DETERMINANTS OF DRUG-RESISTANT TUBERCULOSIS IN MERU COUNTY, KENYA

BY

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DECLARATION

DECLARATION BY CANDIDATE

This research project is my original work and has not been presented in any other institution for any research leading to the award of a degree or any other award.

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This thesis has been submitted to Moi University with our approval as University supervisors.

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DEDICATION

I dedicate this work to my parents for their support and confidence in my academic journey. I also want to dedicate this work to my family (my wife and children) for their support and belief.

ABSTRACT

Background: Tuberculosis (TB) remains a major public health burden globally. In 2022, approximately 10.6 million TB cases and 1.3 million TB-related deaths were reported by the WHO. Globally, there were an estimated 410,000 Drug-resistant tuberculosis (DRTB) cases; Africa accounted for 62,000 cases, while Kenya reported 752 cases. In Meru County, DRTB cases have been increasing, with the county recording 111 cases in 2022, the highest in the country, representing 14.8% of the total cases. The Increasing incidence and complexity of resistance transmission underscore the important need to identify determinants associated with DRTB to inform targeted public health interventions.

Objective: To determine sociodemographic, clinical, behavioural, and socioeconomic factors associated with drug-resistant tuberculosis in Meru County.

Method: A case-control study was conducted among TB patients in Meru County. A case was defined as any drug-resistant TB patient (resistant to at least one or more first-line anti-TB drugs). A control was a bacteriologically confirmed TB patient who turned sputum smear-negative after the treatment course's 2nd, 5th, and 6th month (cured). Drug-resistant tuberculosis registers were reviewed to identify the cases, and were subsequently recruited. Tuberculosis registers were reviewed to identify the controls, and two randomly selected unmatched controls were enrolled per case. Consent was sought from study participants, who were interviewed using a structured questionnaire. Descriptive analysis was conducted where continuous variables were summarized using measures of central tendency and dispersion, while categorical variables were summarized using frequencies and proportions. Crude odds ratio was used to measure association in bivariate analysis. Variables with a p-value of less than 0.2 in the bivariate analysis were subjected to unconditional multivariate binary logistic regression, and stepwise backward elimination was used to develop the final model. In the multivariate model, variables with a p-value of less than 0.05 were independently associated with drug-resistant tuberculosis**.**

Results: A total of 83 cases and 166 controls were enrolled. The mean age of the cases was 39.9±SD12.2 years, and the controls were 37.7 ± SD 13.9 years. Males comprised 57 (68.7%) cases and 118 (71.7%) controls. Age group 25-34 contributed to 43 (51.8%) cases and 93 (56%) controls. The majority of the cases, 63 (75.9%), were mono-resistant DRTB. Having no formal education increased drug-resistant tuberculosis occurrence by 3.37 times (aOR=3.37, 95% CI 1.02–11.75), contact with DRTB case (aOR=3.92, 95% CI 1.54–9.95), not hearing about DRTB (aOR=3.49, 95% CI 1.87–6.52), and alcohol consumption (aOR=2.52, 95% CI 1.25–5.13) were independently associated with drug-resistance tuberculosis.

Conclusion: Having no formal education, contact with DRTB cases, alcohol consumption, and lack of prior information about DRTB increases the risk of DRTB.

Recommendations: Meru County should enhance community health education by integrating TB education into community learning initiatives, expanding awareness campaigns, strengthening contact tracing and screening, and integrating alcohol abuse support programs into TB control efforts to reduce drug-resistant tuberculosis risk.

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ABBREVIATIONS AND ACRONYMS

ADR	Adverse Drug Reaction
BMI	Body Mass Index
CDC	Centers for disease control and prevention
COVID-19	Coronavirus disease 2019
DNLTP	Division of National Leprosy, Tuberculosis and Lung Diseases
DR-TB	Drug-Resistant Tuberculosis
DST	Drug Susceptibility Testing
DS-TB	Drug Susceptible Tuberculosis
EPTB	Extra Pulmonary Tuberculosis
HIV	Human Immunodeficiency Virus
LPA	Line Probe Assay
MDR-TB	Multi-Drug Resistant Tuberculosis
MGIT	Mycobacterium Growth Indicator Tube
MTB	Mycobacterium Tuberculosis
PDR-TB	Poly Drug-Resistant Tuberculosis
PLHIV	People Living with Human Immunodeficiency Virus
PTB	Pulmonary Tuberculosis
RR-TB	Rifampicin Resistant Tuberculosis
SDGs	Sustainable Development Goals

SSA	Sub-Saharan Africa
TAT	Turnaround Time
TB	Tuberculosis
TIBU	Treatment Basic Unit Surveillance System
TPT	Tuberculosis Preventive Treatment
UHC	Universal Health Coverage
WHO	World Health Organization
XDR-TB	Extensively Drug-resistant Tuberculosis

OPERATIONAL TERMS

Bacteriologically confirmed TB case: A person from whom biological specimen is positive by smear microscopy, culture, or WHO-approved rapid diagnostic tests (such as Xpert MTB/RIF).

Close contact: Living in the same household or frequent contact with a source like a caregiver with sputum-positive tuberculosis

Cure Rate: The proportion of cases (TB) registered in a given year that successfully completed treatment without bacteriological evidence of failure.

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

DRTB infection: A type of infection by Mycobacterium tuberculosis resistant to one or more of the first-line anti-TB drugs.

Drug susceptible TB: A biologically confirmed or clinically diagnosed case of TB without evidence of infection with strains resistant to rifampicin and isoniazid.

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

Pulmonary TB: This is TB disease involving the lung parenchyma (segmental or lobar consolidation, TB bronchopneumonia). Miliary TB is a disseminated disease but is classified as PTB because there are lung lesions.

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

Treatment coverage in TB: The proportion of people diagnosed with TB who are successfully enrolled and started on appropriate TB treatment.

Treatment failure: A TB patient whose sputum smear or culture is positive at most months five or later during treatment.

Treatment Success Rate: The sum of cured and treatment completed. This is calculated based on bacteriologically confirmed cases.

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CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Tuberculosis (TB) remains a major public health burden globally, with nearly one-quarter to one-third of the world's population infected by the disease-causing bacterium *Mycobacterium tuberculosis* (MTB). About 5-10% of people infected will eventually get symptoms and develop TB disease. It remains a crucial public health issue as it is among the top infectious disease causes of mortality worldwide. TB is one of the leading causes of death and the second leading infectious killer after COVID-19 (WHO, 2022a).

Due to its airborne nature, tuberculosis can be transmitted from person to person through coughing, spitting, or sneezing when the person releases aerosol droplets containing bacilli, especially in smear-positive pulmonary TB. When an individual develops active TB, symptoms such as cough, fever, night sweats, or weight loss may be mild for many months. Patients present with paucibacillary and non-specific characteristics, leading to higher TB infection worldwide. Unlike TB infection, when people get TB disease, they will have symptoms. These may be mild for many months, so it is easy to spread TB to others without knowing it (WHO, 2022a).

Not everyone who has tuberculosis (TB) shows up for treatment with symptoms or reports being ill. Thus, screening or TB prevalence surveys may be the only ways to identify individuals with asymptomatic forms of the disease, often known as subclinical TB. According to recent assessments, over 50% of individuals with TB identified by national TB prevalence surveys had bacteriologically proven disease but, when asked, did not exhibit any traditional TB symptoms, such as a persistent cough (Frascella et al., 2021;Law et al., 2020;Teo et al., 2024). There is still much to learn about the natural

history of TB. According to current theory, asymptomatic TB is a phase on a continuum that progresses from Mycobacterium tuberculosis complex infection to clinical illness. Less is known about the causes and rates of progression and reversion between these states, despite the fact that both are known to occur. The participants' symptom status has not been sufficiently reported in studies of these events (Richards et al., 2023;Sossen et al., 2023).

Drug-resistant tuberculosis occurs when bacteria become resistant to the drugs used to treat TB. This means that the drug can no longer kill the TB bacteria; the emergence of drug-resistant TB strains poses a significant challenge to its effective control and management (Abraham et al., 2020). Multi-drug-resistant tuberculosis (MDR-TB) remains a public health crisis and health security threat; only 2 in 5 people with drug-resistant tuberculosis accessed treatment in 2022 (WHO, 2023b).

Globally, 1.3 million people have died from TB worldwide (including 167,000 people with HIV). An estimated 10.6 million people got tuberculosis (TB) disease worldwide in 2022, of which 5.8 million were men, 3.5 million were women, and 1.3 million were children. TB is present in all countries and age groups, but it is curable and preventable. Nevertheless, there was a major global recovery in the number of people diagnosed with TB and treated in 2022 after two years of COVID-19-related disruptions, as this has started to reverse the damaging impact of the pandemic on the number of people dying from TB (WHO, 2023b).

In 2022, there were 410,000 incident cases of drug-resistant tuberculosis, a decline from 2021 cases. The decrease in drug resistant tuberculosis cases is attributed to a downward trend in the percentage of TB cases that are drug resistant, especially among previously treated individuals (WHO, 2023b). While in the previous year, 2021, there

were 450,000 incident cases of multidrug-resistant Tuberculosis (MDR-TB)/rifampicin-resistant Tuberculosis (RR-TB), with 191,000 deaths, which is an upward trend of 3.1% from 437,000 in 2020. The main explanation for this increase is an overall increase in TB incidence between 2020 and 2021, which is estimated to have occurred due to the impact of the COVID-19 pandemic on TB detection (WHO, 2022a).

Over the course of the same period, in Africa, there were 62,000 drug-resistant tuberculosis incident cases. Among 77,000 drug-resistant TB cases that occurred in 2021, 10% of them died (WHO, 2023b). Kenya has an estimated TB prevalence of 426 per 100,000 (MOH, 2016) and was listed among the 30 TB, TB/ HIV, and MDR/TB high-burden countries until 2021, but still there is a high burden of DRTB in the country with the emergence of extensively drug resistant tuberculosis (XDRTB) which could reverse the gains made. However, these high burden TB countries collectively account for 87% of global TB cases. In 2022, Kenya reported 752 cases of DRTB out of 1,089 estimated cases, translating to 69% treatment coverage. Among the 804 patients who were initiated on DRTB treatment in 2021, 83 died, representing a case fatality of 10.3%. In Meru County, 82 patients initiated DRTB treatment in 2021, and 3 died, representing a case fatality of 3.7%, while in 2022, the county had the highest number of DRTB cases notified in the country, with 111 cases representing 14.8% of the total DRTB cases notified in the country (DNLTP, 2022).

Drug-resistant TB presents grave public health implications, including the potential for ongoing transmission and the risk of amplification of resistance to extensively drug-resistant TB (XDR-TB) emergence (Dheda et al., 2017). Managing DRTB cases within healthcare facilities can further complicate infection control efforts (Kendall et al., 2017). According to empirical evidence, DRTB is a complex disease with costly treatment plans, harmful drugs, and protracted treatment periods that place a significant

financial strain on the healthcare system (Manjelievskaia et al., 2015;Thiruvalluvan et al., 2017). The treatment of DRTB is lengthy, expensive, and often less effective compared to drug-susceptible TB (WHO, 2020). The World Health Organization (WHO) recommends using shorter, more tolerable regimens for MDRTB treatment (World Health Organization, 2019). However, implementing these regimens remains challenging, especially in resource-constrained settings (Tiberi et al., 2022).

TB remains a public health risk in spite of worldwide efforts to control it. A significant TB disease death rate was primarily seen among patients who were co-infected with HIV, possibly because the two illnesses can be fatal when combined to further each other's progression (Pan et al., 2020). Unfortunately, in East Africa, where TB prevalence and risk factors are highest, HIV co-infection with MDR-TB did not receive much attention until recently (Workicho et al., 2017). MDR-TB is one of the major public health issues that is most commonly the cause of mortality in immune-compromised individuals, and even in high-income countries, cure rates for this disease are still below 100% (Stosic et al., 2018). Even though TB is curable, people with MDR-TB are almost impossible to treat with the usual first-line TB medications, such as isoniazid (INH) and rifampicin (RIF); as a result, the infection persists for a longer period of time. The emergence of MDR-TB raises the possibility that TB may once more be considered an "incurable disease." (Xi et al., 2022). This could be because certain genes linked to medication resistance cause TB germs to develop mutations, although antibiotics that are provided with resistance may reduce the fitness of tuberculosis germs. However, the resistance to drugs eventually occurs, TB strains may have compensatory alterations, which let them survive and eventually develop medication resistance (Xi et al., 2022). Additionally, Gagneux et al. speculate that pan-sensitive forms of drug-resistant TB could spread (Gagneux et al., 2006). The serious

MDR-TB epidemic is a major public health concern in many countries and a major obstacle to global effective TB control, which emphasizes the value of universal drug susceptibility testing (Wang et al., 2020). Although it can help identify active TB disease early on, programmatic surveillance of DRTB patients' contacts without Tuberculosis Preventive Treatment (TPT) does not reduce the likelihood of developing active TB disease (Malik et al., 2021). In contrast to RR/MDR-TB contact management, active household contact management in rifampicin-susceptible tuberculosis required more work to avoid each mortality, according to a modelling research by Dodd and colleagues (Dodd et al., 2022). According to this research, managing active DRTB household contacts needs to be a top priority in the worldwide effort to combat tuberculosis.

Despite international agreements under the Sustainable Development Goals (SDGs), tuberculosis (TB) continues to pose a serious threat to global health. In line with the World Health Organization's End TB Strategy, which establishes challenging interim milestones for 2025, such as a 50% decrease in TB incidence and a 75% decrease in TB-related mortality relative to 2015 levels, SDG Target 3.3 seeks to eradicate the TB epidemic by 2030 (WHO, 2023a). But progress has been slow; from 2015 and 2022, there was only an 8.7% decrease in TB incidence and a 19% fall in TB mortality, which is far less than the 2025 targets (United Nations, 2024). Gains in diagnosis and treatment were reversed by the COVID-19 pandemic, which severely disrupted TB preventive and care services (UN, 2020). Addressing social determinants, including poverty and limited access to healthcare, and expanding access to diagnostics and care, particularly for children, have become increasingly important in global responses. TB remains the second most common infectious agent-related cause of death worldwide in spite of these efforts (United Nations, 2024). Rekindled political will, more financial

resources, and integrated policies that combine biomedical techniques with social protection and equity-based initiatives are all necessary to achieve SDG 3.3, which is to end epidemics of acquired immunodeficiency disease syndrome, tuberculosis, malaria, and neglected tropical diseases by 2030, while also combating hepatitis, waterborne diseases, and other communicable diseases.

From the perspective of health economics, Value-TB research (Kairu et al., 2021) revealed that the cost of treating drug susceptible TB (DSTB), including monitoring tests, in Kenya varied from $135 to $160. Still, treating DRTB was between $3230 and $392. Even with free medications, screening, and treatment for tuberculosis, patients are yet facing unaffordable direct and indirect expenses. This has been further supported by a TB patient cost study conducted in Kenya, which revealed shocking statistics on the number of people who have become destitute from TB as a result of catastrophic out-of-pocket costs. According to the same TB patient cost survey, conducted in line with the World Health Organization (WHO) end TB strategy and the Universal Health Coverage (UHC), 62.5% of drug-resistant TB (DR-TB) patients lost jobs due to TB. Not only this, but some of these DRTB patients undergo the 6 to 8 months medication regimen first before they start the drug-resistant regimen that runs for up to 18 months, making it even more costly. The TB patient cost survey revealed the suffering endured by patients who had to pay an astounding $252 and $1416 for DSTB and DRTB episodes, respectively (MOH, 2018). Furthermore, around 50% of TB patients and their families worldwide have catastrophic total costs (direct medical expenses, non-medical expenses, and indirect costs including income losses) that exceed 20% of their entire family income, much below the WHO End TB Strategy goal of zero (WHO, 2024a).

Kenya is a signatory to the WHO's post-2015 End TB Strategy, adopted by the World Health Assembly in 2014, which aims to end the global TB epidemic as part of the

newly adopted Sustainable Development Goals. Ending TB is not just a public health problem but a development challenge and opportunity. This strategy serves as a blueprint for countries to reduce TB incidence by 80%, TB deaths by 90%, and to eliminate catastrophic costs for TB-affected households by 2030. The Strategy is not a "one size fits all" approach, and its success depends on adaptation for diverse country settings. The rise of immune-disrupting chronic diseases like diabetes hampers the global commitment to eradicate tuberculosis (TB) worldwide (WHO, 2022a). Innovation and research are two strategies to accomplish this aim. *Mycobacterium tuberculosis* is the organism that causes tuberculosis. The variables influencing the disease's dissemination have been the subject of much research. Research on tuberculosis has influenced both prevention tactics and clinical practice. Nonetheless, there is a growing understanding that combating tuberculosis necessitates an adaptive strategy that actively addresses the determinants of the illness. The problem of drug-resistant TB is getting worse. The development and spread of drug-resistant tuberculosis (DRTB) are closely related to the intricacies of tuberculosis (TB) disease dynamics, which include latent infection, active disease progression, host immunological responses, and socio-environmental variables that not only exacerbate transmission but also drive the evolution of Mycobacterium tuberculosis strains resistant to first-line and second-line drugs (Esmail et al., 2014; Lönnroth et al., 2009). The importance of integrated public health strategies that are suited to the control of both TB and DRTB is highlighted by the dynamic interaction between biological, behavioural, and structural determinants. This calls for advancements in patient-centered care, diagnostics, and international policy coordination (Dheda et al., 2017; WHO, 2020)

Although Kenya has made great strides in TB control, the emergence of multidrug-resistant tuberculosis poses a major health security threat that could jeopardize the gains made in tuberculosis epidemic control. According to the nation's TB situation evaluation, insufficient resources are available for planning, executing, and gathering data for evidence-based interventions and initiatives. From a country perspective, TB funding has been drastically reduced, discouraging the development of effective TB programs. (MOH, 2016).

To control and reduce the prevalence of tuberculosis, the World Health Organization (2010) suggested using the directly observed therapy (DOTS) technique, though it has evolved to include strategies like active case finding that promote early TB case detection. The directly observed therapy technique entails giving patients, under the supervision of a healthcare provider or community health worker, an intensive two-month course of effective chemotherapy consisting of ethambutol, isoniazid, rifampicin, and pyrazinamide. Then, patients receive a four-month course of daily rifampicin and isoniazid, known as the continuation phase. All drug susceptible TB patients receive a 6-month treatment except the TB meningitis and osteoarticular TB. Despite this development, drug-resistant tuberculosis has emerged as a major problem in the nation. A nationwide drug resistant TB survey in 2015 found that 2.1% and 0.7% of newly diagnosed and previously treated cases had MDRTB (MOH, 2016).

