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TREATMENT OF MULTI-DRUG-RESISTANT TUBERCULOSIS WITH SECOND-LINE ALL-ORAL DRUGS IN GHANA: INCIDENCE OF ADVERSE EVENTS.

BY:

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DECLARATION

I, Timothy Ebobabaara Bukari, certify that, this dissertation is my work and that no previous submission for a degree has been made here or elsewhere. Also, works by others, which served as sources of information, have been duly acknowledged by referencing the authors where applicable.

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ABSTRACT

Introduction: The treatment of multidrug-resistant tuberculosis (MDR-TB) remains challenging due to the toxicity of second-line medications and suboptimal treatment outcomes. This study aimed to determine the incidence of adverse events and identify factors associated with these events in patients undergoing treatment for MDR-TB with second-line all-oral drugs in Ghana.

Methods: This retrospective cohort study reviewed the medical records of 384 MDR-TB patients treated with second-line all-oral drugs at selected health facilities in Ghana, including the Greater Accra Regional Hospital, Eastern Regional Hospital, and Kumasi South Hospital. Data were extracted using the Kobo Collect tool, capturing patient demographics, baseline clinical and laboratory characteristics, treatment regimens, and adverse events. The study period spanned from 2020 to August 2024.

Results: The mean age of patients was 45 years (SD = 15), with the majority being male (65.78%). Most patients were aged 45–64 years (33.85%), and HIV was the most common comorbidity (19.5%). The most frequent adverse events were diarrhea (14%), dizziness (13.7%), and vomiting (12.3%), mostly mild to moderate in severity. Severe adverse events such as leukopenia and acute kidney injury were rare (<5%). Over time, gastrointestinal symptoms such as vomiting and nausea decreased significantly.

Multivariate analysis revealed that patients with comorbidities such as diabetes or hypertension were significantly more likely to experience adverse events (aRR = 2.65, 95% CI: 1.58–4.43, $p < 0.001$). In contrast, patients aged 65 years and above had a notably lower risk of developing adverse events (aRR = 0.44, 95% CI: 0.25–0.79, $p = 0.005$). Sex was not significantly associated with adverse events (aRR = 1.03, $p = 0.86$). Overall, 74.9% of patients achieved successful treatment outcomes, while 25.1% experienced treatment failure, relapse, or death.

Conclusion: In conclusion, adverse events are common in the treatment of MDR-TB with second-

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line All-Oral drugs, with gastrointestinal adverse events being the most prevalent. These findings highlight the importance of monitoring and managing adverse events to optimize treatment outcomes for MDR-TB patients in Ghana

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LIST OF ABBREVIATIONS

AEs: Adverse Events

ALT: Alanine Aminotransferase

AST: Aspartate Aminotransferase

Bdq: Bedaquiline

BPaL: Bedaquiline, Pretomanid, and Linezolid

BPaLM: Bedaquiline, Pretomanid, Linezolid, and Moxifloxacin

CTCAE: Common Terminology Criteria for Adverse Events

DOT: Directly Observed Therapy

ELISA: Enzyme-Linked Immunosorbent Assay

HIV: Human Immunodeficiency Virus

MDR-TB: Multi-Drug Resistant Tuberculosis

SAE: Serious Adverse Event

TB: Tuberculosis

WHO: World Health Organization

Lfx: Levofloxacin

Mfx: Moxifloxacin

Lzd: Linezolid

Cfz: Clofazimine

Cs: Cycloserine

Tzd: Terizidone

Dlm: Delamanid

Mpm: Meropenem

Sm: Streptomycin

Eto: Ethionamide

Pto: Prothionamide

PAS: Para-Aminosalicylic Acid.

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CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Tuberculosis remains a public health threat in Ghana and Globally. Tuberculosis (TB) is the second leading cause of death from a single infectious agent, after COVID-19, and one of the top 10 causes of death globally, (WHO, 2022a). According to the 2021 estimates from the World Health Organization (WHO), a staggering 10.6 million individuals were afflicted by Mycobacterium tuberculosis. Moreover, there was a significant increase in an estimated burden of 450,000 new cases of rifampicin-resistant TB (RR-TB) in 2021(WHO, 2022a).

Globally, it is estimated that each day, over 3,471 people lose their lives to TB, and close to 30,000 persons fall ill with TB disease. Also in Ghana, about 39 people lose their lives each day from TB and 121 people fall ill daily(WHO, 2023a). A TB survey in Ghana has shed light on the extent of this challenge, emphasizing the need for robust strategies to address the disease (WHO, 2018).

Multidrug-resistant tuberculosis (MDR-TB) refers to strains of Mycobacterium tuberculosis that are resistant to at least isoniazid and rifampicin, the two most potent first-line anti-TB drugs (Lew et al.,2008). According to global estimates, MDR-TB affects a substantial number of individuals, contributing to the overall burden of TB (Migliori & Tiberi, 2022). The incidence of MDR-TB has been on the rise, challenging the progress made in TB control efforts (Falzon et al., 2015).

Inadequate treatment regimens contribute significantly to the emergence and propagation of MDR-TB (Shukla & Chaudhary, 2019). These regimens may result from a variety of reasons, such as early cessation of treatment, suboptimal drug dosages, or erratic medication adherence (Shukla & Chaudhary, 2019). The improper use of anti-TB drugs, whether due to self-

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medication practices or inadequate prescription management, further exacerbates the development of drug resistance (Liang et al., 2012).

Treatment of Mycobacterium tuberculosis infections is classified into first-line drugs used to treat pulmonary TB infections that are not drug-resistant [isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E)] and second-line drugs used to treat multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) (Bendre et al., 2021). In 2016, the WHO endorsed an injectable-based 9- to 12-month short-course regimen for the treatment of MDR-TB, which marked a major shift in the treatment of TB, following the success of the regimen in a cohort study in Bangladesh (WHO, 2016).

In 2018, the next breakthrough came with the transition to an all-oral three groups of antituberculosis drugs: group A consisting of fluoroquinolone [levofloxacin (Lfx)/moxifloxacin (Mfx)], bedaquiline (Bdq) and linezolid (Lzd); group B consisting of clofazimine and cycloserine (Cs)/terizidone (Tzd); and group C consisting of E, delamanid (Dlm), Z, imipenem–cilastatin (Imp-Cln)/meropenem (Mpm), amikacin (Am), streptomycin (Sm), ethionamide (Eto)/prothionamide (Pto) and para-aminosalicylic acid replaced the injectable drug (WHO, 2018).

Furthermore, in 2019, the shorter all-oral BDQ-containing regimen was introduced, initially for operational research but later for wider clinical application. A recent ground-breaking innovation was the novel, 6-month all-oral BPaL and BPaLM regimens, which are recommended for RR/MDR-TB and XDR-TB (WHO, 2019b). The shift from treating Multi- Drug-Resistant Tuberculosis (MDR-TB) with second-line injections to oral drugs occurred for several reasons. Oral drugs are generally more convenient, allowing for easier administration and monitoring, which can contribute to better compliance with the treatment regimen (WHO, 2018). Treatment with second-line injections for drug-resistant cases is expensive, protracted,

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and toxic, with an average treatment success of approximately 56%, compared to 85% for Oral drugs. Additionally, oral medications often have fewer side effects and may offer a more patient-friendly approach, promoting overall treatment success and reducing the risk of complications associated with injectable drugs (WHO, 2019).

1.2 Problem statement

The treatment of MDR-TB has been challenging due to the toxicity of second-line medications and overall poor treatment outcomes. WHO has recommended all-oral drugs for MDR-TB treatment since 2018, marking a major advance compared with previous regimens that included injectable agents. There have been steady improvements in the treatment success rates to 63% globally, up from 60% in 2019 and 50% in 2012 (WHO, 2023a). While second-line all-oral drugs are promising for the treatment of MDR-TB, their use is often hindered by the occurrence of adverse events (AEs), which can compromise treatment outcomes(WHO, 2022). In a retrospective cohort study of 856 MDR-TB patients in Uganda, 43.1% of adverse events were reported; with joint pain (66%), hearing impairment (20%), and vomiting (16%) being the most common AEs(Ategyeka et al., 2023).

The National Tuberculosis Programme (NTP) in Ghana officially transitioned to bedaquiline-containing all-oral MDR-TB regimens in January 2020 as part of efforts to replace injectable-based treatments (National Tuberculosis Programme, Ghana, 2020). Since this implementation, limited peer-reviewed data exist on the incidence and determinants of adverse events (AEs) among Ghanaian MDR-TB patients, despite the known toxicity of second-line drugs such as bedaquiline and linezolid. However, evidence from other African countries shows that AEs are common; for instance, a retrospective cohort study in Uganda reported that 43.1% of MDR-TB patients experienced AEs, with joint pain (66%), hearing impairment (20%), and vomiting (16%) being most frequent (Ategyeka et al., 2023). This gap in Ghana-specific evidence underscores the need to examine the burden and predictors of AEs under the all-oral regimen.

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Patient factors, such as age, sex, underlying medical conditions, nutritional status, and medication adherence, can influence susceptibility to adverse events (Prasad et al., 2021). The occurrence of these AEs poses a challenge to caregivers, as they must strike a balance between achieving patient efficacy and minimizing potential harm (Lan et al., 2020). The AEs can manifest across various physiological systems(Prasad et al., 2021), leading to treatment non-adherence, interruptions, or discontinuation. (Lan et al., 2020).

Treatment guidelines have been disseminated to provide a framework for standardizing treatment protocols and guiding the selection of drug regimens to minimize the risk of AEs (Bendre et al., 2021). Efforts have been made to develop new drugs and treatment regimens forMDR-TB that are more effective and have fewer AEs (Migliori & Tiberi, 2022; WHO, 2022b). This study will provide valuable evidence on the incidence, types, and severity of adverse events associated with second-line all-oral regimens for MDR-TB treatment in the Ghanaian population. This study will provide valuable evidence on the incidence, types, and severity of adverse events associated with second-line all-oral regimens for MDR-TB treatment in the Ghanaian population. The findings are essential for informing clinical practice, such as optimizing patient monitoring, managing drug toxicity, and tailoring treatment for high-risk groups (e.g., those with comorbidities).

1.3 Justification of the study

The emergence of Multiple Drug-Resistant Tuberculosis (MDR-TB) further complicates efforts for effective disease management(Asante-Poku et al., 2015). This emphasizes the urgency of addressing TB, including the growing challenge of MDR-TB treatment. Despite growing concern, limited data exist on comprehensive studies examining the adverse events associated with second-line oral drugs used in MDR-TB treatment in Ghana. The few available studies, such as that of Agyare et al. (2021), primarily focused on small patient cohorts and reported a range of adverse effects including gastrointestinal disturbances, hepatotoxicity, and hearing loss but

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lacked detailed analysis of their frequency, severity, and associated risk factors.

