Centre
29	Sabvure clinic
30	Spring Valley clinic
31	Tombo clinic

Appendix 12: Africa University Research Ethics Committee approval initial topic

AFRICA UNIVERSITY
(A United Methodist-Related Institution)
INVESTING IN AFRICA'S FUTURE

AFRICA UNIVERSITY
RESEARCH ETHICS COMMITTEE (AUREC)

P.O. BOX 1320, MUTARE, ZIMBABWE • OFF NYANGA ROAD, OLD MUTARE • TEL: (+263-20) 60075/60026/61611 • E-MAIL: aurec@africau.edu • WEBSITE: www.africau.edu

25 July, 2018

The Director, Prof Paul Ndebele
Medical Research Council of Zimbabwe
Corner Josiah Tongogara and Mazowe Road
Harare

Dear Sir

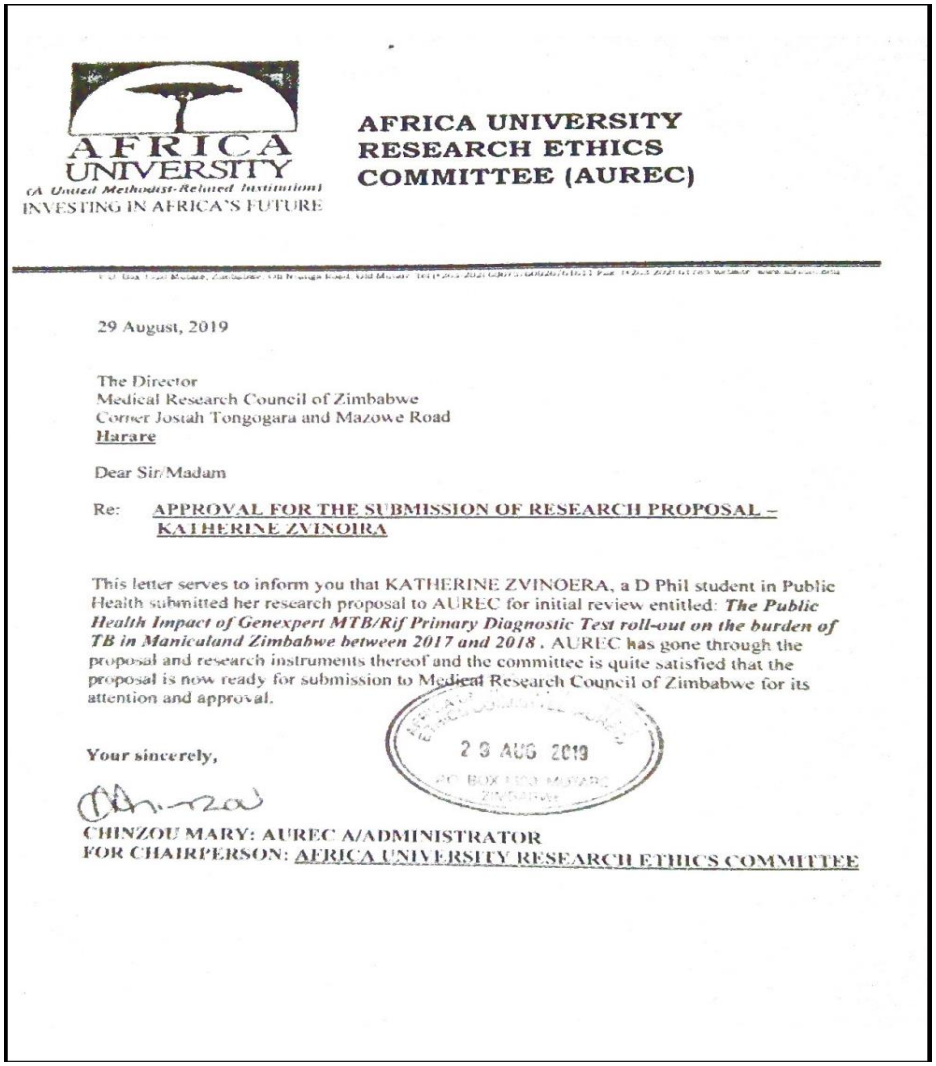
Re: **APPROVAL FOR THE SUBMISSION OF RESEARCH PROPOSAL – KATHERINE ZVINOERA**

This letter serves to inform you that Katherine Zvinoera, a D Phil student in Public Health submitted her research proposal to AUREC for initial review entitled: ***The Diagnostic Utility of Non-invasive Specimens in the Detection of Pulmonary Childhood Tuberculosis by Line Probe Assay and Genexpert MTB/Rif Ultra in Manicaland- a prospective study*** AUREC has gone through the proposal and research instruments thereof and the committee is quite satisfied that the proposal is now ready for submission to Medical Research Council of Zimbabwe Ethics Committee for its attention and approval.

