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Trends in Prevalence of Multi Drug-Resistant Tuberculosis in The Kingdom of Bahrain (2013-2023).

A Thesis Submitted in Partial Fulfilment of the Requirements for the
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Abstract

This thesis examines the trends and prevalence of drug-resistant tuberculosis (DR-TB) in the Kingdom of Bahrain between 2013 and 2023, with a particular focus on multidrug-resistant TB (MDR-TB). MDR-TB, defined by resistance to isoniazid and rifampicin, poses a major challenge to global and local public health systems. Adopting a retrospective design, the research analyzed 1,158 TB-positive samples, with 310 identified as drug-resistant cases. Antimicrobial susceptibility testing (AST) was performed using the BACTEC MGIT 960 system on key drugs including Streptomycin, Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide. The findings reveal that MDR-TB prevalence peaked at 5.48% in 2018 and noted significant Pyrazinamide resistance, reaching 32.65% in 2023. The analysis emphasizes a higher incidence among males (69.7%) and individuals aged 21–40 (60.2%), with non-Bahraini, especially South Asian expatriates, being predominantly affected. Regional comparisons imply that Bahrain's resistance rates are in line with those of Gulf Cooperation Council (GCC) countries and stay below global high-burden regions. Moreover, the COVID-19 pandemic significantly disrupted TB diagnostics, resulting in a lack of resources for AST testing in 2021. These results emphasize the insistent need for enhanced molecular diagnostic methods, effective surveillance systems, and specific public health interventions, along with coordinated regional efforts, to effectively control and reduce the spread of MDR-TB.

Dedication

To Allah, the Greatest and Most merciful, all appreciation is due to You forgiving me the strength and patience to complete this thesis. Through Your heavenly guidance, I have overcome every effectively easily, and in every hard moment, Your mercy sustained me. It is by Your will that I have reached where I am today and where I will be and in You alone, I place my trust for all that is to come. May this thesis benefit and bless other people, and may You accept my efforts as genuine worship.

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Table of Contents

Chapter 1.....	1
1.1 Introduction	2
1.2 Research problem:.....	7
1.3 Research questions:	7
1.4 Research objectives:	8
1.5 Research significance:	8
1.6 The study's setting:.....	8
1.7 Research Terminology:.....	9
Chapter 2.....	12
2.1.1 Literature review	13
2.1.2 Antitubercular Drugs:	14
2.1.3 Regional Analysis of Multi-Drug-Resistant Tuberculosis in the Middle East and North Africa	25
2.1.4 Global Analysis of Multi Drug-Resistant Tuberculosis	33
Chapter 3.....	44
3.1 Study Area/Setting.....	45
3.2 Study Design	45
3.3 Study Subjects.....	46
3.4 Data Collection Methods.....	47
3.5 Laboratory Procedures	47
3.5.1 Primary Drug Susceptibility Testing (SIRE).....	47
3.5.2 Pyrazinamide Susceptibility Testing	47
3.6 Data Cleaning.....	50
3.7 Statistical Methods	52
3.8 Ethical Considerations	53
3.9 Significance of the Public Health Directorate	53
Chapter 4.....	55
Results, Discussion, and Recommendations	55
4.1 Results.....	56
4.2. Discussion	78
4.3.1 General Overview of Resistance Trends	79
4.3.2 Key Years and Significant Trends	79
4.4 Age, Gender and Regional Distribution of Drug-Resistant TB Cases	83
4.4.1 Regional Distribution Patterns.....	84

4.4.2 Age and Gender Distribution Patterns	86
4.4.3 Interplay Between Age, Gender, and Region	88
4.5 The Impact of COVID-19 on TB Diagnosis, Management, and Drug Resistance: A Global and Local Perspective	89
4.6 TB Resistance Patterns in Bahrain Compared to the GCC and North Africa	94
4.7 Global TB Patterns: Focus on High-Burden and Representative Countries	100
4.8 Recommendations.....	100
4.9 Limitations	104
4.10 Conclusion	106
References	107

Table of Tables

Table (1): Summary of Anti-Tuberculosis Drugs the table shows the type of activity, mechanism of action, resistance mechanisms, and key mutations associated with the studied drug..... 22

Table (2): Regional Epidemiological Patterns, Methodologies, and Key Findings of Multi-Drug-Resistant Tuberculosis (MDR-TB) Studies Across the Middle East and North Africa..... 26

Table (3): Global Epidemiological Patterns, Methodologies, and Key Findings of Multi-Drug-Resistant Tuberculosis (MDR-TB) Studies Across the World. 34

Table (4): Trends in Drug Resistance Among TB Patients from 2013 to 2023. The table presents the number and percentage of TB cases resistant to Isoniazid, Rifampicin, Ethambutol, Pyrazinamide, Streptomycin, and MDR (Multidrug-resistant TB: resistance to Isoniazid and Rifampicin at the same time. 66

Table (5): Analysis of Drug Resistance Patterns in TB Patients Across Demographic and Clinical Categories. This table summarizes resistance patterns for five major TB drugs (Streptomycin, Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide) based on sex, age, form of TB and region categories 72

Table (6): Comparative Analysis of DR-TB Epidemiology Across Gulf Cooperation Council (GCC) Countries: Demographic Trends, Resistance Patterns, and Clinical Profiles..... 99

