TREATMENT OUTCOME AND ITS ASSOCIATED FACTORS AMONG MULTIDRUG-RESISTANT (MDR-TB) PULMONARY TUBERCULOSIS PATIENTS IN KENYA: A RETROSPECTIVE COHORT STUDY

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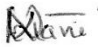
W62/81061/2015

A Thesis submitted to the Institute of Tropical and Infectious Diseases, College of Health Science in partial fulfilment of the requirements for the award of the master's degree in Medical Statistics of University of Nairobi.

November, 2019

DECLARATION

This Thesis is my original work and it has not been submitted / presented for a degree in any institution of higher learning.

Sign:  **Date:** _____

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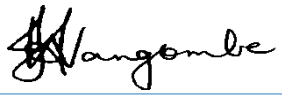
Sign:  **Date:** _____

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DEDICATION

This work is dedicated to my husband John and my son, Christian for their immeasurable support during development of this work and to my parents Francis Kiarie and Fracia Wambui, my siblings: Hellen, Beatrice, Martha, Margaret, Diana and Irene for their encouragement and moral support.

ACRONYMS AND ABBREVIATION

MDR-TB	Multi-Drug resistance tuberculosis
TB	Tuberculosis
WHO	World Health Organization
TIBU	National Tuberculosis electronic case based reporting system
LTFU	Lost to Follow up
AFB	Acid Fast Bacilli
M.TB	*Mycobacterium Tuberculosis*
DST	Drug Sensitivity Test
DAATs	Nucleic Acid Amplification Test
CDC	Centre for Disease Control
NLTP	National Leprosy and Tuberculosis Programme
FBO	Faith Based Organizations
DOT	Direct Observed Therapy
CTLC	County TB and Leprosy Coordinator

ABSTRACT

Introduction: Multidrug resistant tuberculosis is described as tuberculosis caused by a genetic variant of *Mycobacterium Tuberculosis* which is resistant to most potent anti-TB drugs i.e. isoniazid and rifampicin. Kenya is classified among the 30 countries with a high burden of tuberculosis. TB is also among the leading causes of mortality in Kenya. MDR-TB cases continue to rise both globally and in Kenya. In 2016, 445 cases of MDR-TB were diagnosed in Kenya. Treatment success rate decreased from 84% in 2013 to 74% in the 2014 cohort, with a mortality rate of 17% in 2014.

Objective: The objective of this study was to analyze the treatment outcome and associated factors for MDR-TB cases enrolled and completed treatment from 2016-2018.

Methodology: The study was a retrospective cohort study for MDR-TB patients enrolled and completed treatment between 2016 and 2018 in Kenya. The data was obtained from TIBU; an electronic TB case based system that is used to collect routine TB surveillance data in Kenya. A patient was included in the study if he/she was enrolled for treatment between 1st January 2016 and 30th Oct 2018 and the outcome of the treatment assigned The data was exported to excel for preliminary cleaning then exported to Stata 13 for analysis.

Treatment outcomes were analyzed and presented in terms of percentages. Odds ratio were calculated to determine the factors that are associated with the observed outcome. Univariate analysis was conducted to summarize the data while bivariate data was used to check for association. Logistic regression model was fitted for the statistically significant variable at multivariate analysis level.

Results: the results were based on 126 MDR-TB cases. Nairobi County was leading in number of MDR-TB cases. Out of the total number of patients who died 69% were HIV positive. 83.3% of the patients in the study were aged above 24 years. In addition, there were more malels, 58% compared to female 42%.The study found a treatment success rate of 71%, mortality rate of 20%, 2% failed treatment while 6% were lost to LTFU. However, the study found a cure rate of 40% and therefore 31% of the patients did not undertake a sputum smear microscopy test to confirm absence of TB after completion of treatment. The study found that patients who were HIV negative and their BMI was normal (OR=0.03, P-value=0.021) had significantly better treatment success rate. Most of the data analyzed was reported from public facilities with only 8 clients reported from private and FBO. All the patients in the study were tested for HIV.

Conclusion: HIV status and normal BMI are predictors of successful treatment outcome for MDR-TB patients. Private facilities should be capacity build to manage MDR TB cases. In addition, all clients who completes treatment should undergo smear/culture test at the last month of treatment to ascertain cure.

Keywords: MDR-TB, Treatment outcome, tuberculosis

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INTRODUCTION

1.1Background

Tuberculosis has been in existence for a millennia and it continues to be a major health burden in the world(WHO, 2017). It is among the top 10 causes of death worldwide despite the fact that it is a curable disease. In 2018, a total of 6.6 million people in the world with TB were notified to TB programmes in their respective countries (WHO, 2017). Globally, 600,000 cases of MDR-TB and Rifampicin Resistant TB (RR-TB) were notified to TB control programmes (WHO, 2017).

TB burden remains high in Kenya and it is ranked among the 30 countries that account for 87% of world TB cases. According to the TB prevalence survey of 2016, TB prevalence is at 426 people per 100,000 people in Kenya currently. Further, the survey estimated that 169,000 people fell sick with TB in 2016. However, only 46% (77,376) people were diagnosed and put on treatment with TB in 2015. This indicates that 54% of cases remain unnotified (National Tuberculosis Leprosy and Lung Disease Program, 2016). The 2016 TB prevalence survey also led to revision of incidence rate from 233per 100, 000 to 348 per 100,000.An estimated 8,885 deaths (3.15%) are caused by TB currently. The situation is further complicated by emergence of drug resistant TB.

Multi-drug resistant TB is a type of TB that is resistant to Rifampicin and isoniazid drugs. Rifampicin and Isoniazid are powerful first line medication used in treatment of Tuberculosis. This means that once TB becomes resistant to both Rifampicin and isoniazid drugs, a patient should be introduced to second line drugs. Second line treatment is expensive and sometimes a patient may require hospitalization for close monitoring. This imposes an economic burden both to the patient and to the country. MDR-TB threaten the effort to reduce TB burden not only in Kenya but also in the world. In 2016, 490,000 people developed MDR-TB in the world and an additional 110,000 who were resistant to rifampicin and required 2nd line treatment. In Kenya, drug resistant TB has been on the rise with 445 cases notified in 2016 (NLTP, 2016).

