ASSOCIATION BETWEEN DELAY TO TREATMENT INITIATION AND TREATMENT OUTCOMES AMONG RIFAMPICIN RESISTANT TUBERCULOSIS PATIENTS IN SELECTED SITES IN KENYA

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Association between Delay to Treatment Initiation and Treatment Outcomes among Rifampicin Resistant Tuberculosis Patients in Selected Sites in Kenya

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DECLARATION

This thesis is my original work and has not been presented for a degree in any other University

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DEDICATION

To Janai for his continuous support and encouragement during this time. To Nyaboke, Kemunto and Kerubo for always putting a smile on my face while encouraging me to work harder. To my late Mother Sarah, my sister Mbeke and my brother Ngao for their encouragement. I thank Josephine and Kiplimo for reminding me of the goal.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND ACRONYMS

ART	Antiretroviral therapy
DR TB	Drug Resistant Tuberculosis
DST	Drug Susceptibility or Sensitivity testing
FFT	Failure of first line Treatment
FRT	Failure of Retreatment
KAIS	Kenya AIDS Indicator Survey
LPA	Line Probe Assay
MDG	Millennium Development Goals
MDR TB	Multi drug resistant Tuberculosis
NTLD-P	National Tuberculosis, Leprosy and Lung Disease- Program
NTRL	National Tuberculosis Reference Laboratory
PDR TB	Poly-drug resistance
PMDT	Programmatic Management of Drug Resistant Tuberculosis
Pre-XDR TB	Pre Extensively Drug Resistant TB
RAD	Return after Default
RR TB	Rifampicin Resistant Tuberculosis
SDGs	Sustainable Development Goals

STAG-TB	Strategic and Technical Advisory Group for Tuberculosis
TB	Tuberculosis
WHO	World Health Organization
XDR	Extensively Drug Resistant TB

DEFINITION OF TERMS

Delay	This is the time from sample collection to treatment initiation calculated in days, which is on the right side of the median.
END TB Strategy	This is a framework that was developed by the World Health organization after the implementation of the STOP TB Strategy. The END TB Strategy was developed to guide countries globally on the expected structures to put in place towards ending TB by 2050.
Exposure	This is the delay to treatment
Extensively Drug Resistant TB	It is an MDR TB patient resistance to both injectables and quinolones
Treatment failure	This is outcome given to patients who do not respond to treatment
Favourable outcome	This will be the patients who are declared cured or treatment completed at the end of treatment
GeneXpert	A molecular TB diagnostic test that also performs drug sensitivity testing for Rifampicin
Mono-resistance (MR):	Resistance to one first-line anti-TB drug only
Multidrug resistance	Resistance to at least both isoniazid and rifampicin.
Outcome variables	This are the treatment outcome of the patients and the time delay
Poly-drug resistance	Resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).

Pre-Extensively Drug Resistant TB	This is an MDR TB patient who is also resistant to either an injectable or a quinolone but not both
Rifampicin Resistant Tuberculosis	This is resistance to Rifampicin detected using phenotypic or genotypic diagnostic methods, with or without resistance to other anti-TB drugs. These include a person diagnosed with any of the following: rifampicin mono resistant, multidrug resistant, extensively drug resistant TB (XDR TB) and pre-XDR TB.
STOP TB Strategy	This is a framework that was developed by the World Health in Organization in 2006 to guide the various countries in setting targets to achieve the millennium development goals whose target was reduce Tuberculosis burden globally by 2015 through halting and reversing TB incidence
TIBU	It's a surveillance system used by National TB Program. It's not an acronym
Treatment outcomes	A treatment outcome is the name given to the end result of TB treatment. This outcome is given to a patient to exit treatment and close that case in the TB treatment register. The possible outcomes for TB treatment are either cured, treatment completed, out of control, died or failure
Unfavourable outcome	This will be the patients who were declared failure, out of control and died at the end of treatment.

ABSTRACT

Drug resistant TB surveillance aims at early detection and treatment of drug resistant tuberculosis to prevent transmission, morbidity and mortality. The delay to Rifampicin Resistant Tuberculosis (RR TB) treatment initiation remains undefined and its association to treatment outcomes unknown. This study sought to determine association between delay in RR TB treatment initiation and treatment outcomes among patients enrolled on treatment between January 2010 and June 2013 in Kenya. A retrospective cohort of 208 RR TB patients were randomly selected and enrolled in the study. Delay was defined as the time from sample collection to treatment initiation calculated in days, which was on the right side of the median. Chi square statistics and logistic regression was done to establish association between delay and treatment outcomes. Multiple logistic regression analysis was conducted to establish factors associated with delay to treatment initiation. Of the 208 participants, 63% (130) were male giving a male to female ratio of 1.7:1. The average age at registration was 34.5 years [95% CI 32.7,36.3] and 26.9% (56) were HIV positive, 95% (53) of them were on ART. Sixty-four percent 64% of the patients were diagnosed based on culture and conventional DST while 36% by GeneXpert. The median time to treatment (delay) was 66 days. The treatment success rate was 82%. The unfavourable outcomes accounted for 18%. The study showed that there is no significant difference between delay or no delay to treatment outcomes as evidenced by chi-square = (0.1858), p =0.666 which is more than 0.05. The female patient was 0.03 times more likely to have unfavourable outcome than the male patient while patients from North Eastern region were 23.5 times more likely than patients from the central region to have unfavourable outcomes. Use of culture and DST for diagnosis of RR TB was significantly associated with delay to treatment initiation. GeneXpert significantly reduces time to treatment initiation compared to culture and DST. Efforts for early diagnosis and treatment should be enhanced to reduce TB transmission and morbidity.

CHAPTER ONE

INTRODUCTION

1.1 Background Information

Tuberculosis has remained a major public health concern globally with a high mortality rate especially in countries with high HIV burden. HIV is a known driver of the TB burden. Although new HIV infections are coming down, Sub Saharan Africa has the highest burden of HIV globally leading to higher burden of TB and difficulties in TB control (UNAIDS, 2013)

Surveillance of drug resistant tuberculosis is a pillar of Tuberculosis control program as a measure of its performance. It assists countries to make evidence-based policies. Surveillance should be aimed at increasing early drug resistant TB detection and hence early treatment to prevent the transmission of a resistant strain in the community (WHO, 2013).

The Stop TB strategy was a framework developed and launched in 2006 by WHO to build on the success of the DOTS Strategy and address gaps that were unfulfilled in diagnosis and treatment of TB. In addition, there were emerging conditions such as the increase of HIV among TB patients and the emergency of multi drug resistance TB among the unmet needs that needed to be addressed. Further, the STOP TB Strategy was aimed at providing a framework towards achieving the Millennium development goals, MDG six (6) target eight (8), shared the intention to reduce Tuberculosis burden globally by 2015 through halting and reversing TB incidence. The STOP TB partnership targets were to reduce the prevalence and TB mortality by 50% compared to the baseline of 1980 and eliminate TB by 2050 (WHO, 2012). Its objectives were to provide all TB patients with high quality treatment and reduce both human suffering and socioeconomic burden due to TB. It was also supposed to promote human rights , support TB research and innovation and protect people from development of drug resistant TB and TB/HIV confection. Most countries achieved the WHO targets in case detection and treatment

success rate. However, the gains made in TB control are threatened by the emergence of drug resistant Tuberculosis. After the MDGs in 2015, the UN developed the sustainable development goals (SDGs). Tuberculosis is covered under goal 3.3 in which the UN targets to end TB by 2030 (WHO, 2016).

1.1.1 Global Tuberculosis and Rifampicin Resistant Tuberculosis burden

The World Health Organization (WHO) estimated that there were about six (6) million TB cases in 2012. The largest contributors to the TB numbers were Southeast Asia and Western Pacific region at 58%, Africa at 27% while Eastern Mediterranean, European region and the Americas had 8%, 4% and 3% respectively (Glaziou et al 2014). India had the largest absolute number of incident cases in 2012 at an uncertainty range of 2.0-2.4 million (2 6%) of all the global cases, China at 0.9-1.1 million and South Africa at 0.4 – 0.6 million cases. It is estimated that 0.5 million of those notified in 2012 were children (Glaziou, et al., 2014).

The lowest burden of TB is found in high-income countries such as western Europe and America whose incidence is below 50/100,000 as shown in Figure 1.1. Globally, the incidence of TB declined from 1990 to 2001 in an effort to meet the Millennium Development Goals (MDGs) target by 2015 (Glaziou, et al., 2014).

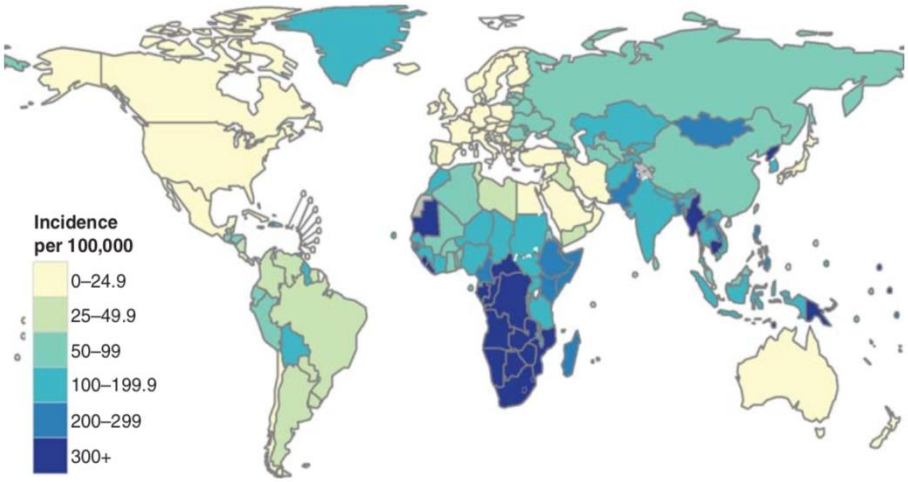


Figure 1.1: Estimated TB incidence rates per 100,000 population in 2012

Source: (Glaziou, et al., 2014)

Tuberculosis is ranked 9th among the leading causes of death globally. One of the MDG targets (MDG 6) was to reduce TB mortality by half compared to the TB mortality in 1990. In 2012, 1.3million people died of whom 320,000 were HIV positive. In the same year, 74,000 HIV negative children died. 75% of the 1.3 million people who died were in Africa. The average mortality globally was at 13/100,000 population and 17/100,000 among HIV positive. This rate is higher in Myanmar, Cambodia, Bangladesh and Africa region at 40/100,000. The mortality rate globally has since then decreased by over 45% (Glaziou, et al., 2014).

The burden of Tuberculosis has been found to be higher than was previously believed following the prevalence surveys that the countries have been carrying out (WHO, 2016). In 2016, 1.3 million HIV negative and 374,000 HIV positive people were estimated to have died from TB (WHO, 2017). This number increased to 10.4 million cases according to the WHO report 2016 of whom 90% were adults and 10% were children. The global report noted that TB was more common among the male at 65% of

the total adult population. The highest number of patients who had dual infection of both TB and HIV was found in Africa, accounting for 74% of the global TB/HIV co infected population. India, Indonesia, China, the Philippines and Pakistan account for 56% of the total TB cases globally (Glaziou, et al., 2014).

The END TB Strategy was developed after the end of the STOP TB Strategy whose target is to eliminate TB by 2050 which will require an annual decline of 20% (Esmail, E. et al, 2014). The World Health Organization therefore advised countries to carry out TB prevalence surveys to ascertain the burden of TB as the burden previously was done using statistical modelling and form a basis for END TB strategy monitoring. Most of the countries showed an increase in TB prevalence. India, China and South Africa were documented as the countries with the highest burden globally (Esmail, et al., 2014)(Glaziou et al 2014). In addition, the classification of countries based on burden has changed from the previous 22 to 30 high burden based on burden of TB, TB and HIV and MDR TB as shown in Figure 1.2. To meet the END TB Strategy countries will be expected to implement novel TB control measures alongside improving their socioeconomic status particularly in high burden and the BRICS countries (Brazil, Russia, India, China and South Africa) (Esmail, et al., 2014).

Drug resistant TB has continued to grow globally becoming one of the threatening emerging microbial resistant disease. It is estimated that 50% of the MDR TB cases are found in India, China and the Russian Federation, (WHO, 2013). Multi-Drug Resistant TB (MDR TB) cases have increased from 450,000 in 2012 to 600,000 in 2016 of whom 170,000 died (WHO, 2017). WHO estimated 4.1% among new TB cases and 19% among previously treated TB cases as having MDR TB (WHO 2017). In the same year, it was estimated that there were 600,000 MDR TB cases of whom 129,000 were initiated on treatment and 240,000 patients died. These cases were reported to be highest in India, China and South Africa. Of those diagnosed with MDR TB, 6.2% were estimated to have Extensively drug-resistant TB (XDR TB) (WHO, 2017).

1.1.2 Burden of Tuberculosis and Rifampicin Resistant Tuberculosis in Africa

Africa bears a larger number of people with Tuberculosis accounting for 25% of the global TB burden. The burden has largely been driven by the HIV pandemic (WHO, 2016). The sub Saharan Africa has seen a pronounced large burden which was associated also with limited resources (Musa, et al., 2017). The incidence of TB in Africa was assumed to be 2,720/100,000 population in 2015 (WHO, 2016).

A metanalysis analysis of TB burden in Sub Saharan Africa showed that pooled prevalence of MDR TB among new cases was lowest in East Africa countries and highest in southern African countries (Musa, et al., 2017). As shown in Figure 1.2, central and southern Africa has a prevalence of higher than 300/100,000, while Kenya, Somalia and Ethiopia follow with an estimated prevalence of between 200 and 299/100,000. The Northern part of Africa is shown to have a low TB.

Among the 30 high burden countries with the largest burden of TB, MDR TB, TB and HIV, 25 countries are in Africa as shown in Figure 1.2. Based on the 22 high burden countries, a previous WHO classification, South Africa was estimated to have the highest prevalence and incidence of TB and has the largest TB, TB/HIV and MDR TB in Africa (Churchyard, et al., 2014). In 2005, the world was shocked by the Tugela Ferry, KwaZulu-Natal outbreak of extensively drug resistant TB (XDR TB) in which, of the 55 patients found to have XDR TB that year, only one survived, consequently raising global awareness on the severity of antimicrobial resistance (Bateman, 2015). In addition, KwaZulu-Natal is also among the regions with the highest burden of rifampicin resistant TB globally (Jayneetha, et al., 2016). Other countries such as Tanzania, Swaziland, Botswana, Lesotho are battling the TB and HIV epidemic

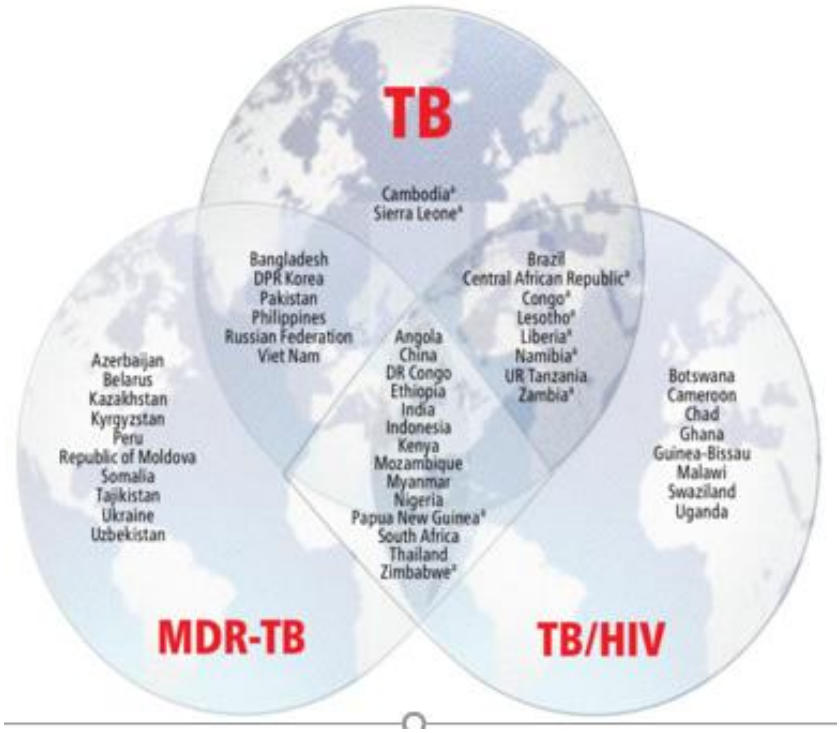


Figure 1.2: Countries in the three high-burden country lists for TB, TB/HIV and MDR-TB.

Source: (WHO, 2017)

1.1.3 Epidemiology of Tuberculosis and Rifampicin Resistant Tuberculosis in Kenya

The prevalence and notification rate of TB in Kenya has been decreasing since 2007 as shown figure 1.3. In 2013, Kenya reported 89,320 TB cases of which 10% were previously treated (WHO, 2013). The recently concluded prevalence survey in Kenya showed that the burden of TB disease in Kenya was higher than was previously estimated with a prevalence of 558 per 100 000 population and an incidence rate of 348 per 100 000 population which accounts for 169 000 people with TB (WHO, 2017), translating to missing over 90,000 people with TB. The country has had to put in strategies to increase the number of people diagnosed and treated in Kenya as shown by the increase in figure 1.3. Kenya is also a high burden HIV country ranked 5th globally

with a prevalence of 5.6% among people aged between 25 and 64 years old (De Cock, et al., 2014). The proportion of patients who were TB HIV co infected reduced from 38% in 2013 (*DLTLD, 2013*) to 31% in 2016 (WHO, 2017).

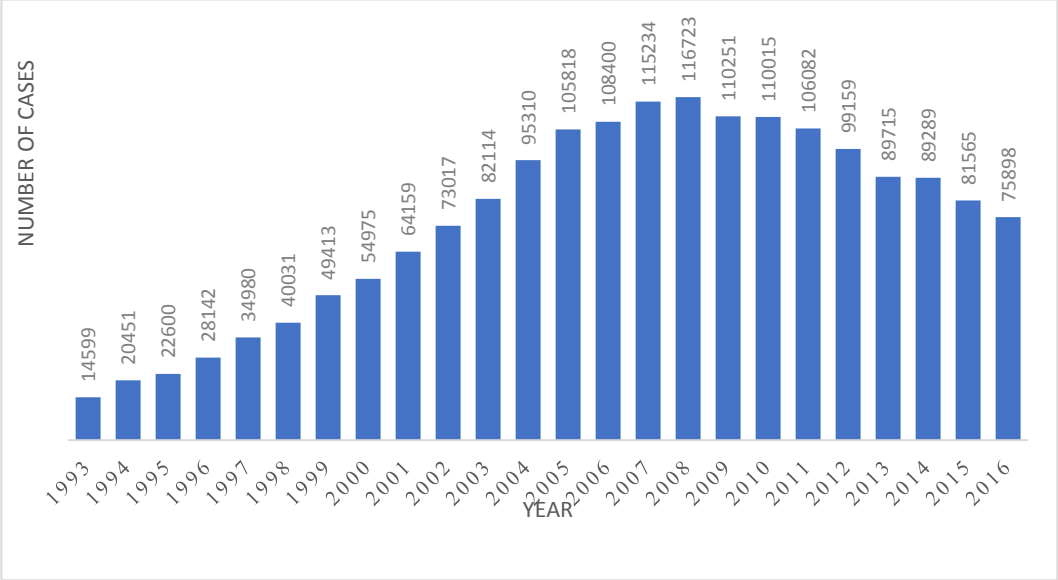


Figure 1.3: TB Case Notification in Kenya from 1993 to 2017,

Source: (National TB Program, 2017)

Rifampicin resistant Tuberculosis (RR TB) is Rifampicin resistance detected using phenotypic or genotypic diagnostic methods, with or without resistance to other anti-TB drugs. These include a person diagnosed with any of the following: rifampicin mono resistant, multidrug resistant, extensively drug resistant TB (XDR TB) and pre-XDR TB.

"Surveillance" is the systematic ongoing collection and analysis of data for public health purposes and the timely dissemination of public health information to assess and respond as necessary to areas of public importance (WHO, 2005). Data from the routine drug resistant surveillance that has been captured over the last two decades has assisted in the response towards drug resistant TB globally. In Kenya RR TB surveillance is carried out using GeneXpert, Line Probe Assay (LPA), culture and Drug Sensitivity

Testing (DST). Over 85% of previously treated TB cases annually are subjected to culture for drug resistance tuberculosis testing. Of those with culture and drug sensitivity test results,_7% are diagnosed with MDR TB (Ndjeka, 2014). Culture and drug sensitivity results are given as a list of drugs one is either resistant to or sensitive to.

Drug resistance TB surveillance has traditionally targeted the high-risk populations in Kenya. The Kenya guidelines states that all risk groups should be tested for drug resistance by GeneXpert and then by culture and DST. The MDR TB surveillance has however been affected negatively by inadequate and low capacity laboratory network. There were three (3) main culture and DST laboratories in Kenya by the end of 2018 but one of these catered only for the refugee population, leaving 2 laboratories to cater for rest of the Kenyan population. According to WHO, the ratio of culture laboratories to the population should be 1:10 million populations. The turnaround time for the culture and DST results is however very long (Battaglioli, et al., 2013). Before 2011, Kenya used both liquid and solid culture for DR TB surveillance. In 2011, Kenya adopted the use of GeneXpert and there are currently over 153 machines scattered in various parts of the country (NTLD-P, 2016). Over 1900 patients (Figure 1.4) have been notified with drug resistant Tuberculosis since 2006. The burden of other resistance patterns other than Rifampicin Resistant TB (RR TB) such as mono-resistant and poly drug resistance has been low in Kenya. In 2014, RR TB diagnosed through GeneXpert increased the number of mono-resistant TB cases detected following the introduction of GeneXpert.