Table of Figures

Figure 1 Diagram illustrates the Mechanisms of Action of Various Drugs.	23
Figure 2 Bar chart Showing the Distribution of Drug-Resistant TB Cases by Region.	57
Figure 3 Bar Chart Showing the Distribution of Drug-Resistant TB Cases by Nationalities	58
Figure 4 Pie Chart Showing the Distribution of Drug-Resistant TB Cases Across Age Groups	59
Figure 5 Bar Chart Showing the Percentage Distribution of Age Groups by Region..	61
Figure 6 Pie Chart Showing the Distribution of Specimen Types in Drug-Resistant TB Cases.	62
Figure 7 Pie Chart Showing the Distribution of Drug-Resistant and Drug-Sensitive TB Positive Cases.	63
Figure 8 Bar Chart Showing the Trend in Drug Resistance Percentages in TB (2013–2023).	68

Abbreviations list

TB – Tuberculosis

DR-TB – drug-Resistant Tuberculosis

MDR-TB – Multi-Drug-Resistant Tuberculosis

XDR-TB – Extensively Drug-Resistant Tuberculosis

pre-XDR-TB – Pre-Extensively Drug-Resistant Tuberculosis

NTM – Non-Tuberculous Mycobacteria

MTBC – Mycobacterium Tuberculosis Complex

PCR – Polymerase Chain Reaction

PZA – Pyrazinamide

PZase – Pyrazinamidase

INH – Isoniazid

RR-TB – Rifampicin-Resistant Tuberculosis

RIF – Rifampicin

EMB – Ethambutol

WHO – World Health Organization

HIV – Human Immunodeficiency Virus

SPSS – Statistical Package for the Social Sciences

MoH – Ministry of Health

PHD – Public Health Directorate

LTBI – Latent Tuberculosis Infection

FAS – Fatty Acid Synthase

MTB – Mycobacterium Tuberculosis

SNP – Single Nucleotide Polymorphism

rpsL – Gene encoding ribosomal protein S12

rpoB – Gene encoding RNA polymerase beta subunit

Chapter 1

Introduction to the study

1.1 Introduction

Mycobacteria are part of the order Actinomycetales, and the only genus within the family Mycobacteriaceae. At present, the genus *Mycobacterium* has more than 100 recognized species (Payeur, 2014). Mycobacteria have distinct cell wall construction and metabolism from other bacteria, necessitating specialized diagnostic procedures, such as stains, culture medium, and identification techniques (Van Ingen, 2017). *Mycobacterium tuberculosis*, which causes tuberculosis (TB) in humans, is the species with the greatest clinical significance. *Mycobacterium bovis* is an uncommon cause of human TB in central Africa, and it also causes disease in cattle and other animals. Despite having significant phenotypic variations, these pathogenic species are genetically quite similar and are sometimes grouped together as the "Mycobacterium tuberculosis complex" (MTBC). non-tuberculous mycobacteria (NTM, atypical mycobacteria, environmental mycobacteria, or mycobacteria other than tuberculosis) is additional pathogenic mycobacteria. Both of these groups frequently act as opportunistic pathogens, especially in immunocompromised people (Percival & Williams, 2014).

With the exception of the plague (*Yersinia pestis*), few illnesses have left such a significant written legacy as TB. The earliest textual remnants were discovered in Indian Vedas and Chinese medicinal manuscripts from before the Xia period, respectively, 5,700 and 3,500 years ago. The origins, development, and transmission of TB were poorly understood until recently, the creation of molecular instruments (Cardona, 2018; Prasad, 2002).

The bacteria *Mycobacterium tuberculosis* is what causes TB, a disease. Through actions like coughing, talking, or singing that release TB germs into the air, people with TB have the ability to spread the disease to others. As they

reach the lungs after being inhaled, these TB germs can cause sickness. The kidneys, spine, and brain are among the numerous body parts that these bacteria can infect by spreading through the circulation (Centers for Disease Control and Prevention, 2014).

According to World Health Organization (WHO) global tuberculosis report 2022, tuberculosis (TB) continues to be a serious worldwide health problem, particularly in areas with inadequate access to healthcare, with a high incidence rate the number of persons who contracted TB was expected to be 10.6 million (95% UI: 9.9-11 million) in 2021, an increase of 4.5% from 10.1 million (95% UI: 9.5-10.7 million) in 2020. The number of new cases of tuberculosis (TB) per 100,000 people increased by 3.6% between 2020 and 2021, reversing annual decreases of roughly 2% for most of the preceding two decades. TB is frequently listed as one of the leading causes of mortality globally, particularly in low- and middle-income nations. World global efforts to fight the disease through better diagnosis, better access to treatment, and protective methods are important (WHO, 2022).

A study conducted between 2000 and 2006 aimed to measure the prevalence of TB in Bahrain. A total of 1,584 cases of TB were found during this time, with 28.2% of the cases were for Bahraini citizens and the rest 71.8% involved non-Bahrainis. The study found that, with some minor changes, TB incidence rates are generally increasing. The incidence rate among Bahrainis ranges from 12.5 to 16.8 per 100,000 per year. Non-Bahrainis had a higher incidence, ranging from 47.4 to 75 per 100,000. The majority of non-Bahraini nationalities with TB were Asian. Males were more often affected, while Bahrainis over the age of 65 were the most affected age groups (Jawad et al., 2014).

Antitubercular medicines are very important in fighting *Mycobacterium tuberculosis* infections and are used in the treatment of TB. Antimicrobial susceptibility testing (AST) is an essential part of TB diagnosis and treatment planning. It helps verify the effectiveness of first-line anti-TB drugs, ensuring the best and most effective treatment selection and checking resistance patterns. The BACTEC MGIT 960 system is a widely used, automated method for detecting *Mycobacterium tuberculosis* growth and assessing susceptibility to key drugs (Siddiqi & Rüscher-Gerdes, 2006). By rapidly identifying drug-resistant strains, AST plays a vital role in preventing treatment failure and controlling the spread of resistant TB.