Drug- resistant TB continue to emerge due to mismanagement of TB treatment and person to person transmission (WHO, 2018). MDR-TB is increasingly hard to treat since the treatment options are limited and drugs are limited especially in the developing countries where resources are scarce. TB treatment is cured by strictly adhering to 6 month drug combinations with close monitoring and support. Incorrect regimen, poor quality drugs and non-adherence of anti-microbial drugs can lead to resistance which can then spread from one person to another especially in congested environments.

1.2 Statement

TB continues to be a major public health crisis and a health security risk. TB is becoming a global public health emergency (O'Neill, Mortimer, & Pepperell, 2015). The situation is further complicated by emerges of MDR-TB. There is also an increasing drug resistant strain of *Mycobacterium tuberculosis* that continue to emerge and spread (O'Neill et al., 2015). Kenya being a developing, is particularly concerned with MDR-TB since the medicines used for treatment are not easily affordable and the patient may require hospitalization for close monitoring. This imposes an economic burden to the country. Kenya is ranked among the high burden MDR-TB countries in the world. In 2016, among the notified cases of TB, 445 cases were multi-drug resistant TB and rifampicin resistant.

TB is an infectious disease and the country has limited capacity to successfully handle the patients to avoid spread. This is due to few isolation wards in the country. The situation is further complicated by a huge population that live in the slums due to poor housing and bad living conditions. This is where the disease is likely to spread if not contained.

The 2016 survey revealed that there is more TB in Kenya than previously estimated. In 2015, WHO estimated a prevalence of 233 per 100,000 while the 2016 TB prevalence survey found 426 per 100,000.This translates to 138,105 TB incidence annually (National Tuberculosis Leprosy and Lung Disease Program, 2016). The survey further found that most people affected by TB epidemic are in the

productive age (15-35 years). In addition, Men, who are mostly the breadwinners in their families, have a higher diseases burden than women. This affects many families social and economic wellbeing.

MDR-TB is characterized by poor treatment outcome, scanty information and late diagnosis due to limited capacity in most health facilities. By studying factors associated with treatment outcome, more information will be available for clinician that could help in improvement of service delivery to MDR-TB patients leading to improved treatment outcomes.

1.3 Justification

MDR-TB poses a health burden and health security risk in the country. The studies reviewed did not attempt to reveal the factors that could be associated with the treatment outcome. For this reason, apart from this study analyzing most recent data on treatment outcome, it will go ahead and establish the factors associated with various outcomes. Therefore, this study will be a great insight in the management of MDR-TB in the country.

1.4 Research question

What are the factors associated with treatment outcome among MDR-TB in Kenya

1.5 General Objective

To determine treatment outcome and associated factors among MDR-TB patients in, Kenya between the years 2016-2018.

1.6 Specific objective

1. To describe demographic characteristics of MDR-TB patients treated in the specified period
2. To determine current treatment outcome of MDR-TB patients treated during the specified period.
3. To evaluate Clinical characteristics associated with outcome of MDR-TB patients
4. To determine Predictors of successful treatment Outcome

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

MDR-TB is defined as resistance to both isoniazid (INH) and Rifampicin. In 2017, WHO estimated a 3.5 % MDR-TB prevalence in Kenya and 20% among previously treated TB cases (WHO, 2017). Emergence of resistant *mycobacterium tuberculosis* strains specifically MDR-TB is a health risk and a high public health concern (O'Neill et al., 2015). According to (WHO, 2017) 130,000 cases of MDR-TB were enrolled for treatment in 2016. Globally, WHO reported a treatment success rate of 54%, mortality of 16 %, 8% failed treatment and 21% were lost to follow up.

2.2 Tuberculosis etiology

Tuberculosis is an airborne disease caused by *mycobacterium tuberculosis (M. tuberculosis)* also known as tubercle bacilli (CDC, 2013). *M. tuberculosis* is presented in form of airborne materials which are known as droplet nuclei measuring 1-5 microns in diameter-wise. The infectious particles are produced when a person already infected with TB coughs, sneeze, shouts or sing.

These tuberculosis causing microorganisms can be sustained in the environment for hours especially when the air circulation is not very good. It is worth noting that the droplet nuclei are not transmitted through surface contact. Therefore, transmission will only occur when a person inhales these disease causing agents and the droplets nuclei reach the lungs. If the disease fighting mechanism of a person cannot regulate the tubercle bacilli they multiply rapidly. It is also worth noting that the infectiousness of a person depends on the number of tubercle bacilli released in the air. Combating TB will require interrupting the transmission cycle from an infected person to a healthy person. This will include personal, clinical and environmental factors that increase the likelihood of transmission.

The Table below shows the probability of transmission of M. tuberculosis.

Table 2. 1 Probability of transmission of M. tuberculosis (Kumar & Kon, 2017)

Factor	Description
Susceptibility	Susceptibility (immune status) of the exposed individual
Infectiousness	Infectiousness of the person with TB disease is directly related to the number of tubercle bacilli that he or she expels into the air. The persons who expel many tubercle bacilli are more infectious than patients who expel few or no bacilli.
Environment	Environmental factors that affect the concentration of M. tuberculosis organisms.
Exposure	Proximity, frequency, and duration of exposure.

2.3 Diagnosis and Management of MDR-TB

Undiagnosed TB is more dangerous since the person remains untreated thus transmitting the disease (Center for Disease Control and Prevention, 2013). TB prevalence survey of 2016 found that 40% of TB cases remain undetected and untreated. This are the cases that are likely to spread the disease. It is estimated that one undetected/ untreated TB case is likely to infect 10-15 people with TB. The symptoms associated with TB disease include persistent cough, chest pain, bloody sputum, weight loss/loss of appetite, fever, chills, night sweat, malaise and fatigue. Diagnosis of Pulmonary TB requires a clinician to take into account clinical history, physical examination, microbiological results and radiological finding (Kumar & Kon, 2017). Both radiological and microscopic methods are used to diagnose TB. Thoracic imaging is critical, both for diagnosing pulmonary TB, and for monitoring response to treatment(Kumar & Kon, 2017).