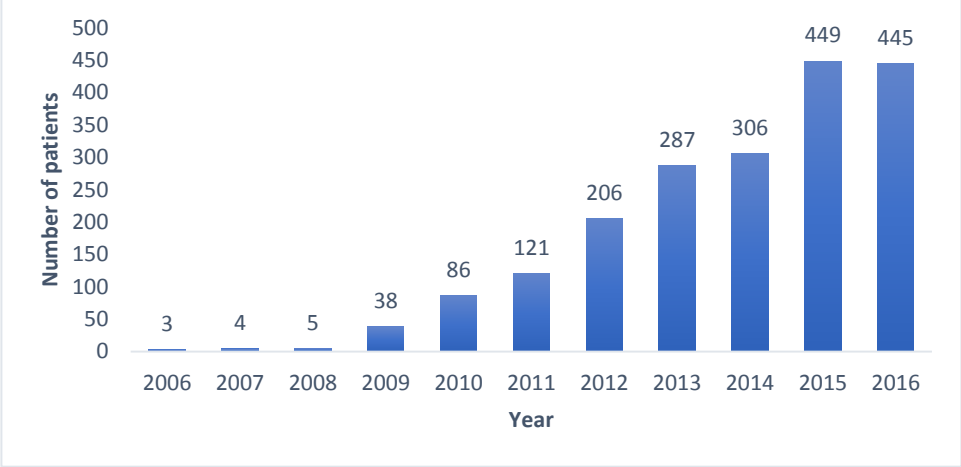


Figure 1.4: Trends in DR-TB notification 2006-2016

Source (NTLD-P, 2016)

1.1.4 TB and MDR TB Diagnostic algorithm

Following the adoption of the use of the GeneXpert, the diagnostic algorithm was revised to include the indications for GeneXpert and the steps to take while diagnosing the cases (Figure 1.5). The algorithm describes the use GeneXpert and other diagnostic tests for TB diagnosis and drug resistant surveillance. The tests are based on populations at higher risk of getting drug resistant TB and guides clinicians on the expected management after receiving results.

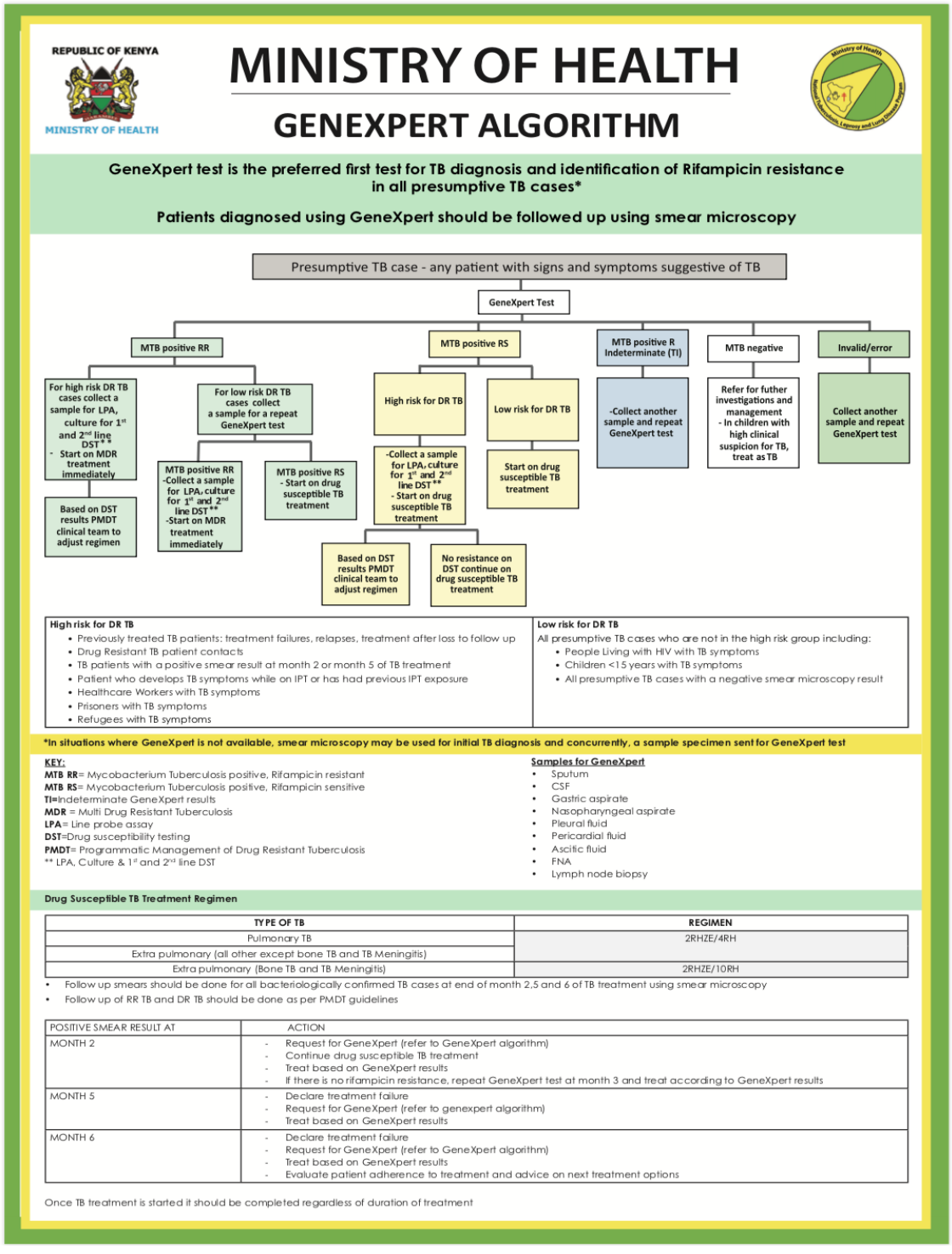


Figure 1.5: DR TB surveillance Algorithm

Source (NTLD-P, 2017)

1.1.5 Rifampicin Resistant Tuberculosis treatment and Care in Kenya

The MDR TB treatment program, in Kenya, started in 2006 in the private sector and in 2008 in public sector. At the time, MDR TB treatment was carried out in isolation facilities which were not available in Kenya. This led to delays in diagnosis and further delays in access to treatment as patients were put on long waiting lists while waiting for drugs (Furin, et al., 2014). The Green Light Committee (Kamene, 2015), a WHO body, during the early MDR TB programs, had to evaluate countries to assess their readiness and capacity to treat MDR TB (Keshavjee, 2009). In 2007, Kenya was evaluated and consequently allowed to treat only 50 MDR TB cases. Subsequently, there was an increase in the number of patients diagnosed without treatment. In 2011, GLC was given a facilitative role instead of supervisory role, allowing countries to procure drugs for all their patients. In addition, isolation of MDR TB patients was no longer encouraged as the best treatment model (WHO, 2018). In an effort to achieve universal access to MDR TB management, Kenya adopted three models of care based on the patient preferences, severity of disease or side effects, convenience and access to quality of care. These included isolation and ambulatory facility or community-based care (DLTLD, 2012). Since then, all patients found to have drug resistance are treated in the nearest facility or at home. This meant that, any treatment Centre would become an MDR TB treatment site once a TB patient in the facility was found to have MDR TB. A review of treatment of MDR TB program in Kenya in February 2014 however showed that despite the presence of drugs, there was an undefined delay to MDR TB treatment (NTLD-P, 2014)

Kenya treated over 1900 MDR TB cases from 2006 to 2016 with favourable outcomes (NTLD-P, 2016). Even with such good progress, there are challenges to access care apart from the physical distance to treatment leading to some undefined delay.

The MDR TB HIV co-infection rate in all treated patients was 25% in Kenya *(DLTLD, 2013).* This rate has however increased to 31% according to the 2017 Global TB report. A hundred percent (100%) of patients who are co infected were on co-trimoxazole therapy and 93% on ART.

1.2 Statement of the problem

Rifampicin resistance refers to resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether in mono-resistance, multidrug resistance, poly-drug resistance or extensive drug resistance (WHO, 2013). Rifampicin is the most potent TB drug and loss of this drug in TB management reduces treatment option for the patients and the patients have to be treated for longer period with injectable and other less potent drugs. Surveillance of Rifampicin resistance with early treatment is important.

Time to treatment from sample collection is part of the WHO indicators (delay to diagnosis and delay to treatment) since 2011. This indicator has not been measured in Kenya. In addition, the relationship between this delay and treatment outcomes is unknown. In Kenya, a midterm review of the Tuberculosis program implementation of the 2011-2015 strategic plan identified that there exists a delay in treatment initiation among MDR and RR TB patients. It was also noted in the 2011 and 2012 outcomes that there were many patients with poor outcomes. The consequences of poor outcomes would mean an increase in mortality with majority of those who die being of reproductive age. Further, poor outcomes would also mean an increase in number of those who fail treatment or who fail to complete treatment hence an amplification of those with drug resistance. The main cause of these poor outcomes is also not known, and delay could be a cause. Therefore, this study was aimed at investigating the association between delay to treatment initiation and treatment outcomes among Rifampicin resistant tuberculosis patients.

1.3. Justification

The Emergency WHO 2008 guidelines state that if drug resistant TB cases are not diagnosed on time, this leads to increase in morbidity, mortality, drug resistance amplification and transmission in the community. Diagnosis of drug resistant TB has been a big challenge due to the long turnaround time of results, the high cost of

diagnostic tools, diagnosis processes such as sample collection, special sample collection bottles, quality assurance (Albert, 2017) and the high cost of the level three (3) bio safety laboratories. Consequently, a lot of efforts have been placed in developing quick, easy to use, point of care diagnostic test for MDR TB. WHO introduced Line Probe Assay (LPA) which had a turnaround time of 48 hours, and late in 2011, the GeneXpert (Xpert MTB RIF) with a shorter turnaround time of two (2) hours was launched. The GeneXpert, is a DNA based tests that is used for the diagnosis of TB and Rifampicin resistance in a single test. WHO adopted this test to diagnose Rifampicin resistance as a proxy of MDR TB. However, it is not known if in practice this translates to a reduction in the duration to treatment initiation from the time the sample was collected. In 2011, WHO developed a reporting framework for drug resistance TB within which MDR TB detection and MDR TB patient enrolment was defined as key. This indicator has so far not been analysed to provide advice to countries on the cut-off point of acceptable time to diagnosis.

A midterm review finding in Kenya February 2014 showed an undefined delay in initiation of MDR TB treatment. There is still no documented evidence of duration to treatment in MDR TB care and the association between duration to treatment and outcome of treatment in Kenya.

To design better drug resistant control policies and interventions, there ~~is~~ was need to measure the delay to treatment initiation and how this delay affects treatment outcomes. The study will also be used to generate hypothesis for intervention studies.

1.4 Research Objective

1.4.1 Broad Objective

To determine association of delay to treatment initiation and treatment outcomes among RR TB patients enrolled on treatment between January 2010 and June 2013 in Kenya in selected TB treatment sites in Kenya.

1.4.2 Specific Objectives

1. To determine the time to RR TB treatment initiation from diagnostic sample collection among Rifampicin resistant TB patients enrolled on treatment between January 2010 and June 2013 in Kenya in selected TB treatment sites in Kenya.
2. To determine the RR TB treatment outcomes among Rifampicin resistant TB patients enrolled on treatment between January 2010 and June 2013 in Kenya in selected TB treatment sites in Kenya.
3. To determine the association between delay to RR TB treatment initiation and treatment outcomes among Rifampicin resistant TB patients enrolled on treatment between January 2010 and June 2013 in Kenya in selected TB treatment sites in Kenya.
4. To determine factors associated with delay to treatment initiation among Rifampicin resistant TB among Rifampicin resistant TB patients enrolled on treatment between January 2010 and June 2013 in Kenya in selected TB treatment sites in Kenya.

1.6 Scope

The study was carried out in selected TB treatment sites in Kenya focusing on rifampicin resistant TB patients. The RR TB patients were those resistant to rifampicin, majority of whom are multi drug resistant TB patients (MDR) or resistant only to rifampicin who were enrolled in treatment between January 2013 and June 2015.

CHAPTER TWO

LITERATURE REVIEW

2.1 Description of Tuberculosis and RR TB

Tuberculosis is an infectious disease that is caused by a bacterium called *Mycobacterium tuberculosis* that affects all parts of the body. It is known to affect mainly the lungs with only a third of people infected with TB having TB outside the Lung, a condition referred to as extra-pulmonary Tuberculosis. The *Mycobacterium tuberculosis* bacteria as we know it today was discovered as a single disease-causing agent by Robert Koch (Koch, 1882) and later described its microbial characteristics in the late 1800s

2.1.1 Characteristics of Mycobacterium Tuberculosis

Mycobacterium is a spore forming, non-motile aerobic and rod-shaped bacterium. It is 2-4 um long. It is known to have slow growth of between 15 to 24 hours, hence takes long to multiply and form disease in human being (Iñaki Comas, 2009). The cell wall of the Mycobacterium is made of mycolic acids and other acids that contribute to the long life of the bacteria and trigger inflammatory reactions from the host (Cole, et al., 1998). The bacterium is resistant to most chemicals and drying making transmission easy. Mycobacterium is a gram-positive spore forming acid fast bacteria considered so since once stained with fuchsin, it resists discolouration by acids hence appears bright red on blue background when examined by use of a microscope (Dye, 2015).

The Mycobacterium has a characteristic of dormancy in which it remains within infected tissues which results from the human cell mediated immunity response. This immunity can contain the bacteria from spreading but it cannot eradicate it till the immunity is weakened by either age or immune suppression when the dormant bacteria reactivate causing the disease (Cole, et al., 1998).

The *Mycobacterium tuberculosis* bacterium is known to be naturally resistant to antibiotics making treatment a challenge. Mycobacterium also develop resistance through chromosomal mutations during the multiplication process. The genes that are affected and in turn result in anti-tuberculosis drug resistance especially changes at the rpob gene causing resistance to Rifampicin, KatG and ihA to Isoniazid (Jayneetha, et al., 2012).

2.1.2 Tuberculosis Transmission

Tuberculosis is transmitted through the air when an infected person coughs and emits the infectious bacteria into the air and an uninfected person inhales the droplets. Sometimes, the bacilli are in small droplets and takes long to settle on the ground, making it easy for one to inhale it hence airflow is important to ensure that there is circulation of air as still air keeps the bacilli in the air longer. In fact, where natural ventilation is not available, a mechanical ventilation with at least 6 to 12 air changes per hour is recommended to ensure prevention of respiratory infections (Matsie, et al., 2015). The two main factors that determine risk of transmission of TB is the quantity of the infected droplets in the air and the duration of exposure to airborne infectious material (Nadia AIT-Khaled, 2003), (Narasimhan, et al., 2013). Talking for 5 minutes and one cough produce almost the same number of bacteria into the air and this can remain airborne for almost 30 minutes (Johnstone-Robertson, et al., 2011).

2.1.3 Latent Tuberculosis

Once the bacterium is inhaled, it settles in the lung alveoli. The body immune system tries to fight the bacteria by eliciting a cell mediated immune response killing majority of them. Some bacteria continue to multiply in the macrophages after phagocytosis forming a granuloma (Suhail, 2010). These bacteria can then be carried to various parts of the body through the lymphatic system. Some granulomas can live in the body for many years without releasing these bacilli. These result in latent TB infection or a dormant infection. By definition, Latent TB is a state of continued immune response to

the present *Mycobacterium tuberculosis* antigens without manifesting any symptoms or signs (WHO, 2018) of TB. A third of the global population is infected with latent TB (Houben & Dodd, 2016). Latent Tuberculosis is not infectious and people with this condition do not transmit disease. Studies have shown that approximately 5-10% (Biraro IA, 2016) of those infected with TB will progress to active TB disease in their life time and usually happens within 5 years of infection (JD, 1993). The risk is high among children (Kenyon, 2002) and it takes a period of less than 2 years to progress to active disease among children since their immunity is weak. Their ability to transmit is however lower as they have less bacterial load than adults (Kasambira, 2011).

2.1.4 Active Tuberculosis Disease

Active TB disease is a progression from latent TB. This is the symptomatic stage. The main presentation is cough which is usually productive with bloody or not bloody sputum, chest pain, loss of body weight, and drenching night sweats. There are many factors that increase one's risk of developing active TB, majority of which are as a result of decreased body immunity (Suhail, 2010). HIV is one of the major drivers of TB disease in Africa (Narasimhan, et al., 2013). TB has been shown to be the most common cause of death among HIV patients. In 2016, TB killed a third of HIV patients (WHO, 2018). Other populations that are predisposed to TB disease are children especially under 5 years of age, people with diabetes and those on chemotherapy (Narasimhan, et al., 2013). Other populations that are at risk of developing TB are young people particularly male, those with low immunity like in diabetes patients, health care workers and prisoners (Nicole, 2015).

2.1.5 Techniques for Tuberculosis Screening and Diagnosis

2.1.5.1 Symptom Screening and Mantoux Test

TB screening primarily involves investigation for presence of TB infection. This is usually done by symptoms screening and Mantoux test. Symptom screening involves

looking for presence of active TB using four cardinal symptoms which are cough, chest pain, night sweats and fever (Claassens, et al., 2017). Mantoux test asses exposure to TB infection especially in low TB burden populations for example children to increase index of suspicion for TB among health care workers. It is also used as a diagnostic test of latent Tuberculosis. Mantoux test, also known as Tuberculin Skin Test (TST), is a purified protein derivative (PPD) that is given through a subdermal injection. An immune reaction occurs resulting in the formation of an induration in a person who is exposed to Tuberculosis. The induration is measured from the 2^{nd} to 3^{rd} day. The induration is considered positive at 5 mm and 15 mm in high and low risk populations respectively (Surajit & Basanti, 2012).

2.1.5.2 Microscopy

TB diagnosis was initiated by Robert Koch who introduced characterised *Mycobacterium tuberculosis* on microscopy (Koch, 1882). Microscopy has remained the only diagnostic method for many years. Two main stains that are used in TB diagnosis using microscopy are Ziehl Nielsen (ZN) and Auramine stain. Ziehl Nielsen staining (Caminero, 2003) was the most popular and easy to use stain for *Mycobacterium tuberculosis*. ZN stain was used mainly with light microscopes which were more available, but the test is less sensitive compared to Fluorescent microscopy that uses auramine. The microscopy has many advantages such as the use anywhere in the world, cheap, easy to use and apply. However, the duration to diagnosis is mainly two (2) days as spot sputum collected at the day of hospital visit, a morning sputum sample the following morning and the spot sputum on second day had to undergo testing prior to releasing the patient results (Hooja, et al., 2011). In addition, the sensitivity of microscopy is very low at 50% leaving out a lot of patients with TB undiagnosed (Quincó, et al., 2013). In HIV patients suspected to have TB, the sensitivity is even lower at about 35% and hence a poor diagnostic tool for this group of patients (Quincó, et al., 2013). The test is also unfriendly in children, has a low sensitivity and is dependent on collection of sputum sample. This is a hard one to collect in children as they are not able to spit out after coughing (Kunkel, et al., 2016).

2.1.5.3 Use of GeneXpert

GeneXpert is a molecular diagnostic test that is specific for *Mycobacterium tuberculosis*. It was launched by WHO in 2010 and its use has since expanded rapidly in many countries with some like South Africa using it in place of the traditional smear microscopy. One of the global targets is to ensure universal access not only to TB diagnosis but also to baseline drug sensitivity testing for all patients prior to treatment initiation (Denkinger, et al., 2014). In addition, there is the "diagnose and treat" approach that has encouraged the adoption of GeneXpert as a diagnostic tool which gives results within 2 hours. GeneXpert placement in low level facilities has been hindered by the absence of electricity. This therefore would mean good sample networking processes. The roll out of GeneXpert has been shown to be hindered by poor system linkages and logistical challenges (Kashmira, et al., 2016). The cost of GeneXpert machine and diagnostic consumables such as cartridges has also been prohibitive. GeneXpert has been shown to test patients with low TB bacillary load, hence patients who have TB can be diagnosed the first day they come to the treatment facility. The introduction of GeneXpert was seen as revolutionary as it reduced waiting time to diagnosis and consequently to treatment initiation with good outcomes.

2.1.5.4 Use of culture

There are two methods of culture used to grow the Mycobacterium in a suitable media for ease of reading and generally considered the gold standard of TB diagnosis. Growth of these bacilli in either solid media or liquid media (Caminero, 2003) proves that there are live bacilli in the sputum sample of the patients and hence the patients should initiate on TB treatment.

Conventional culture and DST methods have remained the diagnostic gold standard until recently when GeneXpert was introduced. Solid culture takes eight (8) weeks and liquid culture six (6) weeks to grow. Due to this delay in diagnosis to treatment, culture is not advised as the first test of diagnosis (Chris Gilpin, 2014). Culture is however a very

essential tool in patient for follow up, especially for patients on second line drugs and for second line DST, as GeneXpert and microscopy can pick dead bacilli.

2.1.5.5 Use of Chest X Ray

Chest X Ray is considered a rapid imaging solution which aids one to identify abnormalities in the chest. The use of radiology particularly the chest X Ray was a preferred option by many clinicians who could not get a bacteriological test to confirm presence of disease due to the fast turnaround time. The commonly visible indications of TB in the X Ray are cavities and upper lung lobe infiltrates (van Cleeff, et al., 2005). The recent prevalence surveys where chest X Ray was used, incidences of asymptomatic TB patients being picked meaning that it had an higher accuracy in identifying TB than use of symptoms alone (Anna, et al., 2012).