Early case detection and treatment are the most effective strategies for tuberculosis programs (WHO, 2020). Nevertheless, their performance is distinct from the expected level globally and worse in high TB-burden countries (Asemahagn et al., 2020;Merid et al., 2019). Accurate drug resistance diagnosis is delayed in settings with limited resources due to limited access to quick diagnostic instruments. Although they have

made it easier to identify rifampicin resistance, molecular diagnostics like GeneXpert are still underutilized in many areas. Because of this, more TB cases remain undetected, those detected do not get complete anti-TB treatment, resulting in poor outcomes including TB recurrent and MDRTB in the developing countries (Turner et al., 2017). Despite significant advancements, several gaps in our understanding of DRTB persist. Ongoing research is needed to elucidate the dynamics of transmission, optimal diagnostic methods, and strategies to improve access to appropriate care.

1.2 Problem Statement

Drug resistant tuberculosis (DRTB) poses a significant global health challenge, with increasing incidence rates and complex patterns of resistance transmission within communities and regions. DRTB is associated with longer and more costly treatment regimens, lower cure rates, and increased mortality rates (WHO, 2022a). The emergence of DRTB hampers efforts to control and eliminate tuberculosis worldwide as its prevalence continues to rise (WHO, 2022a). Meru County had a TB case notification rate of 270 per 100,000 persons in the population, higher than the national average of 168 per 100,000 persons in the population in 2022 (DNLTP, 2022). Also, it is the country's leading county in DRTB case notification, with 111 (14.8%) cases reported from the region in 2022. Over the last few years, the county has experienced a gradual increase in notified DRTB cases from 26 to 73 to 82 to 111 cases in 2019, 2020, 2021, and 2022, respectively, and this indicates an increasing proportion of reported DRTB cases in Meru County of 4%, 7.6%, 10.2% and 14.8% over the last few years compared to those reported nationally (DNLTP, 2022).

1.3 Justification of the Study

Tuberculosis is a curable disease, even though it is highly infectious. The treatment period with multiple antibiotics for drug-susceptible tuberculosis is long (6-8) months, but even longer (18-24) months for drug-resistant tuberculosis. If left untreated, each person with active tuberculosis can infect 10-15 people through close contact (WHO, 2022a).

Meru County has reported a steady increase in DRTB cases, yet the specific factors driving this pattern remain insufficiently understood, coupled with limited studies in the study area. Without localized evidence, it becomes difficult for county health authorities to tailor interventions that target these unique factors contributing to DRTB in this setting. Given the escalating threat of drug-resistant tuberculosis, determining factors associated with this form of tuberculosis can help in identifying patients at risk of transmission, optimizing screening, diagnosis, and treatment strategies, improving treatment adherence, and addressing factors that contribute to drug-resistant tuberculosis. The results and recommendations of this study can lead to better approaches to case finding, managing, and preventing DRTB. It can also lead to personalized care plans and improved treatment outcomes among DRTB patients, leading to a reduction in transmission, hence lowering the burden of DRTB in Meru County and Kenya.

1.4 Research Questions

I. What are the social demographic factors associated with drug-resistant tuberculosis in Meru County?

II. What are the clinical factors associated with drug-resistant tuberculosis in Meru County?

III. What are the behavioral and socio-economic factors associated with drug-resistant tuberculosis in Meru County?

1.5 Objectives

1.5.1 Broad Objectives

To assess determinants of drug-resistant tuberculosis in Meru County.

1.5.2 Specific Objectives

1. To determine social demographic factors associated with drug resistant tuberculosis in Meru County.
2. To assess clinical factors associated with drug resistant tuberculosis in Meru County.
3. To determine behavioral and socio-economic factors associated with drug resistant tuberculosis in Meru County.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Introduction

The infectious disease tuberculosis (TB) is caused by a bacterium called *Mycobacterium tuberculosis.* Latent or asymptomatic MTB infection (LTBI), which could include, for example, a person with bacteriologically unconfirmed TB who did not report symptoms suggestive of TB during screening and can linger for decades, symptomatic "active TB," which includes lung disease and can spread to other people, or resistance or early clearance of the bacillus are the three outcome of coming into contact with an infectious TB case (Uplekar et al., 2015). The typical symptom of active tuberculosis (pulmonary TB) is a severe productive cough. However, fever, weight loss, night sweats, and other symptoms common to respiratory infectious diseases are often present in extrapulmonary tuberculosis, which can also affect other organ systems (Dowdy & Behr, 2022).

When mycobacteria proliferate and evolve at a specific rate, they can withstand anti-TB medications that would typically be successful, leading to drug-resistant tuberculosis. Mycobacterium causes tuberculosis (TB) because of this capacity. There are three main ways that drug resistance might develop. First of all, all living things undergo random genetic changes that result in changed functionality and innate resistance after a specific number of divisions. Second, acquired drug resistance is a sign of insufficient treatment since it arises from the selection of resistant strains of MTB as a result of inadequate therapy, and third, primary resistance happens when a patient encounters and becomes infected by a resistant strain of MTB (MOH, 2021).

2.2 Aetiology and History of Tuberculosis

Although Mycobacterium tuberculosis is thought to have originated 3 million years earlier, the name "tuberculosis" was first used by Johann Schonlein in 1834. Since then, other continents have given the phrase "tuberculosis" different names. The word "phthisis" was used in ancient Greek. It was known as "schachepheth" in both ancient Roman and Hebrew. In the 1700s, the patient was known as "the white plague" due to their pale complexion (Martini et al., 2018). In the 1800s, the term "consumption" was used to describe tuberculosis. Schonlein dubbed it TB, although the term "Captain of all these men of death" was still widely used. A separate name, "scrofula," was given to the illness because it spread to the neck and lymph nodes. The pulmonary disease that plagued people in the Middle Ages is believed to be distinct from this condition. According to its location in the body (pulmonary versus extrapulmonary) and the various treatment options (drug-susceptible, drug-resistant, multidrug-resistant, pre-extensively drug-resistant, extensively drug-resistant), we now have a solid understanding of tuberculosis (CDC, 2016).

Robert Koch won the Nobel Prize in medicine in 1905 after he discovered on March 24, 1882, that the main cause of tuberculosis was the mycobacterium TB. His work was further improved by Ziehl and Nelson, who developed sputum staining methods. One in seven individuals in the US and Europe died of tuberculosis at this time. In order to increase awareness of the disease's worldwide impacts, the International Union Against Tuberculosis and Lung Diseases created World TB Day on March 24th, a century later (Martini et al., 2018) .

In 1944, Albert Schätz, Elizabeth Bugie, and Selman Waksman discovered *Streptomyces griseus*, also known as streptomycin, which was the first antibiotic used to treat tuberculosis. The hypothesis that bacteria will eventually develop antibiotic

resistance as a result of random mutations and natural selection was put forth by biologist Renee Dubos in 1950. It was soon discovered that certain TB patients had streptomycin-resistant TB strains. Additional anti-tuberculosis medications, such as rifampicin, isoniazid, and p-aminosalicylic acid, were developed throughout the course of the following 20 years. However, the increased use of these medications led to the emergence of drug-resistant forms of tuberculosis. Multi-drug resistant TB, or MDRTB, was the term used to describe the discovery of TB strains resistant to isoniazid (INH), para-aminosalicylic acid (PAS), and streptomycin in Great Britain in 1956. As strains resistant to even more drugs were found in later years, the term "extensively drug-resistant TB" (XDRTB) was created (Martini et al., 2018). Because of the nodular lesions they produce in the lungs, the organisms are referred to as tubercles. They are obligate pathogens and the cause of tuberculosis. The bacteria that causes tuberculosis, a disease that is carried by the air, is called *Mycobacterium tuberculosis*. The Mycobacterium tuberculosis complex is created when Mycobacterium tuberculosis combines with seven other closely related mycobacterial species: *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium microti*, *Mycobacterium caprae*, *Mycobacterium pinnipedii*, *Mycobacterium Canetti*, and *Mycobacterium mungi.* Though not all of them are, these species are zoonotic (Gupta et al., 2018).

2.3 Biology and Pathogenesis of Tuberculosis

The causal agent of tuberculosis is *Mycobacterium tuberculosis*, a rod-shaped bacterium with a protective waxy coating lipid cell wall. It's mycolic acid cell wall, which also confers resistance to mild antiseptics, increases its pathogenicity. Since aetiology determines the degree of TB transmission, pathogenesis and transmission are intertwined. M. tuberculosis is almost entirely considered a human pathogen, and its survival depends on how it interacts with its human host. This perspective holds that

the assertion of continued pathogen transmission requires a successful host-pathogen relationship. M. tuberculosis is typically considered a human pathogen, and its persistence is contingent upon its interactions with hosts. This perspective holds that in order to demonstrate ongoing pathogen transmission, a successful host-pathogen interaction is required (Long et al., 2022). This specific form of bacteria is present in human hosts, although other types, including *Mycobacterium bovis*, are found in cattle. In contrast to other bacteria, it takes a long time (15–20 hours) for this one to multiply. Its crimson colour upon acid fast staining serves as an identifier. The pathophysiology of tuberculosis includes the interplay between the infection and the host. Mycobacterium tuberculosis, the organism that causes tuberculosis in humans, is transmitted by droplet nuclei that contain tubercle bacilli. The alveolar macrophages phagocytose the tubercle bacillus after it enters the lungs. The bacteria use a variety of strategies to survive inside their host. One strategy is for the alveolar macrophages to ingest the germs by phagocytosis (Welin, 2011). The bacteria are consumed by tissue dendritic cells as well as the local alveolar macrophages. The infected cells subsequently emit pro-inflammatory cytokines. This release causes more circulating neutrophils, monocytes, and dendritic cells to become infected. Once infected, the blood transfers the infection to the lymph nodes, where it triggers a specific T cell and releases cytokines from the infected cells, including IL-12 and IL-18. As a result, NK cells become more active and release IFN-γ, which causes macrophages to release TNF-α through cytokine and chemokine signaling. This leads to the disruption of other immune cells and the formation of TB-infected granuloma infection. The macrophages in the granuloma differentiate further into epithelioid cells, which then aggregate to form a single, enormous cell. Fibroblasts, lymphocytes, and extracellular matrix proteins envelop the cells. The bacilli remain within the granuloma

until they fail due to immunosuppression. The ability of the host to successfully develop an immune response has a major impact on the illness's natural history and progression. For the treatment of tuberculosis, T-lymphocytes are crucial (Welin, 2011). Thus, active tuberculosis may develop as a result of a substantial deterioration of cell-mediated immunity brought on by HIV. According to research, the number of CD4+ T cells, which are associated with cell-mediated immunity, and other factors like the duration of infection are both directly and indirectly connected with the prevalence of active TB in HIV-positive persons. HIV infection has an impact on the natural progression and clinical presentation of the disease. For instance, it is impossible to distinguish between those who are HIV-positive and in the early stages of HIV infection and those who are HIV-negative but have TB. However, as HIV infection progresses, pulmonary, extrapulmonary, and sputum smear-negative TB becomes more prevalent (Raviglione, 2016). Notably, the host's immunity can sometimes be so strong that it can prevent the growth of the tubercle bacilli and halt the progression of the disease when the extracellular bacilli are eaten by macrophages and exposed to other white blood cells. The immune reaction is initiated, causing white blood cells to either encapsulate or eliminate most of the bacilli, resulting in the formation of a granuloma. By this point, latent tuberculosis infection (LTBI) will have been confirmed. Despite having M. tuberculosis in their systems, people with LTBI do not have TB disease and cannot spread the infection to others. A person who has LTBI is not regarded as having TB. Additionally, studies have shown that 5% of individuals infected with M. tuberculosis will probably contract the disease within the first year or two of infection and another 5% will do so later in life if treatment is not received. Accordingly, 10% of individuals with a healthy immune system who are infected with M. tuberculosis will eventually get tuberculosis (CDC, 2023).

2.4 Tuberculosis Transmission

Tuberculosis (TB) is an infection caused by the bacterium *Mycobacterium tuberculosis*. The method by which the bacillus spreads from person to person is through aerosolized droplets from an infected person through coughing, sneezing, spitting, or talking, and is the same for both drug-resistant and drug-susceptible tuberculosis (CDC, 2023;Nikolayevskyy et al., 2016). While eating unpasteurized dairy products can spread the bacterium, airborne transmission remains the primary mechanism. Although it can affect other organs, the infection mostly affects the lungs. The host immune system is weakened as the germs grow inside the body. A number of variables affect TB transmissibility. Research has indicated that persons with HIV-coinfected TB are not contagious, particularly if they are immunocompromised. Several variables influence the likelihood of Mycobacterium tuberculosis transmission, including environmental conditions, level of exposure, the infectiousness of the source case, and the susceptibility of the exposed individual (Martinez et al., 2021).

2.5 Epidemiology of Tuberculosis

An estimated 25% of the world's population is thought to have contracted MTB. Of those who have contracted tuberculosis, 5–10% will eventually develop symptoms and become unwell. Tuberculosis is a major public health concern as it is one of the most common infectious disease causes of mortality worldwide (WHO, 2022a). As of 2023, 1.25 million people worldwide had died from TB, including 161,000 people with HIV. TB is now the second most common infectious killer and the 13th leading cause of death worldwide, surpassing both COVID-19 and HIV. Globally, an estimated 10.6 million people were estimated to have developed tuberculosis (TB) in 2022, including 5.8 million men, 3.5 million women, and 1.3 million children. One of these cases that requires severe attention is drug-resistant tuberculosis (DRTB). Although tuberculosis

(TB) affects people of all ages and in all countries, it is preventable and treatable. According to estimates, COVID-19-related interruptions led to almost 700,000 more deaths than were anticipated for the three years 2020–2022 (WHO, 2023b).

Global TB control efforts are seriously hampered by drug-resistant tuberculosis (DRTB), particularly extensively drug-resistant tuberculosis (XDRTB) and multidrug-resistant tuberculosis (MDRTB) (Falzon et al., 2018). In 2022, there were 410,000 cases of drug-resistant tuberculosis worldwide. On the other hand, there were 450,000 MDR/RR-TB event cases worldwide in 2021, up 3.1% from 437,000 cases in 2020. This surge is linked to an overall increase in tuberculosis incidence between 2020 and 2021 and is thought to be mostly caused by the impact of the COVID-19 pandemic on tuberculosis case detection (WHO, 2022a). According to WHO projections for 2022, MDR/RR-TB was responsible for 191,000 deaths (WHO, 2023b).

A total of 310,000 people died from tuberculosis in 2022, of the estimated 2.5 million people in Africa who caught the disease, making up roughly 24% of all deaths globally, a somewhat smaller percentage than the 25% it contributed to in 2021. A total of 62,000 incident cases of drug-resistant TB occurred during the same year. In 2021, there were 77,000 drug-resistant TB cases, with 10% of cases leading to death (WHO, 2022a). The possibility to achieve the 2035 targets of a 90% fall in incidence and a 95% reduction in mortality is threatened by the fact that drug-resistant TB is frequently disregarded in Africa. Therefore, quick action is needed to determine the true prevalence of drug-resistant TB in Africa. Since most African countries do not routinely screen all TB cases for rifampicin drug resistance, population-based survey results are needed to obtain the most accurate estimate of the burden of drug-resistant TB across the continent (WHO, 2023a).

According to the Kenya TB prevalence survey (MOH, 2016), there are 426 TB cases for every 100,000 individuals in Kenya. Up to 2021, Kenya was among the 30 countries with the highest burdens of TB, MDR/RR TB, and TB/HIV, which together accounted for 87% of all TB cases worldwide. Kenya still has a significant TB burden in spite of this accomplishment. In 2022, Kenya reported 90,560 cases of TB overall; 8.3% of those reported had previously had TB treatment. This showed that, compared to the 77,854 TB cases reported in 2021, there was a 16.6% increase in TB case reporting in 2022. Since 2020, the number of TB case notifications has steadily climbed every year. In 2021 there were 147 instances of TB per 100,000 people, and the 2022 case notification rate increased to 168 cases per 100,000 people. The WHO estimated that there would be 1089 cases of drug-resistant tuberculosis (DRTB) in Kenya in 2022, compared to 752 cases of DRTB recorded by the country. This amounts to a treatment coverage rate of 69%, which is much less than the WHO treatment coverage goals of 90%. With 111 cases, representing 14.8% of all notified cases, Meru County had the most percentage of reported DRTB cases in the country (DNLTP, 2022).

TB is a disease that can be found anywhere in the world. In 2022, the South-East Asian Region of the World Health Organization reported the highest number of new cases of tuberculosis (46%), closely followed by the African Region (25%) and the Western Pacific Region (18%). About 87% of new cases of tuberculosis were in 30 countries having a high burden of the disease. These countries—Bangladesh, India, Indonesia, China, the Philippines, Pakistan, Nigeria, and the Democratic Republic of the Congo—reported more than two-thirds of the global total, in decreasing order of load. However, the Philippines, India, and Indonesia collectively were responsible for the bulk (>60%) of the global decrease in TB notifications in 2020 and 2021. All of these nations reached 2019 levels in 2022 (WHO, 2023b). Drug-resistant TB is not uniformly spread

throughout the world. High-burden countries in Eastern Europe, Central Asia, and sub-Saharan Africa bear a disproportionately heavy burden of DRTB. Customized therapies are necessary for effective management because the prevalence of DRTB varies among various areas (Dheda et al., 2017).

People with compromised immune systems—such as those with HIV, diabetes, malnourishment, or tobacco use—are at a higher risk of becoming ill. In 2023, it was predicted that undernutrition would be the cause of 0.96 million new cases of TB globally, with alcohol use disorders (0.75 million), smoking (0.70 million), HIV infection (0.61 million), and diabetes (0.38 million) following closely behind. Adults in their prime working years make up the majority of TB patients; those who are most likely to procreate are also the most susceptible. However, all age groups are at risk. Over 80% of diseases and deaths occur in low- and middle-income countries. Despite being preventable and curable, tuberculosis (TB) is anticipated to regain its position as the leading infectious agent-related cause of death worldwide after being surpassed by coronavirus disease (COVID-19) for three years. Furthermore, it was the leading cause of death for people with HIV and the main cause of antibiotic-resistant mortality (WHO, 2024a). Active TB is more common in HIV-positive individuals than in non-infected individuals. Even with the availability of prevention and treatment methods, tuberculosis (TB) is still a major problem. This is particularly true for those infected with HIV, as CD4 cells are essential for fighting infections (WHO, 2023a). Ending the TB epidemic by 2030 is one of the health objectives of the United Nations Sustainable Development Goals (SDGs), despite the fact that worldwide efforts to battle TB have saved an estimated 79 million lives since the year 2000. Multidrug-resistant TB (MDR-TB) is still a threat to health security and a public health emergency, nonetheless. In

2023, only roughly two out of five individuals with drug-resistant TB received treatment (WHO, 2024a).

Recent studies on the natural history of TB, especially in relation to the development and reversion of symptom status, have raised significant issues regarding the most accurate interpretation of TB incidence (Horton et al., 2023). Particularly for the twenty-nine countries whose burden estimates are based on national TB prevalence surveys (which account for about two-thirds of worldwide TB incidence), the incidence of asymptomatic TB is already included in existing estimates of TB incidence and death. These numbers demonstrate that most asymptomatic TB patients eventually develop symptoms based on an expected natural history. There is now further research being done on this modelling, including investigating the potential applicability of conclusions drawn from pre-chemotherapy cohorts in contemporary contexts. In contrast, it is possible that about half of the people with asymptomatic TB may never experience symptoms, according to new modelling that combines data from national TB prevalence surveys with information on the natural course of TB from the pre-chemotherapy era (Horton et al., 2023).