Yours sincerely

CHINZOU MARY. AUREC A/RESEARCH ETHICS PROGRAMME OFFICER
FOR CHAIRPERSON, AFRICA UNIVERSITY RESEARCH ETHICS COMMITTEE

Appendix 13: AUREC approval final topic



AFRICA UNIVERSITY
(A United Methodist-Related Institution)
INVESTING IN AFRICA'S FUTURE

AFRICA UNIVERSITY RESEARCH ETHICS COMMITTEE (AUREC)

29 August, 2019

The Director
Medical Research Council of Zimbabwe
Corner Josiah Tongogara and Mazowe Road
Harare

Dear Sir/Madam

Re: APPROVAL FOR THE SUBMISSION OF RESEARCH PROPOSAL – KATHERINE ZVINOIRA

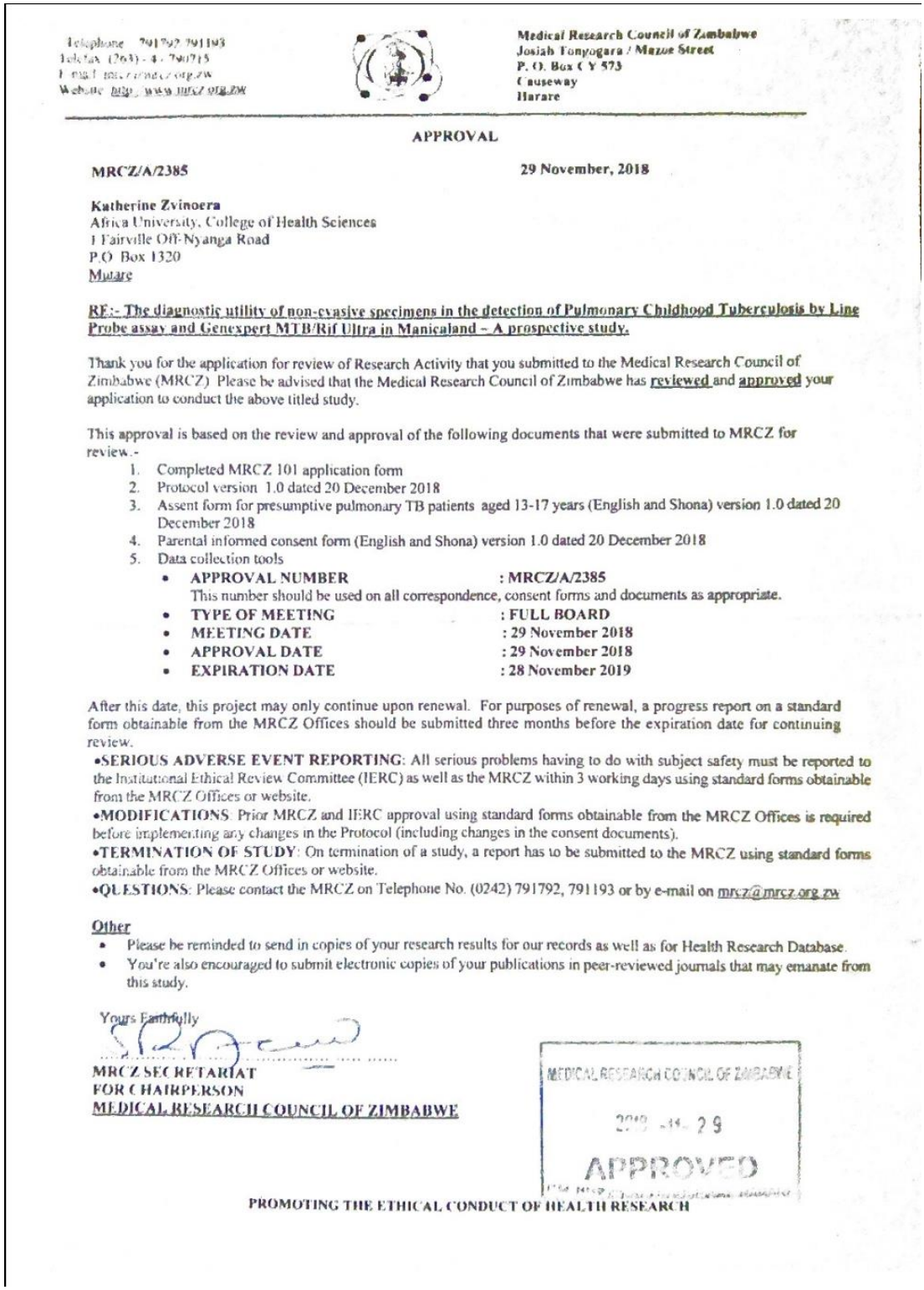
This letter serves to inform you that KATHERINE ZVINOERA, a D Phil student in Public Health submitted her research proposal to AUREC for initial review entitled: ***The Public Health Impact of Genexpert MTB/Rif Primary Diagnostic Test roll-out on the burden of TB in Manicaland Zimbabwe between 2017 and 2018***. AUREC has gone through the proposal and research instruments thereof and the committee is quite satisfied that the proposal is now ready for submission to Medical Research Council of Zimbabwe for its attention and approval.