The chest X Ray has a high sensitivity of 94% in HIV positive and 100% in HIV uninfected but a low specificity. Use of chest X Ray is therefore limited to TB screening, and increasing index of suspicion among health care workers, but not as a TB diagnostic tool due to the low specificity. It has been noted that interpretation of the chest X Ray is reader dependent The X Ray has also been considered a hinderance to access to TB diagnosis due to its cost even though a study carried in Kenya on the role and use of chest X Ray showed that the use of X Ray and ZN microscopy was cost effective (WHO, 2004) (van Cleeff, et al., 2005).

2.1.6 Treatment of Tuberculosis

The treatment of Tuberculosis has been known to take many months. TB treatment is given based on history of exposure to TB and TB medicines. Patients who have never been exposed to TB drugs are treated using WHO accepted regimen for six (6) months using four (4) drugs, namely, Rifampicin, Isoniazid, Pyrazinamide and Ethambutol. The four (4) drugs are taken for the first two (2) months and then two (2) are dropped and the patient continues with Rifampicin and Isoniazid for the remaining four (4) months of

treatment. In some countries, there is still an 8-month regimen that is given to previously treated TB patients who do not have a drug susceptibility test (WHO, 2010). In this regimen, streptomycin is added to the four (4) first line drugs and the regimen is administered with two (2) months of streptomycin, Rifampicin, Isoniazid, Pyrazinamide and Ethambutol, one (1) month of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol and the remaining five (5) months of Rifampicin, Isoniazid and Ethambutol. Treatment monitoring is done using sputum smear microscopy or culture where feasible. Treatment outcome is usually declared at the end of treatment or once the patient leaves the treatment either by death or if lost to follow up. A patient is considered cured if the patients whose sputum test showed presence of bacteria and the last two (2) sputum tests, carried out during the duration of treatment, turned out to be negative. If only one or no test is done or the patient's diagnostic test was negative, the patient gets treatment completed as the treatment outcome.

2.1.7 Anti-tuberculosis Drug Resistance

Drugs are supposed to either kill or inhibit the growth of the organisms for which they are administered. Drug resistance is when the drug that would usually kill or inhibit the growth of an organism is no longer able to do so. Other scholars describe resistance as the ability of an organism to continue growing and multiply in the presence of the drug that would usually kill it at therapeutic levels (Rachel, et al., 2010).

Multi drug resistant TB which is resistance to Rifampicin and Isoniazid is the most important resistance to monitor. The first line treatment of TB is the short-term chemotherapy that takes two (2) months of Isoniazid, Rifampicin, Ethambutol and Pyrazinamide and a continuation phase of rifampicin and Isoniazid for four (4) more months. Studies have shown that with this 6-month regimen (short course chemotherapy), over 80% of patients with TB will cure successfully as recommended by the WHO (Han, 2006). For cure to happen, drugs should either be bactericidal, have sterilizing effect or be able to kill persistent bacilli. In this regimen, Rifampicin has the sterilizing effect, isoniazid is bactericidal (Tawanda G, 2007) while pyrazinamide has

the ability to kill the persistent bacilli (Ying Z, 2013). Resistance to the two drugs means that the patient cannot be treated with the short chemotherapy course. In addition, resistance to Rifampicin alone leaves the short course chemotherapy very weak and for patients to cure treatment should be prolonged for 18 months and the possibility of developing isoniazid resistance is high as it is the only active drug in the continuation phase (Beth T, 2010) According to the British medical bulletin 2005, less than 10% of rifampicin resistant TB cases are monoresistant, this would therefore mean that 90% Rifampicin resistant TB patients are therefore also resistant to Isoniazid. This underscores the role of Rifampicin in TB treatment.

Extensively drug resistant TB (XDR TB) has also been increasingly notified globally following the outbreak that was noted in Kwa Zulu Natal in South Africa in 2005 (Cohen, 2015). XDR TB is the resistance to Rifampicin and Isoniazid (MDR TB), a quinolone and an injectable which form the back-borne of second line TB treatment. Patients with XDR TB therefore benefit from individualised treatment regimen. This is a regimen that is designed based on the patient's resistance pattern and the drug history to ensure only drugs that the patient is sensitive to and are efficacious are given to him.

Anti-tuberculosis drug resistance results mainly from mutations that occur on the genetic makeup of the bacteria. When changes occur at the rpob gene, this results in resistance to Rifampicin resistance, while changes in the KatG and inH probe results in resistance to Isoniazid (Wang, 2018). This can happen naturally during the normal process of multiplication of the bacteria and it is called initial resistance. The rate of development of mutations that are resistant to Rifampicin and Isoniazid is estimated to be at 10^{-9} and 10^{-8} cell divisions respectively, suggesting that, if one is on monotherapy which is exposed to a cavity with 10^{8}, then resistance is bound to occur (Müller, et al., 2013). Once a bacillus is resistant to a particular drug, further resistance will occur through selection. Selection happens when someone with a bacillus that is resistant to a particular drug is exposed to that drug. The drug kills the sensitive bacilli leaving the resistant bacilli to multiply (Müller, et al., 2013). Exposure to this drug again would therefore not kill the bacteria. Hence the reason why monotherapy is discouraged in the

management of Tuberculosis. This type of resistance that occurs when a patient is on treatment is called acquired resistance (Müller, et al., 2013). Acquired resistance is when patient develops drug resistant bacteria following exposure to the medicines and selects the resistant bacteria allowing them to multiply and hence needs different drugs to treat them.

A person who already has resistant bacteria can transmit it to another person. The person who gets this resistant bacillus therefore gets primary resistance as the patient has not been exposed to anti tuberculosis before. The World Health Organization has shown that the risk of resistance is higher among previously treated TB patients and this has been due to the acquired resistance from exposure to anti TB medicines.

2.1.8 Management of Rifampicin Resistant Tuberculosis

The management of drug resistant TB is ideally based on the drugs the patient is exposed to and the drugs are resistant to. Usually, second line TB medicines are added to the regimen. However, due to the public health interventions and ease of administration and monitoring in programmatic settings, the World Health Organization provided guidelines on the use of a standardised regimen. A standardised regimen is the regimen that has been designed to apply to most patients in a given population based on the drug resistance surveys and routine surveillance. The regimen has changed over the years with the first regimen in 2008 being 24 months which was revised to 20 months in 2011 and in 2016 to 9 months (Giovanni, et al., 2017). The regimen in 2008 and 2011 were similar except that the duration of the injectable (Kanamycin (Km), or Amikacin (AM) or Capreomycin (Cm)) was increased from 6 months to 8 months and the continuation phase reduced from 18 months to 12 months (WHO, 2009). The other drugs were used throughout treatment and these included, a quinolone mainly Levofloxacin (Lfx), Cycloserine (Cs), Prothionamide (Pto) and Pyrazinamide (Z or PZA) simply stated as 6Km/Lfx/Cs/Pto/Z;12Lfx/Cs/Pto/Z. This regimen was used for the management of patients with all forms of Rifampicin resistance except XDR TB and pre-XDR TB which get an individualised regimen.

Since 2017 after the introduction of the short term MDR TB regimen, the country has adopted this regimen for all RR TB cases. The drugs used in this regimen include Kanamycin, Moxifloxacin, Clofazimine, Prothionamide, high dose Isoniazid (high dose) and all first line drugs except Rifampicin. The regimen used is now four (4) to six (6) months of intensive phase and five (5) months of continuation phase usually written as 4-6 Km-Mfx-Pto-Cfz-Z-Hhigh-dose-E / 5 Mfx-Cfz-Z-E (DLTLD, 2012).

Polydrug resistant TB also get an individualised regimen. However, the Kenya program developed a standard regimen that could be used for patients with this resistance patterns which was 9 months of Levofloxacin, Rifampicin, Ethambutol and Pyrazinamide (9Lfx/R/E/Z) for the Isoniazid resistant patients. Other first line resistance drugs to more than one drug is treated for 18 months with the following regimen 3Km/Lfx/Cs/Pto/Z;15Lfx/Cs/Pto/Z.

Any other resistance patterns are treated with individualized regimen. Bedaquiline and Delamanid are new drugs that have been introduced in the market and are being added in the MDR TB regimen and XDR TB patients as per the guidance of clinical teams for the management of drug resistant Tuberculosis

2.1.9 Patient Monitoring

The second line drugs are more toxic than the first line treatment hence close monitoring of these patients is paramount. The drugs usually affect the liver, Kidney, heart, thyroid function and other body organs. As such these organ functions are tested prior to treatment initiation and thereafter regularly or as need arises (DLTLD, 2012) (WHO, 2008) (Karen Smith, 2019).

To monitor treatment outcome, drug resistant TB patients are monitored using culture and smear microscopy. Conversion is defined as two consecutive culture negative tests during the intensive phase of treatment taken at least 30 days apart. This condition must be met prior to moving to continuation phase. A patient is considered cured if the patient

has at least 3 negative culture results from samples collected at least 30 days apart during the last 12 months of treatment.

2.2 Conceptual Framework

The diagram below demonstrates how the study was carried out with the exposure and non-exposure variables indicated. In the study the participants who delay to treatment would be exposed and their outcomes would be expected to be unfavourable while those who do not delay to initiate treatment would be expected to have better outcomes

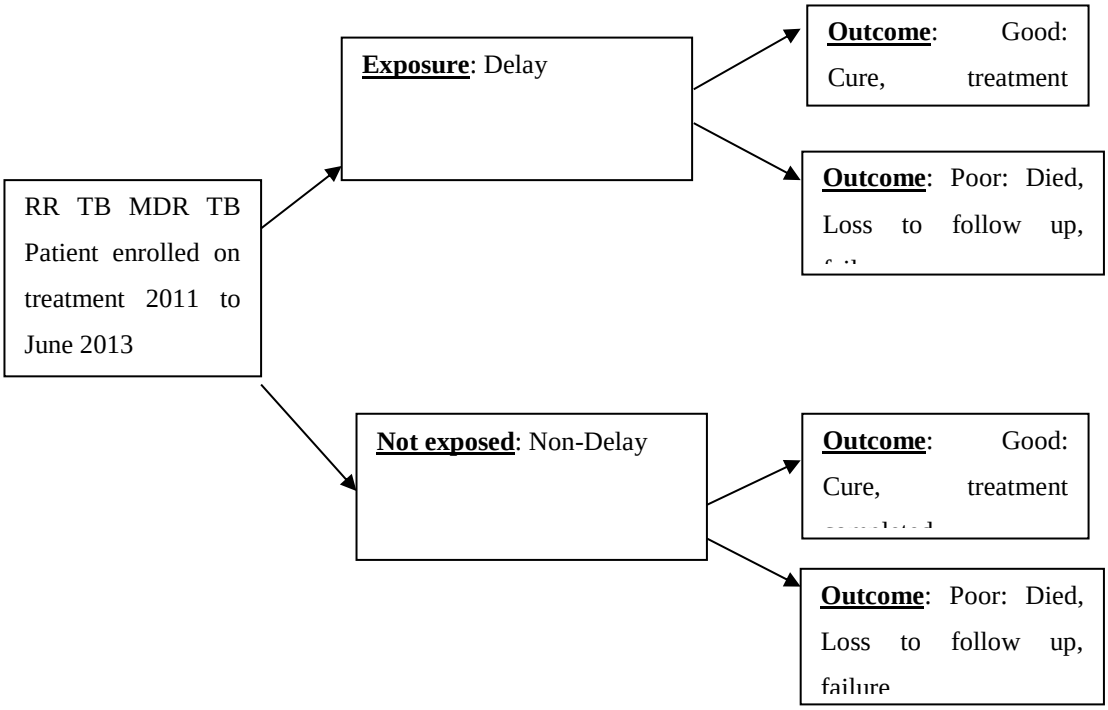


Figure 2.1: Conceptual Framework

2.3 Theoretical Review

2.3.1 Delay to Treatment Initiation

The Emergency WHO 2008 guidelines state that if drug resistant TB cases are not diagnosed on time, this may lead to increase in morbidity, mortality, drug resistance amplification and transmission in the community (WHO, 2008).

There are various types of delay.

1. Patient delay – this is the time from onset of symptoms to the time the patient presents to the health care facility for diagnosis and treatment
2. Health system delay – this is the time taken from the first time the patient presents to the health care facility with TB symptoms to the time the patient is initiated on treatment. This time can be divided into two:
    a. Diagnostic Delay – this is the time that the patient presents to the health care facility to the time the patient is diagnosed to have tuberculosis.
    b. Treatment delay – this the time from the date of diagnosis to the time the patients is initiated on Tuberculosis treatment.
3. Total delay- this the time from onset of symptoms to the time treatment is initiated

The various types of delay are defined as such so as to guide in identification of the bottlenecks at the various steps taken along the patient pathway. It has been observed that diagnostic delay has contributed the most to the total delay (Ettehad, 2012) (Alavi, 2015). Diagnosis of drug resistance Tuberculosis has been a big challenge due to the long turnaround time of results, the high cost of diagnostic tools, diagnosis processes such as sample collection, special sample collection bottles, sample collection settings and the high cost of the level 3 bio safety laboratories (Willy, et al., 2015). There are also a few laboratories globally with the adequately trained personnel to carry out the tests. Consequently, a lot of efforts have been placed in developing quick, easy to use, point of care diagnostic test for MDR TB. WHO introduced LPA, which had a turnaround time of 48 hours, but was only used in high level laboratories and late in 2010, the Xpert MTB RIF was launched commonly known as GeneXpert.

2.3.2 Treatment Outcomes of RR TB

Globally the treatment outcomes of MDR TB has been low with an average treatment success rate of 54% in 2014 (WHO, 2017). However, some countries like Ethiopia

registered high treatment success rates of 78.6% (Daniel M, 2015) while is South Africa the rates remained low at about 46% (Padayatchi, 2014). Delay in the wait for culture results for diagnosis was considered a big challenge. As such the unfavourable outcomes have been high hence understanding the factors leading to poor outcomes is necessary. Unfavourable outcomes have been associated with the HIV status, delay to treatment, quality of drugs, adherence, nutrition status and other comorbidities.

2.3.3 Association between Delay and Treatment Outcomes

Drug resistance delay studies have not been carried out widely except as part of retrospective cohort analysis. Most of the studies carried out have demonstrated that there is a significant delay to treatment. Delay to both diagnosis and treatment of Tuberculosis has been considered one of the failures of TB control (Alavi, 2015). In Tanzania, a retrospective analysis of 69 patients showed a long time between specimen collection for culture & DST and from diagnosis to treatment with a median of 138 & 131 days respectively (Mpagama et al., 2013).

A further study in Western Cape carried out on 39 children with MDR TB showed that delay to MDR TB treatment was 246 days if culture & DST was used as a diagnosis test (Ettehad, 2012). This cohort had poor outcomes of 46%.

In Tel Aviv, a metanalysis study was done to evaluate delay to diagnosis and treatment outcomes of TB among non-national immigrants without health insurance. The mean health system and patient delay was 79±42 and 25±14 respectively. The study did not find any association between treatment success with either health system or patient delay. (Mor, et al., 2013).

In KwaZulu Natal, Narasiimolo carried out a study of 200 MDR TB suspects. The study was aimed at understanding the delay to treatment initiation among patients who were referred for admission in specialized drug resistant centres for treatment. The average

delay from sample collection to initiation of treatment was 12.4 weeks in 75% of the cohort studied (Narasimooloo & Ross, 2012).

An assessment of treatment outcomes in Ethiopia also showed that the HIV TB co infection increased the risk of poor outcomes (Eshetie, 2018). HIV status was also highlighted as a cause of high death rate among MDR TB HIV cases as demonstrated by the study in South Africa which, showed a 10-fold increase among HIV patients (Kliiman & Altraja 2009). Hindi Satti in an evaluation of the 164 MDR TB cohort in Lesotho of whom 96 were HIV co infected. The study concluded that early detection and prompt treatment of both MDR TB and HIV led to improved outcomes (Satti et al., 2012).

MDR TB patients who have been treated severally for TB could have resistance to multiple anti tuberculosis medicines. Studies have shown that, outcomes of patients are not influenced by additional resistance to first line anti tuberculosis medicines other than to Isoniazid and Rifampicin (Migliori et al., 2009).

Other causes of mortality in MDR TB were associated with severity of disease by the time the treatment was initiated, but this was disputed by a study in china that showed that the severity of disease was as a result of delay in diagnosis and hence delay in treatment.

2.4 Critique of the existing literature relevant to the study.

Since treatment of rifampicin resistant has been taking long, a lot of studies have shied away from carrying out studies on delay to treatment initiation and effect on treatment outcomes which are given 12 months after completion. This has therefore had studies relay on retrospective data which is usually incomplete and hence few variables can be investigated in relation to other factors associated to unfavourable treatment outcomes other than delay. In addition, all the studies that have shown association or lack of

association between delay and treatment outcome have failed to actually give a definitive cause and solution to the unfavourable outcomes.

According to the study in Tanzania (Khadija, et al., 2017), delay to treatment leads to unfavourable outcomes while (Hind, 2012) concludes that early detection and treatment initiation would lead to equally good outcomes in HIV co infected patients as those who are not coinfected. The assumption in this conclusion is that late diagnosis and treatment would also lead to unfavourable outcomes.

In 2016, Harries looked at publications to identify the effect of delay to treatment initiation especially with many countries having long waiting lists to treatment and could not find any with a comparative group. The study used 28 days as the cut-off point with those whose treatment was initiated 28 days after diagnosis being considered delayed. All studies lacked patient centred information since all were considered retrospectively. He observed that implementation science study should be used to monitor delay for programmatic management of rifampicin resistant TB patients (Harris, et al., 2016).

2.5 Research gaps

Kenya has had a rifampicin resistant TB program for a long time. All the researches carried out on delay to treatment initiation have happened outside Kenya. The only study carried out on delay was on delay to diagnosis and has not been published yet.

Kenya requires to develop policies that the program can use for decision making on the actual use of new diagnostics versus culture and DST, identify the target for policies such as which gender, age group or even the laboratory network to reduce delay.

CHAPTER THREE

MATERIALS AND METHODS

3.1 Study Site and Population

This study was carried out all TB clinics that provided drug resistant TB treatment in various parts of Kenya, a country in East Africa which borders Somalia to the East, Sudan and Ethiopia to the North, Uganda to the West, Tanzania to the South and the Indian Ocean to the South East. Kenya has a projected population of 47 Million (KNBS, 2009) according to the 2009 census and covers an area of 582,646sq km. The burden of MDR TB, at the time of the study, was estimated to be 2.5% among the new TB cases and 10% among previously treated TB cases(WHO, 2013). Kenya has over 300 DR TB treatment sites according to the 2015 NTLD-P Annual report. The patient information is collected into a national RR MDR TB database through TIBU, an electronic data recording and reporting tool for the TB program in which case-based data is entered by the TB clinicians at the health care facility. The data from all the MDR TB treatment health facilities in Kenya is therefore in TIBU and formed the sampling frame.

The target population was the RR TB patients enrolled on treatment in selected sites in Kenya between January 2010 and June 2013.

3.2 Research Design

A retrospective cohort study was carried out on a sample of 208 Rifampicin resistant TB patients initiated on treatment between January 2010 to June 2013 in which time to treatment and their outcomes were reviewed. The retrospective design was preferred over a prospective study because of the duration it would take the researcher to carry out the study. A prospective study would require a period of 3 years of data collection (a year of patient enrolment and 2 years of treatment before assigning treatment outcome).

The period of review was purposively selected as between January 2010 and June 2013. This is because, treatment of drug resistant TB was only available in 2 facilities before 2010 and the diagnostic method available then was only culture and DST hence the comparison with other regions in the country and other diagnostic tests would not have been possible. Patients initiated on treatment after June 2013 did not have outcomes hence could not participate in the study. Random sampling was used to ensure proper representation of the patients for the study and to ensure generalizability and replication.

3.2.1 Inclusion criteria

i. The following details the participants who were included in the study;
ii. RR TB patients enrolled on treatment between January 2010 and June 2013
iii. RR TB patient with date of sample collection, date of diagnosis, and treatment outcome. The possible treatment outcomes were either favourable or unfavourable.
iv. Patients with bacteriological confirmation

3.2.2 Exclusion Criteria

All the Rifampicin Resistant TB cases who did not meet the inclusion criteria were therefore excluded from the study

3.3 Sampling

3.3.1 Determination of Sample size

The following formula (Naing, et al., 2006) was used to calculate the sample size using random sampling with finite population.

$$n = \frac{N * Z^2 * p(1-p)}{d^2 * (N-1) + Z^2 * p(1-p)}$$

$$n = \frac{550 * 1.96^2 * 0.32(1 - 0.32)}{0.05^2 * (550 - 1) + 1.96^2 * 0.32(1 - 0.32)}$$

$$n = \frac{550 * 3.8416 * 0.32 * 0.68}{1.3725 + 0.83593}$$

$$n = \frac{459.7627}{2.2084}$$

$$n = 208.185 \approx 208$$

Where;

N= Total Rifampicin resistant TB patients enrolled on to treatment between Jan 2010 to June 2013 = 550 (from the National TB database –TIBU)

z=at 95% confidence interval = 1.96

p= expected proportion of poor treatment outcomes =32% =.32 This is based on the 2011 treatment outcomes in which the treatment success rate was 68% (DLTLD, 2013)

d= absolute precision at .05

3.3.2 Sampling procedure

All RR TB patients registered on the national drug resistant TB register who were enrolled on treatment during the period of study and met the selection criteria were entered into excel sheet. Simple random sampling was used to identify 208 patients for the study. The exposure factor in the study was delay to treatment, which was defined as the time to treatment initiation from the time of sample collection, on the right of the median time to treatment. Those on the left side of the median were considered as non-delay and hence non-exposure group. The outcome variable was treatment outcome of the patients. Exposure and non-exposure groups were at a ratio of 1:1 divided at the median duration to treatment from the study sample collection date, hence each group

had 104 patients. The median was calculated by enlisting the time to treatment from sample collection for each patient in ascending order. Median was considered the best to identify delay as the actual definition of delay in TB settings had not been done. In addition, the data collected in delay studies is skewed hence the use of median. Reference made in delay studies referred to the use of median as the best point for measuring delay. In this study, quartiles were evaluated to seek further understanding of the effect of delay in the first and 3rd quartiles to treatment outcomes of the study participants.