The current WHO definition of notifiable TB does not distinguish between symptomatic and asymptomatic TB (WHO, 2024c). On the other hand, asymptomatic TB is becoming recognized as being relevant to current discussions regarding surveillance, infection control, TB eradication, and other issues. In addition to helping with surveillance and enumeration, standard definitions of asymptomatic TB can eventually help guide the use of diagnostic methods (e.g., increasing the use of chest X-rays) and available medicines. The definition of asymptomatic tuberculosis will also highlight its importance in programmatic management (WHO, 2024c). WHO examined

the implications of asymptomatic TB for incidence estimation when it formed the Global Task Force on TB Impact Measurement in 2024 (WHO, 2024b). One of the primary results of the meeting was strong endorsement for the following load estimation method: WHO would first publish incidence figures for each nation that correspond to the prevalence of TB symptoms. In addition to being more applicable to most current TB programs, which prioritize optimizing services for symptomatic TB, this would ensure continuity with previous estimates. Second, the WHO would provide "complementary" figures to recognize the importance of asymptomatic TB for transmission. An estimate of the worldwide prevalence of tuberculosis, broken down by asymptomatic and symptomatic forms, would be part of these estimations. Concurrent with collaborative efforts to validate recently published estimates for natural history parameters, these estimates are now being developed (WHO, 2024b).

Accurate estimates of the annual risk of infection are important for understanding the global disease burden and developing public health strategies to slow the spread of TB (Henry Boom et al., 2021). In order to reduce the incidence of tuberculosis in the population, Dye et al. (2013) state that early treatment of TB patients prevents the disease from spreading and prevents them from becoming contagious (Dye et al., 2013). According to Jurcev-Savicevic et al. (2013). A number of factors, including diagnostic abilities, care-seeking behaviours, and healthcare accessibility, might affect case detection, which is an essential component of tuberculosis programs (Jurcev-Savicevic et al., 2013). The COVID-19 pandemic disrupted TB services globally, leading to underdiagnosis and treatment delays. This disturbance led to an increase in drug-resistant cases because treatment disruptions and barriers to healthcare access allowed resistant strains to proliferate. Passive TB case discovery, in which patients self-refer to clinics and are assessed for tuberculosis (TB) by the attending physician, is the

mainstay of TB programs in many countries. However, in many developing countries with limited access to medical facilities, passive case discovery might not be enough to reach the global objective of a 90% case detection rate (WHO, 2023a).

2.6 Diagnosis of Tuberculosis

Active TB case finding is key in diagnosing TB in adults and adolescents. This involves screening all persons visiting health facilities using key screening questions, which include the presence of cough (of any duration), Hotness of body/ body temperature > 37.50 C, drenching night sweats, unintended weight loss/ BMI less than 18.5 and chest pain. Persons who screen positive for any of the signs and symptoms listed above should undergo a thorough clinical evaluation before classification as a presumptive TB case. Presumptive TB cases should undergo diagnostic evaluation per the TB screening and diagnostic algorithm for adults and adolescents over 10 years old. To diagnose Tuberculosis, the following steps should be followed: History Taking: TB diagnosis begins with taking a thorough medical history. TB should be ruled out in any person presenting with any of the signs and symptoms of TB and a history of contact with a TB patient. The aim of history taking is to rule out other differential diagnoses of TB. Physical Examination: Physical signs of TB on respiratory examination may include tachypnea, bronchial breath sounds, dullness on percussion, reduced air entry, fever > 37.50 C, wasting, haemoptysis and pallor. If the patient does not have any of the signs/ symptoms above or is not found to be a presumptive TB case on further clinical review, evaluate the patient for TB preventive therapy (MOH, 2021).

Investigations to diagnose PTB GeneXpert MTB/ Rif and Truenat tests are used in TB diagnosis and detecting rifampicin resistance. At the same time, TB loop-mediated isothermal amplification (TB-LAMP) is only used for TB diagnosis. All persons with

Presumptive TB should undergo microbiologic testing to confirm the diagnosis. Key considerations in the choice of TB diagnostic test to be used include: When GeneXpert testing is available on site, a sputum sample should be collected and sent for GeneXpert testing. Gene Xpert MTB/Rif detects both Mycobacterium tuberculosis complex bacteria (MTBC) and Rifampicin resistance in sputum and extra-pulmonary tuberculosis specimens, as it has a fast turnaround, which is less than two hours, high sensitivity, low risk in terms of biosafety, and is an automated one-step process with high sensitivity and specificity. However, it requires an uninterrupted and stable electrical power supply and cannot be used to monitor tuberculosis treatment. When Truenat testing is available on site, a sputum sample should be collected and sent for Truenat testing, as it is the first WHO-recommended molecular test for tuberculosis and rifampicin resistance that can be used in peripheral settings with limited infrastructure. It is also used as an initial diagnostic test for tuberculosis. This test can generate results for TB in one hour and rifampicin resistance in one additional hour. However, electricity is still required for charging batteries and uses more manual steps than the XpertMTB/RIF test (WHO, 2024c). TB-LAMP is also used as an initial diagnostic test for tuberculosis. It requires minimal infrastructure and has biosafety requirements similar to smear microscopy. Detection of amplified product is based on the turbidity visualized with the naked eye or under ultraviolet light and requires less than one hour to perform it. However, it is mostly suitable for settings with a low prevalence of HIV and MDRTB, cannot be used to monitor treatment and does not detect drug-resistant Tuberculosis (Ciesielczuk et al., 2020). Acid-fast bacilli (AFB) smear microscopy is used as an initial diagnostic test for the detection of AFB in pulmonary tuberculosis, it is used to monitor treatment, it can be done safely with low risk level and minimal biosafety precautions, and it is inexpensive and widely available. However, it has low

sensitivity (fifty per cent), which is further reduced in HIV positive individuals and children. It has limited specificity as it can detect non-tuberculosis mycobacterial (NTMS) and does not detect drug resistance. When only smear microscopy is available on site, two sputum samples should be collected, one for smear microscopy and the other to be transported to the nearest GeneXpert testing laboratory. If smear microscopy is positive, the patients should be started on DSTB treatment and reviewed once GeneXpert results are received. A negative smear microscopy result does not rule out TB. If both GeneXpert and smear microscopy are not available on-site, a sputum sample should be referred to the nearest GeneXpert testing laboratory. Lipoarabinomannan assay (LF-TB LAM) should be considered for eligible PLHIV as per the diagnostic algorithm. If positive, initiate DSTB treatment and review once GeneXpert results are received. A negative LF-TB LAM result does not rule out TB. All adult patients newly diagnosed with TB should undergo HIV testing as per the national HIV Testing Services algorithm and Diabetes testing as per the Kenya Diabetes guidelines (MOH, 2021).

Tuberculosis investigations include GeneXpert, GeneXpert ultra, and Truenat testing for all presumptive TB cases, diagnosis of TB, and detection of RR TB. TB-LAMP for the diagnosis of TB. Smear microscopy (Fluorescent and Light microscopy) is used where all presumptive Pulmonary TB cases where GeneXpert, Truenat and TB-LAMP are not available, and it is used for all DSTB patients for treatment follow-up to detect TB disease and Monitoring of bacteriologically confirmed TB patients on treatment at months two/three, five and six. Chest X-ray is preferred for all presumptive pulmonary and some extrapulmonary TB, where accessible and affordable, and a screening tool to identify those at high risk of TB disease and supports TB diagnosis, especially in children and when sputum for AFB/ GeneXpert is negative or not applicable. However,

TB is not the only illness that can produce comparable radiographic results on chest X-rays. Histology is used for all presumptive EPTB and tissue diagnosis in suspected extrapulmonary tuberculosis, e.g. TB adenitis. Other supportive tests include the tuberculin skin test and Interferon Gamma Release Assay (IGRA), which are used to detect TB and latent TB infection. Lateral flow urine lipoarabinomannan assay (LF-LAM) is used for Human Immune deficiency-infected patients with severe illness or advanced HIV disease, all hospitalized people living with HIV and for diagnosis of TB as an add-on test to GeneXpert/ GeneXpert ultra to increase the diagnostic yield of TB testing in severely immunocompromised people living with HIV and AIDS. In TB diagnosis, all attempts must be made to make a bacteriological diagnosis of PTB in adults (MOH, 2021).

Though other diagnostic testing methods are not commonly available in low- and middle-income countries like Kenya, the whole genome sequencing test is a good example. The whole-genome sequencing test is a cutting-edge technique that precisely determines the nucleotide base order throughout an organism's whole genome, including M. tuberculosis (MTB). An important turning point in the study of M. tuberculosis was reached when the complete genome of the strain H37Rv, which was the best characterized, was sequenced. Following this sequencing, a thorough study was conducted in order to gain a deeper understanding of the biology of this slowly spreading virus and aid in the creation of novel preventative and treatment measures. With 4,411,529 base pairs and over 4000 genes, the MTB genome has a remarkably high guanine and cytosine concentration. This approach makes it easier to identify all genomic mutations and variants by offering a thorough picture of the bacterial genetic material. The first sequencing study examined anti-tuberculosis medication resistance, first concentrating on the particular M. tuberculosis genes linked to this resistance. Nine

antibiotic resistance-associated locks were sequenced in 314 clinical M. tuberculosis isolates by Campbell et al., of which 52% were multidrug-resistant (MDR) and 3% were extremely resistant (XDR). When the phenotypic and sequencing data were compared, it was discovered that the sequence had a sensitivity of 90.8% and a specificity of 94.7%, respectively, for correctly identifying the resistance phenotype shown in the case of MDR isolates. However, accurate sequence-based identification of XDR isolates was more challenging, with a 99.3% specificity and a sensitivity of only 40.0% (Campbell et al., 2011). Drug-resistant isolates' WGS sequencing research improved our knowledge of the mutations linked to treatment resistance while also emphasizing how difficult it is to interpret the results. Research on ethambutol resistance has revealed that the M. tuberculosis genome can accrue even modest levels of resistance that are typically undetectable by conventional phenotypic antibiotic susceptibility assays (Safi et al., 2013). Another study found that although whole genome sequencing was unable to detect the corresponding mutation, phenotypic testing demonstrated isoniazid resistance (Clark et al., 2013).

Currently, diagnostic methods are still centered on available technologies (e.g., microscopy, culture, and molecular alternatives). Even though the majority of asymptomatic TB patients should have a pulmonary location, extrapulmonary manifestations of the illness may be the only one’s present. A personal history that suggests contact with or a history of TB would support the diagnosis of forms of asymptomatic TB that are bacteriologically unconfirmed by the tests currently available. The diagnosis would be based on chest radiography results or other imaging (such as computed tomography) and histopathological examination. WHO's current TB treatment guidelines do not differentiate between individuals with symptoms and those with asymptomatic TB; further study is required to ascertain whether asymptomatic TB

can be successfully treated with regimens of varying duration or composition. To better account for the possibility of asymptomatic TB, other guidelines for TB screening as well as infection prevention and control would also need to be modified (WHO, 2024b). When diagnosing tuberculosis, integrated diagnostic methods, which include many procedures and approaches, generally yield the best results. The sensitivity, effectiveness, and precision of tuberculosis diagnosis can be increased by enhancing test quality and accessibility and utilizing cutting-edge technologies (WHO, 2024c).

2.7 Classification of Drug-resistant Tuberculosis

There are several ways drug-resistant tuberculosis can be classified, and they include the following: classification due to resistant patterns, classification due to registration group, classification based on anatomical site, and classification based on HIV status.

2.7.1 Classification due to Resist Pattern

The classification was done according to resistance patterns, including: Monoresistance- resistance to one first-line anti-TB medicine only; Poly-drug resistance (PDR) - resistance to more than one first-line anti-TB medicine (other than both Isoniazid and Rifampicin). Multi-drug resistance (MDR) is resistance to at least both Isoniazid and Rifampicin. Rifampicin resistance (RR) is resistance to rifampicin, detected using phenotypic or genotypic methods, with or without other anti-TB drugs. It includes any resistance to Rifampicin, whether mono-resistance, multidrug resistance, or Poly-drug resistance (Tiberi et al., 2022). Isoniazid resistance refers to Mycobacterium tuberculosis strains with resistance to isoniazid and susceptibility to rifampicin confirmed in vitro. Pre-XDR resistance refers to resistance to Isoniazid and Rifampicin, and resistance to any fluoroquinolone. Extensive drug resistance (XDR) refers to resistance to any Fluoroquinolone and at least one of group A drug

(levofloxacin, moxifloxacin, bedaquiline, and linezolid), in addition to multidrug resistance (MOH, 2021).

2.7.2 Classification due to Registration Group

This classification is done due to registration group including; New (N)- this refers to patients who have never received anti-tuberculosis treatment, or who have received anti-tuberculosis treatment for less than one month. Relapse (R) – this refers to patients previously treated for tuberculosis who have been declared cured or treatment completed and then diagnosed with MDRTB. Return after loss to follow up- this refers to patients who return to treatment with confirmed MDRTB after interruption of treatment for two months or more. After the failure of First-Line Treatment (FFT), this refers to patients who return after having failed the first treatment, i.e., smear-positive at the earliest, month 5. After the failure of Retreatment (FRT) are patients who return after having failed the re-treatment (MOH, 2021).

2.7.3 Classification based on anatomical site

This classification is done based on anatomical site, including Pulmonary Drug-resistant TB; this refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. This excludes pleural effusion. Miliary TB is classified as PTB because the lesions are in the lungs. Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without lung radiographic abnormalities, constitutes a case of extrapulmonary TB. Patients with pulmonary and extrapulmonary TB are classified as cases of PTB. Extrapulmonary Drug-Resistant TB refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lung

parenchyma, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, and meninges (MOH, 2021).

2.7.4 Classification based on HIV status

This classification is done based on HIV status, including HIV Positive TB patient: this refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a positive result from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrolment in HIV care, such as enrolment in the pre-ART register or in the ART register once ART has been started. HIV-negative patient; this refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing conducted at the time of TB diagnosis. HIV status unknown TB patient; this refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and no other documented evidence of enrolment in HIV care (MOH, 2021).

2.8 Drug-resistant Tuberculosis Diagnosis

Finding the high-risk individuals for acquiring DRTB or those suspected of having DRTB and obtaining pertinent samples for mycobacteriological testing are the first steps in the diagnosis process. Individuals at high risk for drug-resistant tuberculosis (DRTB) include those who have been exposed to DRTB and have TB symptoms; these include children who have TB symptoms and are in contact with DRTB source persons; failures on drug-susceptible TB treatment (smear positive at months 2 and 5); patients who develop TB while on TPT; health care workers; refugees; prisoners; and all previously treated patients with TB symptoms, failures, relapses, and return after loss to follow-ups are among the individuals at high risk for DRTB tuberculosis (WHO, 2024c).

The definitive diagnosis of drug-resistant TB requires the detection of Mycobacterium tuberculosis bacteria and the determination of resistance to anti-TB drugs using the methods outlined below:

2.8.1 Genotypic

For the genotypic methods, the Xpert MTB/RIF can be used to diagnose rifampicin resistance, and Mycobacterium tuberculosis quickly. It is recommended for all suspected tuberculosis cases as the initial test for TB diagnosis and detection of rifampicin resistance. Compared to culture, it has a sensitivity of 96% and a specificity of 98%. Its advantages include heightened sensitivity, the ability to identify patterns of rifampicin resistance, a quicker turnaround time, and a low need for infrastructure and expertise. Due to its ability to identify both live and dead bacilli, it is not advised for use in monitoring patient response to treatment. Additionally, it may cause discrepancies with phenotypic DST results. (GeneXpert covers 95% of the gene area), with limited capacity to identify tuberculosis resistant to some strains but vulnerable to others (MOH, 2021). The second approach, Line Probe Assay (LPA), uses the same basic principles as GeneXpert as they both use PCR technology. This method is utilized to identify drug sensitivity to both first-line (rifampicin and isoniazid) and second-line (fluoroquinolones and second-line injectable) drugs as well as speciation for Mycobacterium Tuberculosis Complex (MTC) (Ciesielczuk et al., 2020). The fact that LPA can quickly classify patients who have been confirmed to be resistant to rifampicin or to multidrug-resistant tuberculosis into groups for either the shorter MDRTB regimen or the traditional lengthier regimen is one of its strengths. Its limitations include the need for appropriate and sufficient laboratory equipment and infrastructure, as well as competent laboratory personnel (MOH, 2021).

2.8.2 Phenotypic

The gold standard for diagnosing tuberculosis (TB) is the culture method, which can find as low as 10-100 live bacteria/ml. Some instances are: 1. Mycobacterium Growth Indicator Tube for Liquid Culture (MGIT). 2. Lowenstein-Jensen-Solid Culture (LJ). Medication susceptibility testing and culture are necessary for every instance of tuberculosis that is identified bacteriologically. Its advantages include the ability to detect MTB with as few as ten bacilli/ml and to conduct drug susceptibility testing and drug resistance surveillance. Limitations are the slow growth of MTB, thus causing delayed turnaround time and requiring huge infrastructural capacity to set up a laboratory technique called drug susceptibility testing (DST) that assesses whether mycobacteria will proliferate when TB medications are present. Bacterial growth suggests resistance to the medications used to treat tuberculosis; the absence of growth indicates susceptibility. Indications for DST are: First-line DST, previously treated patients; persons who develop active TB after exposure to a patient with documented DRTB, and patients who remain smear-positive at months two and five of therapy. Second line DST: Patients with a DST showing resistance to at least rifampicin, isoniazid, or both rifampicin and isoniazid at baseline, patients who remain culture-positive on or after Month 3 DRTB, persons who develop active TB after exposure to a patient with documented DRTB (MOH, 2021).

2.9 Drug-resistant Tuberculosis Treatment

Drug-resistant strains of tuberculosis are more challenging to cure than drug-susceptible strains, and they pose a danger to global progress toward the objectives established by the World Health Organization's (WHO) End TB Strategy. Thus, based on the most recent research available, there is an urgent need for evidence-based policy recommendations on the treatment and management of people with DRTB. The WHO's

mission to educate medical professionals in Member States on enhancing treatment and care for patients with drug-resistant tuberculosis is fulfilled by the WHO's unified guidelines on drug-resistant tuberculosis treatment (WHO, 2022a).

WHO created and released evidence-based policy guidelines on managing DRTB patients between 2011 and 2018. Numerous WHO publications, such as the WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update, published by WHO in December 2018, contain these policy suggestions. The WHO-convened Guideline Development Groups (GDGs) formulated the policy recommendations in each guideline by summarizing the evidence and developing policy recommendations and supporting remarks using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. The GDGs are made up of afflicted individuals and diverse groups of outside specialists with expertise in various facets of the programmatic and clinical management of DRTB. The WHO's Guideline Review Committee (GRC) approved the procedures used to create the recommendations, and the GRC has been involved in creating each of these guidelines (WHO, 2022a).