Organism possesses a complexly organized cellular architecture that directly mediates its pathogenic potential, resilience, and ability to escape host immune defenses, making it one of the most challenging pathogens encountered in clinical medicine. At the core of its resilience is a unique cell envelope that differs significantly from those of other bacterial species. Unlike the simpler cell walls of many bacteria, the *Mycobacterium* cell envelope features a strong core structure where peptidoglycan is covalently linked to arabinogalactan, which in turn anchors long-chain mycolic acids. These mycolic acids, exceeding 80 carbon atoms in length, build a highly hydrophobic outer layer that acts as a protective barrier against dehydration, chemical damage, and many antibiotics, contributing to its virulence (Daffe & Marrakchi, 2019). The high lipid content also gives rise to the acid-fast staining characteristic of *Mycobacteria*, a diagnostic characteristic that has been helpful in clinical microbiology for over a century (Murray et al., 2020). The bacterium is also coated in a slimy outer layer of proteins, sugars, and lipids. This capsule is a key player in TB infection. It helps the bacteria attach

to host cells and escape past the immune system, masking *M. tuberculosis* from detection and buying it time to establish infection (Murray et al., 2020). The interaction between these structural components not only mediates host colonization and invasive potential but also supports the formation of granulomas—organized aggregates of immune cells that are central to the host’s attempt to contain the pathogen (Cronan, 2022). After inhalation, TB bacilli are transported to the pulmonary alveoli, where they are engulfed by resident macrophages. Unlike typical pathogens, TB disables host defenses through specific cell envelope components that interrupt phagosomal maturation. By inhibiting phagosome-lysosome fusion, the pathogen creates a protected intracellular niche favourable to long-term survival. This ability for latent persistence complicates clinical detection and requires prolonged therapeutic regimens. (Vergne et al., 2005). Clinical investigations have established that this ability to survive intracellularly is closely linked to the physical and chemical properties of the mycobacterial cell wall, which not only limits the penetration of many hydrophilic antimicrobial agents (Jankute et al., 2015). but also keeps the bacterium protected from the cytotoxic effects of reactive oxygen and nitrogen species produced by activated macrophages (Ramon-Luing et al., 2023).

Because of how infectious and tends to progress into a severe illnesses TB continues to be a major interest for world health. Rifampin, isoniazid, pyrazinamide, and ethambutol are among the first-line antitubercular drugs that have been approved by the FDA, and each has a specific function in the treatment of tuberculosis (Padda & Muralidhara Reddy, 2023). According to the WHO, there are 5 types of TB resistance the first one is isoniazid-resistant TB, rifampicin-resistant TB (RR-TB) and multi-drug resistant TB (MDR-TB)

which is defined as resistance to rifampicin and isoniazid extensively drug-resistant TB (XDR-TB) and pre-extensively drug-resistant TB (pre-XDR-TB) are two of the most significant TB resistance types. Pre-XDR-TB is when TB doesn't respond to the drug rifampicin and a type of fluoroquinolone, which are key in fighting TB. XDR-TB is even worse. It means TB can't be treated with rifampicin, any fluoroquinolone, and also ignores either bedaquiline or linezolid. Between 2020 and 2021, more people got TB that can't be treated with usual drugs. In 2021, about 450,000 new cases were reported. (WHO, 2022). MDR-TB is treated with second-line medications such Kanamycin, Streptomycin, Capreomycin, Amikacin, Levofloxacin, Moxifloxacin, and Gatifloxacin (Padda & Muralidhara Reddy, 2023). HIV-positive patients are more susceptible to MDR-TB infection and have a significant chance of turning their infection into active MDR-TB. Patients with HIV frequently die while waiting for test confirmation of MDR-TB and prior to beginning effective medication (Seung et al., 2015).

Pulmonary tuberculosis, the most common manifestation of the disease, typically presents with a chronic cough, chest pain, hemoptysis, fever, and weight loss (CDC,2025). This type of TB happens primarily when droplets are aerosolized by inhalation and these aerosols contain the bacterium and it remains the most important and principal way of transmission among humans (WHO,2025). Aside from pulmonary TB, TB can spread to other parts of the body leading to extrapulmonary and this happens through the bloodstream or lymphatic system, which can cause a range of clinical conditions including dangerous disorders such as tuberculous meningitis, which attacks the central nervous system and is associated with high mortality; skeletal tuberculosis, commonly known as Pott's disease when it involves the spine; genitourinary

tuberculosis, which can impair kidney and reproductive organ function; and miliary tuberculosis, a form characterized by widespread dissemination of the bacteria leading to multiple organ involvement (Gopalaswamy et al., 2021). The ability of the pathogen to alter the host's immune response, which is the basis for the manipulation of the intrinsic immune system of the host is what distinguishes different types of TB (Gopalaswamy et al., 2021). The mycolic acids and several lipid parts not only limit the effectiveness of antitubercular drugs but also stand for the persistence of treatment that the patient has to take for six months or longer (Daffé & Marrakchi, 2019; Jankute et al., 2015).

1.2 Research problem:

Control of *Mycobacterium tuberculosis* must be a priority because the infection's treatment may take a long time to complete. Due to the newly discovered multidrug-resistant strains, the infection has become more difficult to cure. As a result, it is essential that the public health sector continues its routine of tracking the disease's progress.

1.3 Research questions:

1. What is the prevalence of multi-drug-resistant Tuberculosis (MDR-TB) in Bahrain?
2. How common is tuberculosis that is resistant to multiple medications in Bahrain?
3. Which racial and ethnic groups are most affected by DR-TB in Bahrain?
4. Which age groups are most affected by DR-TB in Bahrain?