3.4 Data Collection

Data of all RR TB patients was obtained from electronic national drug resistant TB register commonly known as TIBU based on the period of review. Data from TIBU was matched (using VLOOKUP function in excel) with data from Laboratory information system (LMIS) and the GeneXpert laboratory information systems to include the date of sample collection and date of diagnosis variables. Patients who met the inclusion criteria after matching formed the sampling frame. Study participants were randomly sampled using simple random sampling method in excel.

For data abstraction, two data entry clerks who had been working in other TB research programs were identified and trained on the study, its objectives the data collection and entry by the principal investigator. Data abstraction form (appendix 1) was digitized using Epi info vs. 3.1. The sampled study participants' data was abstracted into data abstraction form and clarification sought from the health care facility workers through phone calls and field visits. Unique identifiers were assigned to each study case for confidentiality and identification by the principal investigator (appendix 2).

3.4.1 List of variables

Delay was the dependent variable and was defined as the duration in days of more than median time from sample collection to treatment initiation (appendix 3). Patient characteristics were collected to better understand the study sample.

The following variables were collected to measure delay in objective 1.

i. Interval between sample collection and treatment initiation

Delay to treatment was the sum of delay to diagnosis and delay to treatment.

To address objective 2, treatment outcomes was the outcome variable and was defined as Good if Treatment success and Unfavourable outcome if failure, death and loss to follow up. The outcome was collected as the dependent variable in this study (appendix IV).

In objective 3, to determine the association of delay to treatment initiation and the treatment outcome, the variables used were therefore Interval between sample collection and treatment initiation and the treatment outcome whether favourable or unfavourable. The patient characteristics were also used to rule out confounders in the study to both treatment outcomes and to the delay to treatment initiation. They also formed some of the independent variables.

The following variables were collected to determine factors associated with delay to treatment initiation among rifampicin resistant TB cases in objective 4.

ii. Demographic – age, sex, Weight (BMI)
iii. HIV status,
iv. ART
v. Diagnostic test used –Xpert Vs Culture & DST
vi. Region
vii. Resistance patterns

viii. Registration group – New (N), Relapse (R), Return After Default (RAD), Failure after Retreatment (FRT) and (FRT) and Failure After Firstline (FFT)

3.4.3 Data Storage

After data collection, the data abstraction forms were stored in a secured cabinet at the National data Centre in the office of the investigator situated in the TB Program office in Nairobi which only the principal investigator has access. Two password protected Windows 7 computers were used for data entry and analysis and was only accessible to the same people.

3.5 Data Management

3.5.1 Data Cleaning

Data was double entered into PHP-MYSQL for analysis using unique identifiers. Data was then imported into Stata version 13 for cleaning and analysis. Data accuracy was verified by the principal investigator and any discrepancies was clarified from the data abstraction forms and TIBU. In cases where the date of treatment initiation was missing, the date of patient registration was used instead.

For regression analysis participants with delay were coded as one (1) while those with no delay were coded as zero (0). Similarly, for treatment outcome, participants who had favourable outcomes were coded as one (1) while those with unfavourable outcomes were coded zero (0)

3.5.2 Data analysis

Descriptive analysis which included mean, median, frequency and contingency tables, charts and graphs were carried out to provide the basic understanding of the participants demographic and clinical characteristics. Kaplan Meier plots were used to estimate the time to treatment initiation to address delay.

Treatment outcomes were calculated and presented in proportions using pie charts.

From various studies, age, sex, HIV status, BMI, ART, RR TB diagnostic test and resistance patterns have been associated with mortality among Rifampicin resistant TB cases while other studies considered the same characteristics as a cause of delay to treatment hence these were considered confounders in this study. Logistic regression was used determine factors associated with delay and those associated with treatment outcomes

Stata version 13 was used for analysis

3.6 Ethical Considerations

Ethical clearance was sought from Kenyatta National Hospital Ethics and Research Committee prior to carrying out the study. Since the data used is from the program, informed consent was not necessary but, the researcher sought clearance from the National TB program head to access the data in the National database. The National TB program is the custodian of the patient data. The research unit at the TB program approves data access and ensures all ethical requirement are met prior to providing approval.

Confidentiality of patient information was ensured by use of patient unique identifiers instead of patient names to ensure that study participants could not be identified. These unique identifiers were generated during digitization of the data abstraction form.

CHAPTER FOUR

RESULTS

4.1 Introduction

This chapter provides a presentation of research findings analysed according to the methodology in chapter three. This include the descriptive analysis of the participants' demographic and clinical characteristics. It also provides presentation on factors that explained delay to treatment initiation and treatment outcomes using logistic regression.

The study targeted RR/MDR TB (Rifampicin Resistant/Multi drug resistant TB) patients who were enrolled on to treatment from January 2010 to June 2013. A total of 208 participants were enrolled into the study from all the patients initiated on treatment during the period of the study in selected sites in Kenya (Appendix 5).

4.2 Characteristics of respondents

The participants' demographic characteristics such as weight, height and final BMI were examined, and the results are shown in Table 4.1.

4.1.1 Distribution of Respondents by Age and Gender

From Table 4.1, the participants' age ranged from 2 to 66 years with an average age of 34.5[95% CI 32.7,36.3]: years at initiation of treatment. It was further noted that 63% (n=130) of the participants were male while 37% (n=78) were female with a male to female ratio of 1.7:1. This indicates that the study captured more male patients with RR TB than there were female ones during the period of study.

Table 4.1: Clinical and demographic characteristics of patients with rifampicin resistant TB put on treatment between Jan 2011 and June 2013: n=208

Variable	N	Min.	Max.	Median	Mean	Std. Err	95% CI	
							Lower	Upper
Age	208	2	66	33	34.5	13	32.7	36.3
Weight (Kgs)	185	15	95	50	49.3	0.8	47.7	50.9
Height (Metres)	177	1	1.9	1.7	1.6	0.0	1.6	1.7
BMI	175	10.2	36.7	18.0	18.0	3.3	17.6	18.6
Time to Treatment[1] initiation (days)	208	0	599	66	98.8	115.8	45.5	86.5

[1]Time to treatment = calculated from the day the sample was collected to the day the person initiated on treatment

Figure 4.1 shows the age and sex distribution of the participants. The males were more in all age groups with most of the participants aged between 15 and 54 which accounts for 88% of the total participants. The highest burden was noted within the productive age of 25 to 34 age group at 33%. Children who were defined as those less than 14 years, accounted for 4 percent and the elderly, over 65 years old accounting for 1%.

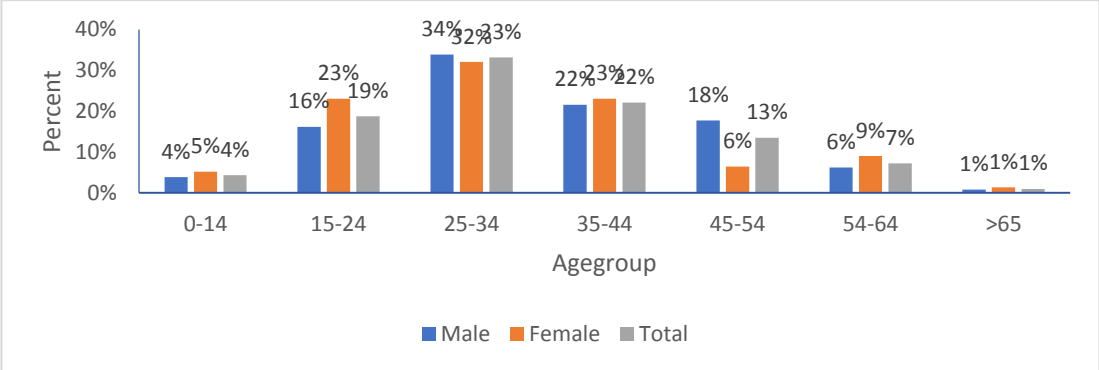


Figure 4.1: The distribution of respondents by age and sex calculated as percentages of total respondents: n=208

4.1.2 Patients' weight and BMI

The minimum weight noted was 15kgs while the maximum was 95kgs with an average of 49.3Kgs [95% CI: 47.7, 50.9]. The patients' average height was 1.64 [95% CI: 1.6, 1.7] meters with average BMI being 18.0 [95% CI: 17.6, 18.6] (Table 4.1). It was further observed that 21.2% and 28.4% were found to have severe and moderate malnutrition respectively accounting for a total of 58% participants with a BMI of less than 18.5 (Figure 4.2). Participants with normal and a BMI above 24 (upper normal) accounted for 3%.

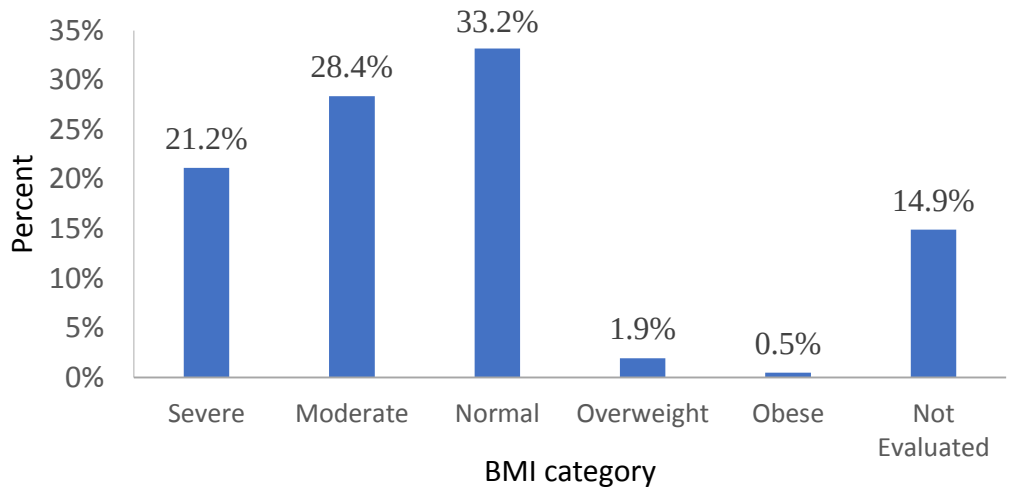


Figure 4.2: This is the nutritional status of RR TB cases

Nutrition status was calculated based on the WHO standards in which severe=<16.0), moderate= [16.0-18.49] normal=18.5-25 overweight=25.1-30.0 obese >30.0

The study further showed that 6 out of 9 children (67%) had severe malnutrition, (Table 4.2). Male were more malnourished compared to women in the categories of moderate and severe malnutrition at 56% and 60% respectively.

Table 4.2: The BMI status of the respondents aggregated by age and sex

BMI Category	Total	0 - 14[6] (children)	Above 14 (Adults)	Female	Male
Moderate[1]	57 (27%)	1 (1%)	56 (98%)	25 (43%)	32 (56%)
Normal[2]	67 (32%)	0 (0%)	67 (100%)	24 (35%)	43 (64%)
Obese[3]	32 (15%)	2 (6%)	30 (93%)	12 (37%)	20 (62%)
Overweight[4]	6 (2%)	0 (0%)	6 (100%)	3 (50%)	3 (50%)
Severe[5]	46 (22%)	6 (13%)	40 (86%)	18 (39%)	28 (60%)
Total	208 (100%)	9 (4%)	199 (95%)	82 (39%)	126 (60%)

Moderate[1] [16.0-18.49], Normal[2] [18.5-25], Obese[3] [>30.0), Overweight[4] [25.1-30.0], Severe[5](<16.0)

0 - 14[6] -Age cut off was 14 for children and above that were considered adults based on the WHO standard for reporting. N=208

4.1.3 HIV status and Anti-retroviral Therapy (ART) uptake of the Patients

From the results, 73.1% (152) of the patients were HIV negative, while 26.9% (56) were HIV positive. Table 4.3 indicates the TB/HIV co-infection rate was 26.9%. Also, the co-infection was higher among female (57.1%). Majority of the adults were co-infected (96.4%).

Table 4.3: The HIV status among RR TB cases sampled demonstrated in numbers and percentages. N = 208

HIV status[1]	N	Sex		Age	
		Male	Female	0 - 14 (children)	Above 14 (Adults)
Positive	56 (26.9%)	24 (42.9%)	32 (57.1%)	2 (3.6%)	54 (96.4%)
Negative	152 (73.1%)	102 (67.1%)	50 (32.9%)	7 (4.6%)	145 (95.4%)

HIV[1] = Human Immunodeficiency Virus

4.1.4 Antiretroviral Therapy (ART)

Table 4.4 indicates that 91% (53) of the patients were initiated on antiretroviral therapy 56% of whom were Female and 43% were Male. Overall 96% of adults were initiated on ART therapy. The findings further indicated that the 2 children who were HIV positive were put on ART however, 3 adults of whom 2 were female and one was male were not put on ART.

Table 4.4: Proportion of respondents who were positive for HIV put on ART. N=56

		Sex		Age	
ART[1]	**N**	**Male**	**Female**	**0 - 14 (children)**	**Above 14 (Adults)**
Positive	53 (91.4%)	23 (43.4%)	30 (56.6%)	2 (3.8%)	51 (96.2%)
Negative	5 (8.6%)	3 (60.0%)	2 (40.0%)	0 (0.0%)	5 (100.0%)

ART[1] = Anti-Retroviral Therapy

4.1.5 Resistance Classification and Pattern

This section of the analysis sought to establish the classification of resistance of TB. MDR was the most common form of drug-resistant TB at 91.8% compared to 6.7% for RR TB (resistant to Rifampicin only) and 1.4% for PRE-XDR. Of the total 9 children, 8 (89.9%) of them had MDR TB. There were more males consistently across all the resistant pattern groups.

Table 4.5: Resistance patterns of respondents presented in numbers and proportion. N=208

Resistance Pattern	Total	0 - 14 (children)	Above 14 (Adults)	Female	Male
MDR	191 (91.8%)	8 (4.2%)	183 (95.8%)	76 (39.8%)	115 (60.2%)
PRE XDR	3 (1.4%)	0 (0.0%)	3 (100.0%)	2 (66.7%)	1 (33.3%)
RR	14 (6.7%)	1 (7.1%)	13 (92.9%)	4 (28.6%)	10 (71.4%)
Total	208 (100%)	9 (4.3%)	199 (95.7%)	82 (39.4%)	126 (60.6%)

The statistics on table 4.6 show the resistance patterns grouped as per the number of drugs the patient developed resistance to. The drugs are Streptomycin (S), Rifampicin (R), Isoniazid (H), Ethambutol (E), Pyrazinamide (Z), Capreomycin (CM) and Quinolone (Q). The table shows that 63.5 % of the patients were resistant to both Rifampicin and Isoniazid (RH), 11.1% were resistant to SRHE, 5.8 % had R resistance. A further 1.4% had either RHZ or RHE. It is important to note patients with Pre-XDR TB (SHREZ/Q, SRHEZ/CM) accounted for 1% among all RR TB patients.

Table 4.6: Number of drugs the respondents are resistant n=208

Resistance pattern	Frequency	Percent
R	12	5.8
REZ	1	0.5
RH	132	63.5
RH/Q	1	0.5
RHE	3	1.4
RHEZ	1	0.5
RHZ	3	1.4
RZ	1	0.5
SHRE	1	0.5
SRH	18	8.7
SRHE	23	11.1
SRHEZ	9	4.3
SRHEZ/CM	1	0.5
SRHEZ/Q	1	0.5
SRHZ	1	0.5
Total	**208**	**100**

*S= Streptomycin; R = Rifampicin; H=Isoniazid; Ethambutol; Z = Pyrazinamide; CM = Kanamycin; Q = Quinolone

4.1.6 Diagnostic Techniques used during the Study Period (2010 – 2013)

During the period under study, drug resistance surveillance was carried out using culture. GeneXpert was still new in the market. According to the findings, 64% of the patients were diagnosed based on culture and conventional DST while 36% were subjected to GeneXpert.

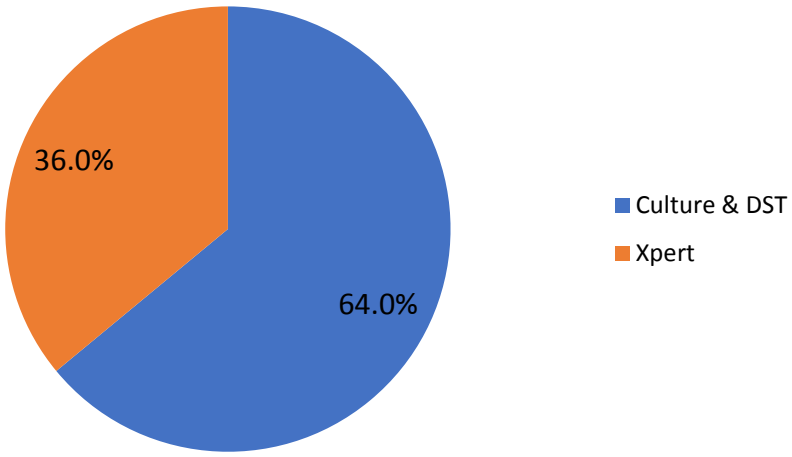


Figure 4.3: Proportions of respondents diagnosed using either culture and DST or GeneXpert

In both children and adults, culture and DST was the main diagnostic test used at 67.7% and 61.3% respectively as shown in Figure 4.4.

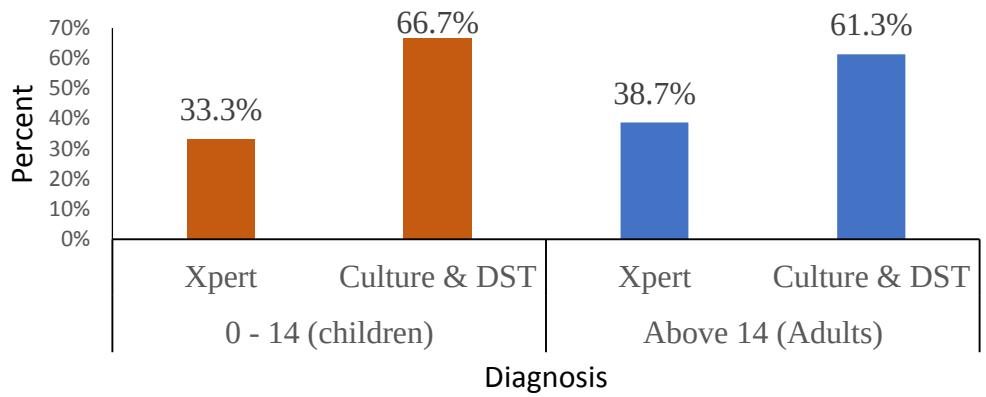


Figure 4.4: Proportion of children (0 - 14 years) and adults(>14) diagnosed using Xpert or culture and DST presented in percentage.

It was interesting to note that the use of GeneXpert increased as shown in Figure 4.5 from 17.9% in 2011 to 71.4% in June 2013 while the use of culture and DST declined from 82.1% to 28.6% during the same time.

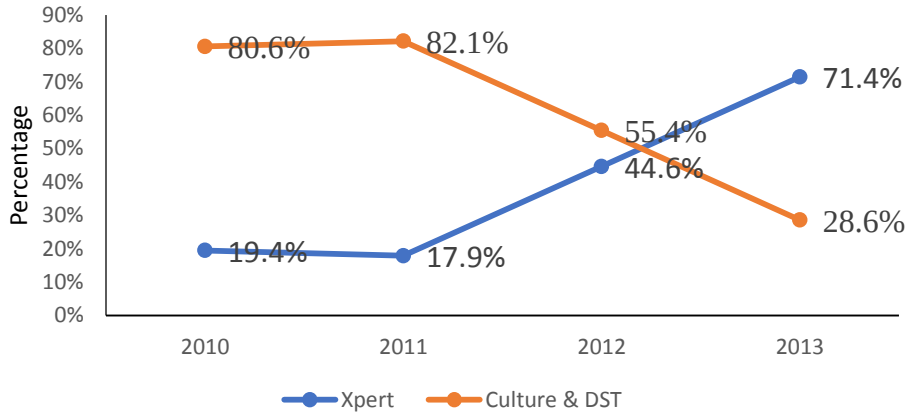


Figure 4.5: Annual percentage uptake of Xpert and Culture & DST tests over the period of study

4.2 Delay to Initiation of Treatment

The study sought to understand delay to treatment initiation. This was defined as the time from time sample was collected to the time patient was initiated on treatment. The median was used to determine delay with those on the right of the median being delay. The median time to treatment (delay) was 66 days, with a mean of 99 days to treatment and a range of 0 to 599 days.

Table 4.7: Mean, median and quartile times to initiation of treatment

Variable	**N**	**Percentile**	**Centile**	**[95% Conf. Interval]**	
		25	14.5	9.5	28.9
Duration	208	50	66	49.4	82.6
		75	131	108	152
Variable	N	Mean	Std. Dev.	Min	Max
Duration	208	98.7885	115.8219	0	599

The 1st quartile was at 14.5[95% CI: 9.5, 28.9] days and the 3rd quartile was at 131[95% CI: 108, 152] days as shown in Table 4.7. The average (median) time to treatment initiation was 66 [95% CI: 49.4, 82.6] days. The minimum time to treatment initiation was same day, that is, the sample was collected, diagnosis was made, and patient initiated on treatment the same day with one of the patients taking up to 599 days to be initiated on treatment.