Following new evidence that the repurposed drugs, Linezolid and Clofazimine, and new molecules, Bedaquiline and Delamanid, were safer and more effective than injectable medicines, the World Health Organization (WHO) recommended the use of injectable free regimens (IFR) for the treatment of drug-resistant tuberculosis in 2018. Kenya made the transition on January 1, 2020, in response to a prompt communication on the same (MOH, 2021).

According to the WHO consolidated treatment guidelines, there were new updates in 2022. The latest update included a 6-month bedaquiline, pretomanid, linezolid and

moxifloxacin (BPaLM) regimen for MDR/RR-TB, WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients. But Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB. Although it should not delay the BPaLM initiation, the test results should guide the decision on whether moxifloxacin can be retained or should be dropped from the regimen. In cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be initiated or continued. This recommendation applies to the following: a. People with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB). b. People with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular, and disseminated (miliary) TB. c. Adults and adolescents aged 14 years and older. d. All people, regardless of HIV status. e. Patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out. This recommendation does not apply to pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid. The recommended dose of linezolid is 600 mg once daily, both for the BPaLM and the BPaL Regimen (WHO, 2022b).

The 9-month all-oral regimen for MDR/RR-TB, WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. The 9-month all-oral regimen consists of bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine (for 4 months, with the possibility of extending to 6

months if the patient remains sputum smear positive at the end of 4 months), followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). Ethionamide can be replaced by 2 months of linezolid (600 mg daily) (Santiago et al., 2020). A 9-month regimen with linezolid instead of ethionamide may be used in pregnant women, unlike the regimen with ethionamide. This recommendation applies to: a. people with MDR/RR-TB and without resistance to fluoroquinolones; b. patients without extensive TB disease and without severe extrapulmonary TB c. patients with less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid and clofazimine; when exposure is greater than 1 month, these patients may still receive this regimen if resistance to the specific medicines with such exposure has been ruled out; d. all people regardless of HIV status; e. children (and patients in other age groups) who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB) (WHO, 2022b).

Despite the WHO recommendation on the treatment of DRTB, the treatment of drug-resistant tuberculosis (DR-TB) in Kenya faces a number of significant obstacles. While Mycobacterial Growth Indicator Tube (MGIT) findings can take up to three months, Line Probe Assay (LPA) results have a noticeably lengthy turnaround time (TAT), averaging three weeks. Furthermore, there is a notable two- to four-week lag between the diagnosis of DR-TB and the start of treatment. Among patients with rifampicin-resistant TB (RR-TB), the coverage of second-line drug susceptibility testing (DST) is still relatively poor. The shorter, all-oral, 9–12-month treatment regimen for multidrug-resistant TB (MDR-TB) that the WHO recommends has not been fully implemented in Kenya. Peripheral neuropathy is solely evaluated through symptomatic screening, and

there are gaps in electrocardiogram (ECG) and visual monitoring, as well as insufficient documentation and reporting of adverse drug reactions (ADRs) in patient files or the Treatment Information Basic unit (TIBU) system. Additionally, monthly follow-up cultures, LPA, and second-line DST findings are not consistently recorded in patient logbooks or DR-TB registers. Additionally, it is uncommon to repeat the test for DR-TB patient contacts three months after baseline, as advised by national standards. Most hospitals do not do routine baseline and follow-up ECG testing for patients with DR-TB. Last but not least, second-line medications' (SLDs') quality assurance requirements are still below ideal (DNLTP, 2024).

2.9.1 Principles and rationale of DRTB treatment

Effective treatment of drug-resistant tuberculosis (DRTB) is grounded in several evidence-based principles. Treatment for TB/DRTB involves the use of drug combinations; as a result of avoiding the selection of naturally occurring resistant mutants, resistance is prevented from emerging. Never utilize monotherapies, whether deliberate or not, as this increases the risk of selecting naturally occurring mutants for the one medication being used. It's crucial to remember that since anti-TB medications don't induce mutations, they choose resistant mutants (Zumla et al., 2013). The medications in the regimen should have both bactericidal and sterilizing properties. Selection for DRTB treatment regimens must ensure that the included medications possess both bactericidal and sterilizing properties. Bactericidal drugs rapidly eliminate actively replicating bacilli, while sterilizing drugs target dormant or slowly replicating populations that are more difficult to eradicate (Nuermberger, 2017). The duration of the treatment should allow for activity against all populations of bacilli (MOH, 2021).

2.9.2 Classification of Anti-TB Drugs in the Management of DRTB

Based on their effectiveness and experience, anti-TB medications used in the treatment of DRTB were categorized by the WHO in 2019 into groups. Group A: Include all three medicines (Unless they cannot be used) Levofloxacin (Lfx) or Moxifloxacin (Mfx), Bedaquiline (Bdq), Linezolid (Lzd). Group B Add both medicines (Unless they cannot be used): Clofazimine (Cfz), Cycloserine (Cs), or Terizidone (Trd). Group C Add to complete the regimen and when medicines from Group A and B cannot be used Ethambutol (E), Delamanid (Dlm), Pyrazinamide (Z), Imipenem (Imp) /Cilastatin (Cln) or Meropenem (Mpn), Amikacin (Am) or Streptomycin (s), Ethionamide (Eto) or Prothionamide (Pto), p-amino salicylic acid (PAS) (WHO, 2022b).

2.9.3 Treatment regimens by Resistant Patterns

The injectable free treatment regimen: is the recommended regimen for MDR/RR and Pre-XDR (resistant to SLIs) TB patients including adults, children, and pregnant women. The Drugs used in these regimens are administered orally. This regimen has two phases:

1. Intensive phase: 6 months

The end of the intensive phase is defined by a negative culture at the end of the 3rd month and three consecutive negative smears taken 30 days apart after month 3. This phase may be extended in consultation with the National PMDT to 7 and/or 8 months in any of the following situations: a) slow clinical response to treatment after clinical evaluation, characterized by: i. Ongoing /worsening TB (pulmonary) symptoms (cough, fever, drenching night sweats, and weight loss/poor weight gain) ii. Worsening radiological features i.e. cavities, infiltrates, opacities b) Delayed smear or culture conversion, c) Cases where baseline SL LPA results are indeterminate/FLQ susceptibility is not confirmed. The extended intense phase should not be continued

after a negative culture at month four, and negative smears at the end of months seven and eight indicate that it is finished (MOH, 2021).

2. Continuation phase: 12 months

Depending on the results of the culture and smear, the continuation phase begins in month seven or, if appropriate, at the conclusion of the extended intense phase. Depending on the DST pattern, the continuation phase lasts for 12 to 14 months. Sputum cultures that reverse (go from negative to positive) signify a failed course of treatment. A multidisciplinary team should evaluate the patient immediately in the event of reversion, and the national clinical team should be notified as soon as possible (MOH, 2021).

Table 1: Drug Resistant tuberculosis treatments

Pattern of Drug Resistance	Regimen	Duration
MDR/RR TB	Intensive phase: 6 months Bdq/Cfz/Lfx/Cs/Lzd Continuation phase: 12 months Cfz/Lfx/Cs	18 months
Paediatric MDR/RRTB (<6yrs and <25kg)	Intensive phase: 6 months Mfx/Cfz/Cs/Lzd Continuation phase; 12 months Mfx/Cfz/Cs	18 months
Pre-XDR-Injectable resistant	Intensive phase: 6 months Bdq/Cfz/Lfx/Cs/Lzd Continuation phase: 12 months Cfz/Lfx/Cs	18 months
Pre-XDR-Fluroquinolones Resistant	Intensive phase: 6 months Bdq/Dlm/Lzd/Cfz/Cs Continuation phases: 14 months Dlm/Cfz/Cs	20 months
Pre-XDR paediatrics* -Fluroquinolones Resistant	Intensive phase: 6 months Bdq**/* Dlm/Lzd/Cfz/Cs Continuation phase: 14 months- Dlm/Cfz/Cs/Z	20 months
Isoniazid mono resistance	6 months RZE/Lfx (with pyridoxine)	6 months
Bedaquiline Intolerance (In cases of Severe Adverse Events or hypersensitivity)	Intensive phase: 6 months Dlm/Lzd/Lfx/Cfz/Cs Continuation phase: 12 months Lfx/Cfz/Cs	18 months
Poly-drug resistance (PDRTB) (HE/HEZ+S)	9 months RZE/Lx (with pyridoxine)	9 months
Pyrazinamide mono-resistant (Z) or Pyrazinamide and Ethambutol (EZ) without INH resistance or Ethambutol Mono-resistance (E)	2 months RHZE, 4 months RH (with pyridoxine)	6 months
Extensively Drug - resistance (XDR)	Individualized regimen	18-24 months

2.9.4 Treatment of Drug-Resistant Tuberculosis in Special Conditions

Drug-resistant tuberculosis (DRTB) often coexists with other medical conditions, presenting significant challenges in managing both TB and the accompanying illnesses. In individuals with HIV coinfection, Bedaquiline cannot be used with efavirenz-based antiretroviral therapy (ART) regimens due to reduced Bedaquiline levels in the bloodstream. In such cases, the ART regimen should be optimized by replacing efavirenz with Dolutegravir. Clinicians must monitor for additive or overlapping toxicities between ART and anti-tuberculosis medications. Linezolid should be avoided in patients with hemoglobin levels below 8 g/dL or pancytopenia. TB treatment should take precedence, and ART should be initiated within 2–8 weeks of starting TB therapy. Additionally, monitoring for Immune Reconstitution Inflammatory Syndrome (IRIS) and managing it according to ART guidelines is essential (WHO, 2022b). Recent meta-analytic evidence supports the inclusion of Bedaquiline and Linezolid in DRTB treatment regimens for patients with HIV, showing higher treatment success rates and reduced mortality when compared to older regimens, though rigorous prospective studies remain limited (Wu et al., 2022).

In paediatric populations, fluoroquinolones are a cornerstone of DRTB treatment due to their potent bactericidal activity. Among these, Moxifloxacin has superior sterilizing activity and tolerability compared to Levofloxacin, and is therefore preferred in paediatric regimens when resistance patterns permit. Children who have been exposed to DRTB should receive empiric treatment guided by the drug-susceptibility test (DST) results of the index case, even in the absence of laboratory confirmation, in keeping with WHO recommendations emphasizing the positive association between the use of WHO Group A drugs (including bedaquiline, moxifloxacin, and linezolid) and

successful treatment outcomes in children and adolescents (Garcia-Prats et al., 2025;MOH, 2021).

Pregnancy is not a contraindication for treating active DRTB, but drug safety profiles must be carefully considered. Class D drugs, such as aminoglycosides, should be avoided. Lactation is permitted, although contact with the child should be minimized to reduce the risk of infection. Nausea and vomiting, which may worsen during treatment, should be monitored and managed accordingly. Medications such as Linezolid, Bedaquiline, Clofazimine, and Delamanid are considered safe during pregnancy and lactation. For patients with diabetes mellitus, blood glucose levels must be closely monitored to ensure glycemic control. Education on diet, treatment adherence, and lifestyle modifications is critical. Screening for complications such as renal insufficiency, neuropathy, and visual impairment is necessary, with referrals to diabetes care clinics as needed. Patients with renal disease should have electrolyte imbalances regularly monitored and corrected according to established guidelines, with referrals to specialized care when necessary (MOH, 2021).

Liver disorders require frequent liver function tests, especially when hepatotoxic drugs such as pyrazinamide, isoniazid, fluoroquinolones, or Bedaquiline are used. Patients with liver dysfunction should be referred to specialized care for comprehensive management. Psychiatric and mental health conditions should be screened using tools like the Patient Health Questionnaire-9 (PHQ-9), and Cycloserine use should be closely monitored due to its potential to exacerbate psychiatric symptoms. Effective dosing and referrals to mental health specialists are vital in such cases. For patients with drug and substance dependence, screening using tools such as the CAGE (cut-down, annoyed, guilty, and eye opener) questionnaire is necessary. In severe cases, inpatient care in specialized isolation facilities may be required. By addressing these considerations,

clinicians can tailor DRTB treatment to meet individual needs, ensuring better outcomes despite the complexities associated with comorbidities (MOH, 2021).

2.10 Tuberculosis prevention and control strategies

A key element of the End TB plan is infection prevention and control, which mainly aims to lower the risk of TB transmission. Therefore, TB infection prevention and control (TB IPC) in healthcare settings is a significant advancement in the fight against TB transmission. By safeguarding patients, clients, healthcare workers, and the community against tuberculosis, good TB IPC practices, which include administrative, environmental, and respiratory controls, can make healthcare safer. IPC also has a bigger role in preventing the spread of TB, drug-resistant TB (DRTB), and other infectious respiratory diseases like COVID-19 and Influenza (MOH, 2021).

Prevention strategies encompass a range of interventions. In Kenya, all children are immunized with BCG at birth. Additional approaches involve screening and promptly treating infected individuals, providing Tuberculosis Preventive Therapy (TPT) to HIV-infected individuals, close contact with TB cases and those at high risk, offering laboratory and diagnostic services, gathering and analyzing data, and delivering training and education. It is essential to ensure TB patients receive appropriate treatment until they are fully cured.

Administrative controls play a pivotal role in limiting the production of droplet nuclei and, consequently, the risk of *M. tuberculosis* exposure for patients and healthcare personnel at the main control level. These administrative actions include the timely identification of patients with tuberculosis who may be contagious, their immediate separation or isolation, and the rapid start of an appropriate anti-tuberculosis treatment. Additional crucial actions include assessing the facility's transmission risk, creating a

written infection control strategy specific to its requirements, and giving healthcare staff thorough training so they can carry out the plan with efficiency (MOH, 2021).

The employment of respiratory protection equipment, environmental controls, and administrative procedures comprises the three tiers of the hierarchy of control measures used in the tuberculosis infection control program. The complete avoidance of exposure is typically not possible. Hence, environmental control approaches are used in high-risk locations to lower the concentration of droplet nuclei in the air, in accordance with the Centers for Disease Control and Prevention (CDC) Tuberculosis Control guidelines. Increasing natural ventilation and aeration is one of these strategies (CDC, 2023).

Using personal respiratory protection devices (PRPDs) to protect healthcare workers from infectious tuberculosis particles while covering their mouths and noses is the third recommended control method. It is noteworthy that typical surgical masks (made of cotton or paper) are frequently used by healthcare personnel, and they do not filter out infectious droplet nuclei. However, if patients wear them to stop the production of TB droplet nuclei when they cough or speak, they might be useful (DNLTP, 2018).

To further control Tuberculosis criteria for isolation of patients, a patient-centered approach should be emphasized throughout the entire course of tuberculosis (TB) treatment. This strategy can be reinforced by community involvement, where treatment supporters play a crucial role in assisting patients with drug adherence and providing holistic care, including psychological, spiritual, and social support. In some situations, isolation for TB may be necessary; however, voluntary isolation is always preferable. Patients should receive proper counselling, adequate information, and sufficient support, with community-based care being the first approach whenever possible. Isolation may be considered in specific cases, such as when a known TB patient refuses effective treatment despite extensive efforts including counselling, health education,

and community support, to ensure adherence. Additionally, isolation may be necessary for TB patients who have agreed to ambulatory treatment but cannot implement proper infection control measures at home, particularly if they are infectious. Furthermore, patients with comorbidities or severe health conditions that require inpatient care, including those with multidrug-resistant TB (MDRTB), pre-extensively drug-resistant TB (pre-XDRTB), extensively drug-resistant TB (XDRTB), or those with a history of drug use, may also require isolation (DNLTP, 2018).

Raising community awareness, identifying presumed TB early, and referring patients for follow-up in a medical context can all help to reduce the spread of TB in the community. Cough cleanliness and etiquette should be taught to identified TB sufferers. Raise community knowledge of the value of following TB treatment guidelines. When it comes to TB infection, prevention, and control, certain high-risk community situations require extra care. Because of the extended potential exposure period, crowded conditions, inadequate ventilation, and restricted access to medical care, tuberculosis spreads more easily in communal settings. It should therefore get extra attention in the prevention and management of tuberculosis (MOH, 2021).

2.11 Factors associated with drug-resistant tuberculosis

Several factors were associated with drug-resistant tuberculosis, including sociodemographic, clinical, behavioral, and socioeconomic factors.

2.11.1 Sociodemographic Factors

Several social demographic factors are associated with drug-resistant tuberculosis, such as age, gender, marital status, and education level. In a study done in Henan Province in China, being of male gender was a risk factor for the development of drug-resistant tuberculosis; sixty-five per cent of study participants were males, and the study

concluded that males tend to have a higher tendency to not adhere to anti-tuberculosis drugs in comparison to females, and their poor health-seeking behaviour, as they delay treatment (Zhang et al., 2016). In a study conducted in Brazil, drug-resistant Tuberculosis cases were also higher in males than females, and those who were in their active age were mostly affected by drug-resistant tuberculosis (Soares et al., 2020). A study in Uganda on gender differences among DRTB patients found that the majority of study participants were male, accounting for sixty-two per cent of study participants, and it predicted that men had a higher mortality of DRTB as well as mortality of DRTB/HIV co-infection (Baluku et al., 2021). A South African study found that being a woman predicted a risk factor for DRTB, especially extensively drug resistant tuberculosis, independent of HIV infection (O'Donnell et al., 2011). In a study conducted in the Oromia region in Ethiopia for risk factors associated with drug-resistant tuberculosis, women of reproductive age represented most of the cases with drug-resistant tuberculosis, which is a public health implication for pregnancy and children (Mulisa et al., 2015).

In a study conducted in Addis Ababa, being single was determined as a risk factor for drug-resistant tuberculosis, as the majority of DRTB cases were single, as the exposure is greater for them than for married people (Assefa et al., 2017). Education level was associated as a risk factor for DRTB, as limited education may result in poor health literacy and understanding of treatment regimens, leading to non-adherence and treatment failure. Urban areas are also associated with higher rates of DRTB due to increased population density, limited healthcare resources, and a higher risk of transmission (Seddon et al., 2012). A study done in Pakistan also found that illiteracy may cause TB patients to have low knowledge of TB and delayed health-seeking

behaviour when the disease occurs. It may also lead to misuse of the medications and make patients not adhere to the TB treatment (Ahmad et al., 2012).

2.11.2 Clinical Factors

We have potential clinical risk factors predisposing one to contract drug-resistant tuberculosis infection. The immune system plays a pivotal role in preventing and fighting tuberculosis. Patients with conditions such as HIV/AIDS or other immunocompromising conditions are more susceptible to drug-resistant forms of tuberculosis. The compromised immune system diminishes the ability to control the infection, increasing the risk of treatment failure and drug resistance (Mulisa et al., 2015). Studies on DRTB in Uganda have shown that the majority of DRTB patients are co-infected with HIV, with fifty-two to sixty-two per cent of them being DRTB/HIV co-infected (Baluku et al., 2020; Okethwangu et al., 2019). Hence, it is a potential risk factor for acquiring drug resistant tuberculosis.