Additionally, Research efforts aimed at optimizing treatment regimens, developing safer alternatives, and improving patient outcomes are imperative to address the complex interplay between MDR-TB treatment and adverse effects. Only through a comprehensive understanding of these dynamics can we hope to overcome the obstacles posed by adverse effects and achieve successful outcomes in managing MDR-TB.

1.4 Primary Objective

To determine the incidence of adverse events and the associated factors in treating Multi-Drug-Resistant Tuberculosis with Second-Line All-Oral Drugs in Ghana.

1.5 Specific objectives of the study

1.To assess the incidence and types of adverse events associated with the use of second-line all-oral drugs for the treatment of MDR-TB in Ghana.

2. To evaluate the clinical outcomes among MDR-TB patients who receive second- line all-oral drug treatment.

3. To identify factors contributing to the occurrence of adverse events during the treatment of MDR-TB with second-line all-oral drugs.

1.6 Conceptual framework

The conceptual framework for the study on the incidence of adverse events in the treatment of multi-drug-resistant tuberculosis (MDR-TB) with second-line all-oral drugs in Ghana, is structured around key variables and their hypothesized relationships. This framework is grounded in the understanding that the incidence of adverse events in the treatment of MDR- TB with second-line all-oral drugs is influenced by a complex interplay of variables (Gray, 2022). By examining the relationships between exposure, outcome, mediating, and confounding factors,

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this framework provides a theoretical basis for understanding the factors contributing to adverse events in MDR-TB treatment, which is in line with what was reported by Gray and colleagues (2022). The selection of variables is informed by existing literature on MDR-TB treatment, adverse events, and related factors (De Vries et al., 2017).

The focus of this study is the use of second-line all-oral drugs for treating MDR-TB. This variable represents the treatment regimen administered to patients diagnosed with MDR-TB (Esmail et al., 2022). This variable delineates the specific medication regimen prescribed to individuals who have been diagnosed with MDR-TB, encompassing a combination of oral medications carefully selected to target the resistant strains of the tuberculosis bacterium(Winoto & Candradikusuma, 2021). Unlike first-line drugs, which are commonly administered as part of standard TB treatment, second-line all-oral drugs are specifically chosen to combat MDR-TB strains that have shown resistance to conventional treatment protocols (Gupta et al., 2020). It is hypothesized that the use of second-line all-oral drugs for the treatment of MDR-TB will be positively associated with the incidence of adverse events

(Koirala et al., 2021) Mediating factors such as patient demographics and clinical characteristics may moderate this relationship, influencing the likelihood and severity of adverse events. Also, confounding factors such as the presence of drug-resistant strains and access to healthcare facilities may confound the relationship between exposure and outcome variables, necessitating appropriate control measures in the analysis (Aslam et al., 2023).

The choice of categories and variables in this framework is informed by existing literature on MDR-TB treatment, adverse events, and related factors by Aslam and colleagues (Aslam et al., 2023). Exposure Variables are factors related to the treatment process itself. According to Wang et al., (2024), in MDR-TB treatment, exposure variables may include the specific second-line all-oral drugs administered, their dosage, treatment duration, and adherence to treatment protocols. Understanding how these variables contribute to adverse events is crucial for optimizing

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treatment outcomes while minimizing risks.

The primary outcome variable in this framework is the incidence of adverse events. Adverse events encompass a wide range of undesirable effects associated with medication use, including but not limited to gastrointestinal disturbances, hepatotoxicity, peripheral neuropathy, and psychiatric manifestations(Wang et al., 2024). Quantifying and characterizing these adverse events is essential for evaluating treatment safety and effectiveness. Mediating Factors are variables that mediate or moderate the relationship between exposure and outcome variables. In the MDR-TB treatment, mediating factors may include patient characteristics such as age, sex, comorbidities, nutritional status, and immune function (Wagnew et al., 2024).

Additionally, healthcare system factors such as access to healthcare facilities, quality of care, and availability of support services may influence the occurrence and severity of adverse events. Confounding factors are variables that may distort or obscure the true relationship between exposure and outcome variables (Wagnew et al., 2024). In the study of adverse events in MDR-TB treatment, confounding factors could include socio-economic status, educational level, cultural beliefs, and environmental factors or household conditions. Accounting for these confounding factors is essential to ensure the validity and reliability of study findings. Several factors may affect the primary outcome of adverse events in the MDR-TB treatment. A study conducted by (Oehadian et al., 2022) and colleagues reported that, the inherent toxicity of second-line all-oral drugs used in MDR-TB treatment can directly contribute to the incidence and severity of adverse events (Oehadian et al., 2022). Patient-specific factors such as age, sex, genetic predisposition, nutritional status, and coexisting medical conditions can influence the likelihood and severity of adverse events (Koirala et al., 2021). Patients with compromised immune systems or pre-existing organ dysfunction may be at higher risk of experiencing adverse reactions to treatment.

Therefore, the conceptual framework for studying the incidence of adverse events in the

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treatment of MDR-TB with second-line all-oral drugs in Ghana provides a structured approach to understanding the multifactorial nature of treatment-related adverse events. By examining the relationships between exposure, outcome, mediating, and confounding factors, researchers can identify opportunities for intervention and optimization of treatment strategies to improve patient outcomes and minimize the burden of adverse events.

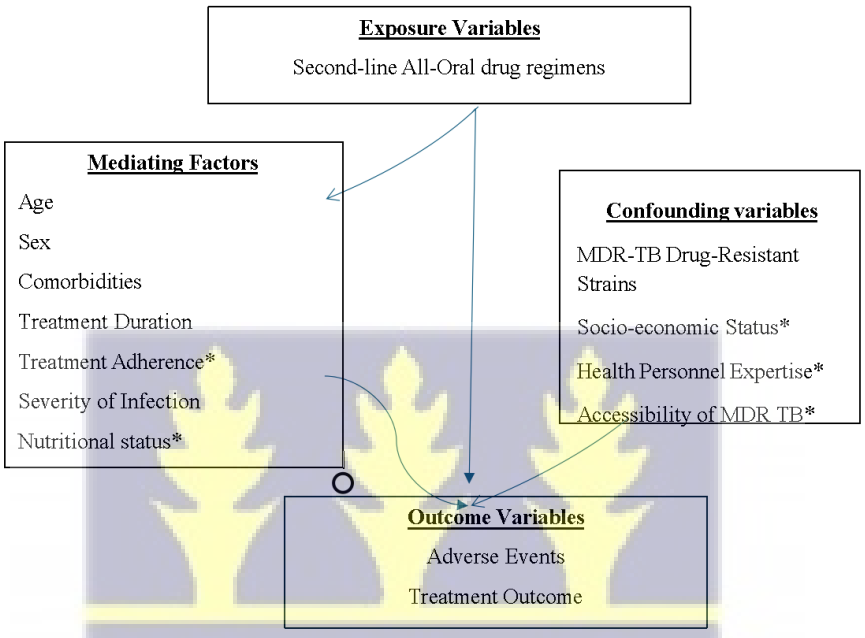

Figure 1; Conceptual Framework of the study.

NB: Asterisk (*) indicates variables that were not measured

1.7 Hypothesized Relationships of The Study

It was hypothesized that the use of second-line all-oral drugs for the treatment of MDR-TB will be positively associated with the incidence of adverse events.

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CHAPTER TWO

2.0LITERATURE REVIEW

2.1 Multidrug-Resistant Tuberculosis (MDR-TB) Treatment

Multidrug-resistant tuberculosis (MDR-TB) is a form of tuberculosis disease caused by bacteria that are resistant to at least two of the most powerful first-line anti-TB drugs, isoniazid, and rifampicin. MDR-TB presents a significant challenge to global TB control efforts due to its complexity, prolonged treatment duration, higher mortality rates, and increased healthcare costs (Ahmad & Mokaddas, 2009). Several factors contribute to the epidemiology of MDR-TB, including incomplete treatment, inappropriate use of antibiotics, poor infection control, HIV co-infection, and challenges within healthcare systems (Sharma & Mohan, 2006). Addressing MDR-TB requires a multiple approach that includes strengthening TB prevention and control efforts, improving diagnostic capabilities, ensuring access to effective treatment regimens, enhancing infection control measures, and addressing social determinants of health (S. Ahmad & Mokaddas, 2009).

The emergence of drug-resistant TB dates back to the mid-20th century, coinciding with the widespread use of antibiotics for TB treatment (Jang & Chung, 2020). Resistance to isoniazid and streptomycin was first reported in the 1950s, followed by resistance to rifampicin in the 1960s (Jang & Chung, 2020). The introduction of combination therapy and directly observed treatment, short-course (DOTS) strategy in the 1990s helped improve TB control but did not adequately address the growing problem of MDR-TB. Historically, MDR-TB treatment regimens relied on injectable drugs such as kanamycin, capreomycin, and amikacin, in addition to second-line oral drugs such as fluoroquinolones and oral bacteriostatic agents (Loddenkemper et al., 2002). These regimens were associated with significant adverse effects, long treatment durations, and low success rates. Moreover, the use of injectable drugs posed

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challenges in terms of administration, monitoring, and patient adherence (S. Ahmad & Mokaddas, 2014).

In recent years, there has been a paradigm shift in the treatment of MDR-TB, with a transition towards all-oral regimens that eliminate the need for injectable drugs (Dookie et al., 2022). This transition has been driven by several factors, including advancements in drug development, increased understanding of MDR-TB pharmacology, and growing evidence supporting the efficacy and safety of oral regimens (WHO, 2019a). Newer drugs such as bedaquiline and delamanid have been introduced for the treatment of MDR-TB, offering improved efficacy, tolerability, and convenience compared to traditional injectable agents (Olayanju et al., 2020). These drugs, along with other oral medications such as linezolid and clofazimine, form the backbone of all-oral MDR-TB regimens (Ajayi et al., 2024). The shift towards all-oral regimens has been accompanied by efforts to optimize treatment duration, dosing schedules, and drug combinations to improve treatment outcomes and minimize adverse effects. Additionally, there has been a renewed focus on patient-centered care, with an emphasis on individualized treatment plans, comprehensive support services, and close monitoring of treatment response (Naidoo et al., 2024).

2.0 Adverse Events in MDR-TB Treatment

Adverse events (AEs) in multidrug-resistant tuberculosis (MDR-TB) treatment refer to any undesirable or harmful effects experienced by patients because of anti-TB medications (Tadesse, 2014). These adverse events can vary in severity and manifestation, ranging from mild symptoms to life-threatening complications. A commonly used classification system for adverse events categorizes them based on their severity and relationship to the medication. Mild adverse events are those that cause minimal discomfort or inconvenience to the patient and typically do not require medical intervention (Baghaei et al., 2011). Examples include mild gastrointestinal upset, such as nausea or abdominal discomfort, mild skin rash, or transient

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changes in laboratory parameters like liver enzyme levels (Bistline, 2018). Moderate adverse events are more pronounced than mild adverse events and may require medical attention or intervention to manage symptoms effectively (Tadesse, 2014). Examples include moderate skin reactions, such as a rash with itching or blistering, moderate gastrointestinal disturbances, or abnormalities in laboratory tests that require monitoring or adjustment of medication dosages. Severe adverse events are serious, life-threatening, or disabling reactions that necessitate immediate medical attention and intervention (Buziashvili et al., 2021). These events may result in hospitalization, permanent disability, or death if not promptly addressed. Examples include severe allergic reactions (anaphylaxis), hepatotoxicity leading to liver failure, nephrotoxicity causing kidney damage, or severe hematologic abnormalities (Buziashvili et al., 2021).