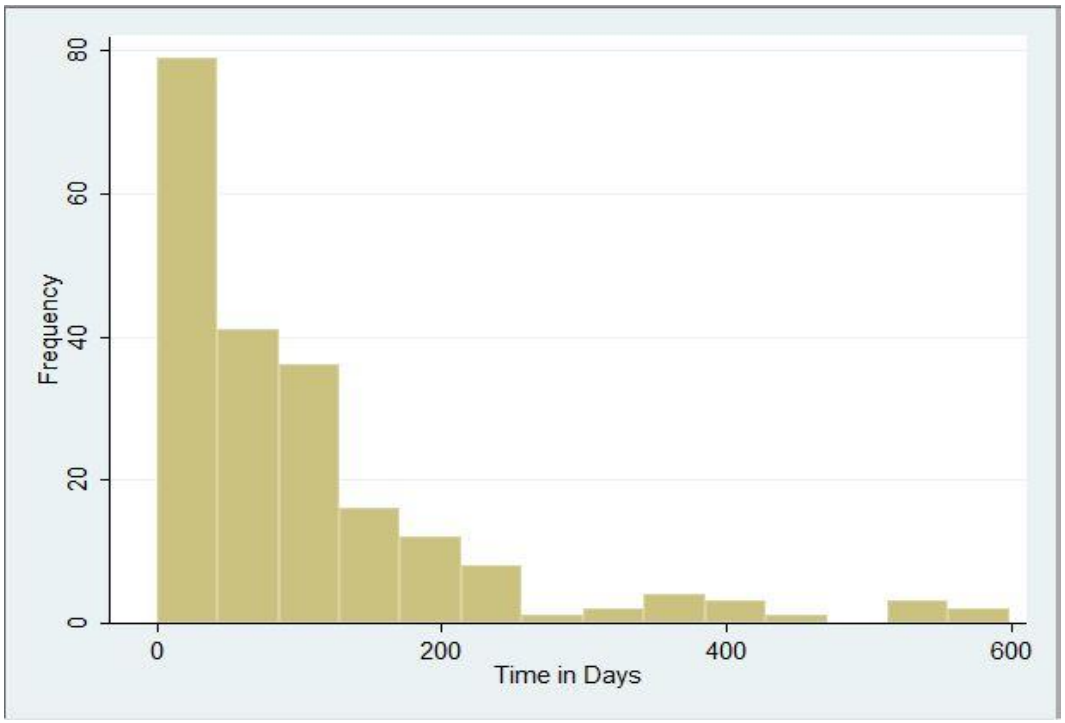


Figure 4.6: Histogram on delay to treatment initiation

Based on the data, the time to treatment (delay) is skewed to the right as shown by Figure 4.6. This means that majority of the patients diagnosed were started on treatment early as shown on the histogram Figure 4.6. However, it is important to note that there are still patients who took long to be initiated on treatment.

Kaplan Meier Plots

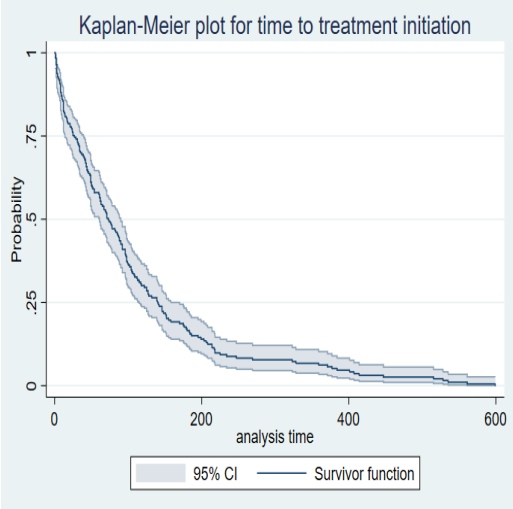


Figure 4.7(a)

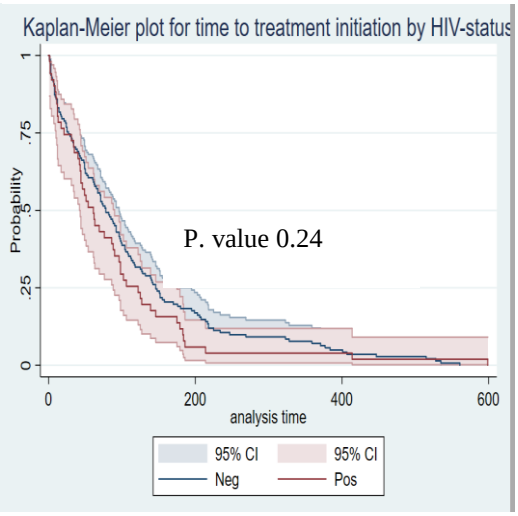


Figure 4.7(b)

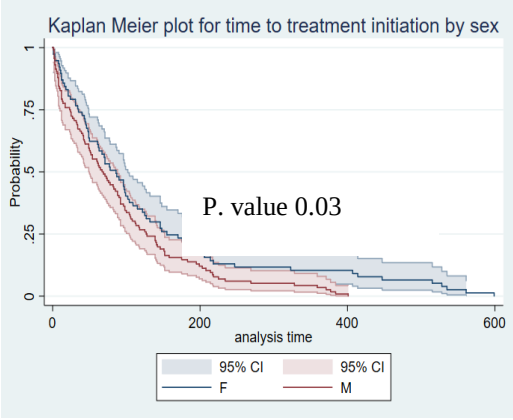


Figure 4.7(c)

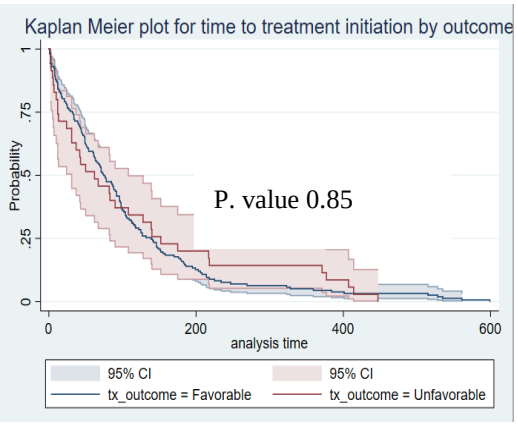


Figure 4.7(d)

Figure 4.7: Kaplan Meier plots for treatment initiation

From the plots in figure 4.7, Figure 4.7(a) shows the time to treatment initiation among the participants. It was observed that the curve drops almost sharply a likely indication that the time to initiation is good. Comparing between HIV positive and negative patients, the HIV positive clients seem to have a shorter time to treatment initiation as

compared to HIV negative clients as shown in Figure 4.7(b). After running a logrank test, the difference was found not to be statistically significant (p-value = 0.24).

A comparison by sex, male seem to be initiated on treatment earlier compared to female as depicted in Figure 4.7(c). This was confirmed as with the logrank test (p-value = 0.03).

In Figure 4.7(d), it was observed that the curve drops almost immediately a likely indication that the time to treatment initiation is good irrespective of outcomes.

4.3 Treatment Outcomes

The treatment outcome was the dependent variable in this study. The results in Figure 4.8 shows that 59% were cured while 23% completed treatment with a treatment success rate of 82.2% (59%+23%). The unfavourable outcomes therefore accounted for 17.8% of the patient enrolled in the study.

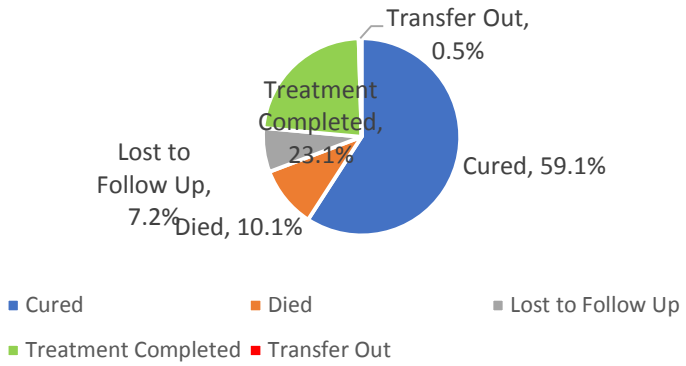


Figure 4.8: Proportion of respondents who received the different of treatment outcomes at the end of treatment

4.4 Delay and Treatment Outcome

4.4.1 Association between Delay and Treatment Outcome

Table 4.8: Cross Tabulation of Delay and Treatment Outcome of study participants. N=208

		Outcome		Total	Chi-Square Tests	p value
		Favourable	Unfavourable			
Delay	No delay	88	18	106	0.19	0.67
	Delay	83	19	102		
	Total	171	37	208		

In Table 4.8, those that had delayed to initiate treatment, 83 (81.4%) of them had a favourable outcome while on the other hand 19(18.6%) of them had an unfavourable outcome. However, for those with no delay, 88 (79%) of them had a favourable outcome while 18(21%) had an unfavourable outcome. There was however, no statistically significant difference between delay or no delay in relation to treatment outcomes as evidenced by chi-square = (0.17), p =0.67 which is greater than 0.05.

4.4.2 Level of duration to delay on the outcomes

Further analysis on the influence of level of duration to delay on the outcomes was carried out by dividing the delay into quartiles. From the table 4.9, 19.2% of those that a time to treatment initiation of less than 14.5 days (1st quartile) had a favourable outcome while 5.8% had an unfavourable outcome. In the 2nd quartile, 21.2% of those that had delay of between 14.5 and 66 days, had a favourable outcome and 3.8% had an unfavourable outcome. Moreover, in the 3rdquartile, 22.2% of those that had a delay of between 66 and 131 days had a favourable outcome while 2.9% had an unfavourable outcome. Finally, for patients in the 4th quartile, 19.7% of those with a delay of over 131 days had a favourable outcome while 5.3% had an unfavourable outcome. Majority (75%) of the patients were initiated on treatment by the 3rd quartile. The p-value is not less than 0.05 and hence there is no statistically significant difference in treatment outcome among those who start treatment early and those who started late.

Table 4.9: Level of duration to delay on the outcomes divided into quartiles. n=208

Quartile (Days to initiation of treatment)	Outcome		Total	Chi-Square Tests	p value
	Favourable	Unfavourable			
1st quartile	40 (19.2%)	12 (5.8%)	52	1.39	0.24
2nd quartile	44 (21.2%)	8 (3.8%)	52		
Total	84	20	104		
	Favourable	Unfavourable	Total	Chi-Square Tests	p value
3rd quartile	46 (22.1%)	6 (2.9%)	52	1.85	0.19
4th quartile	41 (19.7%)	11 (5.3%)	52		
Total	87	17	104		

4.4.3 Association between Treatment Outcomes and HIV Test

The table 4.10 highlights the association between outcome and HIV test. From the results, 125 (50.1%) of those who were HIV negative had a favourable outcome while 27 (19.9%) of them had an unfavourable outcome. The number of those that were HIV positive were lower. It is only 46 (22.1%) of those that were HIV positive that had a favourable outcome while 10 (4.8%) of them had an Unfavourable outcome. There was no statistical significant association between the outcome and HIV test as shown by X^2 = (0.0002), p-value 0.987> 0.05.

Table 4.10: Association between treatment outcome of respondents and HIV test result. n=208

		Treatment outcome		Total	Chi-Square Value	p value
		Favourable	Unfavourable			
HIV status	Negative	125 (50.1%)	27 (19.9%)	152	0.0002	0.99
	Positive	46 (22.1%)	10 (4.8%)	56		
	Total	171	37	208		

Favourable = Cured + Treatment complete; Unfavourable = Died + LTFU + Failure

4.4.4 Association between Treatment Outcome and Anti- Retroviral Therapy (ART)

The study put into account the association between treatment outcome and ART. According to the TB guidelines, All HIV patients with TB should be initiated on ART immediately. Out of the 56 HIV positive patients, 53 patients (94.6%) were put on ART. Of these, 44 (83%) had a favourable outcome. For those that were not undergoing ART, 2 of them had a favourable outcome whereas one had an unfavourable outcome.

Table 4.11: Association between treatment outcome and initiation of ART among respondents with who were HIV positive. N=56

		Treatment outcome			Fisher's exact
		Favourable	Unfavourable	Total	
ART	Yes	44	9	53	0.237
	No	2	1	3	
	Total	46	10	56	

4.4.5 Logistic regression analysis of factors associated with unfavourable Treatment Outcome among Rifampicin Resistant TB cases

The Table 4.12 illustrates results of a logistic regression on the factors associated with treatment outcomes among Rifampicin resistant TB cases. The results showed that males were 0.3 (p-value = 0.033) times less likely to have a favourable treatment outcome compared to females. Patients receiving treatment in the North Eastern Region were 24 times more likely to have favourable outcomes as compared to patients receiving treatment in the central region.

Age, HIV status, caloric food support, type of patient, time to treatment initiation, type of diagnosis and BMI category were not statistically significant in explaining the factors associated with unfavourable treatment outcomes.

Table 4.12: Factors associated with unfavourable outcomes among RR TB cases

Variable	Categorical	B	Std. Dev.	Z	P>z	[95% CI]		EXP(B)
	FFT	REF						
	FRT	0.3	1	0.3	0.8	0.2	9.6	1.3
Type of	LTFU	-1.5	1.1	-1.3	0.2	0	2.1	0.2
patient	Missing	-1	1.2	-0.8	0.4	0	3.9	0.4
	New	1.6	1.2	1.3	0.2	0.5	49.3	4.7
	Relapse	-0.2	0.7	-0.3	0.8	0.2	3	0.8
Time to	No delay	REF						
treatment	Delay	-0.1	0.5	-0.1	0.9	0.3	2.6	0.9
	Central	REF						
	Coast	-0.5	1	-0.5	0.6	0.1	4.3	0.6
	Eastern	-1.2	1	-1.2	0.2	0	2.2	0.3
Region	Nairobi	1.2	1.1	1.1	0.3	0.4	27.9	3.3
	North Eastern	3.2	1.2	2.7	0	2.3	250.7	24.1
	Nyanza	-0.1	1.3	-0.1	0.9	0.1	10.9	0.9
	Western	0.2	1.4	0.1	1	0.1	17.4	1.2
Sex	Female	REF						
	Male	-1.2	0.6	-2.1	0.03	0.1	0.9	0.3
Food	No	REF						
Support	Yes	-0.1	0.6	-0.1	0.8	0.3	2.7	0.9
BMI		0.03	0.02	1.2	0.2	1	1	1
	1	REF						
Quarter	2	1.1	0.7	1.7	0.1	0.6	9.1	3.1
	3	0.8	0.7	1.1	0.3	0.5	14.2	2.2
	4	1	0.9	1.1	0.3	0.5	14.2	2.6
Age		-0.03	0.1	-0.3	0.8	0.8	1.2	1
HIV	Negative	REF						
	Positive	0	0.6	0	1	0.3	3.2	1
	0 – 14	REF					0	8.2	1
	15 – 24	-1.7	1.9	-0.9	0.4	0	95.1	0.2
Age group	25 – 34	-0.5	2.7	-0.2	0.9	0	329.7	0.6
	35 – 44	-0.7	3.3	-0.2	0.8	0	3022.1	0.5
	45 – 54	-0.7	4.4	-0.2	0.9	0	66279.1	0.5

	55 – 54	-0.1	5.73	-0.03	1	1	1	0.9
	Moderate	REF						
BMI Category	Normal	0.3	1.2	0.2	0.8	0	3.4	1.296
	Obese	-2.8	2.1	-1.4	0.2	0	56.7	0.0595
	Overweight	-0.7	2.4	-0.3	0.8	0.4	63.3	0.5
	Severe	1.6	1.3	1.3	0.2	1	1	5.1
Type of Diagnosis	GeneXpert	REF						
	culture & DST	-0.1	0.6	-0.22	0.8	0	303.5	0.9
Constant		0.9	2.5	0.4	0.7	1	1	2.56

Likelihood Ratio (LR) = 54.96 and chi2 Prob > chi2 0.0036

4.5 Factors associated with delay to treatment initiation of RR TB patient

Logistic regression analysis of factors associated with delay to treatment initiation was also carried out. Both bivariable and multiple logistic regression analysis showed that patients initiated on treatment in the second quarter of the year, were more likely to have treatment delay than those initiated on treatment in other quarters of the year with a P value of 0.005 and 0.016 respectively. There was also a strong association between test used for diagnosis and delay to treatment initiation among the RR TB cases. Patients diagnosed with culture and DST had a higher risk of delay than those diagnosed using GeneXpert in both bivariable (p-value =0.000) and multiple (p-value =0.000) logistic regression analysis as shown in Table 4.13.

Table 4.13: Factors associated with delay to treatment initiation of RR TB patient *n=208*

Variable	**Categorical**	**Bivariable logistic regression analysis**					**Multiple logistic regression analysis**				
		B	**Z**	**P>z**	**[95% CI]**		**B**	**Z**	**P>z**	**[95% CI]**	
Type of patient	FFT	REF									
	FRT	1.4	0.6	0.5	0.5	4	0.7	-0.4	0.7	0.1	5.5
	LTFU	0.9	-0.2	0.9	0.2	4.3	0.4	-0.7	0.5	0	7.2
	Missing	1.7	0.9	0.4	0.5	5.6	1.2	0.2	0.9	0.1	11.4
	New	1	0.1	0.9	0.4	2.9	0.4	-0.9	0.4	0.1	2.9
	Relapse	1.1	0.3	0.8	0.5	2.2	1.6	0.7	0.5	0.5	5.6
Region	Central	REF									

	Coast	1.4	0.4	0.7	0.3	7.7	1.5	0.2	0.9	0	331
	Eastern	1.1	0.1	0.9	0.2	5.7	4.7	0.6	0.6	0	966
	Nairobi	3.2	1.4	0.2	0.6	16.1	5.6	0.6	0.5	0	1095.3
	North Eastern	1.1	0.1	0.9	0.2	5.1	2.6	0.4	0.7	0	502.1
	Nyanza	1.8	0.6	0.5	0.3	11.1	3.6	0.5	0.6	0	863.3
	Western	0.5	-0.6	0.6	0.1	4.9	6.3	0.6	0.5	0	1912.6
Sex	Female	REF									
	Male	1.4	1.2	0.2	0.8	2.5	2.3	1.5	0.1	0.8	6.6
BMI		1	0.6	0.5	1	1	1	0.1	0.9	1	1
Quarter	1	REF									
	2	2.9	2.8	0	1.4	6	6.5	2.4	0	1.4	29.9
	3	1.8	1.4	0.2	0.8	3.8	3.2	1.5	0.1	0.7	14.8
	4	1.7	1.2	0.2	0.7	3.9	3.3	1.3	0.2	0.6	19.1
Age		1	-1.4	0.1	1	1	0.9	-0.8	0.4	0.8	1.1
HIV	Neg	REF									
	Pos	1.5	1.4	0.2	0.8	2.9	2.9	1.8	0.1	0.9	9.4
Age group	0 – 14										
	15 – 24	1.7	0.7	0.5	0.4	7.4	5.8	1	0.3	0.2	159
	25 – 34	1	0.1	0.9	0.3	4.2	3.1	0.5	0.6	0	302.6
	35 – 44	2.3	1.2	0.2	0.6	10	14.7	0.8	0.4	0	7537.2
	45 – 54	0.4	-1.1	0.3	0.1	2	5.9	0.4	0.7	0	24397.9
	55 – 54	1.1	0.1	0.9	0.2	5.8	20.8	0.6	0.6	0	756896.1
	65+	1.3	0.1	0.9	0.1	26.9	40.8	0.6	0.6	0	14700000
BMI	Moderate	REF									
Category	Normal	0.7	-0.9	0.4	0.4	1.5	0.7	-0.3	0.8	0.1	6.6
	Obese	1.4	0.8	0.4	0.6	3.5	0.6	-0.3	0.8	0	25.2
	Overweight	0.5	-0.9	0.4	0.1	2.7	1	0	1	0	53.6
	Severe	0.8	-0.6	0.6	0.4	1.7	1.5	0.3	0.7	0.1	16.3
Type of	GeneXpert	REF									
Diagnosis	culture & DST	0	-5.2	0	0	0	0	-5	0	0	0
Constant							6.7	0.5	0.6	0	7372.5

Likelihood Ratio (LR) =27.44 Prob > chi2 = 0.02844

CHAPTER FIVE

DISCUSSION, CONCLUSION & RECOMMENDATIONS

5.1 Discussion

5.1.1 Time to Treatment Initiation from Diagnostic Sample Collection

Drug resistant Tuberculosis is a public health threat with Kenya being among the high burden MDR TB countries globally. Following the new classification, Kenya is among the 14 high TB, MDR TB and HIV burden countries (STAG-TB, 2015).

Delay to diagnosis and eventual treatment initiation has been long in many countries. This was in most cases associated with the diagnostic method used for especially culture and conventional drug sensitivity testing due to the slow growth of bacteria, and the isolation mode of treatment which had many patients in waiting lists for treatment (Martin, et al., 2009) (Padayatchi, 2014).

Delay in this study was defined as the duration from the time sample was collected for diagnosis to the time patient was initiated on treatment. The median was used to determine delay with those on the right of the median being considered as having delayed to initiate treatment. The median time to treatment (delay) was 66 days, with a mean of 99 days to treatment and a range of 0 to 599 days. A possible explanation would be that majority of the patients were diagnosed using Culture and DST which takes a longer diagnostic time as compared to GeneXpert. India has the highest burden of multidrug resistant TB and poor treatment outcomes. A study carried out in India to assess the delay found a median time of 128 days (Nair, 2017) which was much higher than the findings of this study in which the median time was 66. In Kwa Zulu Natal, the author noted a significant delay to treatment with a mean delay of 12.4 weeks (87 days) using culture and DST (Narasimooloo R, 2012). In this study, the mean time to treatment initiation was 98.8 days which was slightly more than in Kwa Zulu Natal and this could be explained by the health systems and programmatic interventions that are in

place for patient referral to initiate treatment and the capacity of GeneXpert in South Africa at the time of the study.