Previous treatment history is one main clinical factor associated with DRTB, as individuals with a history of incomplete or inadequate TB treatment are at an increased risk of developing drug resistance (World Health Organization, 2019). A study conducted in Southern Ethiopia showed that patients with a history of treatment failures had an increased risk of developing drug-resistant tuberculosis; faulty treatment regimens or non-adherence to tuberculosis treatment of first-line anti-tuberculosis drugs leads to treatment failures and might contribute to increased risk of developing drug-resistant tuberculosis. Individuals with a history of tuberculosis relapsing during anti-tuberculosis treatment were more likely to acquire drug-resistant tuberculosis (Biru & Woldesemayat, 2020).

Adherence to treatment, especially poor adherence to the prescribed treatment regimen, is a major contributor to the development of drug resistance. Factors such as pill burden and side effects may affect adherence. Drug-resistant tuberculosis requires a longer time to treat compared to drug-susceptible tuberculosis, and most of the problems of drug resistance originate from the length of treatment. The longer time that is required to treat drug-resistant tuberculosis implies an additional risk of poor treatment adherence and, in turn, leading to treatment failure (Seung et al., 2015).

In another setting, like Sudan, close contact with known DRTB cases was among the determinant factors of one acquiring DRTB. As contact with DRTB cases increases, like in cohabiting in the same household, the risk of transmission of DRTB increases (Elduma et al., 2019). A study done in the Amhara region in Ethiopia also showed that close contact with DRTB patients increased the risk of being infected with drug-resistant mycobacterium tuberculosis, which in turn may lead to the development of DRTB, as the study alluded that tuberculosis is spread through the air from one person to another. The tuberculosis germs are passed through the air when someone is sick with TB disease of the lungs or throat, coughs, speaks, laughs, sings, or sneezes. And anyone near the sick person with DRTB can breathe the germs into their lungs, in turn becoming infected (Mulu et al., 2015).

2.11.3 Behavioral Factors

Behavioral factors contribute significantly to acquiring drug resistant tuberculosis, a person's behaviour has a significant role in their ability to contract TB. Among the factors are, but are not restricted to, health-seeking practices, smoking, drinking alcohol, and using khat.

Certain behaviours, such as smoking, cause additional risk, as smoking damages the lungs and impacts the body's immune system, making them more susceptible to tuberculosis. It also increases the risk of recurrent tuberculosis in people who have already contracted tuberculosis, as it impairs the response to treatment, in turn leading to the development of drug-resistant tuberculosis (Meriki et al., 2013). An unhealthy lifestyle, such as excessive alcohol consumption, has also been vehemently put into the spotlight regarding healthcare-seeking behaviour and leads to non-adherence to anti-tuberculosis drugs, which in turn leads to drug-resistant tuberculosis (Elmi et al., 2015). Findings from a meta-analysis study done in Africa showed stigma and discrimination as factors associated with drug resistant tuberculosis (Cannon et al., 2021). A study done in Pakistan showed that stigmatization of individuals with TB persists and can lead to social isolation, hindering their ability to complete treatment. This social marginalization contributes to the spread of drug-resistant strains (Khan et al., 2022).

A study done in Eastern Cape Province in South Africa found that the majority of DRTB clients show poor knowledge and low awareness levels about DRTB, low literacy levels, and inadequate information among DRTB patients about DRTB infection, in turn showing it to be a potential risk factor for acquiring DRTB (Fana et al., 2019). In other studies, done in Japan (Baral et al., 2014) and Southern Ethiopia (Fikre et al., 2019), not getting counselled was associated with developing drug-resistant tuberculosis, as these indicate that if one is a patient of TB and not counselled adequately on TB and its treatment modalities, it could lead to one acquiring drug-resistant tuberculosis.

2.11.4 Socioeconomic Factors

The development of drug-resistant tuberculosis can be linked to an individual's socioeconomic status (SES). This is because those with lower socioeconomic status may have difficulty accessing healthcare services, which can delay diagnosis and treatment initiation and contribute to the development of drug resistance (Orenstein et al., 2009). Socioeconomically deprived individuals are also at a higher risk of coming into contact with TB-positive individuals; they also have a higher chance of working and living in crowded, poorly ventilated areas, being malnourished, engaging in unhealthy behaviours (such as smoking and alcohol abuse), and having difficulty in utilizing medical services and implies that people suffering were more likely to have low social-economic conditions and status (Duarte et al., 2018). Therefore, access to treatment is limited due to the distance to the medical institution, transportation expenditures, and hospitalization charges, which contribute to the disease burden that impacts disease management and results. Therefore, it is sometimes referred to as the sickness of the poor, as additional risk variables that impact this disease burden include socioeconomic position, job loss, living in congested areas, inadequate cleanliness, immunocompromising disorders, and poor dietary intake leading to undernourishment (Horter et al., 2014; Zhang et al., 2016).

A study conducted in Southern Ethiopia found that poverty was a predictor of drug-resistant tuberculosis (DRTB), partly because it often forces individuals to live in overcrowded one-room houses, which is an additional factor that contributes to the development of DRTB. The concentration of mycobacteria in the air is determined by the space available in the room and adequate ventilation in the house. One-room houses, especially in rural settings, are primarily huts without windows, where livestock and people live together in the same space. This arrangement leads to overcrowded living

conditions and inadequate ventilation, increasing the transmission of *Mycobacterium tuberculosis* and contributing to DRTB (Biru & Woldesemayat, 2020). A meta-analysis study done in Africa on socioeconomic drivers of drug resistant tuberculosis found poverty and financial constraints due to job loss among the risk factors associated with acquiring drug resistant tuberculosis (Cannon et al., 2021).

2.12 Conceptual Framework

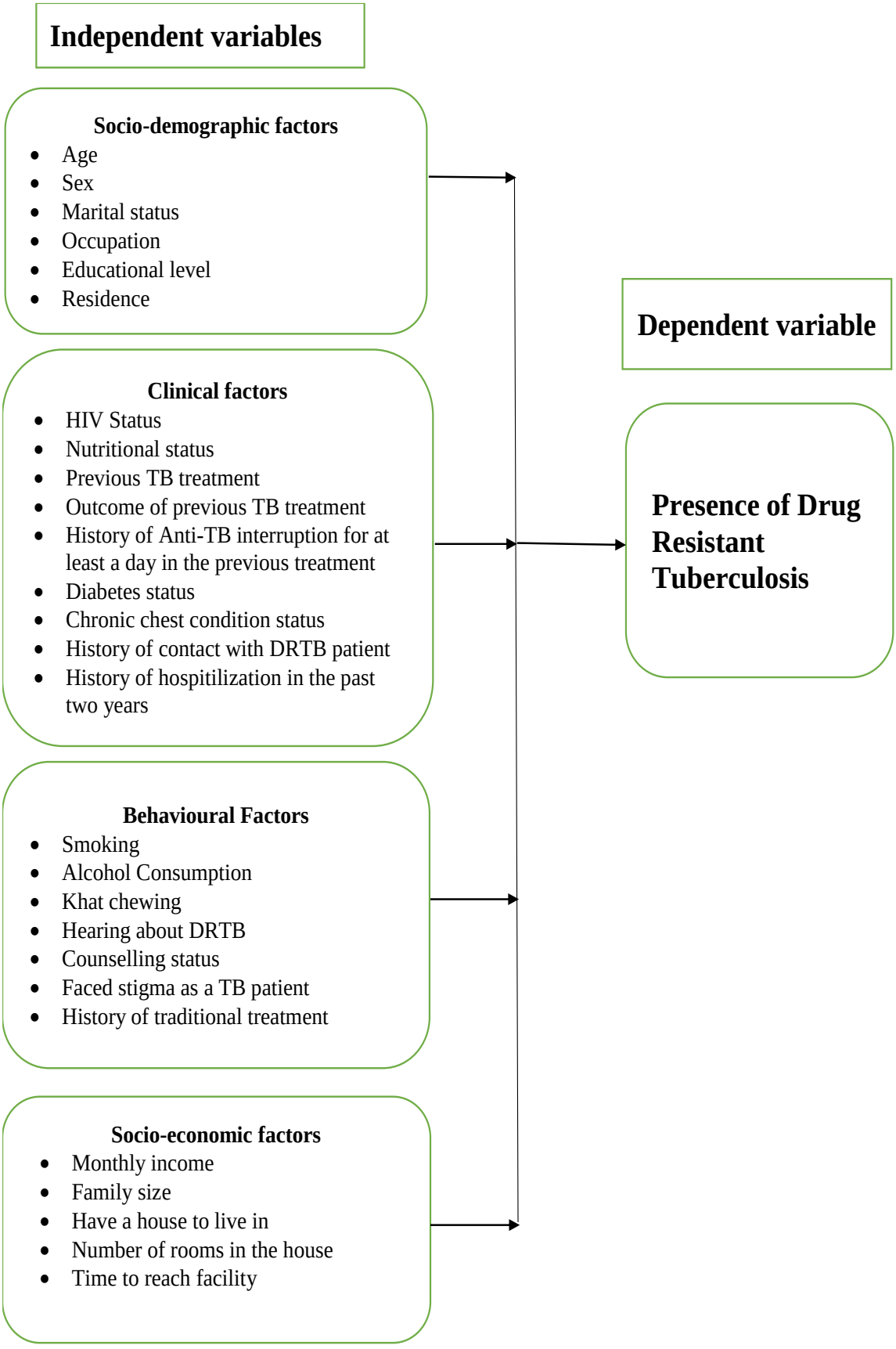

Figure 1: Conceptual framework

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 Study site

The study was conducted in Meru County. Meru County is one of the 47 counties in Kenya. It borders Isiolo County to the north, Tharaka Nithi County to the east, Nyeri County to the southwest, and Laikipia County to the west. As of the 2019 census, Meru County has a population of 1,545,714 people, comprising 777,975 females, 767,698 males, and 41 individuals who identify as intersex. It has a total area of 7,006 km², of which 972.3 km² is gazetted as forest, and comprises a total of 9 sub-counties: Imenti North, Imenti South, Imenti Central, Buuri, Tigania West, Tigania East, Igembe Central, Igembe South, and Igembe North. There are thirty-five divisions, one hundred and sixty-one locations, and three hundred and eighty-six sub-locations (KNBS, 2019). The county headquarters are in Meru town, which is the largest town and main economic hub of Meru County. Below is the map of Meru County (figure 2).

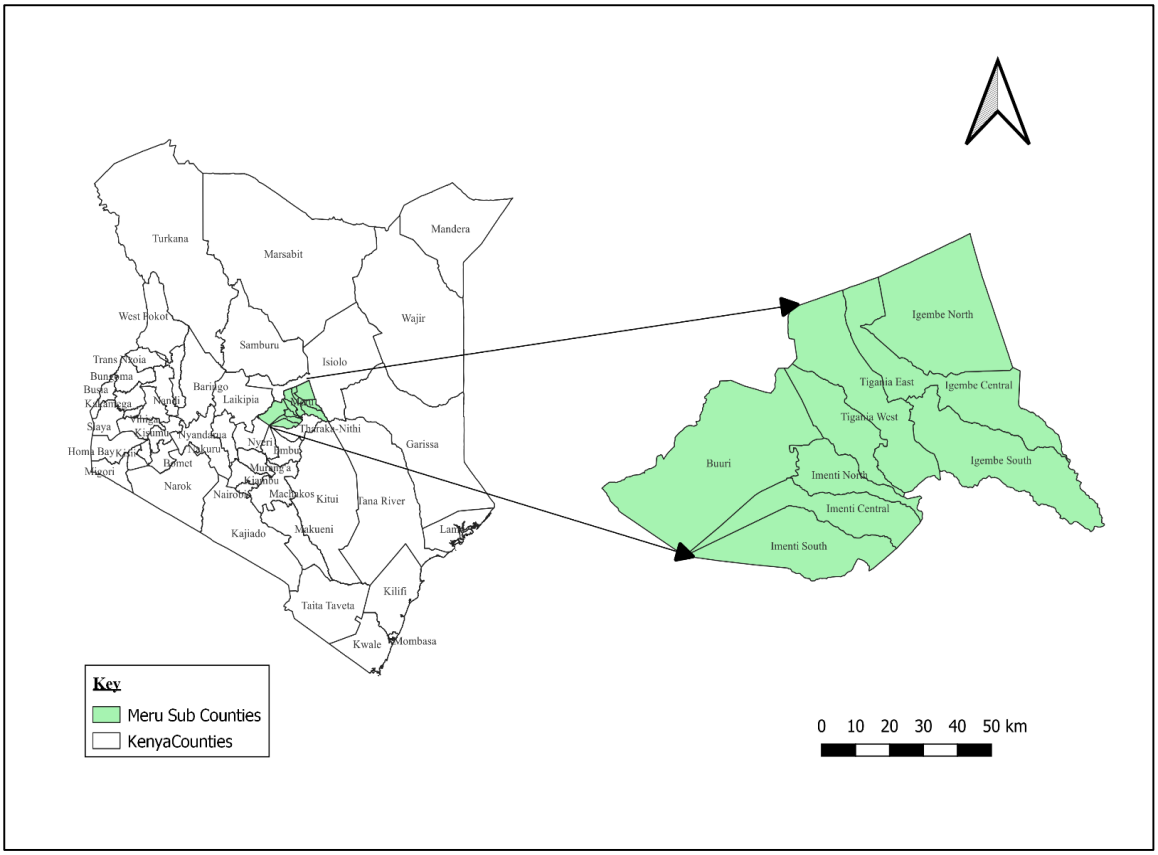

Figure 2: A Map of Meru County

3.2 Study Population

The study targeted DRTB patients from 2023 and 2024 and selected drug-susceptible TB patients at the same sites as the DRTB patients, who were residents of Meru County. The study population consisted of both males and females aged 18 years or older.

3.2.1 Inclusion Criteria

Patients who consented to participate in the study and are residents of Meru County.

Cases are patients who are drug-resistant tuberculosis patients (resistance to at least one or more first-line anti-TB drugs).

Controls are drug-susceptible tuberculosis patients who are bacteriologically confirmed TB patients, have undergone a full course of TB treatment, and turned sputum smear-negative after the second, fifth, and sixth months of treatment, indicating a successful response to the treatment and classification as "cured."

3.2.2 Exclusion Criteria

TB Patients were excluded from the study if they did not reside within the study area at the time of data collection. In addition, patients who were of unsound mind or were critically ill and unconscious were excluded due to their inability to participate adequately in the study. The study further excluded patients who were not bacteriologically confirmed at diagnosis, including those diagnosed with extrapulmonary tuberculosis. Patients with bacteriologically confirmed tuberculosis at initial diagnosis but without laboratory-confirmed sputum conversion at the second, fifth, or sixth months of treatment were also excluded. Finally, patients who declined or were unable to provide informed consent were not included in the study.

3.3 Study Design

The study was a facility-based, unmatched case-control study. This study design was used because it made it possible to compare cases and controls and evaluate any association between several factors and DRTB. It has efficiency in examining rare outcomes and suitability for retrospective assessment of exposures. The design was also appropriate because the study could be completed with limited resources and in a comparatively short time. Data collection was done from August 2024 through November 2024.

3.4 Sample Size Determination

The sample size was determined using the Kelsey formula (Charan & Biswas, 2013;Sullivan & Soe, 2007). A total of 249 study participants (83 cases and 166 controls) were included in the study. A ratio of 1:2 (cases: controls) was employed to detect the least extreme Odds Ratio (OR) of 2.20, at a significance level of 95% and power of 80%, where history of contact with TB represents the exposure, the hypothesized proportion of cases with exposure was 43.08%, and the hypothesized proportion of controls with exposure was 25.6% (Workicho et al., 2017).

Kelsey's formula is shown below:

$$n_1 = \frac{(Z_{\alpha/2} + Z_{1-\beta})^2 \bar{p}\bar{q}(r+1)}{r(p_1 - p_2)^2}$$

$$\bar{p} = \frac{p_1 + rp_2}{r+1} \quad \text{and} \quad \bar{q} = 1 - \bar{p}$$

Variable notations

α-The probability of type I error (significance level), the probability of rejecting the true null hypothesis

β-The probability of type II error (1-the power of the test) is the probability of rejecting the true null hypothesis

p_1 = proportion of cases with exposure

p_2 = proportions of controls with exposure

n_1 = number of cases

n_2 = number of controls =rn_1

r= ratio of controls to cases

Assumptions

Kelsey required sample size for cases using Kelsey's formula

Two-sided confidence level (1-apha) = 95%

Power (%chance of detecting) =80 %

Ratio of controls to cases = 2

Hypothetical proportion of controls with exposure = 25.6%

Hypothetical proportions of cases with exposure = 43.08%

Least extreme Odds Ratio to be detected = 2.20

Based on Kelsey's formulae estimated sample size was

Number of cases =83

Number of controls = 166

Total sample size = 249

3.5 Sampling Technique

A record review of TB treatment registers of all the DRTB cases in Meru County was conducted. A list of all drug-resistant TB cases was abstracted from the TB treatment registers (Treatment Information Basic Unit- TIBU system). Six of the eight TB treatment zones were considered for the study due to the high proportion of DRTB cases in 2022 (Igembe North, Igembe South, Imenti North, Tigania West, Imenti South, and Tigania East). Probability proportional to size sampling was used for a sample size of 249. DRTB cases were selected in the treatment zone according to the table below:

Table 2: Distribution of cases and controls per TB treatment zones in Meru County

Treatment zone	**Reported cases from January to December 2022**	**The target number of cases per Treatment zone**	**The target number of controls per case in the Treatment zones**
Igembe South	15	12	24
Igembe North	25	19	38
Imenti North	12	9	18
Imenti South	23	18	36
Tigania West	13	10	20
Tigania East	20	15	30
Total	108	83	166

The number of respondents targeted per zone was calculated based on the formula below:

Sample size per Treatment zone=

$$\frac{\textit{Treatment zone DRTB cases for 2022 X Total cases sample size}}{\textit{Total DRTB cases reported in 2022 for all six Treatment zones}}$$

E.g., For Igembe South Treatment zone

Treatment zone DRTB cases for 2022=15

Total cases sample Size =83

Total DRTB cases reported in 2022 for all six treatment zones =108

Therefore, Sample Size = $\frac{15^* 83}{108} = 12$

Therefore, the total number of cases and controls needed for Igembe South is 12 and 24, respectively.

Therefore, the total number of cases and controls needed for this study was 83 and 166, respectively, making a sample size of 249.

The study was a hospital-based case-control study, as both DRTB and DSTB treatments are integrated into the same treatment facilities. The targeted population in the study comprised DRTB patients diagnosed in 2023 and 2024, and selected ordinary drug-susceptible TB patients at the same sites as DRTB patients. All the living and accessible DRTB patients as of August 2024 in the treatment registers (TIBU) from each treatment zone were tracked to their respective facilities. Thirty-eight facilities (appendix 6) with DRTB cases across the six TB treatment zones in Meru County were visited for data collection due to the presence of a surviving DRTB patient. These facilities included the county referral hospital, sub-county referral hospitals, health centers, and dispensaries, all of which provide TB treatment services and manage patients with DRTB.