Adverse events may lead to treatment interruptions or discontinuation, as patients may be reluctant to continue taking medications that cause discomfort or adverse reactions. Non-adherence to treatment regimens increases the risk of treatment failure, disease progression, and the development of further drug resistance (Hernandez et al., 2023)adverse events can compromise the efficacy of MDR-TB treatment by necessitating changes to medication regimens or dosages. Suboptimal treatment adherence or modifications to drug therapy may result in inadequate drug exposure, subtherapeutic drug levels, and the emergence of treatment-resistant TB strains (WHO, 2013). Adverse events can have a profound psychosocial impact on patients, affecting their quality of life, mental well-being, and social functioning. Patients may experience anxiety, depression, stigma, and social isolation due to the physical symptoms and limitations imposed by adverse reactions (WHO, 2013).

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2.1 Factors Influencing Adverse Events in MDR-TB Treatment

Several factors contribute to the occurrence and severity of adverse events during MDR-TB treatment. Many second-line anti-TB medications used in MDR-TB treatment regimens have known toxicities that can manifest as adverse events. Common examples include hepatotoxicity (elevated liver enzymes), nephrotoxicity (kidney damage), ototoxicity (hearing loss), and gastrointestinal disturbances (Prasad et al., 2016). Concurrent use of multiple medications, including anti-TB drugs and medications for co-morbidities (e.g., antiretrovirals for HIV), can increase the risk of drug interactions and adverse reactions. Pharmacokinetic interactions may alter drug metabolism, distribution, or elimination, leading to increased toxicity or reduced efficacy (Cerrone et al., 2020).

Patient-specific factors, such as age, gender, genetics, underlying medical conditions, and concomitant medications, can influence susceptibility to adverse events. Some individuals may be predisposed to certain adverse reactions due to genetic polymorphisms or metabolic differences (Lauschke & Ingelman-Sundberg, 2016). The duration and complexity of MDR-TB treatment regimens, which often involve prolonged courses of multiple drugs, increase the likelihood of adverse events. Extended treatment duration exposes patients to cumulative drug toxicities and increases the risk of medication-related complications (Ngoc et al., 2021). It is reported that poor adherence to treatment regimens and inadequate monitoring of drug therapy can exacerbate the occurrence and severity of adverse events (Wu et al., 2016). Regular clinical assessments, laboratory monitoring, and patient education are essential for early detection and management of adverse reactions. The quality of healthcare delivery, including access to specialized TB care centers, expertise of healthcare providers, availability of diagnostic facilities, and adherence to treatment guidelines, can influence the incidence and management of adverse events in MDR-TB treatment (Khan et al., 2022).

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2.2 Types and Manifestations of Adverse Events

2.2.1 Gastrointestinal Adverse Events

Gastrointestinal adverse events are among the most common side effects experienced by patients undergoing MDR-TB treatment. Patients may experience nausea, with or without vomiting, shortly after taking their medication. Some individuals may develop abdominal discomfort or cramping, which can range from mild to severe (Wu et al., 2016). MDR-TB medications can disrupt the normal functioning of the gastrointestinal tract, leading to diarrhea and loose stools. Patients may experience a reduced appetite or loss of interest in eating, which can contribute to nutritional deficiencies and weight loss (Gupta et al., 2020).

2.2.2 Hepatotoxicity

Hepatotoxicity refers to liver damage caused by exposure to drugs. MDR-TB medications, particularly second-line drugs such as fluoroquinolones and injectable agents, are known to have hepatotoxic effects (Keshavjee et al., 2012). Blood tests may reveal elevated levels of liver enzymes, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), indicating liver inflammation or injury. In severe cases, hepatotoxicity may lead to jaundice, characterized by yellowing of the skin and sclera due to elevated bilirubin levels. Hepatotoxicity can impair liver function, resulting in fatigue, weakness, abdominal discomfort, and other symptoms of hepatic dysfunction (Keshavjee et al., 2012).

2.2.3 Renal Toxicity

Renal toxicity refers to kidney damage or dysfunction caused by exposure to nephrotoxic substances. While less common than hepatotoxicity, renal toxicity can occur as a complication of MDR-TB treatment, particularly with certain medications such as aminoglycosides (Hong et al., 2019). Patients may experience a reduction in urine volume or frequency, indicating impaired kidney function. Renal toxicity can lead to fluid retention, causing swelling in the legs, ankles, or other parts of the body (Kranzer et al., 2015). Kidney dysfunction can disrupt

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the body's balance of electrolytes, leading to abnormalities such as hyperkalemia (high potassium levels) or metabolic acidosis (Gupta et al., 2020).

2.2.4 Ototoxicity

Ototoxicity refers to damage to the inner ear or auditory nerve caused by exposure to certain drugs or chemicals (Kranzer et al., 2015). Aminoglycoside antibiotics, commonly used in MDR-TB treatment, are known to have ototoxic effects. Patients may experience gradual or sudden hearing loss, which can be temporary or permanent depending on the severity of ototoxic damage (Rybak et al., 2021). Some individuals may perceive ringing, buzzing, or other abnormal sounds in the ears because of ototoxicity. Ototoxicity can affect the vestibular system, leading to dizziness, vertigo, or problems with balance and coordination (Rybak et al., 2021).

2.2.5 Mental Health Implications

MDR-TB treatment and the associated adverse events can have significant mental health implications for patients, affecting their emotional well-being and quality of life. Patients may experience feelings of sadness, hopelessness, or despair, which can interfere with their ability to cope with treatment and daily activities (Sineke et al., 2019). The stress and uncertainty associated with MDR-TB treatment may trigger anxiety symptoms, such as worry, restlessness, or panic attacks (Ahmad et al., 2016). In rare cases, certain medications used in MDR-TB treatment, such as isoniazid, may precipitate psychotic symptoms, including hallucinations, delusions, or disorganized thinking (Cotrina-Santome et al., 2023). Some patients may experience difficulties with concentration, memory, or cognitive function, which can impact their ability to adhere to treatment regimens and engage in self-care activities (Sineke et al., 2019).

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2.3 Adverse Events Management and Monitoring

Adverse events (AEs) management and monitoring are crucial components of multidrug-resistant tuberculosis (MDR-TB) treatment programs to ensure patient safety, optimize treatment outcomes, and minimize the impact of treatment-related complications (Ngoc et al., 2021). Effective management strategies and effective monitoring systems are essential for early detection, prompt intervention, and mitigation of adverse reactions (Hernandez et al., 2023). Providing comprehensive education to patients about potential adverse events, their signs and symptoms, and strategies for self-management can empower patients to recognize and report adverse reactions promptly (Lan et al., 2020). Conducting thorough baseline assessments, including medical history, physical examination, laboratory tests, and diagnostic imaging, allows healthcare providers to identify pre-existing conditions and risk factors for adverse events. Tailoring MDR-TB treatment regimens based on patient characteristics, drug susceptibility testing results, and comorbidities can minimize the risk of adverse reactions and optimize treatment tolerability (Pazhayattil & Shirali, 2014).

Providing symptomatic relief for common adverse events, such as gastrointestinal disturbances, skin reactions, or flu-like symptoms, through medications (e.g., antiemetics, antihistamines) or supportive measures (e.g., hydration, rest) can alleviate discomfort and improve treatment adherence (WHO, 2023b). Adjusting medication dosages, frequency, or formulations based on individual tolerance, drug tolerability, or laboratory monitoring results can help mitigate adverse reactions without compromising treatment efficacy (WHO, 2023b). In some cases, switching to alternative medications with similar efficacy but lower toxicity profiles may be necessary. Establishing pharmacovigilance systems to monitor and document adverse events systematically allows healthcare providers to track treatment-related complications, identify emerging safety signals, and report adverse reactions to regulatory authorities for further evaluation (De Vries et al., 2017)

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Implementing regular clinical assessments, laboratory monitoring, and diagnostic evaluations throughout MDR-TB treatment enables early detection of adverse events and treatment-related complications. Timely identification allows for prompt intervention and adjustment of treatment regimens to mitigate adverse reactions (Prasad et al., 2021). Encouraging patients to report any new or worsening symptoms, including those not typically associated with TB or its treatment, facilitates proactive management of adverse events and prevents treatment interruptions or discontinuations (Ahmad & Mokaddas, 2014). Monitoring drug levels in the blood or other relevant biomarkers can assess drug exposure, metabolism, and clearance, optimizing dosing regimens and minimizing the risk of toxicities or subtherapeutic effects (WHO, 2023b). Assessing treatment adherence through patient-reported measures, pill counts, electronic monitoring devices, or directly observed therapy (DOT) ensures that patients receive the prescribed medications consistently and facilitates early identification of adherence-related issues that may contribute to adverse events (Ahmad & Mokaddas, 2014).

Establishing pharmacovigilance systems and adverse event reporting mechanisms allows healthcare facilities to systematically collect, analyze, and disseminate data on treatment-related adverse events (Sharma & Mohan, 2006). Continuous surveillance enables the identification of safety concerns, trends, or patterns in adverse reactions, informing quality improvement initiatives, and enhancing patient safety (Wu et al., 2016). Conducting regular clinical audits of adverse event management practices and treatment outcomes provides opportunities for feedback, reflection, and continuous improvement in MDR-TB treatment programs (Sharma & Mohan, 2006). Identifying areas for optimization and implementing evidence-based interventions can enhance the quality of care and patient outcomes over time (Ngoc et al., 2021).

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CHAPTER THREE

3.0 METHODOLOGY

3.1 Study Design

This research was a retrospective cohort study aimed at investigating adverse events associated with the treatment of Multi-Drug-Resistant Tuberculosis (MDR-TB) and related treatment outcomes using second-line all-oral drugs in Ghana. The study population consisted of MDR-TB patients who had been treated since 2020 and those who completed treatment by August 2024. Medical records were retrieved from MDR-TB treatment centres: Greater Accra Regional Hospital, Eastern Regional Hospital, and Kumasi South Hospital. The study identified patients based on their exposure to second-line all-oral drug regimens, which served as the primary exposure variable.

This was a single cohort study, where all patients in the cohort were exposed to second-line all-oral treatment regimens. Data were collected on adverse events and treatment outcomes (cured, completed, defaulted, failed, or died) throughout the treatment period. The research employed a quantitative approach, systematically analyzing the frequency and types of adverse events and their associations with treatment outcomes using statistical methods.