1.4 Research objectives:

1. To determine the prevalence and trends of multi-drug-resistant tuberculosis in Bahrain.
2. To identify the racial and ethnic groups most affected by multi-drug-resistant tuberculosis in Bahrain.
3. To investigate the age groups at the highest risk of multi-drug-resistant tuberculosis in Bahrain.

1.5 Research significance:

This research is critical for educating and updating national health policies to prevent and control tuberculosis, particularly its drug-resistant forms. By identifying demographic groups most at risk, the study supports targeted awareness campaigns and effective intervention strategies. The findings will contribute to strengthening Bahrain's infection control systems and public health policy, ultimately lowering the disease burden.

Furthermore, the study has global relevance by contributing to antimicrobial stewardship efforts, essential for addressing the rising threat of drug resistance. By understanding MDR-TB epidemiology, the research promotes the sustainable use of existing medical treatments and safeguarding their effectiveness for future generations.

1.6 The study's setting:

Our research uses the data resources available within the Ministry of Health's (MoH) databases, the main component that ensures a rich basis for our investigation. A significant aspect of utilizing this data is the MoH's

commitment to ensuring the anonymization of patient information, thereby upholding privacy standards and ethical considerations in our research.

The statistical analysis will be carried out at the University of Bahrain, which is equipped with the necessary technological and academic resources to support our study. Specifically, the data will be analyzed using IBM SPSS Statistics, Version 25, to perform descriptive and inferential statistical analyses.. This phase will benefit from the University's advanced statistical tools and expertise, providing a rigorous analytical framework for our investigation.

1.7 Research Terminology:

Tuberculosis(TB):

TB caused by *Mycobacterium tuberculosis*, is the leading cause of death regarding to infectious diseases globally, notably prevalent in Southeast Asia, Sub-Saharan Africa, and Eastern Europe, with over 8 million new cases each year. This disease primarily Impacts the lungs (pulmonary tuberculosis), Identified by symptoms such as a productive cough, fever, weight loss, hemoptysis, chest pain, night sweats, fatigue, and anorexia. The bacteria's lipid-rich cell wall makes it resistant to disinfectants and hard to stain, but when it stains, they are identified as acid-fast bacilli. TB can also spread outside the lungs (extrapulmonary tuberculosis) through the spread of bacilli, affecting areas such as the genitourinary system, meninges, gastrointestinal tract, skeleton, lymph nodes, and more, leading to diverse symptoms ranging from dysuria and flank pain to severe conditions like tubercular meningitis and skeletal TB, notably Pott's disease (Parija, 2012).

Isoniazid-Resistant TB:

This form of TB exhibits resistance to isoniazid, a first-line anti-TB medication. It does not necessarily imply resistance to other drugs used in the treatment of TB (WHO,2023).

Rifampicin-Resistant TB (RR-TB):

This type includes TB strains that are resistant to rifampicin, a first-line anti-TB drug, which is vital for the treatment regimen (WHO,2023).

Multi-Drug Resistant Tuberculosis (MDR-TB):

MDR-TB describes TB that is resistant to at least isoniazid and rifampicin, which are the two most powerful first-line anti-TB drugs. This resistance makes the condition more complex and difficult to treat (WHO,2023).

Pre-Extensively Drug-Resistant TB (pre-XDR-TB):

Pre-XDR-TB is a form of TB that is resistant to rifampicin and any fluoroquinolone. Fluoroquinolones are a class of second-line anti-TB drugs, suggesting that this type shows a higher level of resistance compared to MDR-TB but is not as resistant as XDR-TB (WHO,2023).

Extensively Drug-Resistant TB (XDR-TB):

XDR-TB is TB that is resistant to rifampicin, plus any fluoroquinolone, and at least one of either bedaquiline or linezolid. This class indicates the highest level of drug resistance, indicating that the TB strain is resistant to both first-line drugs and a critical second-line drug (WHO,2023).

Prevalence:

The prevalence of a disease refers to the likelihood of currently having the disease, without considering how long one has been affected by it (Rosner,2011).

Incidence Rate:

Incidence refers to the rate at which new cases occur within a specific population at risk during a defined period. In medical contexts, it usually represents the number of newly diagnosed cases of a disease or condition per population at risk over a specified timeframe (Noordzij et al., 2010).

Pulmonary Tuberculosis:

Pulmonary Tuberculosis, affecting the lungs, accounts for 80% of all TB cases. It can be further categorized into primary or post-primary types (Bhatia and Ichhpujani, 2008).

Extrapulmonary Tuberculosis:

Extrapulmonary tuberculosis usually occurs when the bacteria spread through the Circulatory system from the primary infection site, which is usually the lungs during the early stages of multiplication. Depending on where the infection spreads, it can affect different parts of the body, such as the genital or urinary tract, the brain and spinal cord (meninges), the gastrointestinal system, bones and joints, lymph nodes, and other areas (Parija, 2012).

Latent Tuberculosis (LTBI):

Latent tuberculosis infection describes a state where there is a sustained immune response to exposure to *Mycobacterium tuberculosis* antigens, but without any signs or symptoms of active TB disease. Individuals with LTBI serve as a potential source for the development of active TB cases (Kiazyk & Ball, 2017).

Chapter 2

Theoretical framework and Literature review

2.1.1 Literature review

Multi-drug-resistant tuberculosis (MDR-TB) presents a Significant threat to global health, described by its resistance to the two most powerful anti-TB drugs. This literature review aims to Investigate into the theoretical framework and empirical research surrounding MDR-TB, with an aim to uncover the Extent of methodological approaches, demographic investigations, and the evolution of findings within both Arabic and foreign contexts. By examining academic studies from its beginning to the most recent studies, this review aims to create a comprehensive overview that supports the formulation of detailed research hypotheses and methodology for investigating MDR-TB.