29 AUG 2019

Your sincerely,

CHINZOU MARY: AUREC A/ADMINISTRATOR
FOR CHAIRPERSON: AFRICA UNIVERSITY RESEARCH ETHICS COMMITTEE

Appendix 14: Medical Research Council of Zimbabwe approval letter



Telephone 791792 791193
Telefax (263) - 4 - 790715
E-mail: mrcz@mrcz.org.zw
Website: http://www.mrcz.org.zw

Medical Research Council of Zimbabwe
Josiah Tongogara / Mazoe Street
P. O. Box C Y 573
Causeway
Harare

APPROVAL

MRCZ/A/2385 **29 November, 2018**

Katherine Zvinoera
Africa University, College of Health Sciences
1 Fairville Off Nyanga Road
P.O Box 1320
Mutare

RE:- The diagnostic utility of non-evasive specimens in the detection of Pulmonary Childhood Tuberculosis by Line Probe assay and Genexpert MTB/Rif Ultra in Manicaland – A prospective study.

Thank you for the application for review of Research Activity that you submitted to the Medical Research Council of Zimbabwe (MRCZ). Please be advised that the Medical Research Council of Zimbabwe has reviewed and approved your application to conduct the above titled study.

This approval is based on the review and approval of the following documents that were submitted to MRCZ for review.-

1. Completed MRCZ 101 application form
2. Protocol version 1.0 dated 20 December 2018
3. Assent form for presumptive pulmonary TB patients aged 13-17 years (English and Shona) version 1.0 dated 20 December 2018
4. Parental informed consent form (English and Shona) version 1.0 dated 20 December 2018
5. Data collection tools

- **APPROVAL NUMBER : MRCZ/A/2385**
  This number should be used on all correspondence, consent forms and documents as appropriate.
- **TYPE OF MEETING : FULL BOARD**
- **MEETING DATE : 29 November 2018**
- **APPROVAL DATE : 29 November 2018**
- **EXPIRATION DATE : 28 November 2019**

After this date, this project may only continue upon renewal. For purposes of renewal, a progress report on a standard form obtainable from the MRCZ Offices should be submitted three months before the expiration date for continuing review.

•**SERIOUS ADVERSE EVENT REPORTING**: All serious problems having to do with subject safety must be reported to the Institutional Ethical Review Committee (IERC) as well as the MRCZ within 3 working days using standard forms obtainable from the MRCZ Offices or website.

•**MODIFICATIONS**: Prior MRCZ and IERC approval using standard forms obtainable from the MRCZ Offices is required before implementing any changes in the Protocol (including changes in the consent documents).

•**TERMINATION OF STUDY**: On termination of a study, a report has to be submitted to the MRCZ using standard forms obtainable from the MRCZ Offices or website.

•**QUESTIONS**: Please contact the MRCZ on Telephone No. (0242) 791792, 791193 or by e-mail on mrcz@mrcz.org.zw

Other

- Please be reminded to send in copies of your research results for our records as well as for Health Research Database.
- You're also encouraged to submit electronic copies of your publications in peer-reviewed journals that may emanate from this study.