WHO guidelines provide that once a patient is suspected to have pulmonary TB, two or three sputum samples should be drawn and send to the laboratory for microscopic investigations and subsequent culture. Further, at least one sputum sample should be drawn in the morning since it contains most Acid Fast Bacilli (AFB). In the cases where a patients is unable to produce sputum, sputum inducing techniques and

bronchoscopy can be applied to obtain specimen. Sputum found positive for AFB are the smear positive cases of TB and should be given attention due to their ability to transmit the disease. This should be followed by contact tracing to avoid further spread of the disease.

MDR-TB is caused by *M. tuberculosis* strains that are resistant to most effective TB drugs. The most effective first line anti-TB medication are isoniazid and rifampicin. However, MDR-TB is treated just like normal TB and it is not more infectious. WHO recommends the use of the phenotypic drug susceptibility test (DST) to diagnose MDR-TB and the nucleic acid amplification test (NAATs). Phenotypic DST is done using either liquid or solid cultures. Liquid cultures are more sensitive and results have higher turnaround time of around 2 weeks. However, the equipment is expensive and extreme measures have to be undertaken to ensure that cultures are not contaminated. On the other hand, use of solid cultures is cheap but it can take up to 8 weeks for pulmonary TB to be confirmed, and a further 6 weeks for final DST results to be obtained. This may contribute to the further spread of the disease since the patient continues taking infective drugs as they await DST results.

When Pulmonary TB is confirmed the patient is started on first line drugs. The treatment phase is divided into two; intensive phase for 2 months, which comprises, rifampicin, isoniazid, pyrazinamide and ethambutol. As with all drugs, safety profile, side effects and interaction with other drugs should be considered before administering these drugs. This is followed by a continuation phase using rifampicin and isoniazid. The table below shows the drugs and their administration for drug-sensitive TB:

Table 2. 2 First-line drugs dosage for treating drug-sensitive TB (Kumar & Kon, 2017).

Drug	Allowable daily dose (mg/kg)	allowable daily dose range (mg/kg)	Maximum daily dose (mg)
Rifampicin	10	8-12	600
Isoniazid	5	4-6	300
Pyrazinamide	25	20-30	-
Ethambutol	15	15-20	-

An assessment for drug resistance is recommended, and it can either be mono resistance; defined as resistance to isoniazid or rifampicin, or poly resistance, which is resistance to both isoniazid and rifampicin. A patient can also have Multi-Drug Resistance (MDR) which is resistance to both rifampicin and isoniazid. Assessment should be based on prevalence of MDR-TB, poor drug adherence and exposure to MDR-TB. The treatment regimen for MDR-TB is constituted by at least five agents: pyrazinamide and at least 4 other second line drugs (group A-C) in table 3. The following table shows drugs used for treatment of MDR-TB:

Table 2. 3 Medication for treatment of MDR TB (Kumar & Kon, 2017)

Group	**Drugs**
Group A: fluoroquinolones	Levofloxacin, moxifloxacin, gatifloxacin
Group B: second-line injectable agents	Amikacin, capreomycin, kanamycin, streptomycin (may be substituted for other second-line injectable agents in certain circumstances)
Group C: other core second-line agents	Ethionamide/prothionamide, cycloserine/terizidone, linezolid, clofazimine
Group D: add-on agents (not part of the core MDR TB regimen)	Pyrazinamide, ethambutol, high-dose isoniazid, bedaquiline, delamanid, p-aminosalicylic acid, imipenem-cilastatin, meropenem, amoxicillin-clavulanate, thioacetazone (provided patient is HIV negative)

2.4 Risk factors for MDR-TB

There are various contributing factors that increase the chances of a person to get infected with *M. tuberculosis*. Risk of exposure is related to the disease burden and the environment people live in (Duarte et al., 2017). The environment, air circulation, and the population will all determine the spread of the disease. Other co-morbidities such as HIV infection, diabetes, silicosis, rheumatoid arthritis, other chronic illnesses and immunosuppressive therapies may increase susceptibility of a person to *M. tuberculosis* infection (Duarte et al., 2017). Others factors include tobacco use, malnutrition and drug abuse. The more the prevalence of a risk factor the higher it's likely to be a risk factor tuberculosis. Therefore, countries with high HIV burden the more HIV is as a risk factor for TB (Duarte et al., 2017).

A study carried out in Kenya found sex and HIV status to be associated with the treatment outcome observed (Mibei, Kiarie, Wairia, Kamene, & Okumu, 2016). Other factors studied in the above study and not to be associated are nutritional status and mode of care.

2.5 TB control strategies in the country

Tb remains a major health challenge in Kenya(Immune & Syndr, 2016) . Further *M. tuberculosis* strains resistant to most potent anti-TB are also increasing globally and Kenya(NTLP, 2017). Therefore the country has adopted a three-pronged approach to reverse these trends. The first approach is integrated patient care and prevention. This entails early diagnosis of not only TB but also of drug susceptibility. In addition, this pillar also advocates for systematic screening of contacts and most at risk populations. This approach also entails treatment of all people diagnosed with TB and MDR-TB. It also advocates for integrated services for TB/HIV activities and management of co-morbidities (NTLP, 2017).

To achieve "End TB" as advocated by WHO, the country has also adopted bold policies, lobbying for political goodwill and commitment and supportive systems. This will require both levels of government

to prioritize TB activities and have a line budget for them. It also requires all stakeholders to work together towards a common goal. The stakeholders include civil societies, communities, government etc. Further universal health coverage, social protection and poverty alleviation will accelerate the efforts in "End TB" strategy"(NTLP, 2017)

The third approach is through intensified research and innovation. This requires continuous review and development of tools, uptake of new interventions and strategies. Continuous research will also optimize implementation and promote impact. These three approaches are aimed at attaining the global targets by 2035. These are 95% reduction of TB deaths by 2035 as compared to 2016, reduction by 90% of the tuberculosis incidence rate, and to ensure that there are no families facing catastrophic costs due to TB (Duarte et al., 2017).