MDR-TB is defined as the resistance to both isoniazid and rifampicin, which are considered the most crucial antitubercular drugs, in 2022, an estimated 410,000 (95% UI: 370,000 to 450,000), individuals were diagnosed with MDR-TB or rifampicin-resistant tuberculosis (RR-TB). In 2022, the Approximated proportion of new TB cases with MDR/RR-TB remained at 3.3% (95% UI: 2.6-4.0%), while among previously treated individuals, it escalated to 17% (95% UI: 11-23%). Comparatively, in 2015, these figures were slightly higher at 4.0% (95% UI: 3.1–4.9%) and 25% (95% UI: 15–36%), respectively. A remarkable number of MDR/RR-TB cases was observed in three countries, with India, the Philippines, and the Russian Federation together accounting for 42% of the global burden. Within these regions, mainly in the Russian Federation and various Eastern European and Central Asian countries, the prevalence of MDR/RR-TB among previously treated cases exceeded 50%, representing a persistent need for interventions and enhanced healthcare infrastructures to combat the spread of drug-resistant tuberculosis. The WHO objective of tuberculosis eradication is only

Streptomycin, similar to other aminoglycosides, belongs to a medicinal and bacteriologic category of traditional gram-negative antibacterial medications. These drugs act as bactericidal agents by disrupting ribosomal peptide or protein synthesis. Streptomycin attaches to a certain site on the 16S rRNA found within the smaller 30S subunit of the bacterial ribosome, thus reducing its activity, and halting the synthesis of new proteins by blocking the formation of peptide bonds, aminoglycosides are considered as hydrophilic substances that unable to directly pass through the hydrophobic bacterial cell membrane. Instead, they need an electron transport system implicated in the cell's respiratory cycle for entry, which explains why aminoglycosides primarily target aerobic bacteria that can grow in an oxygenated environment (Vianna et al., 2019; Germovsek et al., 2017).

Streptomycin resistance in TB occurs mainly because of changes in the *rpsL* gene, which is responsible for producing the S12 protein, because of these changes the binding of streptomycin to ribosome will be affected ultimately reducing the drugs' ability to block protein production. Mutations in the *rrs* gene, which is responsible for the production of 16S rRNA in the ribosome also affect streptomycin resistance by either lowering its binding to the ribosome or disrupting its interaction with the target site. Moreover, efflux pumps such as the Rv1258c pump can aid in streptomycin resistance by removing the drug from cells (Voss, 2023). Furthermore specific mutations in the gene that code for S methionine dependent 7 methylguanosine methyltransferase can confer resistance to streptomycin. Researchers conducted dynamics simulations to explore how three versions of gidB. S70R, T146M and R187M. Contribute to streptomycin resistance (Bharati et al.,

2019). The combined effects of these mechanisms can result in increased levels of streptomycin resistance, in tuberculosis strains.

The cell envelopes of mycobacteria contain an amount of acids making up about 30% of their dry weight. These acids play roles; they create a waterproof barrier that helps the bacteria resist antibiotics and are crucial, for the organisms survival and ability to cause disease. Mycolic acids are typically chain fatty acids with 70–90 carbons often attached to the arabinogalactan layer on the side of the mycolate outer membrane (Batt, Minnikin, & Besra, 2020). The tough impermeable cell wall of *M. Tuberculosis* and the presence of efflux pumps help these bacteria withstand attacks (Abraham, 2020). INH is a drug used to treat tuberculosis (TB) because it works effectively by blocking the production of acids, which are essential components in the bacterial cell wall of MTB (Nongkhlaw, Nongkhlaw, & Bisht, 2022). INH is commonly given as therapy, for latent tuberculosis infection (LTBI) to individuals who have been exposed to TB but do not have an infection.

The purpose of using INH is to decrease the number of LTBI cases that develop into tuberculosis and reduce the spread of the bacteria (Norton & Holland 2012). While the exact way INH works is still uncertain, researchers have suggested mechanisms. One study proposed that the bacteria enter the cell wall through diffusion. Subsequently oxidative activation takes place via the catalase peroxidase enzyme (KatG) leading to the creation of an intermediate called isonicotinyl acyl radical. This process begins with the formation of the INH NAD adduct, which then obstructs InhA (2 trans enyolacyl carrier protein reductase) in MTB (Ejalonibu et al. 2021). InhA, an enzyme organized as a tetramer, in tuberculosis has become a target because of its role in fatty acid synthesis and its association with the short chain

dehydrogenase/reductase family. Being an NADH trans enoyl acyl ACP carrier protein it plays a part, in mycobacterial physiology (Wahan et al., 2024).

Resistance to isoniazid (INH) in *Mycobacterium tuberculosis* (MTB) is primarily caused by mutations that reduce the effectiveness of the bacterial enzyme KatG, which plays a role in converting INH into its form INH NAD. These mutations in the *katG* gene hinder the activation of INH leading to a decreased ability to target and inhibit the enzyme InhA. Some mutations like *katG* FS6 and *katG* W328L partially decrease KatG activity resulting in reduced susceptibility to INH. Also, mutations such as *katG* W198 will completely stop KatG function resulting in high level resistance, to the drug (Gregory et al., 2023; Vladimir et al., 2022).