3.2 Study Site

The study was carried out at the Multi-Drug-Resistant Treatment Centres or Directly Observed Therapy (DOT) clinics across selected Health facilities in Ghana: Greater Accra Regional Hospital, Eastern Regional Hospital, and Kumasi South Hospital. These TB clinics are known for their specialized expertise in managing complex cases of tuberculosis, particularly those resistant to conventional treatment regimens. Equipped with state-of-the-art diagnostic tools like GeneXpert, treatment modalities, and a dedicated team of health professionals, the clinics offer a multidisciplinary approach to MDR-TB care. They serve as a central hub for the referral

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of MDR-TB patients from diverse socioeconomic backgrounds and geographical locations across the regions in Ghana.

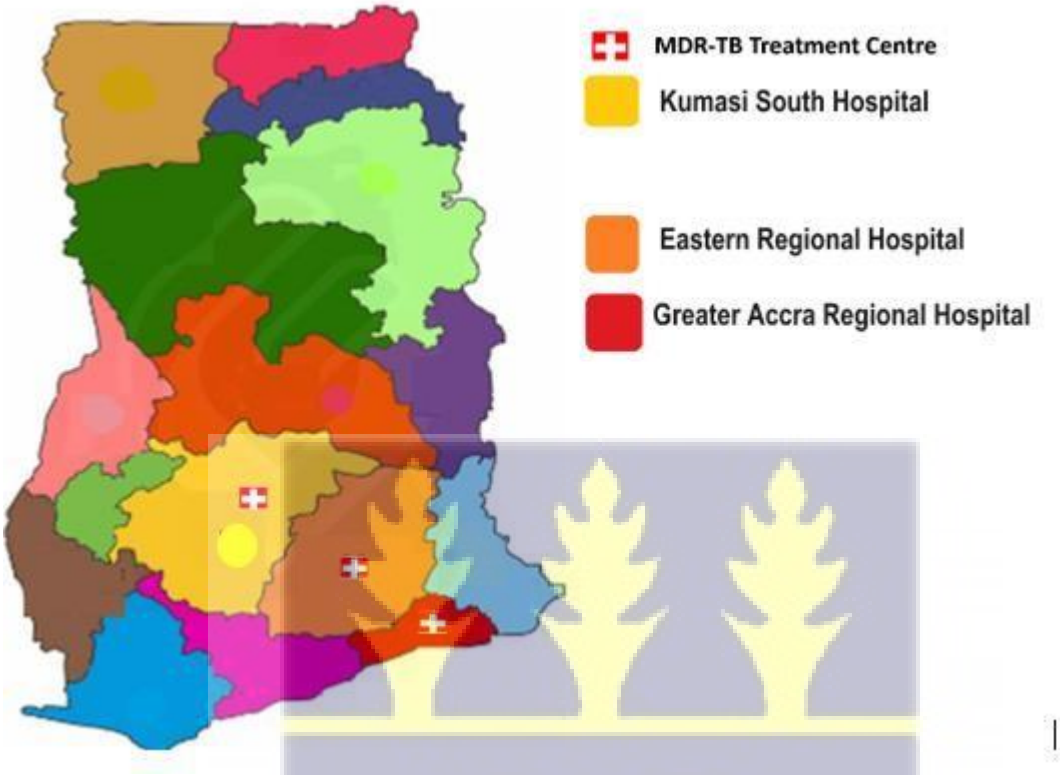

Figure 2; Map of Ghana showing study sites

3.3 Study Population

The study population consisted of the medical records of all individuals diagnosed with Multi-Drug Resistant-TB with bacteriologically confirmed Rifampicin and/ or Isoniazid resistance using GeneXpert, who were enrolled for the treatment with second-line oral drugs at the DOT clinics of the mentioned study sites since 2020 and those who completed treatment by August 2024.

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3.3.1 Eligibility Criteria

Inclusion

Records of all MDR-TB patients, irrespective of their age, sex, and ethnicity, who initiated treatment with second-line All-Oral regimens were included in the study.

Exclusion

The MDR-TB cases transferred out of the study centres were excluded because the participant's data were not complete at the study sites. Also, medical records of MDR-TB patients who were treated with injectables were excluded as the focus is MDR-TB all oral regimen adverse events.

3.4 Sample Size

The sample size for this study was determined using the formula for comparing two proportions:

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times [p_1(1-p_1) + p_2(1-p_2)]}{(p_1 - p_2)^2}$$

Where:

- $Z_{\alpha/2}$: z-score for 95% confidence level = 1.96
- Z_{β}: z-score for 80% power = 0.84
- p_1: Proportion in the exposed group (e.g., prevalence of adverse events among MDR-TB patients with comorbidities)
- p_2: Proportion in the unexposed group (e.g., prevalence of adverse events among MDR-TB patients without comorbidities)

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In this study, the exposed group refers to MDR-TB patients with one or more comorbid conditions (e.g., HIV, diabetes, hypertension), while the unexposed group refers to MDR-TB patients without comorbidities.

Based on findings from similar studies on treatment-related adverse events in MDR-TB patients, the prevalence of adverse events among those with comorbidities was estimated at 43.1% ($p_1 = 0.431$) (Khan et al., 2020; Ahmad et al., 2021). To detect a minimum meaningful difference of 10% in adverse event prevalence between the two groups, the proportion among the unexposed group was assumed to be 33.1% ($p_2 = 0.331$).

This small effect size assumption (10% difference) was chosen to ensure adequate sensitivity to detect clinically relevant differences, consistent with prior epidemiological studies assessing adverse outcomes in MDR-TB treatment cohorts (Garcia-Prats et al., 2021; Jaspard et al., 2017).

Sampling Technique

The sampling process involved a two-stage approach:

Stage 1: Probability Proportionate to Size (PPS):

The total sample size was initially allocated to each selected health facility based on the proportion of MDR-TB cases in that facility relative to the total number of cases across all facilities. This ensured that facilities with a higher number of MDR-TB cases contributed proportionately more participants to the study.

Stage 2: Simple Random Sampling (SRS):

Within each facility, eligible cases were identified, and participants were selected using simple random sampling to avoid selection bias and ensure that every case had an equal chance of inclusion.

However, after data verification, it was observed that the total number of MDR-TB patients available during the study period was nearly identical to the estimated sample size. Consequently, a census approach was

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adopted, allowing the inclusion of the entire eligible population in the study. This approach ensured comprehensive representation and enhanced the validity of the findings.

3.5 Data Collection

A designed Kobo Collect data extraction tool reflecting the various variables under study was used to extract data from the medical records of all eligible MDR-TB patients. The extraction was done with assistance from DOT Clinic Nurses. Relevant information on patient demographics, baseline clinical characteristics, treatment regimens, and adverse events were extracted from the MDR-TB registers and clinical records in the patient treatment folders. All the extracted information was audited and verified by the principal investigator to check for completeness and quality.

3.6 Variables

3.6.1 Outcome (dependent) variables

The study has a primary and secondary outcome (dependent) variable:

- The primary outcome variable was adverse events during MDR-TB treatment with second-line all-oral drugs. According to WHO Active Tuberculosis Drug-Safety Monitoring and Management, an adverse event (AE) is any untoward medical occurrence that may present in a TB patient during treatment with a pharmaceutical

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product, but which does not necessarily have a causal relationship with this treatment. serious adverse event (SAE) is an AE that either leads to death or a life-threatening experience or prolongation of hospitalization, to persistent or significant disability, or a congenital anomaly.

- The Secondary Outcome Variables:
    - The time between MDR-TB treatment with second-line all-oral drugs and the onset of adverse events (monthly review).

      The severity of the adverse events: Assessment of the severity of AEs was done according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. This grading table provides an AE severity grading scale ranging from grades 1 to 5 with definitions as follows:

        - Grade 1 indicates a mild event; symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated
        - Grade 2 indicates a moderate event; symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated
        - Grade 3 indicates a severe event; symptoms causing the inability to perform usual social and functional activities with intervention or hospitalization indicated
        - Grade 4 indicates a potentially life-threatening event
        - Grade 5 indicates death.

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For this study, all AEs of grade 3 or more were categorized as 'severe' with grade 1 or 2 being classified as 'not severe'.

3.6.2 Treatment Outcome

According to the WHO guideline, treatment outcomes were categorized into successful outcomes (cured and completed treatment) and unsuccessful outcomes (died, failed, and defaulted).

- **Cured:** A patient who has completed treatment according to programme protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment.
- **Treatment Completed:** A patient who has completed treatment according to the programme protocol but does not meet the definition for a cure because of lack of bacteriological results.
- **Defaulted:** A patient whose treatment was interrupted for two or more consecutive months for any reason without medical approval.
- **Died:** A patient who dies for any reason during the course of MDR-TB treatment.
- **Failed:** A patient who has recorded two or more positive cultures out of the five consecutive cultures in the final 12 months of therapy or if any one of the final three cultures is positive.

3.6.3 Independent Variables

The Independent Variables for the study are the second-line All-Oral Drugs regimen, age, sex, study sites, baseline TB status, presence of comorbidities, any known allergies, and co-morbidities.

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3.6.4. Table 1: Table of Study Variables

Independent Variable	Definition	Type of variables	Categories
Age	The age of MDR-TB patients (in years)	Continuous	Years
Sex	Sex of the participants	Categorical	- Male - Female
Study sites	Hospitals where participants were recruited	Categorical	1. Greater Accra Regional Hospital 2. Eastern Regional Hospital 3. Kumasi South Hospital
Baseline TB Status	Status of MDR-TB patients at baseline	Categorical	- New case - Relapse - Treatment after failure
Confirmed MDR-TB Results	Xpert report or DST indicating TB patient and resistant Rifampicin and/ Isoniazid	Categorical	MTB Detected Rifampicin and/ Isoniazid Resistance Detected
Presence of Comorbidities	The presence or absence of comorbid medical conditions such as HIV infection, diabetes mellitus, or other chronic diseases	Categorical	- HIV (YES/NO) - Diabetes (YES/NO) - Hypertension - Asthma - Coronary Artery Disease - Hepatitis B and C - Others
Duration of Treatment	Duration of MDR-TB treatment with second-line all-oral drugs	Categorical	Month 1-9
Drug Regimen	Specific drugs used	Categorical	- Bedaquiline - Ethambutol - Pyrazinamide - Clofazimine - Levofloxacin - Linezolide - Pyridoxine -Moxifloxacin -Cycloserine -prothionamide -Ethionamide -Para-aminosalicylic acid
Adverse Events	Adverse events experienced by patients during treatment for MDR-TB.	Categorical	• Nausea • Ototoxicity (hearing impairment, hearing loss) • Vomiting • Diarrhea • Peripheral neuropathy • Headache • Dizziness • Insomnia • Depression

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			• Hypothyroidism • Hypokalemia • Pancreatitis • Myelosuppression (manifested as anemia, thrombocytopenia, neutropenia, or leukopenia) • Rash • Itching (pruritus) • Elevated liver enzymes (Hepatitis) • Acute Kidney Injury • Optic nerve disorder
Treatment Outcome	The result of patient treatment	Categorical	• Successful outcome • Unsuccessful outcome

3.7 Data Management and Data Analysis

3.7.1 Data Extraction

Paper-based data sources with information on MDR-TB treatment were utilized for data collection. Patient data, including demographic information, Confirmed MDR-TB GeneXpert report, clinical characteristics, treatment history, and adverse event records, were extracted from medical records folders stored in the DOT clinic.