2.6 Treatment outcome for MDR-TB

Treatment for MDR-TB is expensive and takes a long time. Successful treatment depends on a patient's characteristics and adherence to medication as prescribed. If a patient does not adhere to medication as prescribed, it may lead to relapse, death, and development of extensive drug resistance.

A study for MDR-TB carried out in western India between 2016 found the success rate to be 38.6% (Patel et al., 2016) . This study looked at cure and completion of treatment as a successful treatment outcome while defaulters, death, switched to category IV, failure and still on treatment were considered unsuccessful treatment outcome. This study also looked at association between socio-demographic factors, and previous treatment profiles with treatment outcomes. This study excluded HIV positivity since only two subjects were HIV positive in the study.

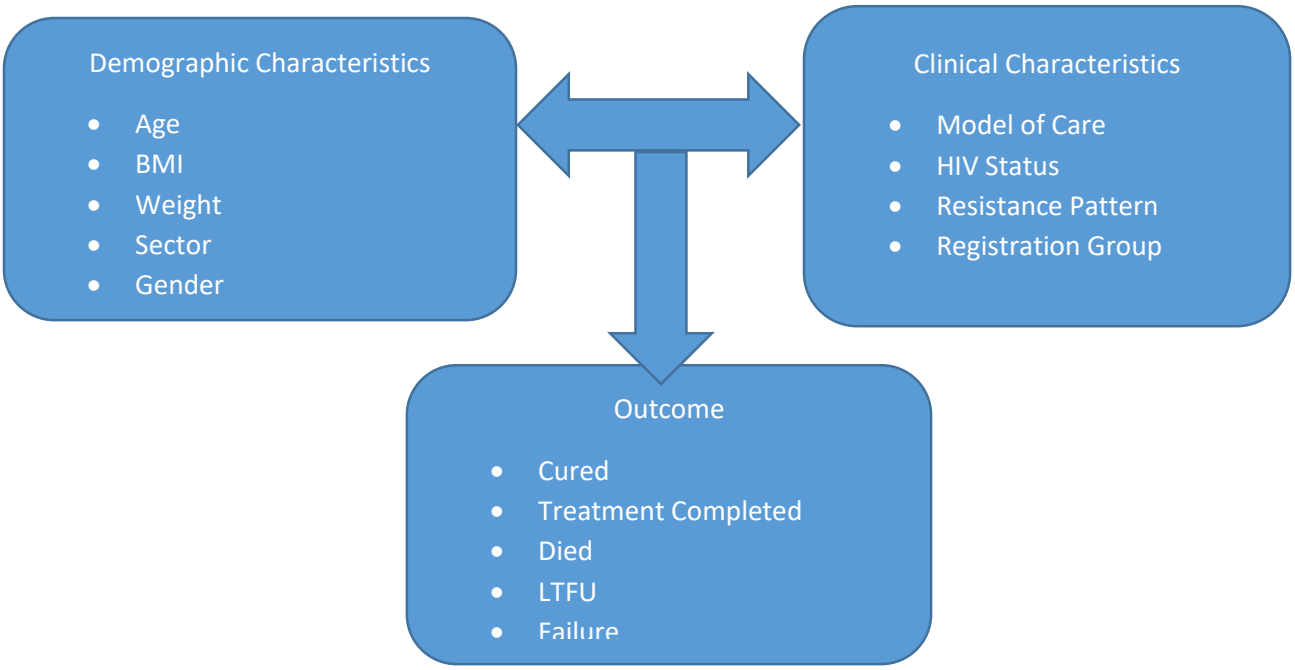
A retrospective study carried out in Ethiopia on survival rates and treatment outcome found that 25.3% of MDR patients were cured, 8.4% had died, 13% had defaulted, and 33.1% were still on treatment. (Girum,

Tariku, & Dessu, 2017). This study also examined gender, age, baseline weight, previous TB treatment, and HIV status among other factors as predictors of treatment outcome.

Another study conducted in Kenya on patients whose treatment was initiated in 2012 found the success rate to be 82.4% but only 47.3% were confirmed to be cured (Mibei et al., 2016). This success rate is higher than WHO estimates of global success rate for MDR-TB which is 59 % (WHO, 2017). The study (Mibei et al., 2016) looked at the association between gender, model of care, HIV status, sector, and age groups with the treatment outcomes. The current study differs with the study (Mibei et al., 2016) in that it will only focus multi-drug resistant tuberculosis. The current study will also analyze the most current data on patients who have completed treatment.

Another study carried out in Tanzania (Leveri, Lekule, Mollel, Lyamuya, & Kilonzo, 2019) which looked at predictors of treatment outcome found low BMI and presence of cavities in the chest to be significantly associated with poor treatment outcome. This study also looked other lifestyle behaviors and regimen that patients were given the study found that smoking and patients on Ethambutol had a significantly low treatment success rate. The study in Tanzania had relatively larger scope of variables as compared to current study.

2.7 Conceptual framework



Dependent variable (outcome) was predicted by either demographic characteristics of the patients, clinical characteristic or interaction between demographic and clinical characteristics.

CHAPTER THREE

METHODOLOGY

3.1 Study population

The study population consisted of bacteriologically or clinically confirmed pulmonary TB cases who had undergone Drug Sensitivity Tests (DST) to confirm presence of *Mycobacterium Tuberculosis* strains resistant to both Rifampicin and isoniazid drugs. The patients included must diagnosed, treated and completed treatment for MDR-TB between Jan 2016 and Dec 2018. The treatment outcome must be known and recorded.

3.2 Study design

The study adopted a retrospective cohort study design. Electronic Records for patients Enrolled and completed treatment between January 2016 and June 2018 for MDR- TB were reviewed. The study definitions were either successful or unsuccessful following WHO guidelines. The Treatment outcome was termed as successful if the patient completed treatment or the patient was cured and unsuccessful if the patient was lost to follow up (LTFU), died or treatment failure/relapse.

The definitions were adopted from WHO definitions 2013 revised in December 2014 (*Definitions and reporting framework for tuberculosis – 2013 revision*, 2014). A patient was termed as cured if a culture or smear tests negative during the last month of treatment or at least one previous occasion. An LTFU was defined as a patient whose treatment was interrupted for two consecutive months or did not start treatment, while a treatment failure was defined as a patient whose culture or smear test are positive after five months of treatment or later during treatment. Finally, Died was a patient who dies for any reason while undergoing TB treatment.