The drug surveillance system in Kenya is currently based on the use of GeneXpert, Line probe assays and culture and DST with GeneXpert being the first test among drug resistant TB high risk groups since 2011 (DLTLD, 2012). GeneXpert was adopted since it takes 2 hours to do the test against culture and conventional drug resistance testing which takes 8 to 12 weeks translating to 56 to 84 days. In this study, only 36% of the patients were diagnosed using GeneXpert. This means that even with GeneXpert, there were patients who took longer than one week to get diagnosis and be initiated on treatment. This could be due to the few a number of GeneXpert machines (11 machines in 2011) in the whole Country. In general, the introduction of GeneXpert reduced the delay to treatment from a mean of 66 to 30 days. This meant that use of GeneXpert as a diagnostic method reduced the overall time to treatment initiation, however it did not necessarily lead to better treatment outcomes as would have been anticipated. A study carried out in Nigeria looking at time to treatment for patients diagnosed using GeneXpert showed a median time of 6 days to treatment initiation (Akanbi, 2017). A univariate analysis carried out on findings of an assessment on the impact of GeneXpert on time to treatment, showed a significant evidence of an association between RR TB detection by GeneXpert and reduced time to treatment initiation (Stagg, 2016).

At the period under review in this study, there were 11 GeneXpert machines in the country and one public culture and DST laboratory that also performed line probe assays. The country relied on both liquid and solid culture methods that take long to make a diagnosis and require specialized laboratories which is expensive for most countries (WHO, 2015). This has also been shown in the study looking at the drug resistant TB program in South Africa, which reported a mean delay of 12.4 weeks to treatment initiation and consequently poor treatment outcomes with a documented treatment success rate of 22% (Padayatchi, 2014). A study comparing the time to treatment using GeneXpert and culture in South Africa showed that the median time to treatment initiation for those diagnosed by GeneXpert was 0(IQR0-0) while that for

culture and DST was 144 days (IQR 28-180) (Hanrahan, et al., 2013). This means that it is possible to initiate patients on treatment on the day of diagnosis, hence reducing morbidity.

5.1.2 Treatment Outcomes of Rifampicin Resistant Tuberculosis Patients

MDR TB which is resistance to the two most important first line anti TB drugs, Rifampicin and Isoniazid has been known to have poor outcomes with only less than 50% having successful outcomes (Cegielski, 2016). The success of treatment in any TB patient is based on microbiological status of a sputum sample from the patient. A patient is considered cured if at baseline they were bacteriologically confirmed by either smear microscopy, culture or GeneXpert and at the end of treatment the smear microscopy test and one previous one is negative for mycobacteria(WHO 2013). Treatment of drug resistance has been a challenge to most clinicians as they depend on the less effective second line medicines. A patient with drug resistant TB is cured if 'a patient has at least 3 consecutive culture negative results taken at least 30 days apart after the intensive period of treatment" (Gunar Günther, 2016).

The world Health organization report showed that the global treatment success rate was at 48% in 2014 (Cegielski, 2016). This improved to 52% in 2016 translating to unfavourable outcomes of between 52% and 48% respectively. The treatment success rate of the patients in this study was 82% (favourable outcome) while 18% had unfavourable outcomes. This is better than global success rate and far above the global target of 75% treatment success rate of MDR TB. The outcomes are comparable to countries such as Ethiopia with a TSR of 78.6% (Meressa, et al., 2015) and higher than Switzerland at 76% (Helbling P1, 2014) and United Kingdom at 70.6% (Anderson, et al., 2013). A study looking at the progress of MDR TB globally studied 30 countries with MDR TB programs and found the median treatment success rate to be 54% (range 75% -84%), indicating that the Kenya rates may have been among the highest globally (Falzon, 2015). Of those with unfavourable outcomes, those who died contributed to 10% while those lost to follow up contributed 7%. Most other studies have found the

lost to follow up as the main contributor of poor treatment outcomes as evidenced by a study looking at treatment outcomes in China in which lost to follow up was at 27% (Alene, 2017) and in South Africa at between 17% and 20%. The male gender was shown to be 0.3 times less likely to have poor outcomes compared to the female. This is comparable to study on gender differences in treatment outcomes among drug sensitive pulmonary TB cases in Kenya that showed that females had a higher risk of poor treatment outcomes compared to male (Kosgei, et al., 2015) but this differs from one done in India in which the male were more likely to have unfavourable outcomes (Nair, 2017).

The results in this study showed that 60% of the patients had BMI below 18.5. This can be attributed to the fact that TB is a body wasting disease and hence the majority of the patients with TB would be expected to have a low BMI. The low BMI in this study unlike in many studies did not contribute to poor treatment outcomes. This could be explained by the fact BMI of the patients in this study was obtained at the beginning of treatment. The patients received nutrition support and counselling during the course of treatment, and this could have prevented the poor treatment outcomes. The main factors that lead to unfavourable treatment outcomes have been named as HIV co infection, low BMI, gender among others. In some studies, it has been observed that a low BMI of less than 18.5 would be associated with unfavourable outcomes, usually death (Shenjie, et al., 2013). In this study, there was no association between the BMI and treatment outcome. This could be attributed to the fact that the BMI was taken at the treatment initiation. Therefore, since majority of the patients got patient nutrition support during this time, this could have reduced the mortality expected among these patients.

HIV AIDS is a driver of TB in Sub-Saharan Africa (Barun, et al., 2017). The MDRTB HIV co infection rate was at 26.23% in 2013 (DLTLD, 2013), compared to 30% among the drug sensitive TB as per the annual report. In most high TB burden countries, MDR TB also has a high burden for HIV (Barun, et al., 2017). Despite many studies reporting that HIV patients with MDR TB are more likely to have poor outcomes, in this study, there was so no significance association between HIV positive patients with MDR TB

and the HIV negative ones. This could be attributed to universal testing of MDR TB patients for HIV and early initiation of ART among the coinfected patients. This agrees with the Lesotho findings that showed that MDR TB patients treated with early ART initiation could achieve same outcomes as the HIV negative (Hind, 2012).

Patents from the North-Eastern region were 23.46 times more likely than patients from the central region to have unfavourable outcomes. More than 30% of drug resistant TB patients in Kenya are found in North Eastern (Kevin, et al., 2015). These patients are mainly refugees of Somalia origin who travelled to Kenya to seek treatment after diagnosis with drug resistant TB in Somalia before Somalia got a treatment program. The burden of drug resistant TB in Somalia following the drug resistance survey done in 2011 showed that the prevalence of MDR TB was 5% among new patients and 40% among previously treated TB patients (Kevin, et al., 2015). This could explain the high burden of drug resistant TB in North Eastern.

5.1.3 Factors Associated with Unfavourable Treatment Outcomes Among Rifampicin Resistant TB Cases

It has been logical to associate poor treatment outcomes especially mortality to delayed diagnosis and treatment of tuberculosis (Rebecca, et al., 2016). The World Health Organization also set an indicator on time to diagnosis and time to treatment initiation to monitor this delay since it had been expected to result in morbidity and mortality of TB patients. In addition, early case detection and prompt treatment initiation have been emphasized, for example The DOTS strategy (Thomas & Sonal, 2005) that was developed by Kylo Styblo was based on a model that showed that with a case detection of 75% and treatment success rate of 85% there would be elimination of TB globally. The strategy was based on early TB case detection and early treatment using short term chemotherapy. In this model, the mortality declined, and most TB patients were initiated on TB treatment with good outcomes.

In the last 2 years studies have been carried out to assess the effect of delay to treatment outcomes. Various studies have, however, demonstrated that the long duration before initiation of MDR TB and XDR TB increased the risk of poor outcomes (Wrishmeen, 2012) (Shenjie et al, 2013).

The question has on association with time to treatment has not been studied (Rebecca, et al., 2016). This study covers a period in which many countries did not have functional drug resistant tuberculosis programs hence the number of patients who had been on long waiting lists for treatment were many hence the time to treatment was long and there was a lot of concerns around mortality due to lack of treatment. This study shows that there is no association between delay to treatment and treatment outcomes. This compares with the finding of a systematic review on effects of early versus late treatment initiation after diagnosis in which 1978 research papers were reviewed and could not find any paper that demonstrated a positive relationship between delay to treatment and treatment outcomes (Rebecca, et al., 2016). This is because irrespective of time to treatment initiation, quality of patient care during treatment is the same. In addition, patients could have had comorbidities despite early treatment initiation. In Vietnam, the study looked at the treatment outcomes of patients on GLC and Non GLC programs. Those in the GLC program had a significant delay of 12.8 days more than the non GLC program, however, the treatment outcomes were better among patients in the GLC program with a TSR of 84.8% compared to non GLC at 53.7% (Hoa, et al., 2014).

5.1.4 Factors associated with Delay to Treatment Initiation among Rifampicin Resistant Tuberculosis Patients

Delay to diagnosis has been the main factor associated with delay to treatment initiation as evidenced by India that showed that delay was associated to use of culture and conventional drug sensitivity testing (Nair, 2017). A similar finding was observed in KwaZulu Natal in which delay to treatment was associated to the long period than of culture and DST took for diagnosis to be made (Narasimooloo & Ross, 2012). In this study, in both bivariable and multiple logistic regression analysis, diagnosis using

culture and DST was associated with delay compared to use of GeneXpert. This could be attributed to the fact that mycobacteria take long to grow, the sample collection and transport to the laboratory can take long. This can be explained by the fact that the number of culture laboratories found in most countries are few and in centralised places requiring proper laboratory networks and sample transport mechanisms.

The male gender in this study did not show statistically significant difference in time to treatment initiation compared to women. However, according to Kaplan Meier analysis, the male gender had a shorter time to be initiated on treatment compared to the female gender. This can be compared to a metanalysis that was carried out in 17 countries and regions looking at 40 studies on factors associated with patient delay and found that the male gender had shorter delays to treatment (Jing, et al., 2015). This could be explained by the fact that there were few facilities that could offer MDR TB treatment requiring diagnosed patients had to travel long distances to obtain treatment. It was therefore easier for males to access treatment than female who faced barriers such as household chores, stigma, physical and financial constraints (Lakshmi, et al., 2014).

HIV patients have regular access to health care. In this study, HIV status did not have statistical evidence of any shorter time to treatment according to both the bivariable and multiple logistic regression analysis, however the Kaplan Meier analysis shows a possibility of having a shorter time to treatment initiation. A study carried out in Ethiopia on the factors that were associated with delay to TB diagnosis and treatment demonstrated that HIV patients took a shorter time to initiate treatment than those who were not infected (Bogale, et al., 2017).

5.1.5 Importance of the study

This kind of study has not been carried out in Kenya previously. It therefore sought to clarify if delay to treatment initiation is associated to unfavourable treatment outcomes. It identifies that there is a gap in understanding the factors associated to treatment outcomes beyond treatment initiation. It creates a need to examine further the

transmission rates and quality of life post treatment completion. Further it encourages studies on the implication of delay in treatment on the possible post treatment complication.

5.1.6 Strengths of the study

The study was carried out on a stable program that has the best outcomes globally. The study was on a national scale covering 3 years and all RR TB patients were included hence the study is generalizable. The sample size was adequate compared to other countries with similar burden as Kenya and in programs that are starting treatment of drug resistant TB cases, hence young DR TB programs can benefit from the findings of this study. The study methodology is comparable to other studies of similar nature in which the assessment is carried out retrospectively. Being an academic study, sample selection was based on random sampling, although in most program evaluations, all patients are studied. This, however, did not compromise the study or findings in anyway as the sample size was adequate and the selection criteria scientific. Patient confidentiality and ethical principles have been applied in the study.

5.1.7 Limitations of the study

The definition of delay is study-specific and based on sample parameters and country context. This may affect comparability of some indicators with other studies.

The study relied on secondary data; records that missed diagnostic tests were excluded from the study. Since the data was retrospectively collected, some information was missing reducing the number that was eligible for the study. The wide confidence intervals in the sub-analyses indicate that the study may have lacked adequate power to detect differences. More subjects were needed in this case. Based on the later years, the treatment outcomes in Kenya have gone down to 73% in 2014. This study could be expanded into subsequent years.

5.1.8 Areas for Further Research

This study does not account for severity of disease in the individuals and delay to sample collection. This is proposed as an area of study to answer if the severity of disease had any association with delay in sample collection and eventual patient outcomes. This is not data usually collected by national Tuberculosis Programs and hence would need to be included in patient treatment cards.

Treatment outcomes are based on the bacteriological results of a patient at diagnosis and end of treatment but does not look at quality of life. As such, though the patient might complete treatment successfully, the patient might be left with complications such as lung collapse that might have been as a result of disease progression while awaiting treatment. The study identifies the second quarter as associated with delay to treatment initiation, a factor that should be studied in programmatic setting and identify the reasons why this is so.

5.2 Conclusion

The study found out that delay to treatment initiation among RR TB patients is not associated with treatment outcomes. Patients with Rifampicin Resistance in Kenya had a high treatment success rate when compared to other countries indicating a strong program. There was no significant association between delay to treatment initiation and outcome, however, it would be important to note that unfavourable treatment outcome was associated with being male and also being diagnosed and treated in the North Eastern regions (which was previously called north Eastern Province) of the Kenya. Other demographic and clinical characteristics such as age, HIV status, type of patient, time to treatment, being on nutritional support, type of diagnosis was not associated with unfavourable treatment outcome.

There was strong evidence that patients diagnosed with culture and DST were more likely to delay in treatment initiation compared to those diagnosed using GeneXpert.

GeneXpert significantly reduces time to treatment initiation. The use of GeneXpert for surveillance should be increased and barriers to its access addressed, as it has been shown to reduce delay to treatment. Efforts for early diagnosis and treatment should be enhanced to reduce TB transmission and morbidity.

Patients initiated on treatment during the second quarter of the year were more likely to delay in treatment initiation. HIV status, gender, resistance pattern, BMI and region where treatment was initiated had no association to delay to treatment initiation.

Recommendation

The researcher recommends that use of GeneXpert for surveillance should be increased and barriers to its access addressed, as it has been shown to reduce delay to treatment. Since it is a point of care test, its availability should be ensured to maintain the short turnaround time. The number of treatment sites offering Rifampicin Resistant TB treatment need to be increased to reduce time to initiation of treatment consequently cutting down the transmission rates for drug resistant TB. The treatment outcomes were generally good but an adherence and mortality studies to assess the main causes of unfavourable outcomes at the facility and patent level of various drugs and GeneXpert should be carried out to improve further the treatment outcomes. Patients initiated on treatment during the second quarter of the year were more likely to delay in treatment initiation. A study would need to be done to understand why this time of the treatment calendar resulted in a delay to diagnosis. This study looked at the delay at the health care setting. Patient delay study should be carried out to identify challenges that patients face to access health facilities for diagnosis and treatment such as economic costs and other social barriers. The researcher therefore hopes that the National Tuberculosis program will take up the following recommendations for policy implementation to improve the diagnostic turnaround time, reduce time to treatment initiation and improve treatment outcomes.

REFERENCES

Akanbi, M. O. (2017). Evaluation of GeneXpert for routine diagnosis of HIV-associated tuberculosis in Nigeria: A prospective cohort study. *BMC Pulmonary Medicine, 17*(87), 430-436.

Alavi, S. M. (2015). Factors Associated with Delay in Diagnosis and Treatment of Pulmonary Tuberculosis. *Jundishapur Journal of Microbiology, 8*(3).

Albert, H. d. (2017). Implementation of quality management systems and progress towards accreditation of National Tuberculosis Reference Laboratories in Africa. *African Journal of Laboratory Medicine, 6*(2), 490.

Alene, K. A. (2017). Treatment outcomes of patients with multidrug-resistant and extensively drug resistant tuberculosis in Hunan Province, China. *BMC Infectious Diseases, 17* (573).

Anderson, L. F., Tamne, S., Watson, J. P., Cohen, T., Mitnick, C., Brown, T., Abubakar, I. (2013). Treatment outcome of multi-drug resistant tuberculosis in the United Kingdom: retrospective-prospective cohort study from 2004 to 2007. *Euro Surveillance, 18*(40), 1028-1035.

Anna, H. v., Helen, K. M., Kayla, F. L., Janet, A. A., Benson, G. M., Willie, A. G., Martien, W. B. (2012). Screening Strategies for Tuberculosis Prevalence Surveys: The Value of Chest Radiography and Symptoms. *PLoS*.

Barun, M., Jason, R. A., Ted, C., Martien, W. B., Marcel, B., Judith, R. G., Robin, W. (2017). Drivers of Tuberculosis Transmission . *The Journal of Infectious Diseases, 216*(6), s644 - s653.

Bateman, C. (2015). Tugela Ferry's extensively drug-resistant tuberculosis - 10 years on. *South African Medical Journal, 105*(7), 517-520. Retrieved from

Battaglioli, T., Rintiswati, N., Martin, A., & Palupi, K. (2013). *Comparative performance of Thin Layer Agar and Lo ̈wenstein–Jensen culture for*

diagnosis of tuberculosis. Clin Microbial Infect.

Beth Temple, et al., 2010. Rate and Amplification of Drug Resistance among Previously-Treated Patients with Tuberculosis in Kampala, Uganda. *Clinical Infectious Diseases,* pp. 1126-1134.

Biraro IA, K. S. (2016). The Use of Interferon Gamma Inducible Protein 10 as a Potential Biomarker in the Diagnosis of Latent Tuberculosis Infection in Uganda. . *Plos One*(11).

Bogale, S., Diro, E., Shiferaw, A. M., & Yenit, M. K. (2017). Factors associated with the length of delay with tuberculosis diagnosis and treatment among adult tuberculosis patients attending at public health facilities in Gondar town, Northwest, Ethiopia. . *BMC, 17*(145).

Caminero, J. A. (2003). Diagnosis of Tuberculosis. In CDC (Ed.), *A Tuberculosis Guide for Specialist Physicians* (pp. 81-84). Paris France: International Union Against Tuberculosis and Lung Disease.

Cegielski, P. (2016). Multidrug-Resistant Tuberculosis Treatment Outcomes in Relation to Treatment and Initial Versus Acquired Second-Line Drug Resistance. *Clinical Infectious Diseases, 62*(4), 418-439.

Churchyard, G., Mametja, L., Mvusi, L., Ndjeka, N., Hesseling, A., Reid, A., Pillay, Y. (2014). Tuberculosis control in South Africa: successes, challenges and recommendations. *South African Medical Journal., 104*(3), 244-8.

Claassens, M. M., Schalkwyk, V. C., Floyd, S., Ayles, H., & Beyers, N. (2017). Symptom screening rules to identify active pulmonary tuberculosis: Findings from the Zambian South African Tuberculosis and HIV/AIDS Reduction (ZAMSTAR) trial prevalence surveys. *PLOS one*.

Cohen, K. A. (2015). Evolution of Extensively Drug-Resistant Tuberculosis over Four Decades: Whole Genome Sequencing and Dating Analysis of Mycobacterium tuberculosis Isolates from KwaZulu-Natal. *Plos Medicine, 12*(9), 1-14.

Cole, S. T., Brosch, R., Parkhill, J., Garnier, T., Churcher, C., Harris, D., Barrell, B. (1998). Deciphering the biology of Mycobacterium tuberculosis from the complete genome sequence. *Macmillan Publishers Ltd, 393*(11), 537-544.

Dag Gundersen Storla, S. Y. (2008, January 14). A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC Public Health, 8*(18).

Daniel Meressa1, 2. R. (2015). Achieving high treatment success for multidrug-resistant TB in Africa: initiation and scale-up of MDR TB care in Ethiopia—an observational cohort study. *BMJ Journals, 70*(20), 1181-1188.

De Cock, D., Rutherford, G., & Akhwale, W. (2014). Kenya AIDS Indicator Survey 2012. *PubMed*, 66.

Denkinger, C., Schumacher, S., Boehme, C., Dendukuri, N., Pai, M., & Steingart, K. (2014). *Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis.* PubMed.

DLTLD. (2012). *Standard Operating Procedures for Programmatic Management of Drug Resistant Tuberculosis - (PMDT) Kenya. Nairobi: Ministry of Health.* Nairobi: Ministry of Health.

DLTLD (2013). *National TB and Leprosy Annual Report.* Nairobi: Ministry of Health.

DLTLD. (2013). *Guidelines for Management of Tuberculosis and Leprosy in Kenya.* Nairobi: Ministry of Health.

Dye, C. (2015). *The Population Biology of Tuberculosis Publisher: Pg 28.* New Jersey: Princeton University Press.

Eshetie, S. G. (2018). Tuberculosis treatment outcomes in Ethiopia from 2003 to 2016, and impact of HIV co-infection and prior drug exposure: A systematic review and meta-analysis. *PLoS ONE, 13*(3).

Esmail, H., E., B. C., Young, D. B., & Wilkinson, R. J. (2014). The ongoing challenge of latent tuberculosis. *Philosophical Transactions of the Royal Society B: Biological Sciences, 369*(1645). Retrieved from http://doi.org/10.1098/rsTB.2013.0437

Ettehad D, S. H. (n.d.). Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis [Internet]. 2012 Jun [cited 2014 Jul 24];12(6):449–56.*

Falzon, D. M. (2015). Multidrug-resistant tuberculosis around the world: what progress has been made? *The European Respiratory Journal, 45*(1), 150–160.

Furin, J., Isaakidis, P., Reid, A. J., & Kielmann, K. (2014). 'I'm fed up': experiences of prior anti-tuberculosis treatment in patients with drug-resistant tuberculosis and HIV. *The International Journal of Tuberculosis and Lung Disease, 18*(12), 1479-84.

Giovanni, S., Simon, T., Rosella, C., LiaD, A., Zhenia, F., Alimuddin, Z., & Giovanni, B. (2017). Applicability of the shorter 'Bangladesh regimen' in high multidrug-resistant tuberculosis settings. *International Journal of Infectious Diseases, 56*, 190-193.