3.5.1 Selection of cases and controls at the facility level

Cases were drug-resistant TB patients and were selected from consenting participants attending TB clinics in the thirty-eight facilities (appendix 6) selected across the six Meru County TB treatment zones. To achieve the sample size of 83 cases, all cases were recruited consecutively as they visited the facilities. Upon the cases' consent, a structured questionnaire (appendix 5) was administered to the respondents to collect information on determinants of DRTB; however, additional clinical information (for cases) was collected from the registers (DRTB register).

Controls were bacteriologically confirmed TB patients who turned sputum smear-negative after the 2^{nd}, 5^{th}, and 6^{th} months of the treatment course (cured) and were selected from consenting participants attending TB clinics in the thirty-eight facilities (appendix 6) selected across the six Meru County TB treatment zones. During their visit at month 5, sputum test before the 6-month mark. Patients were informed by the facility's TB chest clinician that they would be contacted for a follow-up interview. Interviews were scheduled during the last sputum test visit and conducted immediately after the patients had undergone their 6-month sputum tests. This way, patients were directly approached while still at the clinic. For each case selected, two controls were selected from the same facility. A line list for all DSTB patients (cured) was generated; each control in the line list was assigned a number, and then a random number was generated using Microsoft Excel 2019. Upon the control's consent, a structured questionnaire (appendix 5) was administered to the respondents; however, additional clinical information (for controls) was collected from the registers (DSTB register). All cases and controls fulfilling the inclusion criteria were included in the study until the sample size was achieved.

3.6 Pilot Testing

The developed questionnaire was pilot-tested at the Nkubu dispensary, which was not included in the study. The facility was selected because it also had a DRTB case in Meru County, according to the 2022 report. The purpose was to validate the data collection tools for quality assurance.

3.7 Data Collection

The data for the study was obtained by conducting interviews with the study participants (cases and controls) using a structured questionnaire (appendix 5). Sub-county TB coordinators were notified of the patient interviews and requested to provide a schedule of the monthly clinic days for the facilities they supervise. They were also requested to trace DRTB cases before the interview. Trained and competent research assistants speaking proficiently in English or Kiswahili and the local dialect, “Meru” language, were trained to administer the questionnaire at the beginning of data collection to ensure consistency. Clinical data were collected from the drug-resistant tuberculosis registers (cases) and drug-susceptible tuberculosis registers (controls). Data was entered in the Microsoft Excel 2019 spreadsheet after verification. To maintain and uphold confidentiality, personal identifiers were removed, and new unique identifiers were assigned to the dataset for analysis. Variables collected are social demographics, including age, sex, marital status, occupation, education status, and residence. Clinical information, including Nutritional status (Body Mass Index (BMI), HIV status, previous TB treatment, outcome of previous TB treatment, history of anti-TB Interruption for at least a day in the previous treatment, history of contact with DRTB, diabetes status, chronic chest condition status, and previous history of hospitalization for the past two years. Behavioural factors include smoking, alcohol consumption, Khat chewing, hearing about DRTB, counselling status, facing stigma as

a TB patient, and history of traditional treatment. Socioeconomic factors include monthly income, family size, living in a household, number of rooms in the household, and time to reach the facility.

3.8 Data Management and Analysis

Firstly, data cleaning was done, which involved deletion of all formatting, removal of duplicates, change of text cases, identifying and correcting of errors, spell check, the conversation of numbers stored as texts into numbers, selecting and filling of the blank cells and getting rid of extra spaces among others was executed then data coding was done, the coding of variables was aimed at changing qualitative data into a quantitative format. The lead researcher did it after data cleaning to facilitate ease in computer processing with statistical software during data analysis. Coded data was entered into Microsoft Excel 2019.

Data analysis was done using STATA version 15. Results was presented in tables. Measures of central tendency, like mean and median. Measures of dispersion (standard deviation) were calculated for continuous variables, frequencies, and proportions for categorical variables. Bivariate analysis and multivariate analysis for factors associated with DRTB (odds ratio, 95% confidence interval, and p-value <0.05) was used to see the strength of the association. In order to evaluate the independent determinants of DRTB among study participants, the factors that exhibited a significant correlation in bivariate analysis (variables with a p-value ≤ 0.2) were incorporated into a backwards stepwise logistic regression process for multivariable logistic analyses.

3.9 Ethical Considerations

Approval was obtained from MOI University Ethical Review Board (IREC) FAN:0004808 (appendix 1), a permit from the National Commission for Science,

Technology, and Innovation (NACOSTI) NACOSTI/P/24/37775 (appendix 2), and administrative approval from the Meru County Health Department (appendix 3) before approaching the participant. Consent was sought from study participants before interviewing them by signing the consent form (appendix 4). Strict confidentiality was maintained, and all personal identifiers were removed from the data during analysis. There are no known risks or benefits for the study participants in the study. However, the overall impact on the community may be significant because the risks associated with drug-resistant tuberculosis, among other tested objectives, may be crucial in addressing the public health problems associated with drug-resistant tuberculosis.

CHAPTER FOUR

4.0 RESULTS

4.1 Sociodemographic characteristics of cases and controls

The study analyzed data from 83 cases and 166 controls. Among study participants, 57 (68.7%) of the cases and 118 (71.1%) controls were male. The mean age of the cases was 39.9 years (SD±12.2 years), while the control was 37.7 years (SD±13.9 years). The age group with the most cases was the age group 25-44 years, with 43 (51.8%) cases and 93 (56%) of the controls, followed by those in the age group 45-64, accounting for 28 (33.7%) of the cases and 36 (21.7%) of the controls, with those above 65 years comprising of 3 (3.6%) of cases and 7 (4.6%) of controls. Males were 57 (68.7%) of the cases and 118 (71.1%) of the controls. Those married in the study were 33 (39%) cases and 74 (44.6%) controls, and widowed comprised of 4 (4.8%) of cases and 10 (6%) of controls. Those in informal employment accounted for the majority of the cases, 59 (71.1%), and controls 104 (62.7%). In terms of education, those who finished primary school education had the majority, 39 (47%) of the cases and 66 (39.8%) of the control, as shown in the table below (Table 3)

Table 3: Socio-demographic characteristics of cases and controls

Variable	Cases n=83 (%)	Controls n=166 (%)
Age		
Mean age	39.9 (SD±12.2 years)	37.7 (SD±13.9 years)
≤ 24 years	9 (10.8)	30 (18.1)
25–44 years	43 (51.8)	93 (56)
45–64 years	28 (33.7)	36 (21.7)
≥ 65 years	3 (3.6)	7 (4.2)
Gender		
Male	57 (68.7)	118 (71.1)
Female	26 (31.3)	48 (28.9)
Marital status		
Married	33 (39.8)	74 (44.6)
Single	27 (32.5)	57 (34.3)
Divorced	19 (22.9)	25 (15.1)
Widowed	4 (4.8)	10 (6)
Occupation		
Formal employment	3 (3.6)	13 (7.8)
Informal employment	59 (71.1)	104 (62.7)
Student	3 (3.6)	6 (3.6)
Unemployed	18 (21.7)	43 (25.9)
Educational status		
No formal education	29 (34.9)	24 (14.5)
Primary	39 (47)	66 (39.8)
Secondary	10 (12)	51 (30.7)
Tertiary	5 (6)	25 (15.1)
Sub County		
Imenti south	18 (22)	36 (22)
Imenti north	9 (11)	18 (11)
Igembe south	12 (14)	24 (14)
Igembe north	19 (23)	38 (23)
Tigania west	10 (12)	20 (12)
Tigania east	15 (18)	30 (18)

4.2 Clinical Characteristics of Cases and Controls

For the clinical characteristics of cases and controls, the majority of cases, 68 (81.9%), and controls, 141 (84.9%), were negative for Human Immunodeficiency Virus infection. Contact with known DRTB was reported by 17 (20.5%) of cases and 12 (7.2%) of controls. Based on the Body Mass Index (BMI), 32 (38.6%) of cases and 57 (34.3%) of controls were underweight (<18.5 kg/m^2), while 49 (59%) of cases and 106 (63.9%) of controls had a normal BMI (18.5–24.9 kg/m^2). 2 (2.4%) of cases and 2

(1.2%) of controls were overweight (25.0–29.9 kg/m^2), and only 1 (0.6%) of controls was obese (≥30.0 kg/m^2). Previous TB treatment was reported among 20 (24.1%) of cases and 39 (23.5%) of controls. Among these, 11 (55%) of cases and 32 (82%) of controls were cured and completed treatment. 4 (20%) of cases and 7 (18%) of controls defaulted, and 5 (25%) of cases had treatment failure, with none of the controls having treatment failure. Regarding the history of anti-TB interruption for at least a day in the previous treatment, 11 (55%) of cases had such a history, with 9 (45%) adhering to anti-TB medication. For controls, 13 (33.3%) had a history of anti-TB interruption for at least a day in the previous treatment, with the majority, 26 (66.7%), adhering to anti-TB medications. Comorbidities in the study included diabetes; 2 (2.4%) among cases and 4 (2.4%) among controls, and a chronic chest condition before TB diagnosis; 4 (4.8%) of cases and 8 (4.8%) of controls. Only 8 (9.6%) of cases and 17 (10.2%) of controls had a history of hospitalization in the past two years. In terms of resistance patterns among drug-resistant tuberculosis patients, 63 (75.9%) were mono-resistant, with 15 (18.1%) rifampicin-resistant and 5 (6%) multidrug-resistant, as shown in the table below (Table 4).

Table 4: Clinical factors of cases and controls

Variable	Cases n=83 (%)	Controls n=166 (%)
HIV status		
Positive	15 (18.1)	25 (15.1)
Negative	68 (81.9)	141 (84.9)
Contact with DRTB		
Yes	17 (20.5)	12 (7.2)
No	66 (79.5)	154 (92.8)
Nutrition status (BMI(Kg/m^2)		
Underweight (<18.5Kg/m^2)	32 (38.6)	57 (34.3)
Normal (18.5–24.9Kg/m^2)	49 (59.0)	106 (63.9)
Overweight (25.0–29.9Kg/m^2)	2 (2.4)	2 (1.2)
Obese (≥30.0Kg/m^2)	0 (0)	1 (0.6)
Previous TB treatment		
Yes	20 (24.1)	39 (23.5)
No	63 (75.9)	127 (76.5)
Outcome of previous TB treatment		
Cured/completed	11 (55)	32 (82)
Defaulted	4 (20)	7 (18)
Failure	5 (25)	0 (0)
History of Anti-TB Interruption for at least a day in the previous treatment		
Yes	11 (55)	13 (33.3)
No	9 (45)	26 (66.7)
Have diabetes		
Yes	2 (2.4)	4 (2.4)
No	81 (97.6)	162 (97.6)
Had chronic chest condition		
Yes	4 (4.8)	8 (4.8)
No	79 (95.2)	158 (95.2)
History of hospitalization in the past two years		
Yes	8 (9.6)	17 (10.2)
No	75 (90.4)	149 (89.8)
Resistance pattern (n=83)		
Mono-resistant TB	63 (75.9)	
Rifampicin resistant TB	15 (18.1)	
Multi-drug resistant TB	5 (6)	

4.3 Behavioral factors of cases and controls

Regarding behavioral factors, most cases, 56 (67.5%), and more than half of the controls, 95 (57.2%), were Khat chewers. More than half of the cases were smokers, 44 (53%), compared with 69 (41.6%) of the controls. Most cases, 68 (81.9%), and controls, 92 (55.4%), consumed alcohol. Regarding hearing about DRTB, the majority of cases, 57 (68.7%), had not heard about DRTB, compared with 50 (30.1%) of the controls. Most cases, 80 (96.4%), and 162 (97.6%) of controls had a counseling session during treatment. Most cases, 49 (59%), and 91 (54.8%) of controls faced social stigma during TB treatment. The majority of cases, 76 (91.6%), and controls, 151 (91%), did not seek traditional or herbal treatment during their TB treatment, as shown in the table below (Table 5).

Table 5: Behavioral factors of cases and controls

Variable	Cases n=83 (%)	Controls n=166 (%)
Khat chewing		
Yes	56 (67.5)	95 (57.2)
No	27 (32.5)	71 (42.8)
Smoking		
Yes	44 (53)	69 (41.6)
No	39 (47)	97 (58.4)
Alcohol Consumption		
Yes	68 (81.9)	92 (55.4)
No	15 (18.1)	74 (44.6)
Heard of DRTB		
Yes	26 (31.3)	116 (69.9)
No	57 (68.7)	50 (30.1)
Ever counselled by a Healthcare worker on TB		
Yes	80 (96.4)	162 (97.6)
No	3 (3.6)	4 (2.4)
Faced stigma as a TB patient		
Yes	49 (59)	91 (54.8)
No	34 (41)	75 (45.2)
History of traditional treatment for TB		
Yes	7 (8.4)	15 (9)
No	76 (91.6)	151(91)

4.4 Socioeconomic Factors of Cases and Controls

Regarding socioeconomic factors for the cases and controls, the majority of cases, 64 (77.1%), and controls, 110 (66.3%), earned less than Ksh 10,000 per month, and 51 (61.4%) cases and 114 (68.7%) controls lived with their families. All study participants had a house to live in, and those with fewer than five family members comprised the larger proportion, with 50 (60.2%) of the cases and 101 (60.8%) of the controls. In the majority of cases, 78 (94%) and controls 156 (94%), reaching the facility to seek TB treatment took less than two hours, as shown in the table below (Table 6).

Table 6: Socio-economic factors of cases and Controls

Variable	Cases n=83 (%)	Controls n=166 (%)
Monthly income		
Less than Ksh. 10,000	64 (77.1)	110 (66.3)
Kshs. 10,000 to 20,000	18 (21.7)	43 (25.9)
More than Ksh. 20,000	1 (1.2)	13 (7.8)
Living status		
Individually	32 (38.6)	52 (31.3)
With family	51 (61.4)	114 (68.7)
Do you have a house to live in		
Yes	83 (100)	166 (100)
No	0 (0)	0 (0)
How Many rooms does your house have		
One	34 (41)	57 (34)
Two	24 (29)	57 (34)
Three	15 (18)	41 (25)
Four	6 (7.2)	9 (5.4)
Five and above	4 (4.8)	2 (1.2)
Family size		
Less 5 members	50 (60.2)	101 (60.8)
Five or more members	33 (39.8)	65 (39.2)
Time to reach facility		
≤ 2 hours	78 (94)	156 (94)
>2 hours	5 (6)	10 (6)

4.5 Bivariate Analysis of Socio-demographic Factors

The variables were analyzed at the bivariate level to determine the socio-demographic variables with a p-value ≤0.2, which were then subjected to multivariate analysis, where

stepwise backward elimination was applied, and logistic regression was used to determine factors associated with drug-resistant tuberculosis in the study setting. Age category (≤24, 25–44, 45–64, and ≥65 years), sex, marital status (married, single, and widowed), occupation (formal employment, student, and unemployed), and educational status (secondary and tertiary) were not associated with the risk of drug-resistant tuberculosis at the bivariate level in the study. However, being divorced was 1.7 times more likely to be associated with drug-resistant tuberculosis among cases compared to controls (cOR=1.70, 95% CI 0.83–3.52, p=0.149). Having a primary school education and having no formal education were also associated with drug-resistant tuberculosis, with 2.95 times (cOR=2.95, 95% CI 1.05–8.35, p=0.041) and 6.04 times (cOR=6.04, 95% CI 2.01–18.19, p=0.001) more likely to get DRTB, respectively. Among those in informal employment, cases had an odds of 2.46 times of getting DRTB (cOR=2.46, 95% CI 0.67–8.98, p=0.149) compared to controls, as shown in Table 7.

Table 7: Bivariate analysis of sociodemographic factors

Variable	Cases n=83 (%)	Controls n=166 (%)	Crude odds ratio (95%CI)	P-value
Age				
≤ 24 years	9 (10.8)	30 (18.1)	0.70 (0.15-3.28)	0.651
25–44 years	43 (51.8)	93 (56)	1.08 (0.27-4.37)	0.915
45–64 years	28 (33.7)	36 (21.7)	1.81 (0.43-7.66)	0.417
≥ 65 years	3 (3.6)	7 (4.2)	Reference	
Sex				
Male	57 (68.7)	118 (71.1)	0.54 (0.50-1.58)	0.695
Female	26 (31.3)	48 (28.9)	Reference	
Marital status				
Married	33 (39.8)	74 (44.6)	Reference	
Single	27 (32.5)	57 (34.3)	1.06 (0.57-1.96)	0.847
Divorced	19 (22.9)	25 (15.1)	1.70 (0.83-3.52)	0.149
Widowed	4 (4.8)	10 (6)	0.896 (0.26-3.07)	0.862
Occupation				
Formal employment	3 (3.6)	13 (7.8)	Reference	
Informal employment	59 (71.1)	104 (62.7)	2.46 (0.67-8.98)	0.149
Student	3 (3.6)	6 (3.6)	2.17 (0.33-14.06)	0.418
Unemployed	18 (21.7)	43 (25.9)	1.81 (0.46-7.14)	0.394
Educational status				
No formal education	29 (34.9)	24 (14.5)	6.04 (2.01-18.19)	0.001
Primary	39 (47)	66 (39.8)	2.95 (1.05-8.35)	0.041
Secondary	10 (12)	51 (30.7)	0.98 (0.30-3.18)	0.980
Tertiary	5 (6)	25 (15.1)	Reference	

4.6 Bivariate analysis of Clinical Factors

In this study, contact with drug-resistant tuberculosis cases was found to be associated with DRTB at the bivariate level. Those with contact with a DRTB case were 3.30 times more likely to have DRTB than those with no contact (cOR=3.30, 95% CI 1.50–7.32, p=0.003). 20.5% of cases had contact with a DRTB case, and 7.2% of controls had contact as well. Being HIV positive, having a body mass index less than 18.5 kg/m^2, being previously treated for tuberculosis, having diabetes, having a chest condition

before TB diagnosis, and being hospitalized for the last two years were not factors associated with drug-resistant tuberculosis, as shown in the table below (Table 8).