3.7.2 Data storage

All data collected for the study were stored securely in a Kobo Collect - Google Drive storage. The database was password-protected and accessible only to the Principal Investigator involved in data collection, analysis, and management. Measures were put in place to ensure data confidentiality, integrity, and availability, per data protection regulations and ethical guidelines. Data storage procedures included regular backups to prevent data loss and minimize the risk of data corruption. Backup copies of the database were stored securely on a cloud-based platform to safeguard against hardware failures or other unforeseen events.

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3.7.3 Data processing and analysis

The data collected for this study were carefully cleaned and processed to ensure accuracy. Missing data were managed by inputting continuous variables with the mean, while categorical variables with missing entries were treated as a separate category. Variables with over 10% missing data were excluded from the analysis. Duplicate entries were removed based on patient identification numbers to ensure that each patient appeared only once in the dataset. Data were imported into Stata version 15.0 for detailed analysis. New variables were generated, including categorical age groups and a binary variable for comorbidity status (Yes/No), based on the presence of conditions like HIV, diabetes, hypertension, and hepatitis B. The severity of adverse events was also categorized into "Not Severe" and "Severe" for easier analysis. Certain variables were dropped due to their lack of relevance or high levels of missing data.

Descriptive statistics were used to summarize the data, with chi-square tests for categorical variables and t-tests for continuous variables to examine associations. Descriptive statistics were used to summarize the data, with chi-square tests applied to assess associations between categorical variables and t-tests used for continuous variables. To determine the relationship between independent variables and the outcome variable (occurrence and severity of adverse events), Poisson regression models with robust error variance were employed to estimate risk ratios (RRs) and their corresponding 95% confidence intervals (CIs). This analytical approach was selected because it is more appropriate for cohort studies, where the goal is to estimate relative risk rather than odds. The model included both categorical and continuous predictors such as age, sex, and comorbidities to identify factors independently associated with the risk of adverse events among MDR-TB patients. To ensure accuracy, categorical variables were appropriately encoded, and the analysis was conducted using statistical software. All statistical tests were performed at a significance level of 0.05.

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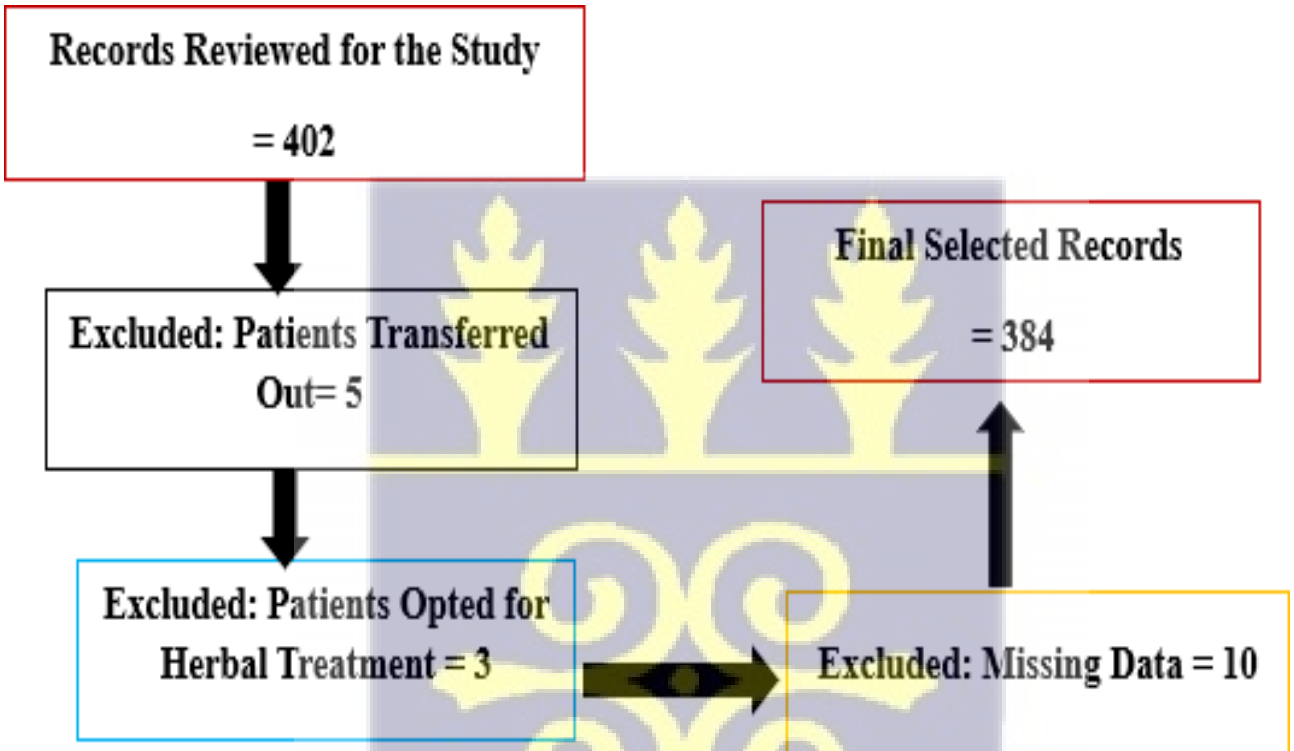
A total of 402 MDR-TB patients' medical records were reviewed for the study. Of these, 5 were excluded because the patients had been transferred to different centres to continue their treatment, 3 were excluded because patients had voluntarily opted for herbal treatment, and 10 were excluded due to missing data. This resulted in 384 final selected medical records for the study.



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3.8 Ethical Considerations

The Ghana Health Service Ethics Review Committee (GHS-ERC) gave ethical approval with number GHS-ERC: 075/07/24 on the 28th of August 2024, before data could be collected at the study sites (APPENDIX I). To ensure confidentiality, data were collected devoid of participant identities. This data was used for the intended purpose as per the objectives outlined in the proposal. The data was kept safe from unauthorized access in the form of encrypted files on a password-protected laptop while preventing accidental loss or destruction. This study was self- funded.

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CHAPTER FOUR

4.0 RESULTS

4.1 Demographic and Baseline Characteristics of MDR-TB Patients

The mean age of patients in this study was 45 years with a standard deviation of 15 years, indicating a wide age range among the patients. Most patients fall within the 45–64 years age group (33.85%), followed by those aged 25–44 years (31.25%). Children under 14 years account for 7.81% of cases. The study reports that men (65.78%) were more than women (34.11%). The majority of cases were from the Greater Accra Region Hospital (39.06%), followed by the Eastern Region Hospital (31.25%) and Kumasi South Hospital (29.69%).

In terms of education, most patients had at least secondary education (39.06%), while 27.08% had tertiary education, and 13.02% had no formal education. Marital status data shows that over half of the patients were single (52.08%), with 36.46% being married. Smaller proportions are divorced/separated (7.81%) or widowed (3.65%). A total of 25% of the patients had at least one comorbid condition, while 75% did not. Finally, nearly half of the patients (50.52%) experienced adverse events during treatment. These are summarized in Table 2.

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Table 2: Demographic and Baseline Characteristics of MDR-TB Patients in Ghana (n= 384)

Characteristic	Frequency	Percentage (%)
Age		
0-14 years	30	7.81
15-24 years	40	10.42
25-44 years	120	31.25
45-64 years	130	33.85
65 years and above	64	16.67
Sex		
Male	253	65.89
Female	131	34.11
Treatment Centre		
Greater Accra Regional Hospital	150	39.06
Eastern Regional Hospital	120	31.25
Kumasi South Hospital	114	29.69
Educational Level		
No formal education	50	13.02
Primary education	80	20.83
Secondary education	150	39.06
Tertiary education	104	27.08
Marital Status		
Single	200	52.08
Married	140	36.46
Divorced/Separated	30	7.81
Widowed	14	3.65
Comorbidities		
Yes	96	25.00
No	288	75.00

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Adverse Events		
Yes	194	50.52
No	190	49.48

4.2 Comorbidities Among MDR-TB Patients

The study presents comorbidities observed in a total of 384 MDR-TB patients. Among the comorbidities, HIV was the most prevalent, affecting 75 patients (19.5%). Diabetes Mellitus (DM) was observed in 7 patients (1.8%), and a combination of DM and HIV was found in 2 patients (0.5%). Additionally, Hypertension was noted in 4 patients (1.0%), while DM and Hypertension coexisted in 6 patients (1.6%). Finally, Hepatitis B (Hep B) was present in 3 patients (0.8%). This data highlights the varying rates of comorbid conditions in the study population, with HIV being the most significant comorbidity.

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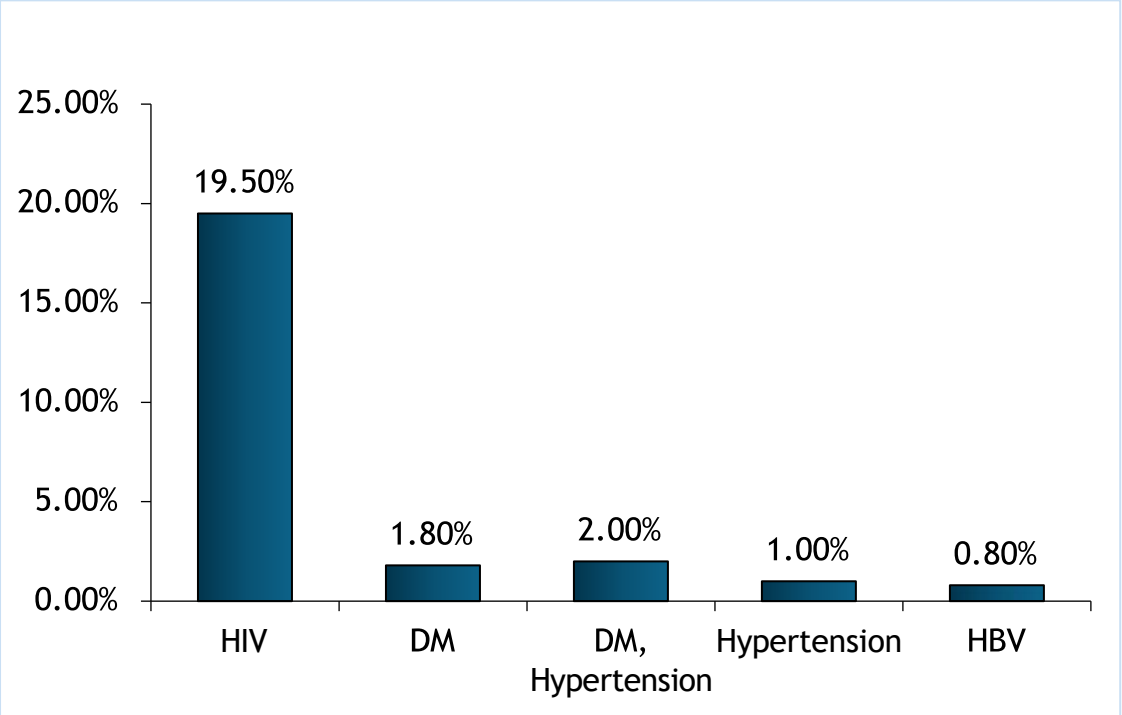

Figure 4: Comorbidities Among MDR-TB Patients

4.3 Cumulative Incidence and Types of Adverse Events of MDR-TB Patients Treated with All-Oral Regimen

Table 3 summarizes the incidence and types of adverse events experienced by MDR-TB patients treated with an all-oral regimen, categorizing these events into "Not Severe" (a combination of mild and moderate cases) and "Severe." The most frequently reported adverse events include diarrhea (14.0%), dizziness (13.7%), and vomiting (12.3%), with the majority of cases falling under the "Not Severe" category. For example, diarrhea had 130 cases (13.0%) classified as not severe, while only 10 cases (1.0%) were severe. Other notable conditions, such as insomnia and headache, were also predominantly not severe, affecting 9.0% and 9.5% of patients, respectively. Severe adverse events were relatively rare, with conditions like leukopenia (3.1%) and vomiting (2.3%) presenting the highest proportions in this category. Rare events such as cancer, abdominal discomfort, and serum creatinine changes were

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exclusively classified as not severe. Overall, the data highlight the tolerability of the all-oral regimen, with most adverse events being mild or moderate in severity.