Yours Faithfully

MRCZ SECRETARIAT
FOR CHAIRPERSON
MEDICAL RESEARCH COUNCIL OF ZIMBABWE

MEDICAL RESEARCH COUNCIL OF ZIMBABWE
2018 -11- 29
APPROVED

PROMOTING THE ETHICAL CONDUCT OF HEALTH RESEARCH

Appendix 15:Extension Medical Research Council of Zimbabwe

Telephone: 791792/791193
Telefax: (263) - 242 - 790715
E-mail: mrcz@mrcz.org.zw
Website: http://www.mrcz.org.zw

Medical Research Council of Zimbabwe
Josiah Tongogara / Mazowe Street
P. O. Box CY 573
Causeway
Harare

MRCZ/A/2385 **07 November, 2019**

Katherine Zvinoera
Africa University
P.O. Box 1320
Off Nyanga Road
Mutare

RE: The public health impact of Genexpert MTB/Rif Primary Diagnostic Test roll-out on the burden of TB in Manicaland Zimbabwe between 2017 and 2018

We refer to your correspondence dated 11 September, 2019 on the above mentioned subject.

Please be advised that the Medical Research Council of Zimbabwe has **reviewed** and **approved** your request for extension of the study period up to 30 November, 2020. On the same note, please be reminded that the study should have a valid MRCZ approval during study round up and data analysis.

Yours Faithfully

.....

MRCZ SECRETARIAT
FOR CHAIRPERSON
MEDICAL RESEARCH COUNCIL OF ZIMBABWE

MEDICAL RESEARCH COUNCIL OF ZIMBABWE
2019 -11- 07
APPROVED
P.O. BOX CY 573 CAUSEWAY, HARARE

Appendix 16: List of four publications

#	Manuscript Name	Journal Details
1	Comparative Analysis of Genexpert MTB/Rif Version 4 and Genexpert Ultra on Frozen Sputum	Central African journal of Medicine Vol 66 No. 1-6 (2020)
2	The Impact of Changing the Diagnostic Test for Tuberculosis in Manicaland	Public Health Action Vol 11 no 4 published December 2021
3	Geo Spatial Distribution of Genexpert MTB/Rif Results in Manicaland For 2017 and 2018	Medical Journal of Zambia , Vol.48(2):78-84 (2021)
4	Investigating Gains in TB Detection During Rollout of Genexpert MTB/Rif Universal Access to Drug Susceptibility Testing Test in Manicaland Zimbabwe, 2017 to 2018	Central African journal of Medicine (Page 40-45) Vol. 68 No. 7-12 (2022)

Appendix 17: DPHIL: appointment of internal and external examiners for Katherine Zvinoera

AFRICA UNIVERSITY
A United Methodist-Related Institution

Investing in Africa's Future

COLLEGE OF HEALTH, AGRICULTURE & NATURAL SCIENCES

To: **I/Dean CHANS – Dr S. Mutambu**

From: **HOD DPHN – Dr E. Mugomeri**

Date: **12 October 2022**

RE: **DPHIL PUBLIC HEALTH: APPOINTMENT OF INTERNAL AND EXTERNAL EXAMINERS FOR CATHERINE ZVINOERA**

The above matter refers,

DPHN is kindly asking for the appointment of two internal and two external examiners for Katherine Zvinoera, a DPhil. Public Health student in CHANS. The student has now accrued four publications that are listed in the progress report attached. The student's first registration was in January 2018. Her thesis looks sound for it to go through the examination process. The topic of the thesis is: Public Health Impact of Genexpert MTB/Rif Primary Diagnostic Test Roll out on the Burden of TB in Manicaland Zimbabwe, 2017 to 2018

Kind Regards

Dr Eltony Mugomeri (DHSc.)
Senior Lecturer & HoD - Department of Public Health & Nursing (DPHN)
E-mail: mugomerie@africau.edu
Website: www.africau.edu
Ext: 1116, G11 Health Sciences Building

Appendix 18: TB screening questions to routinely identify patients belonging to the TB high risk groups

To be administered routinely at all entry points

Have you ever worked as or lived with (tick appropriate response)

1. Health worker Yes/ No If yes give relevant detail
2. Miner Yes/ No If yes give relevant detail
3. Artisanal miner Yes/ No If yes give relevant detail

Patient is

4. Diabetic Yes/ No If yes give detail
5. Over 60 years Yes/ No If yes give relevant detail
6. Under 5 years Yes/ No If yes give relevant detail
7. Malnourished Yes/ No If yes give relevant detail
8. HIV positive Yes/ No If yes give relevant detail