Table 8: Bivariate analysis of Clinical Factors

Variable	Cases n=83 (%)	Controls n=166 (%)	Crude odds ratio (95% CI)	p-value
HIV status				
Positive	15 (18.1)	25 (15.1)	1.24 (0.62-2.51)	0.542
Negative	68 (81.9)	141 (84.9)	Reference	
Contact with DRTB				
Yes	17 (20.5)	12 (7.2)	3.30 (1.50-7.32)	0.003
No	66 (79.5)	154 (92.8)	Reference	
Nutrition status				
$< 18.5 kg/m^2$	32 (38.6)	57 (34.3)	1.20 (0.70-2.07)	0.513
$\geq 18.5 kg/m^2$	51 (61.4)	109 (63.7)	Reference	
Previous TB treatment				
Yes	20 (24.1)	39 (23.5)	1.03 (0.56-1.92)	0.916
No	63 (75.9)	127 (76.5)	Reference	
Have diabetes				
Yes	2 (2.4)	4 (2.4)	1.00 (0.18-5.57)	1.000
No	81 (97.6)	162 (97.6)	Reference	
Had chronic chest condition				
Yes	4 (4.8)	8 (4.8)	1.00 (0.29-3.42)	1.000
No	79 (95.2)	158 (95.2)	Reference	
History of hospitalization in the past two years				
Yes	8 (9.6)	17 (10.2)	0.93 (0.39-2.77)	0.881
No	75 (90.4)	149 (89.8)	Reference	

4.7 Bivariate Analysis for Behavioral Factors

In this study, we analyzed 83 cases and 166 controls. For behavioral factors associated with drug-resistant tuberculosis, khat chewing was found to be associated with DRTB, with those who chewed khat being 1.55 times more likely to have DRTB than others (cOR=1.55, 95% CI 0.89–2.69, p=0.120). A total of 67.5% of cases and 57.2% of controls chewed khat. Smoking cigarettes was also found to be associated with DRTB, with smokers being 1.58 times more likely to have DRTB than nonsmokers (cOR=1.58, 95% CI 0.93–2.70, p=0.087). A total of 53% of cases and 41.6% of controls smoked cigarettes. Among study members, alcohol consumption was found to be a risk factor for contracting drug-resistant tuberculosis, and alcohol consumers were 3.65 times more likely to have DRTB than non-consumers (cOR=3.65, 95% CI 1.50–7.32, p=<0.001). A total of 88% of cases and 55.4% of controls were alcohol consumers. Those who did not hear about DRTB included 68.7% of cases and 30.1% of controls, and they were 5.09 times more likely to have DRTB than those who did hear about DRTB (cOR=5.09, 95% CI 2.88–8.99, p=<0.001). Facing stigma as a TB patient, being counseled by a health care worker while being a TB patient, and a history of herbal treatment were found not to be associated with DRTB at the bivariate analysis level, as shown in Table 9 below.

Table 9: Bivariate Analysis of Behavioral Factors

Variable	Cases n=83 (%)	Controls n=166 (%)	Crude odds ratio (95% CI)	p-value
Khat chewing				
Yes	56 (67.5)	95 (57.2)	1.55 (0.89-2.69)	0.120
No	27 (32.5)	71 (42.8)	Reference	
Smoking habit				
Yes	44 (53)	69 (41.6)	1.59 (0.93-2.70)	0.087
No	39 (47)	97 (58.4)	Reference	
Alcohol Consumption				
Yes	68 (81.9)	92 (55.4)	3.65 (1.50-7.32)	<0.001
No	15 (18.1)	74 (44.6)	Reference	
Heard of DRTB				
Yes	26 (31.3)	116 (69.9)	Reference	
No	57 (68.7)	50 (30.1)	5.09 (2.88-8.99)	<0.001
Ever counselled by a Healthcare worker on TB				
Yes	80 (96.4)	162 (97.6)	Reference	
No	3 (3.6)	4 (2.4)	1.52 (0.33-6.95)	0.590
Faced stigma as a TB patient				
Yes	49 (59)	91 (54.8)	1.19 (0.70-2.03)	0.527
No	34 (41)	75 (45.2)	Reference	
History of traditional treatment for TB				
Yes	7 (8.4)	15 (9)	0.93 (0.36-2.37)	0.875
No	76 (91.6)	151 (91)	Reference	

4.8 Bivariate Analysis of Socioeconomic Factors

In this study, a monthly income of less than 10,000 Kenyan shillings was associated with 7.56 times higher odds of DRTB compared with other income earners (cOR=7.56, 95% CI 0.97–5.92, p=0.054). Among cases, 77.1% earned less than 10,000 shillings, and among controls, 66.3% did. Those earning between 10,000 and 20,000 were also associated with a higher likelihood of contracting DRTB (cOR=5.44, 95% CI 0.66–44.75, p=0.115). Living status (living individually or with family), the number of rooms in the house, family size, and time to reach the facility were not associated with the risk of contracting DRTB, as shown in Table 10 below.

Table 10: Bivariate Analysis of Socioeconomic Factors

Variable	Cases n=83 (%)	Controls n=166 (%)	Crude odds ratio (95% CI)	p-value
Monthly income				
<ksh. 10,000	64 (77.1)	110 (66.3)	7.56 (0.97-5.92)	0.054
Kshs. 10000-20,000	18 (21.7)	43 (25.9)	5.44(0.66-44.75)	0.115
>Kshs. 20,000	1 (1.2)	13 (7.8)	Reference	
Living individually or with family				
Individually	32 (38.6)	52 (31.3)	1.37 (0.79-2.39)	0.256
With family	51 (61.4)	114 (68.7)	Reference	
How Many rooms does your house have				
1	34 (41)	57 (34.3)	1.33 (0.77-2.28)	0.307
≥ 2	49 (59)	109 (65.7)	Reference	
Family size				
< 5 members	50 (60.2)	101 (60.8)	Reference	
≥ 5 members	33 (39.8)	65 (39.2)	1.03 (0.60-1.76)	0.927
Time to reach facility				
≤ 2 hours	78 (94)	156 (94)	Reference	
>2 hours	5 (6)	10 (6)	1.00 (0.33-3.03)	1.000

4.9 Multivariable Logistic Regression Model

Socio-demographic: There was no association with sociodemographic variables such as age, sex, marital status, and occupation. At the bivariate level, those in informal employment, those who were divorced, those in primary school, and those with no formal education were closely associated with the occurrence of drug-resistant tuberculosis. Only those with no formal education remained statistically significant in the final multivariate model ($p<0.05$).

Clinical: Among the clinical variables, contact with DRTB remained statistically significant in both the bivariate and the final multivariate model. Being HIV-positive, being previously treated for TB, having comorbidities, and having a low body mass index were not statistically significant.

Behavioral: This study examined behavioral variables at the bivariate level. Key findings include: those who chew khat were associated with drug-resistant tuberculosis.

Individuals who smoke have an increased risk of acquiring drug-resistant tuberculosis. Those who consume alcohol were also associated with drug-resistant tuberculosis. Not hearing about DRTB was also associated with contracting DRTB. Alcohol consumption and not hearing about DRTB remained statistically significant in the final multivariate model.

Socioeconomic: At the bivariate analysis level, monthly income of less than 10,000 shillings and income between 10,000 and 20,000 shillings were closely associated with drug-resistant tuberculosis. No variable remained statistically associated in the final multivariate analysis model**.**

Final model: A step-wise backwards elimination method was used, and the unconditional logistic regression analysis revealed factors associated with drug-resistant tuberculosis. Having no formal education, having contact with a DRTB case, not hearing about DRTB, and alcohol consumption were significantly associated with drug-resistant tuberculosis, as shown in Table 11.

The final study findings include: study participants with no formal education were 3.37 times more likely to contract drug-resistant tuberculosis (aOR=3.37; 95% CI 1.02–11.18, p=0.047) than those with formal education. Among study respondents who reported contact with a DRTB case, the risk of drug-resistant tuberculosis transmission was 3.92 times higher (aOR=3.92; 95% CI 1.54–9.95, p=0.004) than among those who did not have contact with a DRTB case. Not hearing about DRTB was associated with a 3.49-fold increase in the development of drug-resistant tuberculosis (aOR=3.49; 95% CI 1.87–6.52, p=<0.001). Among study participants, those who consumed alcohol were 2.53 times more likely to contract DRTB (aOR=2.53; 95% CI 1.25–5.13, p=0.010) than those who did not consume alcohol.

Table 11: Multivariate Logistic Model

Variable	Cases n=83 (%)	Controls n=166 (%)	Adjusted odds ratio (95% CI)	p-value
Education status				
No formal education	29 (34.1)	24 (14.5)	3.37 (1.02-11.18)	0.047
Primary	39 (47)	66 (39.8)	1.89 (0.61-5.81)	0.268
Secondary	10 (12)	51 (30.7)	0.96 (0.27-3.37)	0.949
Tertiary	5 (6)	25 (15.1)	Reference	
Contact with DRTB				
Yes	17 (20.5)	12 (7.2)	3.92 (1.54-9.95)	0.004
No	66 (79.5)	154 (97.8)	Reference	
Heard of DRTB				
No	57 (68.7)	50 (30.1)	3.49 (1.87-6.52)	<0.001
Yes	26 (31.3)	116 (69.9)	Reference	
Alcohol consumption				
Yes	68 (81.9)	92 (55.4)	2.53 (1.25-5.13)	0.010
No	15 (18.1)	74 (44.6)	Reference	

CHAPTER FIVE

5.0 DISCUSSIONS

Drug-resistant tuberculosis is a serious public health issue that jeopardizes the advancements in TB management, which is an infectious disease. In this study, not having a formal education, having contact with drug-resistant tuberculosis, lack of awareness about drug-resistant tuberculosis, and alcohol consumption were independently associated with increased risk of drug-resistant tuberculosis in the study setting. At the bivariate level of analysis, several variables were significantly associated with drug-resistant tuberculosis: Being divorced, informal employment, primary education, khat chewing, smoking, and low monthly income. These findings from the study are linked to increased drug resistance to tuberculosis in the study setting.

5.1 Socio-Demographic Factors

Among the socio-demographic factors, education status is one of the determinants of drug-resistant tuberculosis. The study revealed that having no formal education was significantly associated with the development of drug-resistant tuberculosis; this could be attributed to one not having formal education being a risk factor for acquiring drug-resistant tuberculosis. Without formal education, individuals may lack the confidence or knowledge to seek appropriate care, leaving them vulnerable to substandard treatment practices that promote drug resistance. It is quite possible that patients with no or less education might not know the importance of adhering to treatment. It thus may prematurely stop treatment either when the symptoms disappear or when side effects appear, thus facilitating the development of DRTB. Several studies have also significantly associated having no formal or low education with the development of drug-resistant tuberculosis. A study conducted in China at Hernan province by (Zhang et al., 2016) associated low formal education with the development of drug-resistant

tuberculosis, and another study done in India on factors associated with drug-resistant tuberculosis linked low formal education with acquiring drug-resistant tuberculosis (Sharma et al., 2019). Another study done in urban Pakistan on risk factors for multidrug-resistant tuberculosis also associated no formal education with getting DRTB (Ahmad et al., 2012). But a study done in Bangladesh had a contrary finding, whereby the study linked those with higher levels of education were associated with the development of DRTB (Rifat et al., 2014).

The study did not find an association between age, marital status, gender, and occupation with the development of drug-resistant tuberculosis. This could be attributed to study participants having similar characteristics since they come from the same locality. Similarly, a case-control study done in southern Ethiopia did not find an association between age and sex with the development of drug-resistant tuberculosis (Fikre et al., 2019). However, there are studies with contrary findings to this study, where age and sex are predictors of drug-resistant tuberculosis in the Amhara region (Mulu et al., 2015) and Addis Ababa in Ethiopia (Assefa et al., 2017).

5.2 Clinical *F*actors

In this study, having contact with a known DRTB case was associated with the development of drug-resistant tuberculosis. These findings are similar to those of a study done in Addis Ababa, Ethiopia (Assefa et al., 2017) and another study done in the Oromia region of Ethiopia (Mulisa et al., 2015). Another study done in Northern Portugal associated having a history of contact with DRTB with the development of DRTB (Gomes et al., 2014). Findings from a study done in Peru (Brewer et al., 2011) also agree with the study. This can be attributed to the longer delays in diagnosing and treating MDRTB patients compared to those with DSTB, particularly in low-income countries. This situation arises from the inadequate availability of diagnostic and

treatment services, along with insufficient infection prevention measures, both in domestic settings and within healthcare facilities. These circumstances increase the duration of the infectious period while producing additional infections from which future cases of MDRTB will develop. One could acquire DRTB through close contact as a family member; hence, living in the same household as a person with DRTB increases exposure to the airborne bacteria. Other studies done in different settings have associated having contact with DRTB with the development of drug-resistant tuberculosis in Sudan (Elduma et al., 2019) and Burundi (Iradukunda et al., 2020).

Active tuberculosis is usually linked to clinical and/or radiological abnormalities. M. tuberculosis can be spread by an individual who has active pulmonary tuberculosis. Controlling the TB pandemic requires managing the reservoir of potential TB cases, including DRTB cases, which are more often associated with the direct transmission of DRTB strains than with acquired drug resistance (Ershova et al., 2015; Yang et al., 2017). Therefore, a key element of the plan for TB eradication is preventing the development of a DRTB infection into disease (Rangaka et al., 2015). Given that 90% of active cases among MDRTB contacts occur within the first two years following exposure, promptly screening and treating close contacts of patients with DRTB is of utmost importance (Kherabi et al., 2022). Due to their extended exposure to index cases, household contacts of a patient with active pulmonary TB are at a heightened risk of contracting TB infection and illness, and according to a meta-analysis by Shah and associates, most of the household contacts of DRTB patients are infected (Shah et al., 2014).

Being HIV positive, having low BMI (< 18.5 kg/m^2), previous treatment of TB, having diabetes mellitus, having chronic chest condition prior to TB treatment, and being hospitalized for the past two years were not associated with the development of DRTB. A systematic review and meta-analysis of a study on comorbidities and risk factors for the development of DRTB had similar findings to our study, and did not associate having HIV and diabetes mellitus with the development of DRTB (Samuels et al., 2018). Also, another case-control study done in Mexico on diabetes and other risk factors for multidrug-resistant tuberculosis did not associate diabetes and HIV with the development of DRTB (Gómez-Gómez et al., 2015). The study done in Addis Ababa did not associate HIV and diabetes mellitus with the development of DRTB (Assefa et al., 2017). To hypothesize as to why DRTB was not associated with diabetes mellitus, report on the findings of a Swedish study that examined the development rate of each strain of *Mycobacterium tuberculosis* and the differences in susceptibility to natural immunity between susceptible and resistant strains, which is essential for speculating on the causes. According to the findings, even in cases where the host immune system is weakened, resistant mutants are probably more likely to rely on natural immunological defense mechanisms than drug-susceptibility ones (Toro et al., 2006). However, there are other contrary findings to our study, which associated being HIV positive and having Diabetes mellitus with the development of DRTB (Van Zyl Smit et al., 2010).

The study did not associate low BMI (< 18.5 kg/m^2) with the development of DRTB, but a multi-center case-control study on determinants of multidrug-resistant tuberculosis in southern Ethiopia had contrary findings (Badgeba et al., 2022). In this study, previous TB treatment was not associated with the development of DRTB. However, contrary to the findings of this study, a study done in Saudi Arabia (Al

Ammari et al., 2018) and a study done in Serbia (Stosic et al., 2018) also associated previous TB treatment with the development of DRTB.

5.3 Behavioural and Socio-economic Factors

The study found an association with DRTB, including alcohol consumption. Alcohol increased 2.5-fold the risk of acquiring drug-resistant tuberculosis among study participants. A systematic and meta-analysis study on risk factors for drug resistance also linked the consumption of alcohol as a risk factor for the development of multi-drug resistant tuberculosis (Pradipta et al., 2018). The majority of the cases were alcohol consumers. A systematic review done on tuberculosis and chronic respiratory disease also associated alcohol consumption with the development of drug-resistant tuberculosis (Byrne et al., 2015). Several other studies linked alcohol consumption with the acquisition of drug-resistant tuberculosis, a study done in East Shoa, Ethiopia (Desissa et al., 2018), in North India (Sinha et al., 2017), and West Bengal, India (Dutt et al., 2022). Alcohol impairs the body's defenses against Mycobacterium TB by weakening the immune system. The activity of immune cells that help prevent TB infection, such as macrophages, is suppressed by long-term alcohol consumption. Weakened immunity makes a person more vulnerable to infection and can result in insufficient bacterial removal during therapy, contributing to the development of resistance. Alcohol users may not follow recommended TB treatment plans because they are inebriated, forgetful, or lack self-discipline. The TB bacteria can thrive and become resistant to the drugs if treatment is not received completely or consistently. Alcohol consumption raises the likelihood of reinfection with drug-resistant strains of tuberculosis and is frequently linked to substandard living conditions, malnourishment, and close contact with other TB patients. Due to shame, neglect, or limited access to healthcare, people who drink alcohol may put off getting help for their TB symptoms.

A delayed diagnosis increases the bacterial burden and the risk of resistance by allowing the condition to worsen. It is also linked to leading to adverse drug reactions during DRTB treatment (Miller et al., 2012). However, there was a contrary finding to our study, which did not link alcohol consumption to the development of drug resistant tuberculosis (Vyawahare et al., 2024).

The study also found that there was an association with the development of DRTB for those who did not hear about DRTB; not having any information about DRTB was associated with the development of drug-resistant tuberculosis. A study done in Pakistan had similar findings to our study, that not hearing about DRTB was associated with the development of DRTB (Javed et al., 2016). Also, another study in southern Ethiopia associated not having information about DRTB with acquiring DRTB (Fikre et al., 2019). However, in this study, smoking was not associated with the development of drug-resistant tuberculosis, but there are contrary findings to our study. A study done in Saudi Arabia associated smoking with the development of DRTB (Sambas et al., 2020), as well as one done in Russia (Miller et al., 2012).

Although the study setting is a Miraa (Khat) growing area, with most of the cases and most of the controls being Khat chewers, the study did not associate chewing it with the development of drug-resistant tuberculosis, similar findings to a study done in Ethiopia (Biru & Woldesemayat, 2020). In this study, not getting counselled was not associated with developing drug-resistant tuberculosis, contrary to studies done in Japan (Baral et al., 2014) and Southern Ethiopia (Fikre et al., 2019). In this study, facing stigma was not associated with one acquiring DRTB, but there are contrary findings to this study (Liboon Aranas et al., 2023) which is associated facing stigma with the development of drug resistant tuberculosis. In this study, socioeconomic factors were not significantly associated with drug-resistant tuberculosis in the adjusted analysis.

However, contrary findings to this study, a study done in Serbia (Stosic et al., 2018) linked having a low monthly income with acquiring drug-resistant tuberculosis.

5.4 Limitations of the Study

Recall bias

Recall bias could be viewed as a potential limitation of the study since some of the data was based on the study participants' recollections of past events. Attempts were made to minimize this problem by ensuring that the exposures evaluated did not rapidly change over time. It was assumed that cases were not more likely to recall the exposures than controls; thus, if recall problems existed, then it would affect both groups equally and, therefore, underestimate the strength of association.

Sampling and representativeness

Because this was a case-control study, the study sites were chosen based on the locations of cases (DRTB patients) rather than a random selection of TB care facilities. Although efforts were made to reach all cases, controls were chosen randomly within the selected facilities. Therefore, more facilities were chosen in some areas than others, potentially limiting the representativeness of the results.

CHAPTER SIX

6.0 CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

6.2.1 Sociodemographic factors

The study concludes that the following sociodemographic factor (having no formal education) is significantly associated with the development of drug-resistant tuberculosis. This underscores the critical role of education in public health. People who lack formal education often have less access to health information, are less knowledgeable about TB prevention and treatment, and are less able to follow recommended treatment plans. This disparity worsens vulnerabilities, such as insufficient treatment and delayed diagnosis, which lead to the development of drug resistance.