Glaziou, P., Sismanidis, C., Floyd, K., & Raviglione, M. (2014). Global epidemiology of tuberculosis. *Cold Spring Cold Spring Harbor Perspectives in Medicine., 5*(2).

Gunar Günther, L. C. (2016). Treatment Outcomes in Multidrug-Resistant Tuberculosis. *The New England Journal of Medicine , 375*(11), 1103-1105.

H S Schaaf, K. S. (n.d.). Culture confirmed multidrug resistant tuberculosis: diagnostic delay, clinical features, and outcome. *Arch Dis Child 2003 88: 1106-1111: doi: 10.1136/adc.88.12.1106*.

Hanrahan, C., Selibas, K., Deery, C., Dansey, H., Clouse, K., Bassett, J., Sanne, I. (2013). Time to treatment and patient outcomes among TB suspects screened by a single point-of-care xpert MTB/RIF at a primary care

clinic in Johannesburg, South Africa. *PLoS One.*, 64.

Han, T., 2006. Effectiveness of standard short-course chemotherapy for treating tuberculosis and the impact of drug resistance on its outcome. *International Journal of Evidence-Based Healthcare*, 4(2), pp. 101-117.

Harris, R. C., Louis, G., Laura, J. M., Alexander, J. P., Miller, J.-E. N., Nkang, V. A., David, A. J. (2016). The effect of early versus late treatment initiation after diagnosis on the outcomes of patients treated for multidrug-resistant tuberculosis: a systematic review. *BMC, 16*(193).

Helbling P1, A. E. (2014). Treatment outcomes of multidrug-resistant tuberculosis in Switzerland. *Swiss Medical Weekly*, 144.

Hind, S. (2012). Ooutcomes of Multi drug Resistand Tuberculosis Treatment with Erly initiation of Antiretroviral Therapy for HIV Co-infected Patients in Lesotho. *PLOS ONE, 7*(10), 1-7.

Hoa, N., Khanh, P., Chinh, N., & Hennig, C. (2014). Prescription patterns and treatment outcomes of MDR-TB patients treated within and outside the National Tuberculosis Programme in Pham Ngoc Thach hospital, Viet Nam. *Tropical Medicine and International Health, 19*(9), 1076-1081.

Hooja, S., Pal, N., Malhotra, B., Goyal, S., Kumar, V., & Vyas, L. (2011). Comparison of Ziehl Neelsen & Auramine O staining methods on direct and concentrated smears in clinical specimens. *Inidan J Tuberculosis, 58*, 72-76.

Houben, R., & Dodd, P. (2016). The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. 13(10): e1002152. https://doi.org/10.1371/journal.pmed.1002152. *PubMed*(13).

Iñaki Comas, S. G. (2009). The Past and Future of Tuberculosis Research. *PLOS pathogen, 510*, 1371.

Jayneetha, M., Andrew, R., Niren, R. M., & and Laura, C. (2012). Drug resistance-related mutations in multidrug-resistant Mycobacterium tuberculosis isolates from diverse geographical regions. *International*

Journal of Mycobacteriology, 124- 130.

Jayneetha, M., Andrew, R., Niren, R. M., & Laura, C. (2016). Multidrug-resistant tuberculosis in KwaZulu-Natal, South Africa: An overview of patients' reported knowledge and attitudes. *African Journal of Primary Health Care & Family Medicine, 8*(1), 1089.

JD, K. (1993). Mycobacterium tuberculosis in household contacts of human immunodeficiency virus type 1–seropositive patients with active pulmonary tuberculosis in Kinshasa, Zaire. *Journal of infectious Disease, 1*, 106-111.

Jing, C., Xianhua, W., Aiguo, M., Qiuzhen, W., Xiuxia, H., & Yong, L. (2015). Factors Associated with Patient and Provider Delays for Tuberculosis Diagnosis and Treatment in Asia: A Systematic Review and Meta-Analysis. *PLoS* .

Johnstone-Robertson, S., Mark, D., Morrow, C., Middelkoop, K., Chiswell, M., Aquino, L., Wood, R. (2011). Social mixing patterns within a South African township community: implications for respiratory disease transmission and control. *American Journal of Epidemiology*, 174(11), 1246-55.

Kamene, M.K., 2015. GLC Mission Kenya 2015 Presentation, Nairobi.

Karen Smith, D. S. D. G., 2019. *Drug-Resistant Tuberculosis: A Survival Guide For Clinicians.* 3rd ed. California: Curry International Tuberculosis Center.

Kasambira, T. (2011). QuantiFERON–TB Gold In–Tube for the detection of Mycobacterium tuberculosis infection in children with household tuberculosis contact. *International Journal of Tuberculosis and Lung Disease, 15*(5), 628-634.

Kashmira, S. C., Cecilia, K., Abineli, M., Mitch, M., Irving, H., Jonathan, N., & Mina, C. H. (2016, May 1). Policy to practice: impact of GeneXpert MTB/RIF implementation on the TB spectrum of care in Lilongwe,

Malawi. *Transactions of The Royal Society of Tropical Medicine and Hygiene, 110*(5), 305–311.

Kenyon, T. (2002). Risk factors for transmission of Mycobacterium tuberculosis from HIV–infected tuberculosis patients, Botswana. . *International Journal of Tuberculosis and Lung Disease, 6*(10), 843-850.

Keshavjee, S. (2009). Role of the Green Light Committee Initiative in MDR-TB Treatment Scale-up. *Green Light Committee* (pp. 1-16). Beijing: WHO.

Kevin P. Cain, 1. ,. (2015). The Movement of Multidrug-Resistant Tuberculosis across Borders in East Africa Needs a Regional and Global Solution. *PLoS Medicine, 12(2), e1001791. http, 12*(2).

Kevin, P. C., Nina, M., Maureen, K., Joseph, S., Subroto, M., Aleksandar, G., Kevin, M. D. (2015). The Movement of Multidrug-Resistant Tuberculosis across Borders in East Africa Needs a Regional and Global Solution. *Plos One, 12*(2).

Khadija, S., Jerry, H., Grace, M., Mary, C., Edward, M., Thomas, M., Lukas, F. (2017). Diagnostic delay and associated factors among patients with pulmonary tuberculosis in Dar es Salaam, Tanzania. *Infectious Diseases of Poverty Journal, 6*(64).

Kliiman K, A. a. (2009). Predictors of poor treatment outcome in multi- and extensively drug-resistant pulmonary TB. *Eur Respir J, 33(5),* 1085–94. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19164345

KNBS. (2009). *2009 Kenya Polpulation and Housing Census: Annalytical Report on Population Projections.* Nairobi, KNBS.

Koch, R. (1882). Die Äetiologie der Tuberkulose. *Berliner klinische Wochenschrift, 15*, 221–230.

Kosgei, R., Sitienei, J., Kipruto, H., Kimenye, K., Gathara, D., Odawa, F., Carter, E. (2015, Oct). Gender differences in treatment outcomes among 15-49 year olds with smear-positive pulmonary tuberculosis in Kenya.

International of Tuberculosis and Lung Disease, 19(10), 1176-1181.

Kunkel, A., Pia, A. z., Ruvandhi, R. N., Florian, M. M., Helen, E. J., & Ted, C. (2016). Smear positivity in paediatric and adult tuberculosis: systematic review and meta-analysis. *BMC, 16*, 282.

Lakshmi, K., Tokunbo, A., Anita, V. S., Katherine, N. M., Celine, R. G., Amita, G., & Wei-Teng, Y. (2014). Gender-Related Barriers and Delays in Accessing Tuberculosis Diagnostic and Treatment Services: A Systematic Review of Qualitative Studies. *Tuberculosis Research and Treatment, 2014*, 14 pages. Retrieved from http://dx.doi.org/10.1155/2014/215059

Long, N. H., Johansson, E., Lönnroth, K., Eriksson, B., Winkvist, A., & Diwan, V. K. (1999). Longer delays in tuberculosis diagnosis among women in Vietnam. *The International Journal of Tuberculosis and Lung Disease, 3*(5), 388-393.

Martin, A., Paasch, F., Von Groll, A., Fissette, K., Almeida, P., Varaine, F., .Palomino, J.-C. (2009). The Union Thin-layer agar for detection of resistance to rifampicin, ofloxacin and kanamycin in Mycobacterium tuberculosis isolates. *International Journal of Tuberculosis and Lung Disease (IJTLD)* , 13(10), 1301-1304.

Matsie, M., Ashwin, S. D., Paul, A. J., Stephen, N. R., Tobias, H. v., Marcello, A. P., . . . Edward, A. N. (2015). Institutional Tuberculosis Transmission. Controlled Trial of Upper Room Ultraviolet Air Disinfection: A Basis for New Dosing Guidelines. *American Journal of Respiratory and Critical Care Medicine., 192*(4), 477 - 484.

Meressa, D., Hurtado, R., Andrews, J., Diro, E., Abato, K., Daniel, T., Aderaye, G. (2015). Achieving high treatment success for multidrug-resistant TB in Africa: initiation and scale-up of MDR TB care in Ethiopia--an observational cohort study. *British Medical Journals, 70*(12), 1081-1088.

Migliori GB, S. G. (2009). MDR-TB and XDR-TB: drug resistance and treatment outcomes. *European Respiratory Journal*, 34(3), 778–9. Retrieved from Available from: http://www.ncbi.nlm.nih.gov/

Mor, Z., Kolb, H., Lidji, M., Migliori, G., & Leventhal, A. (2013). Tuberculosis diagnostic delay and therapy outcomes of non-national migrants in Tel Aviv, 1998-2008. *Euro Surveillance., 18*(12).

Mpagama SG, H. S. (2013). Diagnosis and Interim Treatment Outcomes from the First Cohort of Multidrug-Resistant Tuberculosis Patients in Tanzania. *PLoS ONE 8(5): e62034. doi:10.1371/journal.pone.0062034.*

Müller, B., Borrell, S., Rose, G., & Gagneux, S. (2013). The Heterogeneous Evolution of Multidrug-Resistant Mycobacterium tuberculosis. Trends in Genetics. *29*(3). Retrieved from http://doi.org/10.1016/j.tig.2012.11.005

Musa, B. M., Adamu, A. L., Galadanci, N. A., Zubayr, B., Odoh, C. N., & Aliyu, M. H. (2017). Trends in prevalence of multi drug resistant tuberculosis in sub-Saharan Africa: A systematic review and meta-analysis. *PLoS ONE, 12*(9). Retrieved from http://doi.org/10.1371/journal.pone.0185105

Nadia AIT-Khaled, D. A. (2003). *Tuberculosis Manual for medica students* . Paris, France: UNION, WHO.

Naing, L., Winn, T., & Rusli, B. (2006). Practical issues in Calculating the Sample Size for Prevalence Studies. *Medical Statistics, 1*, 9 - 14.

Nair, D. V. (2017). Predictors of unfavourable treatment outcome in patients with multidrug-resistant tuberculosis in India. *Public Health Action, 7*(1), 32-38.

Narasimhan, P., Wood, J., MacIntyre, C. R., & Mathai, D. (2013). Risk Factors for Tuberculosis. *Pulmonary Medicine, vol. 2013*(Article ID 828939,). Retrieved from https://doi.org/10.1155/2013/828939.

Narasimooloo R, R. A. (2012). Delay in commencing treatment for MDR TB at a specialised TB treatment centre in KwaZulu-Natal. *South Africa*

Medical Journal, 102(6), 360-2.

Narasimooloo, R., & Ross, A. (2012). Delay in commencing treatment for MDR TB at a specialised TB treatment centre in KwaZulu-Natal. *South African Medical Journal* , 360-2.

Ndjeka, N. (2014). *MONITORING REPORT Programmatic Management of Drug Resistant TB in Kenya.* Nairobi: WHO.

Nicole, F. (2015). Tuberculosis: A disease without boundaries. *Tuberculosis*, 527-531.

Nomonde R Dlamini-Mvelase, L. W. (2014). Effects of introducing Xpert MTB/RIF test on multi-drug resistant tuberculosis diagnosis in KwaZulu-Natal South Africa. *BMC Infectious Diseases, , 14:442*. doi:doi:10.1186/1471-2334-14-442

NTLD-P, 2014. *Mid-Term Review Of The National Tuberculosis, Leprosy& Lung Health Unit Of The Ministryof Health, Kenya,* Nairobi: MOH.

NTLD-P. (2016). *Annual Report.* Nairobi: Ministry of Health.

NTLD-P. (2017). *Annual Report.* Nairobi.

NTLD-P. (2017). *Guidelines for Public-Private Mix in Kenya* (1 ed.). Nairobi, Kenya: Ministry of Health.

Olivier Neyrolles, L. Q.-M. (2009). Sexual Inequality in Tuberculosis. *PLOS Medicine, 6*(12), 1-6.

Padayatchi, N. N. (2014). Drug Resistant Tuberculosis Control in South Africa – Scientific Advances and Health System Strengthening are Complementary. *Expert Opinion on Pharmacotherapy, 15*(15), 2113–2116.

Qiao Liu†, L. Z. (2013). Rates and risk factors for drug resistance tuberculosis in North Eastern China. *BMC Public Health, 13*, 1171.

Quincó, P., Samira, B.-S., Walber, B., Rossiclea, M., Silvia, L. S., Valeria, S., Marcelo, C.-S. (2013). Increased Sensitivity in Diagnosis of Tuberculosis in HIV-Positive Patients through the Small-Membrane-

Filter Method of Microscopy. *Clinical Microbiology, 51*(9), 2921-2925. doi:doi:10.1128/JCM.00683-

Rachel, N., Emma, B., & Alexandra, B. (2010). *The Race Against Drug Resistance.* Washington: Center for Global Development.

Rebecca, C. H., Louis, G., Laura, J. M., Alexander, J. P., Joseph-Egre, N. N., Victoria, A., David, A. J. (2016). The effect of early versus late treatment initiation after diagnosis on the outcomes of patients treated for multidrug-resistant tuberculosis: a systematic review. *BMC Infectious Diseases, 16*(193).

Satti H, M. M.-G. (n.d.). Outcomes of multidrug-resistant tuberculosis treatment with early initiation of antiretroviral therapy for HIV co-infected patients in Lesotho. *PLoS One [Internet]. 2012 J.*

Shenjie, T., Shouyong, T., & Lan, Y. (2013). Risk Factors for Poor Treatment Outcomes in Patients with MDR-TB and XDR-TB in China: Retrospective Multi-Center Investigation. *PLOS ONE*(12), 1-8.

STAG-TB. (2015). *Use of high burden country lists for TB by WHO in the post-2015 era.* WHO. Geneva: World Health Organization.

Stagg, H. R. (2016). Decreased time to treatment initiation for Multidrug - Resistant Tuberculosis Patients after use of Xpert MTB/RIF test, Latvia. *Emerging Infectious Diseases, 22*(2), 482-490.

Suhail, A. (2010). Pathogenesis, Immunology, and Diagnosis of Latent Mycobacterium tuberculosis Infection. *PMC*.

Surajit, N., & Basanti, A. (2012). Mantoux test and its interpretation. *PMC, 3*(1), 2 - 6.

Tawanda Gumbo, et al., 2007. Article Navigation Isoniazid's Bactericidal Activity Ceases because of the Emergence of Resistance, Not Depletion of Mycobacterium tuberculosis in the Log Phase of Growth. *The Journal of Infectious Diseases,* 195(2), pp. 194-201

Thomas, R. F., & Sonal, S. M. (2005, June). The DOTS Strategy for Controlling the Global Tuberculosis Epidemic. *Clinics in Chest*

Medicine, 26(2), 197-205.

UNAIDS. (2013). Global report: UNAIDS report on the global AIDS epidemic 2013. Geneva.

van Cleeff, M., Kivihya-Ndugga, L., Meme, H., Odhiambo, J., & Klatser, P. (2005). The role and performance of chest X-ray for the diagnosis of tuberculosis: A cost-effectiveness analysis in Nairobi, Kenya. *PMC*.

Wang, H. Y. et al., 2018. *Detection of Rifampicin- and Isoniazid-Resistant Mycobacterium tuberculosis Using the Quantamatrix Multiplexed Assay Platform System.*:Annals of laboratory medicine.

WHO Tuberculosis Chemotherapy centre. (1961). An investigation of household contacts of open cases of pulmonary tuberculosis amongst the Kikuyu in Kiambu, Kenya. *Bulletin of the World Health Organization, 25*(6), 831–850.

WHO, 2013. Definitions and reporting framework for tuberculosis – 2014 Revision 1st ed., Geneva: WHO Library.

WHO. (2015). WHO's recommended techniques for diagnosing TB. In W. H. Organization, *Implementing Tuberculosis Diagnostics Policy Framework* (pp. 16-18). Geneva, Switzerland: World Health Organization .

WHO. (2004). How reliable is smear microscopy. In T. Frieden (Ed.), *Toman's Tuberculosis case-finding and chemotherapy. Questions and Answers. First Edition* (pp. 51 - 65). Geneva: WHO.

WHO. (2005). *WHO International Health Regulations* (3 ed.). Geneva: WHO Library Cataloguing.

WHO. (2008). *Guidelines for the programmatic management of drug-resistant tuberculosis; Emergency Update.*

WHO. (2009). *Management of MDR-TB: A Field Guide A Companion Document to Guidelines for Programmatic Management of Drug-Resistant Tuberculosis Integrated Management of Adolescent and Adult*

Illness (IMAI). Geneva.

WHO. (2010). *Treatment of Tuberculosis: Guidelines. 4th edition.* Geneva: WHO. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK138743/

WHO. (2013). *Global Tuberculosis Report.*

WHO. (2015). *Global Tuberculosis Report.* Geneva: WHO.

WHO. (2016). *Global Tuberculosis Report.* Geneva, Switzerland: WHO.

WHO. (2016). *Multi-drug Resistant TB (MDR-TB).* Geneva: World Health Organization.

WHO. (2016). *SDG Health and related targets*

WHO. (2017). Multidrug Resistant-TB (MDR-TB). *2017 Update*, pp. 1-3.

WHO. (2017). *Global Tuberculosis Report.* Geneva, Switzerland: WHO.

WHO, 2018. *Ambulatory care and infectiousness in tuberculosis.* Geneva.

WHO. (2018). *Latent tuberculosis infection Updated and consolidated guidelines for programmatic management* (ISBN 978-92-4-155023-9 ed.). Geneva: Creative Commons Attribution.

WHO. (2018). *Latent tuberculosis infection Updated and consolidated guidelines for programmatic management.* Geneva: World Health Organization.

Willy, S., Sebastian, J. G., Gerald, M., Anne, W., Carolyn, N., Philippa, M., . . . Moses, L. J. (2015). Feasibility of establishing a biosafety level 3 tuberculosis culture laboratory of acceptable quality standards in a resource-limited setting: an experience from Uganda. *Health Respiratory Policy System, 13*(4).

Wrishmeen, S., Hajime, S., & Yasuki, K. (2012). Delay in the treatment of pulmonary tuberculosis: a report from Afghanistan. *Environ Health Prev Med, 17*(1), 53-61.

Ying Zhang, et al., 2013. Mechanisms of Pyrazinamide Action and Resistance. *Microbiology Spectrum,* 2(4), pp. 1-12.

APPENDICES

Appendix I: Data Abstraction Form

Code:

The following form will be used to collect the listed variables from the patient electronic register, facility PMDT register and the laboratory register. Insert the provided code in the black spaces on the right. Where the code is absent, insert the exact text.