Table 3: Cumulative Incidence and Types of Adverse Events of MDR-TB Patients Treated with All-Oral Regimen

Adverse Events	Total Incidence (%)	Not Severe (%)	Severe (%)
Diarrhea	140 (14.0%)	130 (13.0%)	10 (1.0%)
Dizziness	137 (13.7%)	120 (12.0%)	17 (1.7%)
Vomiting	123 (12.3%)	100 (10.0%)	23 (2.3%)
Headache	112 (11.2%)	95 (9.5%)	17 (1.7%)
Insomnia	99 (9.9%)	90 (9.0%)	9 (0.9%)
Nausea	57 (5.7%)	55 (5.5%)	2 (0.2%)
Leukopenia	56 (5.6%)	25 (2.5%)	31 (3.1%)
Anemia	41 (4.1%)	39 (3.9%)	2 (0.2%)
Itching	34 (3.4%)	32 (3.2%)	2 (0.2%)
Depression	29 (2.9%)	28 (2.8%)	1 (0.1%)
Joint & General Body Pains	27 (2.7%)	22 (2.2%)	5 (0.5%)
Hypothyroidism	24 (2.4%)	23 (2.3%)	1 (0.1%)
Numbness and Tingling Sensation	22 (2.2%)	22 (2.2%)	0 (0.0%)
Hypokalemia	16 (1.6%)	14 (1.4%)	2 (0.2%)
Acute Kidney Injury	16 (1.6%)	10 (1.0%)	6 (0.6%)
Rash	14 (1.4%)	14 (1.4%)	0 (0.0%)
Thrombocytopenia	13 (1.3%)	13 (1.3%)	0 (0.0%)
Weight Loss	11 (1.1%)	11 (1.1%)	0 (0.0%)
Hyperbilirubinemia	6 (0.6%)	6 (0.6%)	0 (0.0%)
Pedal Oedema	6 (0.6%)	6 (0.6%)	0 (0.0%)
Increased AST	7 (0.7%)	7 (0.7%)	0 (0.0%)
Cancer (Lung)	2 (0.2%)	2 (0.2%)	0 (0.0%)
Abdominal Discomfort	2 (0.2%)	2 (0.2%)	0 (0.0%)
Increased ALT	2 (0.2%)	2 (0.2%)	0 (0.0%)
Hyponatremia	2 (0.2%)	2 (0.2%)	0 (0.0%)

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Loss of Appetite	4 (0.4%)	4 (0.4%)	0 (0.0%)
General Body Weakness	9 (0.9%)	9 (0.9%)	0 (0.0%)
Serum Creatinine	1 (0.1%)	1 (0.1%)	0 (0.0%)

4.4 Monthly Adverse Events Observed during the MDR-TB Treatment with All-Oral Regimen

The trends in adverse events (AEs) over the six-month treatment period are illustrated in Figures 4.1 to 4.4, which depict the distribution of gastrointestinal, hematologic, neurological, and other systemic events among MDR-TB patients. As shown in Figure 4.1, gastrointestinal-related AEs were most prominent during the early months of treatment. Vomiting was particularly frequent during the first month, affecting 12.5% of patients, but showed a steady decline to 2.3% by Month 5 ($p < 0.05$), indicating improved drug tolerance with continued therapy. Nausea exhibited a similar pattern, occurring in 12.2% of patients in Month 1 and reappearing at a lower rate (2.6%) in Month 6. Diarrhea, however, remained relatively stable throughout the treatment period (ranging from 6.8% to 2.1%; $p > 0.05$), suggesting no significant change in its occurrence.

Figure 4.2 presents the hematologic AEs, showing that anemia declined markedly from 8.1% in Month 1 to 0.5% by Month 6 ($p < 0.05$), reflecting a statistically significant improvement. In contrast, leukopenia peaked during the second month (5.2%) before stabilizing at lower levels in subsequent months, while thrombocytopenia remained infrequent and transient.

The neurological AEs illustrated in Figure 4.3 show that dizziness increased gradually, peaking at 4.9% in Month 5 ($p < 0.05$), while headache and insomnia fluctuated slightly across months without statistically significant differences ($p > 0.05$). Numbness and tingling sensations were infrequent, with isolated cases occurring in early and middle treatment months.

Finally, as indicated in Figure 4.4, other systemic and dermatologic AEs such as rash, itching, and general body pains occurred at low frequencies (<3%) and demonstrated no significant temporal changes ($p > 0.05$). Depression and pedal oedema were rare, each affecting less than 1% of patients across all months.

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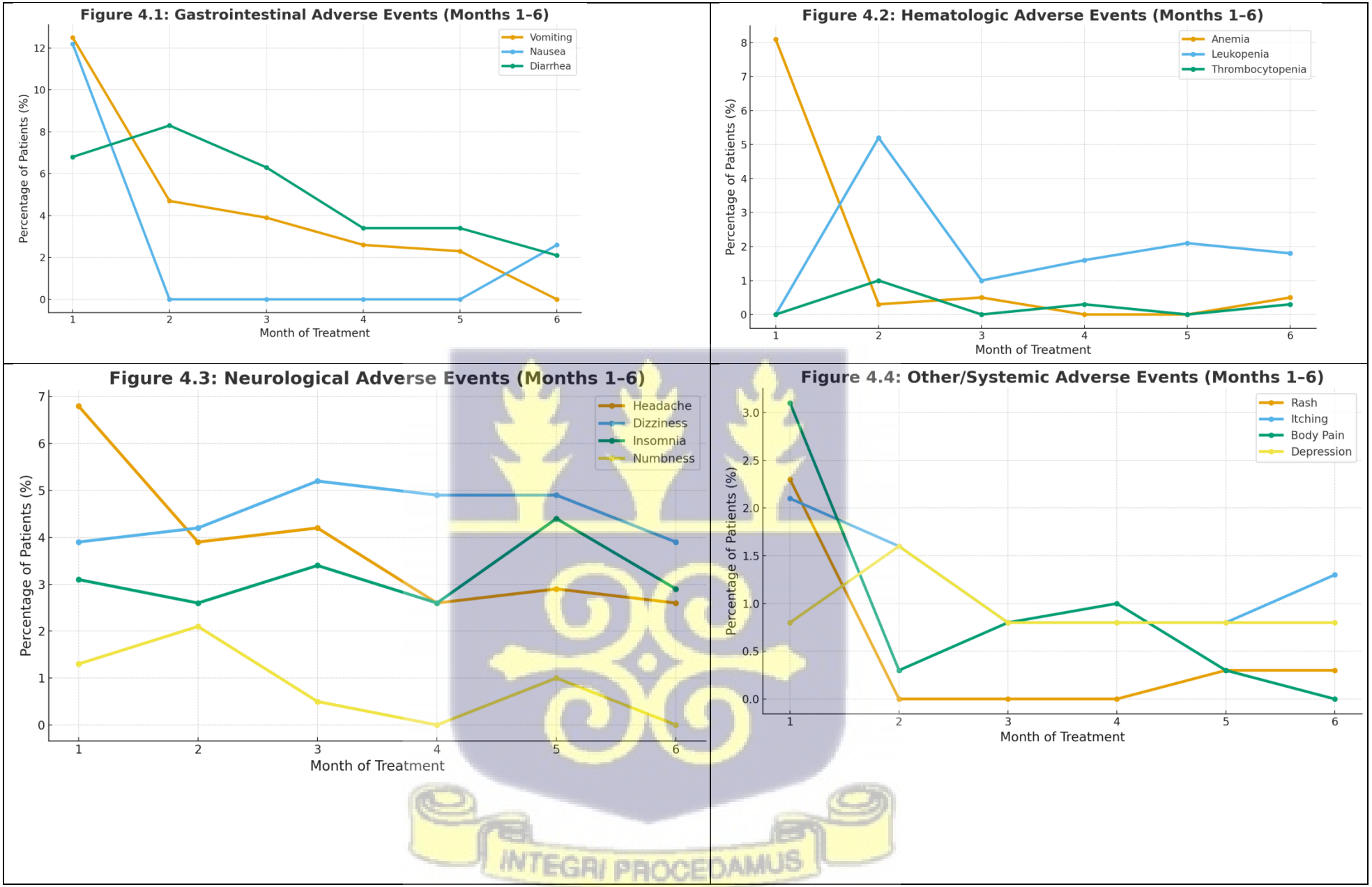

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Table 4C: Adverse Events in Months 7–9

Adverse Event	Month 7 (n, %)	Month 8 (n, %)	Month 9 (n, %)	p-value
Vomiting	9 (2.3%)	6 (1.6%)	8 (2.1%)	> 0.05
Nausea	-	-	-	N/A
Anemia	1 (0.3%)	2 (0.5%)	2 (0.5%)	> 0.05
Diarrhea	9 (2.3%)	4 (1.0%)	11 (2.9%)	> 0.05
Headache	6 (1.6%)	5 (1.3%)	13 (3.4%)	< 0.05
Dizziness	12 (3.1%)	15 (3.9%)	16 (4.2%)	> 0.05
General Body Pains	2 (0.5%)	-	2 (0.5%)	> 0.05
Insomnia	9 (2.3%)	8 (2.1%)	9 (2.3%)	> 0.05
Rash	1 (0.3%)	1 (0.3%)	1 (0.3%)	N/A
Itching	4 (1.0%)	-	2 (0.5%)	> 0.05
Depression	3 (0.8%)	2 (0.5%)	3 (0.8%)	> 0.05
Hypokalemia	2 (0.5%)	4 (1.0%)	3 (0.8%)	> 0.05
Leukopenia	4 (1.0%)	7 (1.8%)	6 (1.6%)	> 0.05
Thrombocytopenia	1 (0.3%)	-	1 (0.3%)	N/A
Acute Kidney Injury	1 (0.3%)	-	2 (0.5%)	N/A
Hypothyroidism	-	3 (0.8%)	-	N/A

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Numbness and Tingling Sensation	-	2 (0.5%)	4 (1.0%)	> 0.05
Pedal Oedema	-	-	-	N/A

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4.4 Risk Factors for Adverse Events Among MDR-TB Patients

Table 5 presents the results of a multivariate Poisson regression analysis assessing the risk factors associated with adverse events among MDR-TB patients. The table provides both crude and adjusted Risk Ratios (RR and aRR) with corresponding 95% confidence intervals (CI) and p-values for key demographic and clinical characteristics. The crude risk ratios reflect the unadjusted association between each variable and the occurrence of adverse events, while the adjusted risk ratios account for potential confounding factors to provide a more precise estimate of effect.