3.3 Sampling technique

The sample included all the MDR-TB in the country whose data is contained in the electronic data collection system. A case was included if the treatment outcome was recorded in the system.

3.4 Sample size determination

The aim of this study was to obtain a countrywide representative sample, therefore all the patients that were enrolled and were expected to have completed treatment during the study period were included in the study. A patient must have had laboratory confirmed MDR-TB and had been assigned treatment outcome in TIBU.

3.5 Recruitment criteria

Inclusion criteria

A patient was included in the study if he/she was enrolled for treatment and expected to have completed treatment between 1st January 2016 and 31th Dec 2018 and the outcome of the treatment assigned.

Exclusion criteria

A patient was excluded from the study if the treatment outcome was not recorded, the assigned treatment outcome not either died, cured, treatment completed and failure

3.6 Data collection

In Kenya routine surveillance data is collected and stored in electronic form under National TB Electronic Case Based Reporting System (TIBU). TIBU enables real time data for all TB patients to be available at any given time. The variables of interest were predetermined. The data was exported to Excel, deindentified then exported to STATA for analysis. Incomplete recorded were deleted before exporting the data to STATA.

3.7 Data management plan

The data was exported to STATA 13 then it was cleaned, recoded and analyzed. The data was stored in the computer and back up for the data was stored using both a flash disk and an external hard drive. The data was protected by use of a password and only the people involved in this study were allowed access.

3.8 Statistical analysis

Quantitative variables were summarized: means with their corresponding confidence intervals were calculated and presented in tables. Their minimum and maximum values were calculated and presented. The normality of continuous variable was checked using the Shapiro-Wilks test and histograms. Shapiro-Wilks tests the null hypothesis that data is obtained from a population that is normally distributed. During the univariate analysis proportions of each treatment outcome was calculated and presented in terms of percentages. Both the quantitative and categorical variables were individually assessed for association with the treatment outcome. The successful treatment outcome rate was calculated by adding the cured and those who have completed treatment divided by total number of cases multiplied by 100.

$$\text{Treatment Success rate}=\frac{Cured+Treatment\ Completed}{Total\ number\ of\ cases}\times 100$$

Bivariate analysis is a technique used to check for association between two variables (Sims, 2000). For categorical variables Chi-square tests were conducted and their likelihood ratio and corresponding P-values presented. Chi-square test was used to test for goodness of fit between observed values and expected values theoretically. A variable was statistically significant if P-value < 0.05. Logistic regression was used to assess association between quantitative variables and treatment outcome.

Multivariate analysis was used to test for association for more than two variable. Predictors with a P-value ≤ 0.7 during bivariate analysis was used to fit multiple logistic model. This model was used to test

for association, fit a model for predicting treatment outcome, check for interaction between variables and control for confounding.

The fitted model will be of the form

$$\ln\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_k X_k$$

Where:

$\beta_1 and\ \beta_2\ and\ \beta_k$ = partial regression coefficients

$X_1\ and\ X_2$ are the model predictors which in this study will be, HIV status, BMI, gender, sector, patient type and Model Of Care.

p= probability of successful treatment outcome i.e. cured or treatment completion

The significance of model fit was determined using the likelihood ratio and p-value. The statistically significant variables were interpreted using the P-value for calculated odd ratio. Effects modification was assessed by fitting interaction between variables during logistic regression. If the interaction term was significant, its odd ratio, and confidence interval was interpreted. A P-value of <0.05 was termed as statistically significant.

3.9 Quality assurance

The study team, included statisticians and TB experts whose input were sought throughout the study. Laikipia County TB coordinator who has vast knowledge of Tuberculosis reviewed the study protocol.

3.8 Ethical consideration

Relevant approvals were sought before carrying out the study. This included approval from NLTP (National Leprosy and TB Programme) in the country and the Ethical Review Committee board of

Kenyatta National Hospital / University of Nairobi (KNH/UON). Waiver to obtain informed consent from patients was also obtained from the Ethical Review Committee (ERC). Confidentially and data security was maintained. This was done by ensuring that patient's identification information connected to the individual patient was deleted after the data was exported to excel. The data was password protected and was not shared with any person not involved in the study.

CHAPTER 4

RESULTS

4.1 Introduction

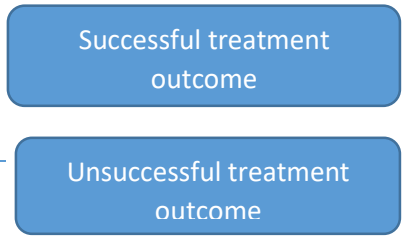
The finding presented in this study are based on 126 patients who were diagnosed with MDR tuberculosis and fit the inclusion criterion. The average Age for the cohort was 36 years (SD=12) with minimum age being 10 years and maximum age being 72. The data was found to be normally distributed since the value for Shapiro wilks had a P-value of greater than 0.05.

4.2 Treatment Outcome

According to the WHO definitions adopted for this study, the data showed that 71.4% (90/126) of total MDR patients had successful treatment outcome against 28.6% who had unsuccessful outcome. Out of 71.4% who had successful outcome, 40.5% of them were confirmed cured for the cohort that was followed. This is shown in the table below

Table 4. 2 Treatment Outcome

Treatment Outcome	Percent
Cured	51(40.48%)
Treatment Completed	39 (30.95%)
Died	26 (20.63%)
Failure	2 (1.59%)
LTFU	8 (6.35%)