6.2.2 Clinical factors

On the clinical factors, the study concludes that having contact with a DRTB case was associated with acquiring DRTB in the study setting. The relevance of transmission dynamics in the spread of drug-resistant tuberculosis (DRTB) is shown by the fact that contact with a case of DRTB is a substantial risk factor for developing DRTB. Close contact makes it easier for resistant strains to spread directly. This emphasizes the necessity of effective infection control strategies, such as the prompt detection and isolation of DRTB cases, regular screening of close contacts, and the administration of preventive treatment when necessary.

6.2.3 Behavioural and socioeconomic factors

The **s**tudy concludes that alcohol consumption had a significant association with the development of drug-resistant tuberculosis, highlighting its significance as a behavioural risk factor. Alcohol intake impairs immunity, increasing a person's

vulnerability to diseases, including TB. Additionally, alcohol consumption is frequently associated with noncompliance with TB treatment plans, which raises the risk of insufficient treatment and the development of drug-resistant tuberculosis.

Not hearing about DRTB was also strongly associated with the development of drug-resistant tuberculosis, underscoring the importance of health education and awareness campaigns in addressing this public health issue. People who don't know enough about DRTB are less able to comprehend how it spreads, its symptoms, and how important it is to follow treatment plans—all of which are crucial in preventing drug resistance. This lack of awareness is frequently more noticeable in underprivileged communities, where access to health education and information is restricted.

6.2 Recommendations

6.2.1 Socio-demographic factors

1. The national TB program and the County government of Meru should incorporate DRTB control methods, customized literacy and education initiatives to equip people with the knowledge they need to identify symptoms, seek prompt medical attention, and follow treatment plans.
2. In order to guarantee fair access to information regarding DRTB prevention and management, community-based awareness programs should also focus on groups with poor educational attainment. In order to lessen the effect of low levels of formal education on DRTB outcomes, this recommendation emphasizes the necessity of inclusive and easily available educational interventions.

6.2.2 Clinical factors

1. Through the Department of Health, the county government boosts follow-up and contact tracking systems to find people exposed to drug-resistant tuberculosis (DRTB) patients early. Put preventive measures in place, such as regular health monitoring, enhanced prophylactic medication (TB preventive treatment) where necessary, and instruction on infection control procedures for family members and close contacts.
2. Through the community health promoters, raise community awareness of the value of isolation and early detection in preventing the spread of DRTB. This suggestion strongly emphasizes preventative measures to reduce the risk of transmission among DRTB case contacts.

6.2.3 Behavioural and socioeconomic factors

1. To raise knowledge of drug-resistant tuberculosis, the national TB program and the county government of Meru should conduct extensive public health education efforts that emphasize the disease's causes, transmission, prevention, and treatment.
2. Use local leaders, community health workers, and the media to spread the word, particularly in underserved and high-risk areas. In order to guarantee accessibility for people with little formal education or exposure to health information, educational initiatives should be culturally aware and customized. This suggestion emphasizes the necessity of inclusive and focused awareness campaigns to close knowledge gaps and encourage DRTB-related preventative practices.
3. Meru County, through the health department, to introduce regular counseling and screening, and follow up closely on regular alcohol use screening at the

facility. Patients with TB who drink alcohol should receive specialized counseling and support. Create treatment programs that address substance abuse and tuberculosis together. Provide therapies for alcoholism, such as cognitive-behavioral therapy (CBT), and psychological support. Inform TB patients about the dangers of alcohol use, particularly how it can make treatment more difficult.

4. To promote behavioral change, use messaging that is sensitive to cultural differences by using area chiefs and local leaders. To increase alcohol users' commitment to TB treatment, fortify community-based support systems by strengthening the direct observation therapy. Encourage patients to cut back on their alcohol consumption by including family members and peer groups.
5. The county government of Meru to support and institute laws restricting the availability of alcohol and encouraging harm reduction techniques.

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APPENDICES

Appendix 1: IREC *Approval*

MTRH/MU-INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/826/2024
Approval Number: 0004808

27th June, 2024

Abdiaziz Mohamed Mohamud,
Moi University,
School of Public Health,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Mr. Mohamud,

DETERMINANTS OF DRUG-RESISTANT TUBERCULOSIS IN MERU COUNTY, KENYA

This is to inform you that ***MTRH/MU-IREC*** has reviewed and approved the above referenced research proposal. Your application approval number is ***FAN: 0004808.*** The approval period is **27th June, 2024 – 26th June, 2025.**
This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, Material Transfer Agreements (MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by ***MTRH/MU-IREC***.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to ***MTRH/MU-IREC*** within 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to ***MTRH/MU-IREC*** within 72 hours.
v. Clearance for export of biological specimens must be obtained from ***MOH at the recommendation of NACOSTI*** for each batch of shipment.
vi. 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.
vii. Submission of an executive summary report within 90 days upon completion of the study to ***MTRH/ MU-IREC.***

Prior to commencing your study, you will be required to obtain a research license from the National Commission for Science, Technology and Innovation (NACOSTI) https://oris.nacosti.go.ke and other relevant clearances from study sites including a written approval from the CEO-MTRH which is mandatory for studies to be undertaken within the jurisdiction of Moi Teaching & Referral Hospital (MTRH) and its satellites sites.

INSTITUTIONAL RESEARCH ETHICS COMMITTEE
27 JUN 2024
APPROVED
P. O. Box 4606 - 30100 ELDORET

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc	CEO	-	MTRH	Dean	-	SOP	Dean	-	SOM
	Principal	-	CHS	Dean	-	SON	Dean	-	SOD

Appendix 2: NACOSTI Approval

REPUBLIC OF KENYA

NATIONAL COMMISSION FOR SCIENCE,TECHNOLOGY & INNOVATION

Ref No: **881017**

Date of Issue: **12/July/2024**

RESEARCH LICENSE

This is to Certify that Mr.. Abdiaziz Mohamed Mohamud of Moi University, has been licensed to conduct research as per the provision of the Science, Technology and Innovation Act, 2013 (Rev.2014) in Meru on the topic: Determinants of drug resistant tuberculosis in Meru County, Kenya for the period ending : 12/July/2025.

License No: **NACOSTI/P/24/37775**

881017

Applicant Identification Number

Director General
NATIONAL COMMISSION FOR SCIENCE,TECHNOLOGY & INNOVATION

Verification QR Code

NOTE: This is a computer generated License. To verify the authenticity of this document, Scan the QR Code using QR scanner application.

See overleaf for conditions

Appendix 3: Meru County *A*pproval

COUNTY GOVERNMENT OF MERU
DEPARTMENT OF HEALTH

Telegrams: "HEALTH" Meru
Telephone: Meru
Fax: 31242
Email: hospitalmeru@gmail.com
When replying should be to:
County Director Medical Services

COUNTY DIRECTOR HEALTH SERVICES
MERU COUNTY
P.O. BOX 8 – 60200
MERU

Ref: MRU/GEN/GEN/C.50

30th August, 2024

To,
Abdiaziz Mohamed
P.O. BOX 7846-00610
Nairobi
Mobile No. 0720323026

Email address: addulsuper86@gmail.com

RE: RESEARCH AUTHORIZATION

Your request for permission to conduct a study on your topic **"DETERMINANTS OF DRUGS-RESISTANT TB At MERU TEACHING AND REFERRAL HOSPITAL AND SUB COUNTY HOSPITALS WITHIN MERU COUNTY.** is hereby granted. Having gone through the Research and Ethics Committee successfully."

Kindly ensure adherence to the ethical guidelines of your research and of the hospital.

You are required to share with my office the results of your research. Please note that this is a preliminary approval; the final approval will be issued upon sharing a copy of your study results.

Also note that the Meru Teaching and Referral Hospital charges a research fee of Ksh. 7.000/= which you are required to pay prior to commencing your study.

Thank you.

Dr. Koome Muthuri
For Director Health Services
County Government of Meru

DIRECTOR HEALTH SERVICES
MERU COUNTY GOVERNMENT
30 AUG 2024
P. O. Box 120 -60200
MERU

Appendix 4: Consent Form
Moi University
PO Box 3900-30100
Eldoret
Dear Respondent,
Re: Research

Introduction/ Utangulizi

My name is……, and I am a student at Moi University, and I am carrying out a research study titled "***Determinants of Drug-resistant Tuberculosis in Meru County.*****".** The study is being conducted among Drug-resistant Tuberculosis patients in Meru County with the support of the Kenya Field Epidemiology Training Program and Moi University. If you agree to participate in this study, you will be asked to provide a written consent to denote your agreement.

Jina langu ni……..na, nimekuja kwa niaba ya Wizara ya Afya na chuo kikuu cha Moi kufanya utafiti juu ya "Sababu zinazohusiana na usugu wa dawa miongoni mwa wagonjwa wa ugonjwa wa kifua kikuu, kaunti ya Meru" Utafiti huu utafanywa minogoni mwa wagonjwa wa ugonjwa wa kifua kikuu wenye usugu wa dawa katika Kaunti La Meru. Kwa msaada wa Mpango wa Mafunzo ya Epidemologia ya Kenya na Chuo Kikuu cha Moi, kufuatia idhini yako, ningependa ushiriki katika utafiti huu.

Purpose/ Kusudi

We would like to understand the factors contributing to Drug resistance to tuberculosis in Meru County.

Ili kubaini kama umewahi kutambua Sababu zinazohusiana na usugu wa dawa miongoni mwa wagonjwa wa ugonjwa wa kifua kikuu, kaunti ya Meru

Procedures/ Taratibu

If you agree to participate in the study, we will ask you some questions about you. These questions will help us to understand why we have high Drug-resistant tuberculosis cases in Meru County. This process will take about 30 minutes of your time or less if you agree to be part of the study.

Ukikubali kushiriki katika utafiti, tutakuuliza baadhi ya maswali kuhusu wewe na taarifa juu ya sababu zinazohusiana na usugu wa dawa ya ugonjwa wa kifua kikuu. Maswali yote yatatusaidia kuelewa ni kwa nini tumekuwa na maambukizi mengi ya usugu wa dawa ya ugonjwa wa kifua kikuu katika kaunti ya Meru .Tutachukua kama dakika 30 za wakati wako kufanya au chini ya hapo.

Benefits/ Faida

The findings of this study will help the implementers of tuberculosis control to understand the determinants of Drug-resistant tuberculosis and hence put in place measures to ensure the cases are reduced in Meru County and beyond.

Matokeo ya utafiti huu yatawasaidia watekelezaji wa kuzuia ugonjwa wa kifua kikuu ili kuelewa sababu zinazohusiana na usugu wa dawa miongoni mwa wagonjwa wa kifua kikuu kwa minajili ya kuweka mikakati ya kupunguza idadi ya visa vya kifua kikuu katika kaunti ya Meru na kwingineko.

Risks/ Discomfort:

We do not anticipate any risk associated with participating in this study. We may, however, ask you questions that you may consider private to you. The information asked will not be linked to you in any way as all the data will be coded with a study number and not your individual name. In this case, the potential loss of confidentiality will be minimized.

Hamna hatari zinazotarajiwa kwako kama mshiriki katika utafiti huu kwa kuwa hakuna mkusanyiko wa sampuli za binadamu au majina. Kupitia usimbaji hatari zozote zinazohusiana na uwezakano wa kupoteza usiri zitapunguzwa.

Confidentiality/ Usiri

All the information you give will not be accessed by anyone else except the researcher, and your names will not be used in the research. All the data will be stored in a computer that is password protected and is accessible to the research team only. The report that will be given to the institution and other stakeholders will not be based on individuals but on all the participants.

Habari yote utakayotoa haitafikiwa na mtu mwingine yeyote isipokuwa mtafiti na majina yako hayatatumika katika utafiti. Ripoti ambayo itapewa taasisi na wadau wengine haitategemea watu binafsi bali washiriki wote.

Cost / compensation/ Gharama / fidia

You will not be paid for participating in the study. Neither, you will not be reimbursed the cost of travelling from your home to the health facility where the interview will be conducted whether you consent to the study or not.

Hutalipwa kwa kushiriki katika utafiti.Hata hivyo, vile vile, hutarejeshewa gharama ya kusafiri kutoka nyumbani kwako hadi kituo cha afya ambapo mahojiano yatafanyika ikiwa umekubali utafiti huu au la.

Right to Refuse/ Haki ya Kukataa

You are free to choose to agree to participate in the study or not. Please note that, if you choose not to participate, your services within the facility and elsewhere will not be affected at all. We however, believe that the information you hold will be very helpful in guiding us in the process of finding ways of preventing transmission of DRTB in this county and beyond.

Uko huru kuchagua kukubali kushiriki katika utafiti. Walakini, maoni yako ni muhimu sana katika utafiti huu.

Consensus/ Makubaliano

I would like to know if there are areas about this study that you have any questions or need clarifications?

Natumahi umeelewa utaratibu mzima. Je! Una maswali yoyote au ufafanuzi?

DECLARATION/ TAMKO

I…….having been given information and time to ask questions about this study, I have read and understood. I, therefore, agree to participate by signing, verbally or by thumbprint/verbally, to give consent for the study to be carried out on me.

Mimi……kwa kupewa habari na wakati wa kuuliza maswali juu ya utafiti huu, nimesoma na nimeelewa. Kwa hivyo, ninakubali

kushiriki kwa kusaini, kwa maneno au kwa kidole gumba / kwa maneno kutoa idhini ya utafiti ufanyike kwangu.

Interviewee signature/ thumbprint/verbal_____

Saini ya aliyehojiwa / kuchapa kidole gumba / mawasiliano _____

Principal researcher: Sign_____date_____

Mtafiti mkuu: Saini_____tarehe _____

Contacts In case you have any questions regarding the study, contact Abdiaziz Mohamed; the Principal investigator - Tel no: 0720323026

Mawasiliano Ikiwa una maswali yoyote kuhusu utafiti wasiliana na Abdiaziz Mohamed; Mpelelezi Mkuu - Simu- 0720323026

Appendix 5: Questionnaire

Study Title: Determinants of drug-resistant tuberculosis in Meru County, Kenya.

1) Questionnaire number_____

2) Indicate if the interviewee is a case or a control

Case ☐ Control ☐

3) If Case indicate the Type/Classification of DRTB

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4) Date of the interview(dd/mm/yyyy) _____ / _____ /_____

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5) Time of the interview(hh/mm/) _____ / _____

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6) Name of the research assistant

Section A: Sociodemographic characteristics

7) Age in years? _____

8) What is your sex?

a) Male ☐ b) Female ☐

9) Residence /Sub-county of interviewee_____

Health facility_____

10) What is your marital status?

a) Married ☐ b) Single ☐ c) Widowed ☐ d) Divorced ☐

11) What is your occupation?

a. Formal employment ☐ b. Informal employment ☐

c. Unemployed ☐ d. Student ☐

12) What is the highest level of education you have completed?

a. No formal education ☐

b. Primary ☐

c. Secondary ☐

d. Tertiary ☐

Section B: Clinical factors

14) What is your HIV status?

a) Positive ☐ b) Negative ☐ c) Unknown ☐

15) Have you had any contact with DRTB case?

a) Yes ☐ b) No ☐

16) History of previous TB treatment?

a) Yes ☐ b) No ☐

17) Outcome of TB treatment before?

a) Cure/Complete ☐ b) Defaulted ☐ c) Failure ☐

18) History of anti-TB medication interruption for at least a day in the previous treatment?

a) Yes ☐ b) No ☐

If yes, please state the reason_____

19) Height (cm) _____

20) Weight (Kgs) _____

21) Nutritional status?

a. Underweight ☐

b. Normal ☐

c. Overweight ☐

d. Obese ☐

22) Had diabetes Mellitus?

a) Yes ☐ b) No ☐

23) Had chronic chest condition?

a) Yes ☐ b) No ☐

24) Any other comorbidity, please specify

_____

25) Have you had a history of hospitalization in the past two years?

a) Yes ☐ b) No ☐

Section C: Behavioural factors

26) Do you smoke?

a) Yes ☐ b) No ☐

27) Do you drink alcohol?

a) Yes ☐ b) No ☐

28) Do you chew khat?

a) Yes ☐ b) No ☐

29) Ever counselled by health care worker about TB?

a) Yes ☐ b) No ☐

30) Ever faced stigma (as TB patient)?

a) Yes ☐ b) No ☐

31) Heard about DRTB?

a) Yes ☐ b) No ☐

32) History of traditional treatment?

a) Yes ☐ b) No ☐

Section D: Socioeconomic factors

33) What is your monthly income?

a) <Ksh 10,0000 ☐

b) Ksh 10,000- 20,0000 ☐

c) >Ksh 20,0000 ☐

34) Living (Individually or with family)?

a) Individually ☐

b) With family ☐

35) Do you have a house to live in?

a) Yes ☐ b) No ☐

36) How many rooms does your house have?

a. One ☐

b. Two ☐

c. Three ☐

d. Four ☐

e. Five and above ☐

37) How many members are residing in the household?

a. < 5 members ☐

b. ≥ 5 members ☐

38) Time to reach facility?

a. ≤ 2 hours ☐

b. > 2 hours ☐

Appendix 6: Study Site Facilities

Facility number	TB treatment zone/facility	Cases enrolled(n)	Controls enrolled (n)
	Igembe south	**12**	**24**
1	Nyambene sub-county hospital	4	8
2	Kiraone dispensary	3	6
3	CCS(ASK) dispensary	1	2
4	Kiegoi dispensary	1	2
5	Maua Methodist Hospital	1	2
6	Kililii dispensary	1	2
7	Akachiu Health Center	1	2
	Igembe north	**19**	**38**
8	Mutuati sub county hospital	5	10
9	Laare Health Center	2	4
10	Theere Health Center	2	4
11	Kaelo dispensary	2	4
12	Thamare dispensary	4	8
13	Machungulu dispensary	2	4
14	Kina dispensary	1	2
15	Kawira dispensary	1	2
	Imenti north	**9**	**18**
16	Meru County Referral Hospital	3	6
17	Giaki sub county hospital	1	2
18	Gokoromone dispensary	3	6
19	Igoki dispensary	1	2
20	Kiburine dispensary	1	2
	Imenti south	**18**	**36**
21	Kanyakine sub county hospital	6	12
22	Consolata Hospital (Nkubu)	5	10

23	Kionyo dispensary	1	2
24	Uruku Health Center	1	2
25	St Ann hospital	1	2
26	Kieni Kia Ndege dispensary	1	2
27	Gaatia dispensary	1	2
28	Mitunguu dispensary	2	4
	Tigania west	**10**	**20**
29	Mutionjuri Health Center	2	4
30	Limaru dispensary	1	2
31	Makendi dispensary	1	2
32	Mbeu Health Center	1	2
33	Mwerokogi dispensary	2	4
34	Miathene sub county hospital	1	2
35	Kunene dispensary	2	4
	Tigania east	**15**	**30**
36	Mukinduri sub county hospital	9	18
37	Muthara sub county hospital	4	8
38	Kiguchuwa dispensary	2	4