Resistance to isoniazid (INH), a fundamental component in tuberculosis treatment can develop not due to *katG* mutations but through other pathways. One of the interesting routes involving the action of acetyltransferase Rv2170 in MTB which introduces a mechanism of resistance. This particular enzyme causes INH resistance by the process of acetylation, so it will cause the drug to become ineffective as it becomes metabolites that do not inhibit cell wall synthesis. One study reveals that Rv2170 acetylates INH interferes with the drug's ability to inhibit the InhA which is the enzyme for mycolic acid production in the wall (K.B. Et al., 2020). The change in INH caused by Rv2170 results in the bacterium manifesting total resistance to the drug which is in turn an example of the conversation of bacterial survival tactics against antibiotic pressure. The comprehension of these resistance modes is essential for the development of new antitubercular drugs to treat TB as the issues from drug resistant strains are continuously increasing.

The identification of PatA, a membrane bound acyltransferase sheds light on an unknown method of lipid synthesis that is essential for maintaining biofilm stability and allowing it to adapt to different environmental conditions. Interestingly the absence of PatA appears to enhance resistance to INH suggesting its role in the production of acid through a pathway that has not yet been identified diverging from the known fatty acid synthase pathway. This unexpected discovery reveals an interaction between the functions of PatA and the survival strategies employed by mycobacteria providing fresh insights, into how lipid metabolism influences drug resistance and biofilm formation (Kun et al., 2023).

Rifampin, also known as Rifampicin, works by targeting DNA dependent RNA polymerase to kill bacteria. It does this by either blocking RNA growth at the 5' end or reducing the enzymes attraction, to RNA segments. This targeted inhibition affects RNA production while sparing DNA dependent RNA polymerase minimizing side effects in humans. Unlike prokaryotes that have single polymerase, eukaryotes have α like heterodimers and three specialized Pols (I III) with unique subunits. Eukaryotic RNA polymerases share conserved features. Differ in sites from prokaryotic counterparts offering potential for developing new drugs against bacterial infections. Rifampin is effective against both extracellular forms of M tuberculosis showcasing its bactericidal abilities. Rifampicin hinders the RNA synthesis elongation phase by attaching to RpoB, the beta subunit of DNA dependent RNA polymerase, in MTB. It is generated by the gene preventing bacteria from making proteins. This interference disrupts functions ultimately causing bacterial cell death. Mutations in the gene can lead to rifampicin resistance with mutations like H451D, H451Y and H451R in MTBs RNA polymerase

playing a role in this resistance development. Research utilizing dynamics simulations and various analytical methods reveals that these mutations reduce rifampicin binding affinity to the RNA polymerase. The diminished binding affinity results from changes in interactions and flexibility within the enzymes binding site shedding light on the mechanisms behind rifampicin resistance. Another study by Arnold et al. (2022) discusses mutations in the gene impacting rifampicin resistance.

Their research highlights six variations; Asp441Val, Ser456Trp, Ser456Gln, Arg454Gln, His451Gly and His451Pro. These mutations have an impact on how rifampicin binds to RNA polymerase. Using docking and dynamic simulations they explain how these genetic changes influence the binding process and disrupt interactions at the drugs target site. This study emphasizes the nature of rifampicin resistance mediated by *rpoB* in MTB emphasizing the urgency for novel treatment strategies to address these strains. Additionally, mutations like S456L and D441V also affect rifampicins binding affinity by reducing interactions particularly altering the contribution of energy, from the R454 residue (Zhang et al., 2020).

Ethambutol or EMB works similarly to isoniazid (INH) by targeting the cell wall of the tuberculosis bacterium. Unlike INH EMB is considered a drug that slows down growth, than killing them outright. It achieves this by interacting with enzymes called arabinosyl transferases that play a role in building certain components of the bacterial cell wall. By disrupting the polymerization process of arabinan in the cell wall EMB causes a buildup of a substance that interferes with cell wall integrity and inhibits growth. Additionally, EMB also targets another enzyme called racemase (MurI) which's essential for building peptidoglycan in the bacterial cell wall. Through inhibition EMB blocks

MurIs site and prevents glutamate from undergoing necessary changes for maintaining cell wall integrity. This interaction alters MurIs structure. Impairs its function pointing to an antibacterial effect of ethambutol, beyond its originally known mechanisms.

In a research project scientists pinpointed genes that play a role in combating EMB, a crucial drug used to treat tuberculosis. Within these genes—*embB*, *embA*, *embC*, *embR* and *ubiA*—the *embB* gene was notably linked to levels of EMB resistance. Mutations at points like codons 306, 406 and 497 within the gene were prevalent in strains that showed resistance to the drug. Interestingly mutations at *embB*306 were identified as indicators of EMB resistance with a sensitivity rate of 57.8% and specificity rate of 78.8%. The impact of genes on causing the TB to be resistant to EMB has been emphasized by recent discoveries. Additionally, while mutations were also observed in the gene they occurred frequently compared to those in the *embB* gene indicating a lesser role in mechanisms of EMB resistance (Xu et al., 2015).

Another study focused on looking into the factors affecting EMB resistance in MTB found two genes —*mbtD* and *celA1*—that showed association with EMB resistance due to its irregular methylation patterns affecting their expression levels. This study highlights the complexity of drug resistance in MTB by not highlighting the mutations only but also epigenetic alterations, like DNA methylation that impact gene expression without changing the underlying DNA sequence.

MTB strains that were mono EMB resistant were created by researchers in the resistance mechanism study and the protein expression effects were measured by the team on drug-exposed bacteria. A greater understanding of the

mechanisms of action of TB drugs will be reached through the targeting of mutations and epigenetic changes for implementations of more effective treatments (Zhuhua et al., 2022).

The way PZA operates involves transforming into acid its form when the drug enters MTB cells. This transformation is made possible by the enzyme pyrazinamidase (PZase) which is coded by the *pncA* gene of MTB. The converted pyrazinoic acid disrupts the membrane potential. Hampers the energy production of cells making it a strong agent, against dormant tubercle bacilli particularly in the acidic conditions found within a host's macrophages where the bacteria may dwell (Khan et al., 2019).