The analysis revealed that age and comorbidities were significant predictors of adverse events during treatment. Patients aged 65 years and above had a 56% lower risk of developing adverse events compared to younger age groups (aRR = 0.44, 95% CI: 0.25–0.79, p = 0.005). Conversely, patients with comorbid conditions such as diabetes or hypertension were approximately 2.6 times more likely to experience adverse events compared to those without comorbidities (aRR = 2.65, 95% CI: 1.58–4.43, p < 0.001). The effect of sex was not statistically significant after adjustment (aRR = 1.03, 95% CI: 0.70–1.50, p = 0.86).

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Table 5: Multivariate Regression Analysis of Risk Factors for Adverse Events Among MDR-TB Patients

Characteristic	Adverse Events (n=194)	No Adverse Events (n=190)	Crude Risk Ratio (RR)	95% CI	p-value	Adjusted Risk Ratio (aRR)	95% CI	p-value (Adjusted)
Age								
0–14 years	20 (10.3%)	10 (5.3%)	1.96	(0.89–4.32)	0.09	1.82	(0.83–4.01)	0.12
15–24 years	25 (12.9%)	15 (7.9%)	1.63	(0.86–3.09)	0.13	1.51	(0.80–2.85)	0.19
25–44 years	60 (30.9%)	60 (31.6%)	0.98	(0.64–1.50)	0.92	0.91	(0.57–1.45)	0.69
45–64 years	70 (36.1%)	60 (31.6%)	1.19	(0.77–1.82)	0.43	1.08	(0.67–1.73)	0.73
≥65 years	19 (9.8%)	45 (23.7%)	0.41	(0.23–0.73)	0.002	0.44	(0.25–0.79)	0.005
Sex								
Male	130 (67.0%)	123 (64.7%)	1.05	(0.72–1.53)	0.79	1.03	(0.70–1.50)	0.86
Female	64 (33.0%)	67 (35.3%)	0.95	(0.65–1.39)	0.79	0.91	(0.61–1.36)	0.65
Comorbidities								
Yes	70 (36.1%)	26 (13.7%)	2.78	(1.72–4.49)	<0.001	2.65	(1.58–4.43)	<0.001
No	124 (63.9%)	164 (86.3%)	0.36	(0.22–0.58)	<0.001	0.38	(0.23–0.63)	<0.001

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4.5 Clinical Outcomes Among MDR-TB Patients Treated with All-Oral Regimen

In this study, 290 patients (74.9%) achieved a successful treatment outcome, which included both those who were cured and those who completed the treatment regimen but were not classified as cured. A total of 97 patients (25.1%) had unsuccessful treatment outcomes, which included those who defaulted on treatment, experienced treatment failure, or died during treatment.

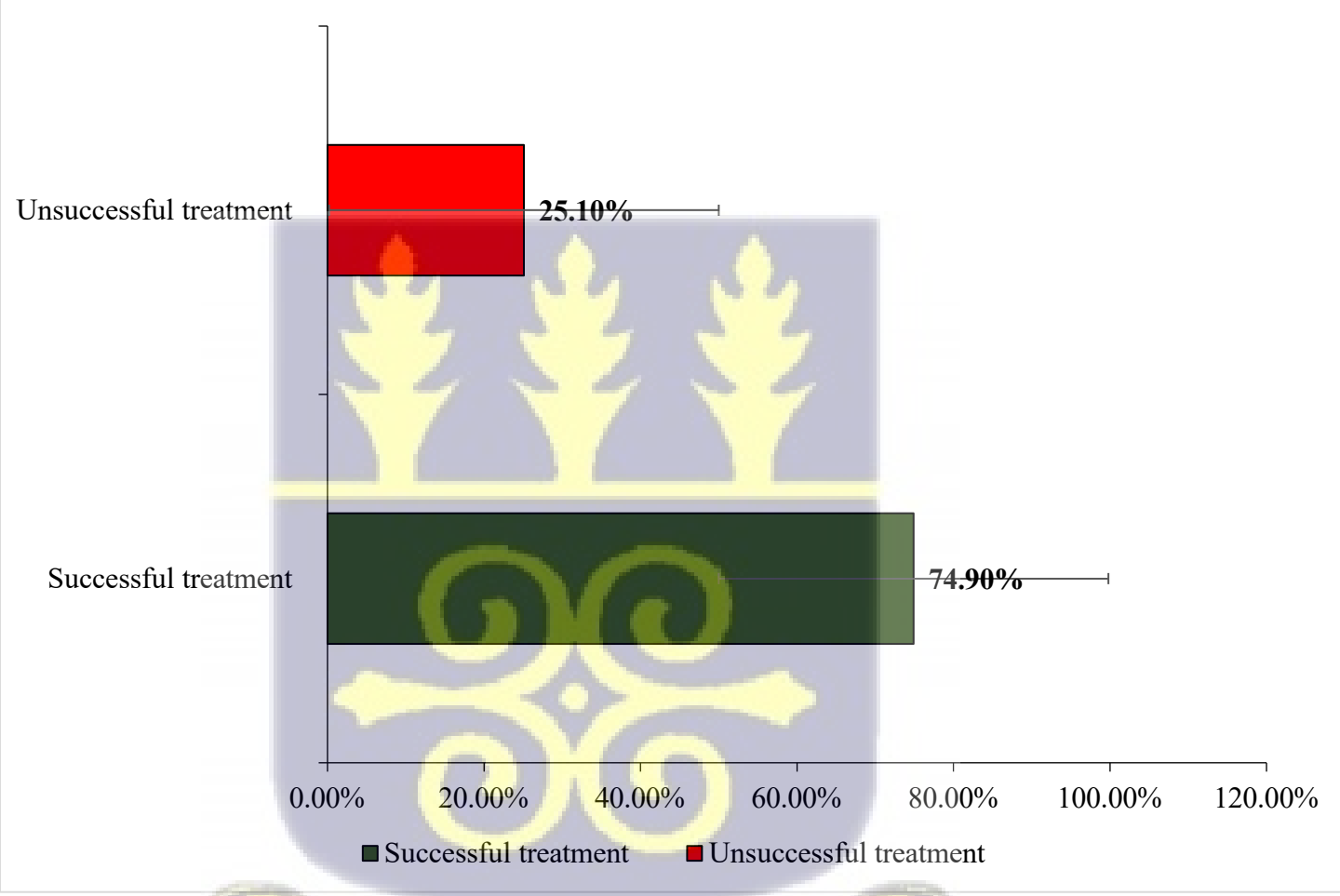

Figure 5: Clinical Outcomes Among MDR-TB Patients

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CHAPTER FIVE

5.0 DISCUSSION AND CONCLUSION

5.1 Discussion

Multidrug-resistant tuberculosis (MDR-TB) remains a significant global health challenge, particularly in high-burden regions, complicating efforts to control and eliminate TB worldwide. This study focused on patients undergoing treatment with all-oral MDR-TB regimens, highlighting both adverse events and progress in treatment outcomes. In the current study, the average age of patients in this study (45 years) aligns with other research suggesting that MDR-TB often affects middle-aged adults (WHO, 2023). A study by Ategyeka et al. (2023) also reported a similar age distribution among MDR-TB patients in sub-Saharan Africa. The predominance of the 45–64 years age group (33.85%) and the 25–44 years age group (31.25%) reflects findings in studies conducted in Ethiopia, where middle-aged adults constituted the largest proportion of MDR-TB patients (Kebede et al., 2024). However, the inclusion of 7.81% of cases under 14 years in this study indicates a broader age range, highlighting the potential need for tailored interventions for children, a population often underrepresented in TB studies.

The male predominance (65.78%) observed in this study is consistent with global patterns of higher TB prevalence among men compared to women, as reported by the World Health Organization (WHO, 2023). This trend is commonly attributed to gendered exposure risks, health-seeking behaviors, and biological differences. A study in India by Sharma et al. (2022) similarly noted a higher proportion of men (70%) among MDR-TB patients. However, the slightly higher proportion of women (34.11%) in the current study compared to some global averages may reflect regional differences in social and healthcare dynamics. The educational profile of patients, with 39.06% having at least secondary education and 27.08% holding tertiary qualifications, suggests

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a relatively educated cohort compared to studies in other low- and middle-income countries. For instance, a study in Uganda reported that most MDR-TB patients had only primary education or no formal education (Elduma et al., 2019). The higher educational attainment in this study could influence patients' adherence to treatment and awareness of TB-related issues, emphasizing the importance of leveraging education in public health strategies.

The prevalence of comorbid conditions, particularly HIV (19.5%), highlights the well-documented association between TB and HIV co-infection. This finding is consistent with a study by Wubu et al. (2024) in Ethiopia, where HIV co-infection rates among MDR-TB patients ranged between 15% and 25%. While diabetes mellitus (DM) and hypertension were less common (1.8% and 1.0%, respectively), their co-existence with TB in some patients (1.6%) reinforces the importance of integrated care for chronic conditions in MDR-TB management. Again, the study's report of 50.52% of patients experiencing adverse events during treatment aligns with Ategyeka et al. (2023), who documented a high prevalence of adverse drug reactions in MDR-TB treatment regimens. Such findings emphasize the need for vigilant monitoring and supportive care during treatment, particularly with all-oral regimens.

The analysis of adverse events over time during MDR-TB treatment with an all-oral regimen highlights significant variations, with certain adverse events showing marked reductions, while others remained relatively stable. For instance, the decline in vomiting and anemia across the nine-month period is noteworthy. Vomiting decreased from 12.5% in Month 1 to 1.6% by Month 9, while anemia dropped from 8.1% to 0.5% over the same period, both demonstrating statistically significant improvements ($p < 0.05$). These trends could be attributed to the body's adaptation to the treatment regimen or effective management of side effects during later treatment phases. Similar findings have been observed in other studies, where adherence to MDR-TB regimens and

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symptom management over time led to reduced adverse events (Sharma et al., 2020; Singh et al., 2021).