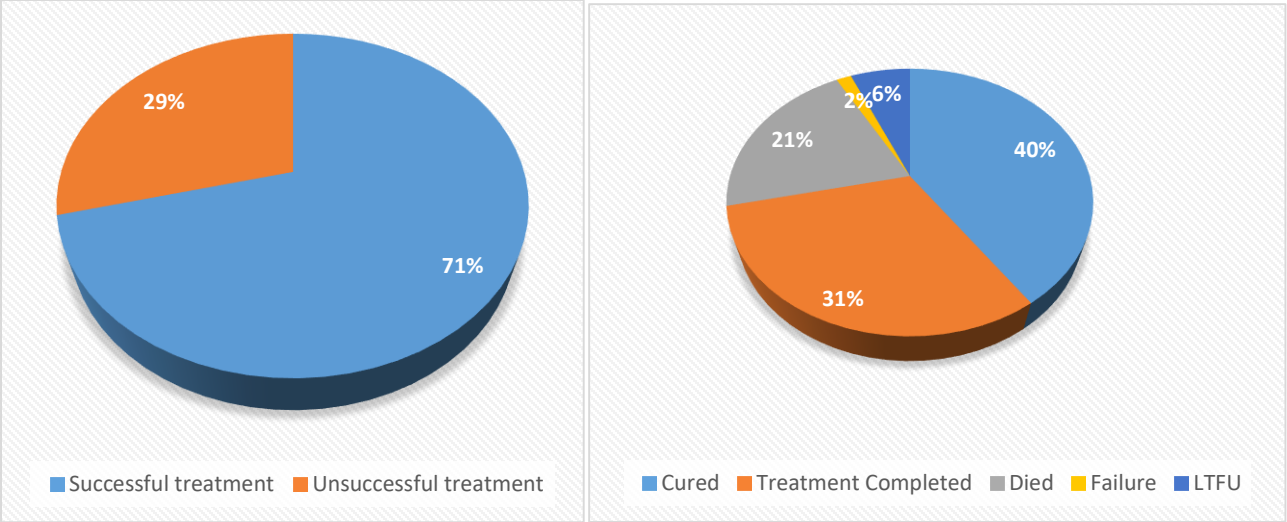


Figure 4. 2 Pie chart Showing Treatment Outcomes

Out of the patients initiated on treatment in 2016 the cure rate was 40 % (51/126). On the other hand 21% (26/126) died while undergoing treatment for MDR tuberculosis. 31% (39/126) of the patients initiated on treatment completed treatment but it was not ascertained whether they were cured or not.

Leading MDR-TB Counties

Cases reported from various counties were tabulated in the tale below. Nairobi County was leading with 17 cases followed by Machakos, Meru and Kirinyaga County.

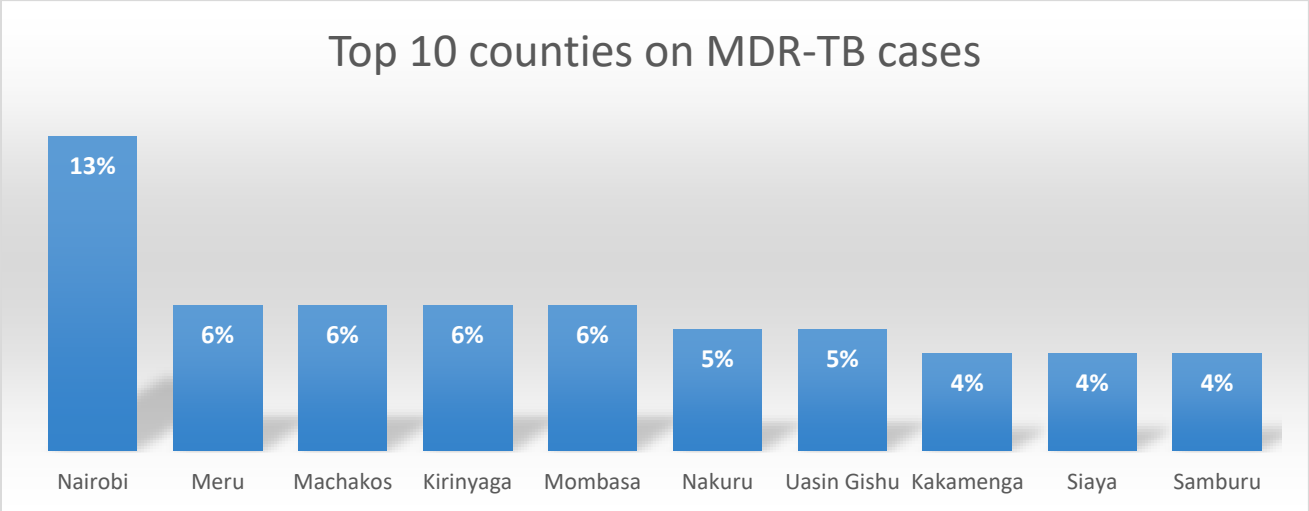


Figure 4. 1 Counties leading in MDR-TB cases

4.3 Patients characteristics

Table 4. 1 Patients characteristics

	Cured n (%)	**Treatment completed n (%)**	**Dead n (%)**	**Failure n (%)**	**LFTU n (%)**	**Total n (%)**
Age						
10-19years	5 (4)	1(0.8)	0	1(0.8)	0	7 (5.6)
20-24year	8 (6.6)	2(1.6)	2(1.6)	0	2 (1.6)	14 (11.1)
>=25year	38 (30.2)	36 (28.6)	24 (19.1)	1(0.8)	6 (4.8)	105 (83.3)
Gender						
Female	22 (17.5)	14 (11.1)	11 (8.7)	0	5 (4.0)	52 (41.7)
Male	29 (23.0)	25 (19.8)	15 (11.9)	2 (1.6%)	3 (2.38)	74 (58.7)
Nutritional status						
Underweight	23 (18.5)	23 (18.3)	17 (13.5)	1 (0.8)	5 (4.0)	69 (54.8)
Normal	24 (19.1)	13 (10.3)	7 (5.6)	0	2 (1.6)	46 (36.5)
overweight	0	1 (0.8)	0	0	1 (0.8)	2 (1.6)
Model of Care						
Community based	35 (27.8)	29 (23.0)	22 (17.5)	2 (1.6)	5 (4.0)	93 (73.8)
facility Based	14 (11.1)	8 (6.4)	4 (3.17)	0	3 (2.4)	29 (23.0)
Individual	2 (1.6)	2 (1.6)	0	0	0	4 (3.2)
HIV Status						
Positive	17(13.5)	19 (15.1)	18 (14.3)	0	4 (3.2)	58 (46.0)
Negative	34(27.0)	20 (15.9)	8 (6.4)	2 (1.6)	4 (3.2)	68 (54.0)
ART						
No	0	0	1 (1.7)	0	0	1 (1.7)
Yes	17 (29.3)	19 (32.8)	17 (29.3)	4 (6.9)	0	57 (98.28)
Type of Facility						
public	46 (36.5)	33 (26.2)	23 (18.3)	2 (1.6)	8 (6.35)	112 (88.9)
private	2 (1.6)	6 (4.8)	2 (1.6)	0	0	10 (7.9)
prisons	1	0	0	0	0	1 (0.8)
Faith-based	2	1	0	0	0	3 (2.4)