Resistance to PZA in MTB mainly stems from mutations that impede the functioning of the enzyme PZase for activating PZA into pyrazinoic acid. These mutations within the *pncA* gene hinder the conversion process reducing its ability to kill bacteria effectively. Alterations in the coding section of *pncA* can impact PZases structure, hence lowering its activity. Moreover, mutations in *pncA*s promoter region might result in decreased enzyme production. Even if PZase maintains its structure inadequate levels can hamper metabolism of PZA. Variants, like *pncA* G76S and *pncA* D49V cause a decrease in PZase activity resulting in resistance. On the hand mutations like *pncA* R140H disable PZase function leading to significant resistance against PZA (Hadi et al., 2023; Khan et al., 2019; Sodja et al., 2022).

A comprehensive summary of all drugs, including their type of activity, mechanism of action, resistance mechanisms, and key mutations, can be found in Table 1, while Figure 1 provides a detailed visual breakdown of the mechanistic pathway

Table (1): Summary of Anti-Tuberculosis Drugs This table outlines the type of activity, mechanism of action, resistance mechanisms, and key mutations associated with Streptomycin, Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide, which target processes such as protein synthesis, cell wall formation, RNA synthesis, and membrane integrity

Drug Name	Type of activity	Mechanism of Action	Resistance Mechanisms	Key Mutations
Streptomycin	Bactericidal and Bacteriostatic	Inhibits protein synthesis by binding to 16S rRNA of the 30S ribosomal subunit	Mutations in rpsL and rrs genes, efflux mechanisms	rpsL, rrs, Rv1258c
Isoniazid	Bactericidal	Inhibits synthesis of mycolic acids, crucial components of the bacterial cell wall	Mutations in katG and InhA genes, acetylation by Rv2170 enzyme	katG (e.g., katG FS6, W328L, W198), inhA
Rifampicin	Bactericidal	Binds to the beta-subunit of DNA-directed RNA polymerase, inhibiting RNA synthesis	Mutations in rpoB gene affecting the drug's binding affinity	rpoB (e.g., H451D, H451Y, H451R, Asp441Val, Ser456Trp)
Ethambutol	bacteriostatic	Inhibits arabinosyl transferases, disrupting cell wall integrity	Mutations in embB and related genes, epigenetic changes affecting gene expression	embB (e.g., 306, 406, 497), ubiA
Pyrazinamide	Bactericidal and Bacteriostatic	Converted into pyrazinoic acid by PZase, disrupts membrane potential and energy production	Mutations in pncA gene affecting enzyme PZase function	pncA (e.g., G76S, D49V, R140H)