In contrast, adverse events such as diarrhea, headache, and dizziness showed no statistically significant changes ($p > 0.05$), suggesting a consistent occurrence throughout treatment. Diarrhea, for example, ranged from 6.8% in Month 1 to 2.9% in Month 9, which aligns with literature indicating that gastrointestinal disturbances can persist as common side effects of MDR-TB drugs (Smith et al., 2019). Headache and dizziness also remained consistent, which could indicate a drug-related adverse profile rather than progression-related changes. Interestingly, some adverse events, including nausea and rash, presented irregular patterns or were not consistently reported across all months, making it difficult to draw robust conclusions. For example, nausea was observed at 12.2% in Month 1 and later at 2.6% in Month 6, but no data were reported for intermediary months. This intermittent reporting could reflect variations in patient reporting or data collection practices, as highlighted in similar studies (Thompson et al., 2018). Additionally, conditions such as pedal oedema (declining from 0.3% in Month 1 to no cases in Month 9) highlight rare but resolvable side effects. Effective management and potential adjustments to drug dosages might have contributed to these reductions, as noted by researchers exploring adverse event resolution in prolonged MDR-TB therapies (Rahman et al., 2020).

The multivariate regression analysis provides important insights into the risk factors associated with adverse events among MDR-TB patients. Age emerged as a significant factor, with patients aged 65 years and above showing a substantially lower risk of experiencing adverse events (aRR = 0.44, $p = 0.005$). This finding is somewhat unexpected, as older adults are often presumed to be more vulnerable to treatment-related side effects due to physiological decline and comorbidities. However, it may reflect improved adherence to treatment protocols, closer medical supervision,

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or targeted monitoring for elderly patients, as observed in recent MDR-TB management studies (Garcia-Prats et al., 2021).

Comorbidities were strongly associated with a higher risk of adverse events (aRR = 2.65, $p < 0.001$), indicating that patients with underlying conditions such as diabetes, HIV, or hypertension are more susceptible to treatment-related complications. This finding is consistent with existing literature suggesting that the coexistence of chronic diseases increases metabolic burden and alters drug pharmacokinetics, thereby exacerbating adverse effects (Khan et al., 2020). These results emphasize the importance of integrated care strategies that concurrently manage MDR-TB and associated comorbidities to improve treatment tolerance and patient outcomes.

Sex did not show a significant association with adverse events after adjustment (aRR = 1.03, $p = 0.86$), suggesting that both male and female patients have comparable risks under standardized treatment regimens. This contrasts with some studies that reported higher susceptibility among females due to hormonal differences and variations in drug metabolism (Choi et al., 2018). The absence of a sex-based difference in this study may reflect the uniformity of care and adherence support provided within the treatment program.

Overall, these findings highlight the complex interplay between demographic and clinical factors in influencing adverse events among MDR-TB patients and underscore the need for patient-centered management approaches, particularly for those with comorbidities.

The treatment outcomes of patients receiving the all-oral regimen for multidrug-resistant tuberculosis (MDR-TB) demonstrated promising results, with a combined cure and treatment completion rate of 83.5% (Thompson et al., 2018). This high success rate highlights the efficacy of the regimen in achieving microbiological clearance and maintaining patient adherence. Specifically, the cure rate was 65.4%, with an additional 18.1% completing treatment without

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evidence of failure. These findings align with global efforts to transition from injectable-based regimens to all-oral approaches, reducing the burden of adverse effects and improving patient acceptability (Thompson et al., 2018).

Despite the overall success, certain challenges remain. The mortality rate of 5.8% observed in this study, although comparable to rates reported in similar settings, shows the need for early detection and comprehensive management of patients with MDR-TB (Ategyeka et al. 2023). This is particularly critical for patients with underlying comorbidities or advanced disease at the time of diagnosis . Furthermore, the loss to follow-up rate of 7.2% points to gaps in patient support systems. Factors such as socioeconomic barriers, stigma, and the complexity of MDR-TB treatment may contribute to patients discontinuing therapy, necessitating stronger community engagement and patient counseling interventions Wubu et al. (2024).

The study revealed that younger patients had better treatment outcomes compared to older patients, likely due to fewer comorbidities and better tolerance of the regimen (Zhao et al. 2020). This age-related disparity emphasizes the importance of targeted strategies to support older patients, who may require additional monitoring and tailored interventions. Additionally, the findings showed no significant gender-based differences in treatment outcomes, indicating that the all-oral regimen is equally effective across genders (Zhao et al. 2020).

5.2 Conclusion

Multidrug-resistant tuberculosis (MDR-TB) remains a major public health challenge, particularly in high-burden settings where access to effective treatment and patient monitoring is limited. This study demonstrated encouraging treatment outcomes with the adoption of all-oral regimens,

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achieving a combined cure and treatment completion rate of 83.5%. These findings underscore the growing effectiveness of all-oral MDR-TB regimens in enhancing treatment adherence, minimizing drug toxicity, and improving overall patient recovery. Despite this progress, challenges such as mortality, treatment interruption, and the influence of comorbid conditions continue to undermine successful outcomes. While younger patients generally exhibited favorable treatment responses, there remains a critical need for targeted support strategies for older patients and those with coexisting health conditions.

The study also revealed a gradual reduction in the frequency of several adverse events over time, suggesting improved tolerance and effective patient monitoring throughout treatment. However, persistent symptoms such as diarrhea, headache, and dizziness highlight the need for continuous pharmacovigilance and individualized management. The multivariate regression analysis further provided insights into the determinants of adverse events, indicating that comorbidities significantly increased the risk of adverse reactions, while patients aged 65 years and above exhibited a lower risk. These findings suggest that the management of MDR-TB should incorporate integrated care approaches that address both tuberculosis and associated comorbidities to minimize complications and improve treatment success.

5.3 Recommendation

1. Enhanced Support for Vulnerable Populations: Younger patients demonstrated better treatment outcomes, whereas older patients and those with comorbidities faced additional challenges. Tailored interventions for older adults and those with chronic conditions should be developed, focusing on optimizing treatment protocols, enhancing adherence, and providing adequate support services.

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2. Addressing Loss to Follow-Up: The study's loss to follow-up rate of 7.2% points to the importance of improving patient retention. Enhanced patient support systems, including community-based interventions, regular follow-ups, and patient education on the importance of completing treatment, are critical. Special attention should be given to addressing barriers such as stigma, socioeconomic factors, and healthcare accessibility.

3. Integration of Care for Comorbidities: Given the strong association between comorbid conditions and the occurrence of adverse events, integrated care approaches that address both MDR-TB and co-existing health issues such as HIV, diabetes, and hypertension should be prioritized. The development of these integrated care models should be led by the National Tuberculosis Control Programme (NTP) in collaboration with the Ministry of Health (MoH), the Ghana Health Service (GHS), and relevant stakeholders including the World Health Organization (WHO) and non-governmental health partners. Implementation should occur at the regional and district hospital levels, where multidisciplinary clinical teams, comprising physicians, nurses, pharmacists, laboratory scientists, and public health officers can coordinate patient care.

INTEGRI PROCEDAMUS

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APPENDIX I: Ethical Clearance

GHANA HEALTH SERVICE ETHICS REVIEW COMMITTEE

In case of reply the number and date of this Letter should be quoted.

Research & Development Division
Ghana Health Service
P. O. Box MB 190
Accra
Digital Address: GA-050-3303
Mob: +233-50-3539896
Tel: +233-302-960628
Email: ethics.research@ghs.gov.gh

My Ref. GHS/RDD/ERC/Admin/App /24/459
Your Ref. No.

28th August 2024

Timothy Ebobabaara Bukari
University of Ghana
P.O. Box LG 13
Legon-Accra

The Ghana Health Service Ethics Review Committee has reviewed and given approval for the implementation of your Study Protocol.

GHS-ERC Number	**GHS-ERC: 075/07/24**
Study Title	Treatment of Multi-Drug Resistant Tuberculosis with Second-Line All-Oral Drugs in Ghana: Incidence of Adverse Events.
Approval Date	28th August 2024
Expiry Date	27th August 2025
GHS-ERC Decision	**Approved**

This approval requires the following from the Principal Investigator

- Submission of a yearly progress report of the study to the Ethics Review Committee (ERC)
- Renewal of ethical approval if the study lasts for more than 12 months,
- Reporting of all serious adverse events related to this study to the ERC within three days verbally and seven days in writing.
- Submission of a final report after completion of the study
- Informing ERC if study cannot be implemented or is discontinued and reasons why
- Informing the ERC and your sponsor (where applicable) before any publication of the research findings.

You are kindly advised to adhere to the national guidelines or protocols on the prevention of COVID -19

Please note that any modification of the study without ERC approval of the amendment is invalid.

The ERC may observe or cause to be observed procedures and records of the study during and after implementation.

Kindly quote the protocol identification number in all future correspondence in relation to this approved protocol

SIGNED.....
Mr. Kofi Wellington
(GHS ERC Chairperson)

Cc: The Director, Research & Development Division, Ghana Health Service, Accra

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APPENDIX II: Data Extraction Tool

Treatment of Multi-Drug Resistant Tuberculosis with Second-Line All-Oral Drugs in Ghana: Adverse Events.

Data Extraction Form

Principal Investigator: Timothy Ebobabara Bukari
Supervisor: Dr. Harriet Affran Bonful

General Information	Name of Treatment Centre	
	Collaborator's Name	
	Date of Data Extraction	
	Patient ID	
Patient Background Characteristics	Patient Age (years)	
	Patient Sex	
	Marital Status	
	Educational level	
	Occupation	
	Patient Residential Region	
	Residential Address	
Baseline Assessment	Referring Health Facility	
	Patient MDR-TB GeneXpert results	
	Patient Weight (Kg)	
	Patient Height (cm)	
	Body Mass Index (BMI)	
	Nutritional Status	
	Previous TB treatment history	
	Duration of previous TB treatment (in months)	
	Type of previous TB treatment	
	The outcome of previous TB treatment	
	Presence of comorbidities as diagnosed by Medical Doctor	
	History of Smoking	
	Alcohol use history	
	History of substance abuse	
	Baseline patient characteristics as evaluated by a medical doctor including laboratory investigations.	
All-Oral Second-line MDR-TB Treatment	Commencement Date of MDR-TB treatment with second-line all-oral drugs.	
	Duration of treatment (months)	

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	Adherence to treatment as prescribed	
	If no, reasons for non-adherence (as documented)	
Adverse Events Assessment (Adverse Events as recorded by the clinician for each monthly review)	Month 1 Review	
	Month 2 Review	
	Month 3 Review	
	Month 4 Review	
	Month 5 Review	
	Month 6 Review	
	Month 7 Review	
	Month 8 Review	
	Month 9 Review	
	Other months, specify	
Treatment Outcome	Final treatment outcome	
	Reason for treatment discontinuation (if applicable)	

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