Delay in MDR TB Abstraction Form

A. Patient Demographics

Patient district registration number _____

Date of registration_____

Data Clerk Name _____

Facility Name_____

District/Zone _____

County _____

Region _____

Age in years _____

Sex: Male _____ Female_____

Weight _____ Height _____ BMI_____

B. Diagnosis

Site of TB: PTB_____ EPTB _____

Resistance pattern – tick appropriate pattern

RR TB	R		MDR TB	RH	
	RE			RH	
	RES			RHE	
	RS			RHES	
XDR				RHS	

Date sample was collected_____

Date of diagnosis _____ by Xpert

Date of diagnosis _____ by LPA (where available)

Date of diagnosis _____ by culture &DST

Date treatment started _____

Diagnostic test used – select the test used to initiate patient on treatment

GeneXpert	
LPA/HAIN	
Culture & DST	

Name of diagnosing lab _____

Days to diagnosis (date sample was collected to date of diagnosis- both days inclusive) _____

Days to treatment (date of diagnosis to date treatment was started- both days inclusive) _____

Treatment outcome

Treatment outcome- select as appropriate

Cured	
Treatment completed	
Died	
Loss to follow up	
Failed	
Transferred out	
Still on treatment	

C. HIV Details

HIV Status Positive _____Negative _____ Unknown _____

If HIV positive, is the patient on ART Yes_____ No _____

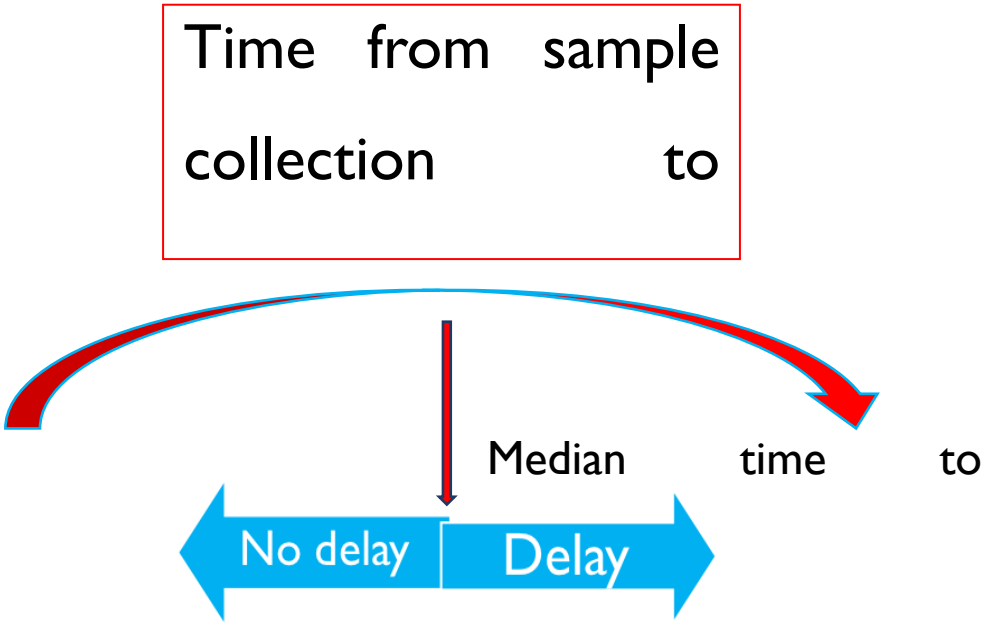
IF HIV positive, is the patient on Cotrimoxazole Yes_____ No _____

Appendix II: Unique Identifiers

Patient No	Unique ID		Patient No	Unique ID		Patient No	Unique ID		Patient No	Unique ID		Patient No	Unique ID
1	1367		43	1273		85	1340		127	1204		169	1030
2	1408		44	1270		86	1214		128	1182		170	1099
3	1357		45	1322		87	1215		129	1053		171	1149
4	1353		46	1221		88	1227		130	1098		172	904
5	1390		47	1313		89	1337		131	1191		173	1075
6	1346		48	947		90	1218		132	1181		174	1151
7	1359		49	1283		91	1336		133	1126		175	1060
8	1383		50	1292		92	1295		134	1032		176	1070
9	1414		51	1303		93	1225		135	1169		177	1156
10	1410		52	1229		94	1324		136	1056		178	1041
11	1352		53	1329		95	1260		137	1147		179	1063
12	1363		54	1306		96	1245		138	1008		181	1172
13	1343		55	1332		97	1213		139	1205		182	990
14	1417		56	1327		98	1293		140	1074		183	864
15	1369		57	1285		99	1252		141	1174		184	868
16	1422		58	1312		100	1302		142	1186		185	943
17	1427		59	966		101	1137		143	1127		186	715
18	963		60	1220		102	1162		144	1193		187	902
19	1402		61	1212		103	1142		145	1140		188	842
20	1366		62	1265		104	901		146	1155		189	899
21	1349		63	1244		105	1154		147	1086		190	920
22	1371		64	1286		106	1211		148	1051		191	928
23	1387		65	1222		107	1150		149	1200		192	722
24	1365		66	1246		108	1019		150	1152		193	952
25	1355		67	1282		109	1120		151	1184		194	1006
26	1345		68	1243		110	1122		152	1187		195	956
27	1361		69	1279		111	922		153	1209		196	900
28	1413		70	1299		112	1109		154	1106		197	721
29	1364		71	939		113	1128		155	1117		198	1001
30	1405		72	1250		114	1129		156	1134		199	909
31	1397		73	1238		115	1124		157	1145		200	973

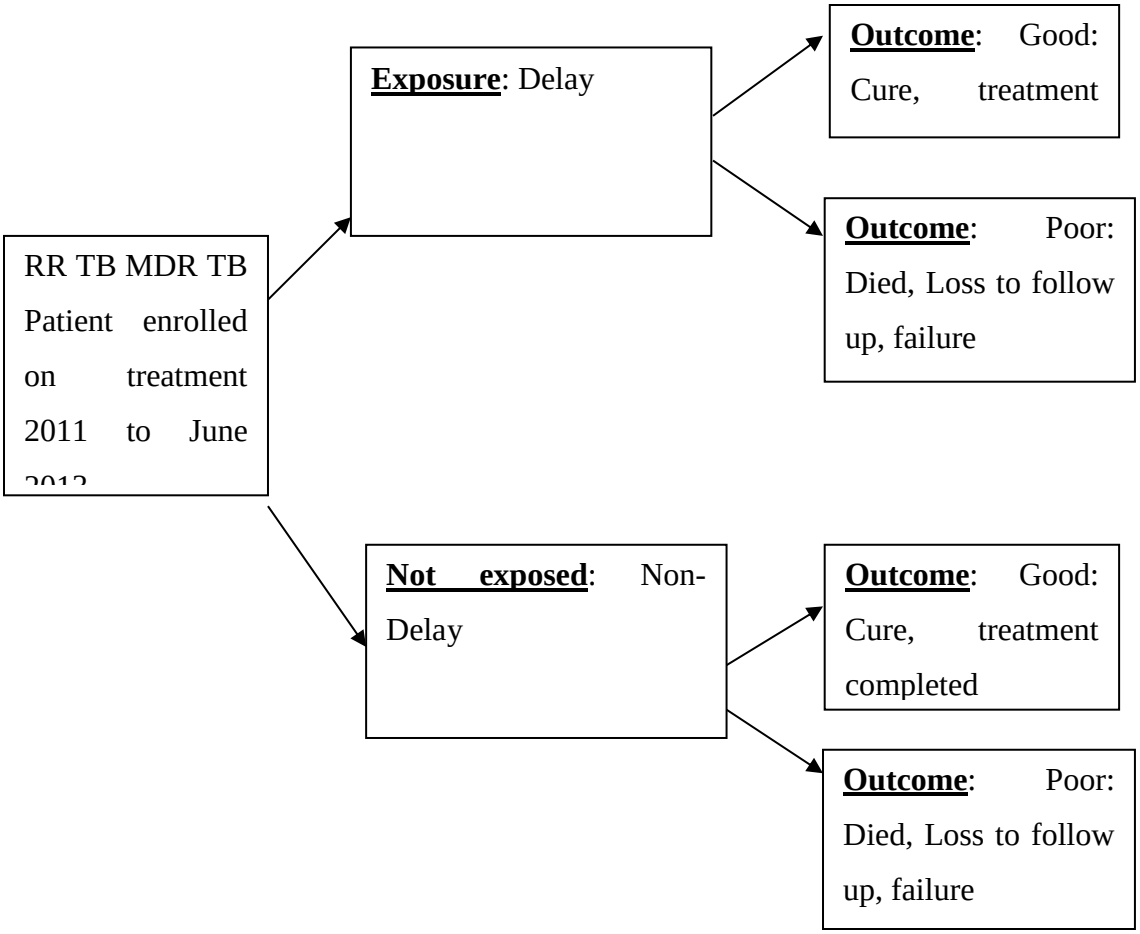
32	1370		74	1284	116	938	158	1210	201	921
33	1416		75	1217	117	1048	159	904	202	942
34	968		76	1311	118	1138	160	1115	203	935
35	1358		77	1314	119	1057	161	1159	204	945
36	1344		78	1328	120	1123	162	1144	205	974
37	1394		79	1307	121	904	163	1116	206	856
38	1426		80	1323	122	1192	164	1121	207	896
39	1354		81	1251	123	1076	165	1072	208	960
40	1348		82	1271	124	1166	166	1132		
41	1428		83	1321	125	1021	167	1025		
42	1310		84	1288	126	1148	168	1031		

Appendix III: Schematic definition of delay



The study defines delay as the median time from date of sample collection to the date the patient was started on treatment calculated in days.

Appendix IV: Study design framework



Appendix V: List of facilities

Province	County	Facility	Sampled
Central	Kiambu	Kiambu District Hospital	1
Central	Kiambu	Kiambu District Hospital	1
Central	Kiambu	Kiambu District Hospital	1
Central	Kiambu	Tigoni District Hospital	1
Central	Kirinyaga	Kagumo Health Centre	1
Central	Kirinyaga	Kerugoya District Hospital	4
Central	Murang'a	Kangari Health Centre	1
Central	Murang'a	Kenyatta National Hospital	1
Central	Murang'a	Naromoru Health Centre	1
Central	Nyeri	NYERI PGH	1
Coast	Kilifi	Kilifi District Hospital	2
Coast	Kilifi	Malindi District Hospital	4
Coast	Kilifi	Mariakani District Hospital	1
Coast	Kilifi	Mtwapa Health Centre	1
Coast	Kilifi	Rabai Rural Health Demonstration Centre	1
Coast	Kwale	Tiwi Rhtc	1
Coast	Lamu	Lamu District Hospital	1
Coast	Mombasa	Coast Province General Hospital	3
Coast	Mombasa	Katulani Sub District Hospital (Kitui)	1
Coast	Mombasa	Kongowea Health Centre	1
Coast	Mombasa	Likoni District Hospital	2
Coast	Mombasa	Mtwapa Health Centre	1
Coast	Mombasa	Port Reitz District Hospital	4
Coast	Mombasa	Thika Nursing Home	1
Coast	Mombasa	Tudor District Hospital (Mombasa)	1
Coast	Taita Taveta	Mwanda Dispensary	1
Coast	Taita Taveta	Shelemba	1
Eastern North	Isiolo	Apu Dispensary	1
Eastern North	Marsabit	Moyale District Hospital	2
Eastern South	Embu	Ena Dispensary	1
Eastern South	Embu	Kiamuringa Dispensary	1
Eastern South	Embu	Kiritiri Health Centre	1
Eastern South	Embu	Runyenjes District Hospital	1
Eastern	Kitui	Ikutha Health Centre	1

South Eastern			
South Eastern	Kitui	Kitui District Hospital	1
South Eastern	Kitui	Mbitini (ACK) Dispensary	1
South Eastern	Kitui	Muthale Mission Hospital	1
South Eastern	Kitui	Mutomo Mission Hospital	1
South Eastern	Kitui	Mwingi District Hospital	1
South Eastern	Machakos	Kangundo District Hospital	1
South Eastern	Machakos	Kitheuni Dispensary	1
South Eastern	Machakos	Machakos Level 5 Hospital	1
South Eastern	Machakos	Mitaboni Health Centre	1
South Eastern	Makueni	Kibwezi Sub District Hospital	2
South Eastern	Makueni	Kilala Health Centre	1
South Eastern	Makueni	Makindu District Hospital	1
South Eastern	Makueni	Mtito Andei Sub District	2
South Eastern	Makueni	Stone Athi Medical Clinic	1
South Eastern	Meru	Kangeta Health Centre	1
South Eastern	Meru	MAUA MTO HOPS	1
South Eastern	Meru	Meru District Hospital	1
South Eastern	Meru	Nyambene District Hospital	1
Nairobi	Nairobi	Alice Nursing Home	1
Nairobi	Nairobi	Dandora (EDARP) Clinic	2
Nairobi	Nairobi	Dandora I Health Centre	1
Nairobi	Nairobi	Huruma (EDARP)	1
Nairobi	Nairobi	Kangemi Health Centre	1
Nairobi	Nairobi	Kenyatta National Hospital	1
Nairobi	Nairobi	Nairobi Remand Prison Health Centre	1

Nairobi	Nairobi	Rhodes Chest Clinic	2
Nairobi	Nairobi	Babadogo (EDARP)	1
Nairobi	Nairobi	Baraka Dispensary (Nairobi)	2
Nairobi	Nairobi	Blue House Dispensary	14
Nairobi	Nairobi	Dandora (EDARP) Clinic	2
Nairobi	Nairobi	DANDORA II HC	1
Nairobi	Nairobi	Dandora II Health Centre	1
Nairobi	Nairobi	Eastleigh Health Centre	3
Nairobi	Nairobi	Embakasi Health Centre	1
Nairobi	Nairobi	Hagadera Hospital	1
Nairobi	Nairobi	Huruma (EDARP)	1
Nairobi	Nairobi	Jericho Health Centre	2
Nairobi	Nairobi	Mathare 3A (EDARP)	2
Nairobi	Nairobi	Matharite Dispensary	1
Nairobi	Nairobi	Mbagathi District Hospital	1
Nairobi	Nairobi	Mukuru Clinic	1
Nairobi	Nairobi	NEW NYANZA PGH	1
Nairobi	Nairobi	Nyumbani Diagnostic Laboratory and Medical Clinic	1
Nairobi	Nairobi	PGH TB MANYATTA	1
Nairobi	Nairobi	Pumwani Majengo Dispensary	1
Nairobi	Nairobi	Reuben Mukuru Health Centre	1
Nairobi	Nairobi	Silanga (MSF Belgium) Dispensary	1
Nairobi	Nairobi	Umoja Health Centre	1
North Eastern	Garissa	Blue House Dispensary	1
North Eastern	Garissa	Dagahaley Hospital	4
North Eastern	Garissa	DAGAHALTY	1
North Eastern	Garissa	Eastleigh Health Centre	1
North Eastern	Garissa	Hagadera Hospital	8
North Eastern	Garissa	Ifo Hospital	10
North Eastern	Garissa	MANDERA DH	1
North Eastern	Garissa	MANDERA DISTRICT HOSPITAL	1
North Eastern	Garissa	PGH TB MANYATTA	1
North Eastern	Garissa	Reuben Mukuru Health Centre	1

North Eastern	Garissa	Taveta District Hospital	1
Nyanza North	Homa Bay	Homa Bay District Hospital	10
Nyanza North	Homa Bay	Ndhiwa Sub-District Hospital	1
Nyanza North	Homa Bay	Nyanza Provincial General Hospital (PGH)	1
Nyanza North	Homa Bay	Nyatoto Health Centre	1
Nyanza North	Homa Bay	PORTREITZ	1
Nyanza North	Homa Bay	Rachuonyo District Hospital	2
Nyanza North	Kisumu	Chulaimbo Sub-District Hospital	1
Nyanza North	Kisumu	Dandora (EDARP) Clinic	1
Nyanza North	Kisumu	GARISSA	1
Nyanza North	Kisumu	KANGEMI HC	1
Nyanza North	Kisumu	KISUMU	1
Nyanza North	Kisumu	KISUMU D/H	1
Nyanza North	Kisumu	Nyanza Provincial General Hospital (PGH)	1
Nyanza North	Kisumu	Rae Dispensary	1
Nyanza North	Siaya	HOMA BAY	1
Nyanza North	Siaya	Ligega Health Centre	1
Nyanza North	Siaya	Mawere Dispensary	1
Nyanza North	Siaya	Nyangu Dispensary	1
Nyanza North	Siaya	Nyanza Provincial General Hospital (PGH)	1
Nyanza North	Siaya	SIAYA D H	1
Nyanza North	Siaya	Sifuyo Dispensary	1

Nyanza South	Kisii	Gucha District Hospital	1
Nyanza South	Kisii	Kionyo Medical Clinic	1
Nyanza South	Kisii	Nyamache District Hospital	1
Nyanza South	Migori	EDARP	1
Nyanza South	Migori	Kadem Tb & Leprosy Dispensary	1
Nyanza South	Migori	Nyakuru Dispensary	1
Nyanza South	Migori	Rongo District Hospital	1
Nyanza South	Migori	Saro Dispensary	1
Nyanza South	Nyamira	Kisii Hospital (Level 5)	1
Rift Valley Nor	Elgeyo Marakwet	Sergoit Dispensary (Keiyo)	1
Rift Valley Nor	Nandi	Kapkangani Health Centre	1
Rift Valley Nor	Trans Nzoia	Kapsitwet Dispensary	1
Rift Valley Nor	Uasin Gishu	Moi Teaching Refferal Hospital	1
Rift Valley Nor	Uasin Gishu	Turbo Health Centre	1
Rift Valley Sou	Kajiado	Fatima Maternity Hospital	1
Rift Valley Sou	Kajiado	Kajiado District Hospital	1
Rift Valley Sou	Kericho	Kericho District Hospital	1
Rift Valley Sou	Kericho	Sosiot Health Centre	1
Rift Valley Sou	Nakuru	Bahati District Hospital	1
Rift Valley Sou	Nakuru	Nakuru Provincial General Hospital (PGH)	1
Rift Valley Sou	Nakuru	Njoro Health Centre	1
Western	Busia	Busia District Hospital	2
Western	Busia	Holy Family Oriang Mission Dispensary	1

Western	Busia	Nambale Health Centre	1
Western	Kakamega	Kakamega Provincial General Hospital (PGH)	1
Western	Kakamega	Shikunga Health Centre	1
Western	Vihiga	HAMISI DH	1
Grand Total			208

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NLTP/DEV/10/34 VOL IV

20th June 2013

Dr. Maureen Kamene Kimenye
P. O. Box25212-00603
Nairobi

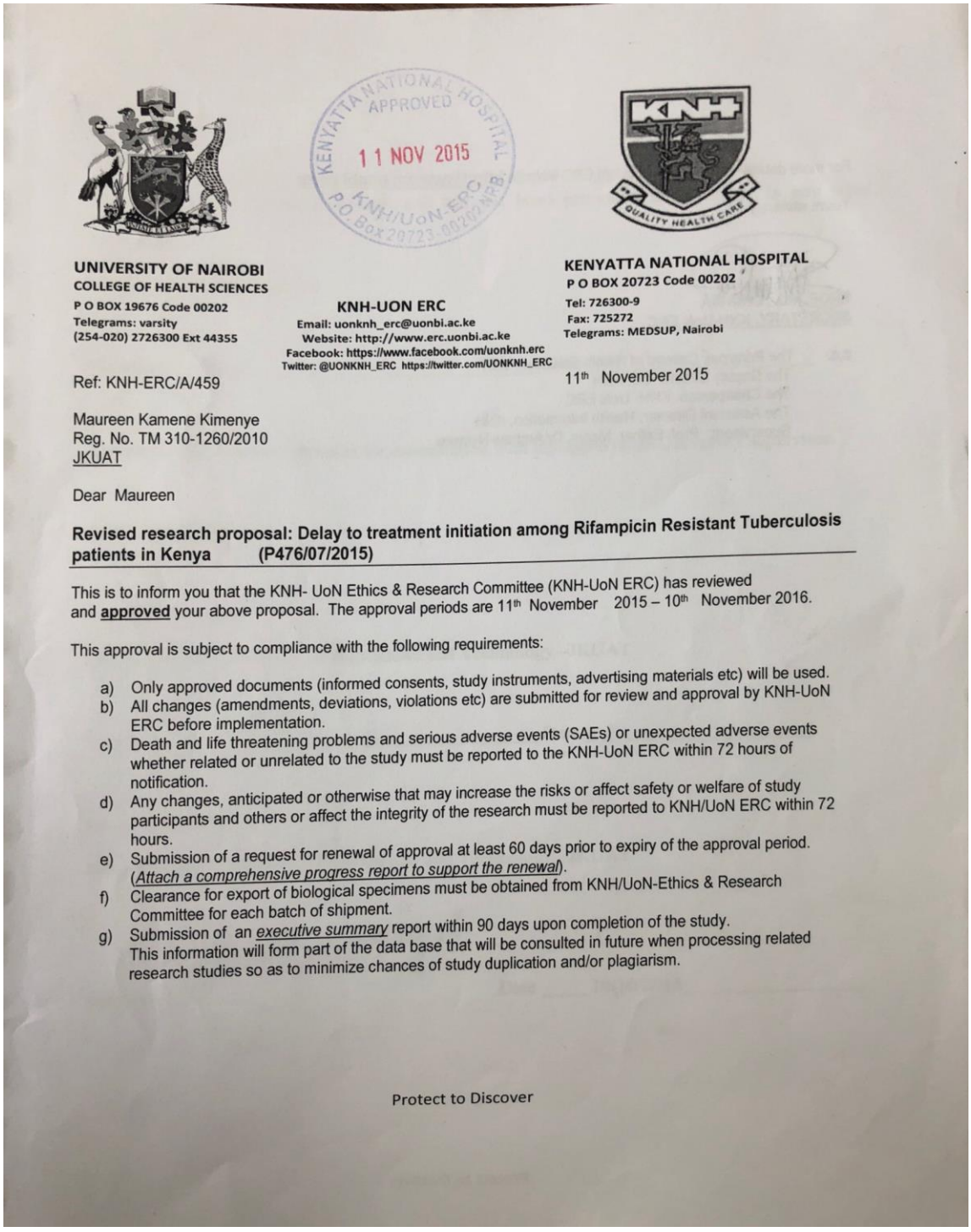
RE: REQUEST FOR ACCESS TO TB DATA FOR A RETROSPECTIVE STUDY ON DELAY TO TREATMENT INITIATION AMONG RIFAMPICIN RESISTANT TUBERCULOSIS PATIENTS IN KENYA

The National Tuberculosis Leprosy and Lung Disease Program is in receipt of your letter dated 10th May 2013 requesting for approval to access the case-based data on TIBU to carry out a retrospective study on Delay to Treatment initiation among Rifampicin Resistant Tuberculosis patients in Kenya. You have also requested for introduction to the TB clinics and diagnostic Laboratories.

Approval is hereby granted to your request to access TB data for your study through TIBU. You are expected to ensure all ethical considerations and confidentiality are adhered to. Further, by copy of this letter, approval is granted to access facilities and TB laboratories for data collection and verification.

Dr Joseph Sitienei
HEAD, NATIONAL TUBERCULOSIS, LEPROSY AND LUNG DISEASE PROGRAM

Appendix VI: Ethical Approval Letter



KENYATTA NATIONAL HOSPITAL APPROVED 11 NOV 2015 KNH/UoN-ERC P.O Box 20723-00202 NRB

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Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
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Ref: KNH-ERC/A/459

11th November 2015

Maureen Kamene Kimenye
Reg. No. TM 310-1260/2010
JKUAT

Dear Maureen

Revised research proposal: Delay to treatment initiation among Rifampicin Resistant Tuberculosis patients in Kenya (P476/07/2015)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH-UoN ERC) has reviewed and **approved** your above proposal. The approval periods are 11th November 2015 – 10th November 2016.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

Protect to Discover

For more details consult the KNH/UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M.L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
Supervisors: Prof. Esther Magiri, Dr.Andrew Nyerere