LFTU=lost to follow-up; HIV=human immune-deficiency virus; ART=Antiretroviral therapy

Age

Age was categorized into adolescent (10-19years), young adults (20-24yrs) and adults above 25 yrs. Most of the patients in the cohort were adults (age>24 years) with an average age of 36 years (SD=12). Majority of the patients 83.3% ((105/125) were aged above 24 years of which 58.8% (74/105) had successful treatment outcome having been cured or completed treatment.

Gender

The cohort consisted of more male i.e 58% compared to female at 42%. Out of 74 males in the cohort 73% of them were classified as having successful outcome. On the other hand, out of 52 females in the cohort 69% of them had successful treatment outcome. 21% of females died during treatment while 20% of the male died.

Nutritional status

The nutritional status of the patient were classified according to their BMI. They were categorized into three categories; either a patient was underweight, normal or overweight. From the finding 54.8% (69/117) patients were underweight while 36.5 % (46/117) had normal weight. Only 1 % (2/117). 9 of the patients were babies whose nutritional status are determined using the Z-score. Out of all the patients classified as underweight 67% of them had successful treatment outcome. However, 17 of the underweight patients died in the course of treatment. Out of the patients classified to have normal weight, 80% has successful treatment outcome. On the other hand 7 patients classified as normal died during treatment.

Model of Care

Majority of the patients 73.8 (93/126) undertook their treatment in the community. MDR treatment is supposed to be Direct Observed therapy (DOT) either in the facility or in the community. Those who undertook treatment in the community 69% (64/93) had successful treatment outcome while 24% (22/93) died during treatment. This is compared to 76% (22/29) who undertook treatment in the facility and had successful treatment outcome while 14% (4/29) died during treatment.

HIV Co-morbidity

More than half 54% (68/126) of the patients in the cohort were HIV negative. while 46% (58/126) of them were HIV positive. 99% (57/58) HIV positive clients were on ART. Out of total clients who died during treatment 69% (18/26) of them were HIV positive.

Type of Facility

Majority of the reported cases 88.9% (112/126) were from public sector. This could be explained by the fact that most of the private and faith-based facilities do not report into the Health management systems as required by the government.

4.4 Test of Association

The data was subjected to fisher's exact test to check for association between patient characteristics and treatment outcome. This is presented in table 7 below.

Table 4. 2 Association between patient characteristics and treatment outcome

Patient characteristic	**Successful (n)**	**Unsuccessful (n)**	χ^2	**P- value**
Age				
10-19years	6	1	0.747	0.688
20-24year	10	4		
>=25year	74	31		
Gender				
Female	36	16	0.210	0.647
Male	54	20		
BMI				
Underweight	46	23	3.14	0.370
Normal	37	9		
overweight	1	1		
Model of Care				
Community based	64	29	2.190	0.335
facility Based	22	7		
Individual	4	0		
HIV Status				
Negative	54	14	4.613	0.032*
positive	36	22		
ART				
No	0	1	1.665	0.197
Yes	36	21		
Sector				
public	79	33	0.837	0.841
private	8	2		

*Significance at α=0.05

HIV=human immune-deficiency virus; ART=Antiretroviral therapy

As shown in table 4.4, only HIV status ($\chi 2$=4.613 Pr=0.032) was found to have a statistical significant association with treatment outcome.

4.5 Predictors of successful treatment outcome

A Logit model was fitted for the factors that had a P-value of <7 in bivariate analysis. The results are presented in the table below.

Table 4. 3 Predictors of successful treatment outcome

Patient characteristic	Successful (n)	OR (CI)	P- value
Gender			
Male	54	1.13 (.45-2.84)	0.788
Female	36	Reference	
Age			
10-19years		Reference	
20-24year		23.17(0.61-873.5)	0.09
>=25year		16.5(0.60-452.0)	0.097
BMI			
Underweight	46	0.16(0.01-2.22)	0.172
Normal	37	0.08(0.005-1.17)	0.065
Overweight		Reference	
HIV status			
Negative	54	2.66(1.07-6.64)	0.036*
Positive	36	Reference	
Model of care			
Facility	22	0.73 (0.25-2.15)	0.570
Community	64	Reference	
Constant		1.61 (.09-27.76)	0.743

*Significance at α=0.05
HIV=Human Immune Deficiency Virus; BMI=Body Mass Index

The results in table 4.5 again shows that only HIV status (OR=2.66, Pr=0.036) is a predictor of successful treatment outcome. This implies that TB patients who are HIV negative are 2.66 times more like to have a successful treatment outcome as compared to HIV positive clients.

4.6 Predictors of successful treatment outcome with Effect modification

The researcher suspected there could be interaction between HIV status of patients and the nutritional status. Therefore a model was fitted with an interaction term between HIV status and nutritional status. This is presented in the table 9 below.

Table 4. 4 Predictors of successful treatment outcome with effect Modification

Patient characteristic	AOR (CI)	P- value
Gender		
Male	0.74(.28-1.97)	0.546
Female	*Reference*	
Age		
10-19years	Reference	
20-24year	15.94(0.48-525)	0.12
>=25year	11.4(0.47-274.8)	0.134
BMI	0.88(0.76-1.01)	0.069
BMI#HIV status		
Underweight #negative	0.39(0.05-3.18)	0.385
Underweight #positive	0.54(0.06-4.59)	0.570
Normal #negative	0.03(.002-0.60)	0.021*
Normal #positive	0.56(0.06-5.19)	0.607
Overweight #negative	0.95(0.03-29.7)	0.976
Overweight #positive	*Reference*	
Model of care		
Facility	0.82(0.28-2.38)	0.718
Community	*Reference*	
Constant	0.48 (0.05-4.65)	0.743

*Significance at α=0.05
HIV=Human Immune Deficiency Virus; BMI=Body Mass Index

Table 4.6 presents results after fitting a model with interaction term between HIV status and Nutritional status. HIV status was either positive or Negative while nutritional status was defined as underweight, normal weight or underweight. The results shows that, patients with Normal weight and are HIV negative are likely to have better treatment outcomes as compared to other categories.

CHAPTER 5

DISCUSSION

This study found that the success rate for the cohort of patients that were followed was 71% which is below the recommended 75% by (WHO, 2017). The cure rate was 40%, mortality rate at 20% and 6% lost to follow-up. This treatment success rate differ from a study carried out at KNH that showed a success rate of 87%. However, this study looked at all drug resistant TB in general and not specific to MDR -TB. A similar study carried out in Tanzania (Leveri et al., 2019) showed a cure rated of 62.7% which means that the cure rate for this study was very low. This could be attributed to weak health system since there was a cohort of patient that completed treatment but they were not confirmed whether they were cured. This study however observed a higher treatment success rate compared to that of a meta-analysis study done in Ethiopia (Eshetie et al., 2018) which observed a treatment success rate of only 59 %.

The percentage of LTFU was slightly lower than that found by a study by(Mibei et al., 2016). This could be attributed to TB case finding effort and improved community health services. Further, the failure rate was very low which indicates effective regimen and good adherence to treatment due to insistence on Direct Observed therapy whether in the facility or in the community.

More males had a higher treatment success rate compared to female this could be attributed to the fact that there were more male diagnosed with MDR-TB compared to females. Out of 58 seropositive clients 36 had successful treatment outcomes while 54out of 68 sero negative had successful treatment outcome. This implies that more HIV negative patients' had a good treatment outcome compared to HIV positive patients. It is worth noting that HIV status of all the 126 patients were tested for HIV and their results recorded. This implies that the Health Care Providers were following the guideline of ensuring all TB

patients are tested for HIV. This is also critical since the study found HIV status as a predictor of successful treatment outcome.

All the patients were also assessed for nutritional status using BMI and were classified as Underweight, normal or overweight. 46 clients who were underweight had successful treatment outcome while 37 who had normal weight had successful treatment outcome. This study did not find significant association between nutritional status and treatment outcome. This differs from the study by Laveri et. al done in Tanzania which found nutritional status to be significantly associated with treatment outcome. However, the study is consistent with finding of a study by (Mibei et al., 2016) that found no association between treatment outcome and nutritional status.

This study went further to investigate whether nutritional status acting together with HIV status could predict the treatment outcome. It was found that HIV negative and normal BMI (>18.5 and <=24.5) was significantly associated with successful treatment outcome. This is critical information in management of MDR-TB patients and in offering necessary interventions. Other studies reviewed did not look at the interaction between HIV status and nutritional status.

Out of those who had successful treatment outcome 62% (79/126) were from public sector while 0.11% (14/126) were from private, prison and FBO facilities. This could imply most private, FBO and prison facilities lacks capacity to handle MDR-TB cases due it complex management. It is therefore important for the government empower and capacity build private facilities to manage MDR-TB cases.

This study found that 69% (64/93) clients who had successful treatment outcomes were using community model of DOT while 76% (22/29) were using facility Model of DOT. However, this study did not find any significant difference in treatment outcome between the two models. Of importance to note is that, for treatment adherence a patient is required to have a treatment supporter who observes daily as the clients

takes his/ her drugs. This is important as non- adherence can lead to treatment failure and drug resistance. Therefore, Implementation of DOT whether at facility or in the community is critical for successful treatment outcome for MDR-TB

This study found more males to have presented themselves with MDR-TB compared to female which is consisted with a previous study by (Mibei et al., 2016). However, the study did not find a significant association between gender and treatment outcome. This is unlike Mibei's study which found females to have a significantly better treatment compared to males.

The findings of this study are likely to suffer some limitations since it is a retrospective study and the data is obtained from routine data stored in electronic format. Routinely collected data is sometimes incomplete for instance in this study some individuals were not be assigned a treatment outcome even after completing treatment. In addition, this study only utilized predictors that were predetermined or routinely collected in TIBU. Therefore, other socio demographic factors like education status, income and residence which might be important predictors were omitted in this study. Further, reliability of recorded and routinely collected data cannot be ascertained, and excluded records due to incompleteness can be a potential source of bias.

CHAPTER 6

CONCLUSIONS AND RECOMENDATIONS

Conclusions

This study found that although 71% of the patients in the study were found to have had successful treatment outcome only 40% had been confirmed cured. This implies that 30% of the patients who completed treatment did not have laboratory confirmation of whether they were cured or not.

The study also found that patients who are HIV negative and their BMI is normal have a statistically significant successful treatment outcome. Therefore, HIV status is a predictor of successful treatment outcome. In addition, the study did not find BMI alone to be a predictor of successful treatment although HIV status interacting with Normal BMI to were found to be predictors of successful treatment outcome.

The study found that most the data was reported from public facilities even though a bigger percentage of those obtaining care from Private and FBO facilities had successful treatment outcome. However, type of facility was not a predictor of successful outcome.

More males were diagnosed with MDR but Gender was not a predictor of successful treatment outcome.

Most of the patients were aged more than 25 years even though age was not found to associate with treatment outcome.

Recommendations

Patients HIV status and BMI should be done routinely as part of patient monitoring while undergoing treatment for MDR TB

The TB programme in the country should ensure that all patients who have completed treatment have their sputum taken to confirm cure and the results recorded in the surveillance tools. This will reflect the true treatment success rate since the goal of TB treatment is to ensure the patient is cured.

This study also recommends that the TB programme to build capacity and empower private facilities to Manage MDR-TB cases in the country.

A Further study is also recommended that will incorporate other potential factors that are not routinely collected in the usual surveillance systems for instance environmental factors and social economic status.

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APPEDIX1: ETHICS APPROVAL

APPENDIX 2: DATA ANALYSIS DO FILE