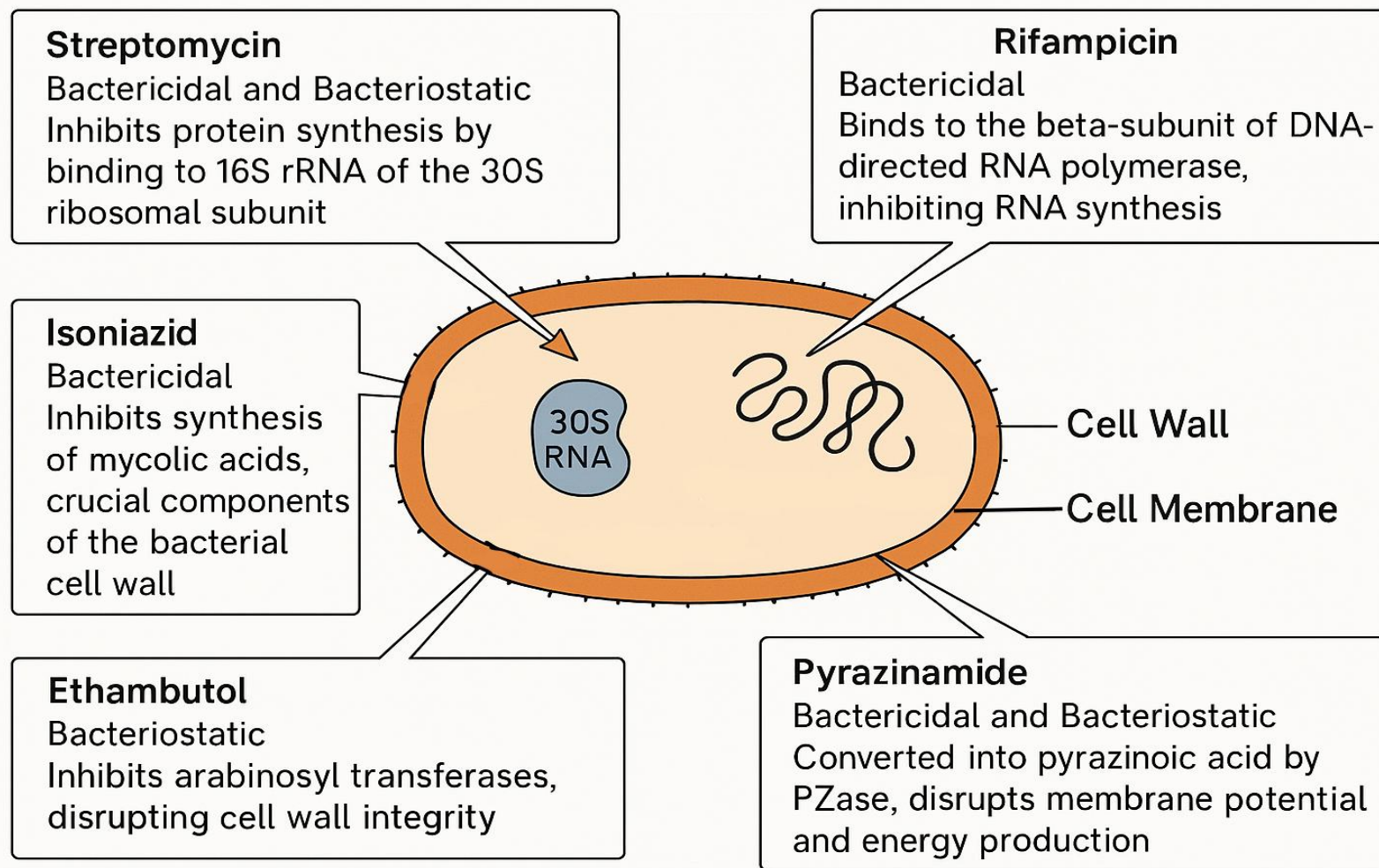


Figure 1 Diagram illustrates the Mechanisms of Action of Various Drugs, including Streptomycin, Isoniazid, Ethambutol, Rifampicin, and Pyrazinamide, targeting processes such as protein synthesis, cell wall formation, RNA synthesis, and membrane integrity. (Adapted from Rasmi et al., 2020; Devaraj, 2023; Haldar, 2021; Hasan, 2019; Vianna

et al., 2019; Germovsek et al., 2017; Batt et al., 2020; Abraham, 2020; Nongkhlaw et al., 2022; Ejaionibu et al., 2021; Wahan et al., 2024; Arnold et al., 2022; Zhang et al., 2020; Xu et al., 2015; Zhuhua et al., 2022; Khan et al., 2019; Hadi et al., 2023; Sodja et al., 2022).

2.1.3 Regional Analysis of Multi-Drug-Resistant Tuberculosis in the Middle East and North Africa

The rise of MDR-TB poses a public health issue especially in areas heavily affected by TB like the Middle East and South Africa. This analysis delves into the prevalence and resistance trends of MDR-TB, in countries within these regions, drawing insights from studies.

Table (2): Regional Epidemiological Patterns, Methodologies, and Key Findings of Multi-Drug-Resistant Tuberculosis (MDR-TB) Studies Across the Middle East and North Africa

Researcher(s)/year	Title	Country	Methodological Approach	Research Tools and Methods	Main Results
(Alkhawaja, 2020)	Epidemiology of drug-resistant tuberculosis in Bahrain, five years review	Bahrain	Retrospective study	National TB surveillance database, public health laboratory, phenotypic sensitivity testing, molecular diagnostics, Statistical analysis	TB incidence decreased from 17 to 11 per 100,000 from 2014 to 2018. Detected 3% MDR-TB with varied resistance patterns including 9% isoniazid monoresistance.
(Alshahrani et al., 2021)	Prevalence of Primary Drug Resistance to Tuberculosis Drugs at a Tertiary Center in Saudi Arabia and Associated Risk Factors	Saudi Arabia	Retrospective study	Phenotypic and molecular diagnostic methods, drug sensitivity testing ,statistical analysis	901 cases studied, 21.4% showed drug-resistant TB. High resistance to pyrazinamide at 33.4%, significant age-related correlation noted.

(Al Hayani et al. 2021)..	Drug Resistance to Anti-Tuberculosis Drugs: A Cross-Sectional Study From Makkah, Saudi Arabia	Saudi Arabia	Retrospective cross-sectional study	Phenotypic and molecular diagnostic methods, drug sensitivity testing, statistical analysis	Among 472 cases, low MDR-TB prevalence at 1.5% with resistance mostly in males. Highest resistance observed for isoniazid and streptomycin at 3.4%.
(Habous et al., 2020)	Pattern of primary tuberculosis drug resistance and associated risk factors at Dubai health authority in Dubai	UAE	Retrospective analysis	Dubai Health Authority's, TB lab, Phenotypic testing, molecular testing, Statistical analysis	First-line drug resistance at 17.3% in 901 cases; specific rates included 3.6% for INH and 2.95% for streptomycin. Diabetes significantly associated with increased risk of TB drug resistance.
(Mohammed et al., 2022).	Prevalence and Drug Resistance Pattern of Mycobacterium tuberculosis Isolated from	Iraq	Retrospective analysis	Clinical records, microbiological testing, Statistical analysis	Notable increase in drug resistance among retreated TB cases; MDR-TB rates significantly increased over the study period. The prevalence of MDR-TB

	Tuberculosis Patients in Basra, Iraq				increased from 0.17% in cases to 1.6% by the end of the research period
(Alfaham et al., 2022)	A study on Pulmonary Tuberculosis and risk factors in New and Re-Treated Presumptive Patients at Wad Madani Tuberculosis Center, Sudan	Sudan	Retrospective analysis	Clinical records, microbiological testing for drug resistance, Statistical analysis of resistance trends	Higher drug resistance rates in retreated TB cases, with significant increases in multi-drug resistance, Of these 9.7% (10/103) had MDR-TB over the study period.
(Soliman, 2021)	Prevalence of Multidrug-Resistant Tuberculosis Using Phenotypic Drug Susceptibility Testing and GeneXpert MTB/RIF with Characterization of Non-tuberculous Mycobacteria Using MALDI-TOF	Egypt	Cross-sectional study	Phenotypic and molecular diagnostic methods, drug sensitivity testing, statistical analysis	MDR-TB prevalence was 7.16% among cultures positive for Mycobacterium tuberculosis, with 27.2% showing rifampin resistance. NTM infections were also reported.

A study titled "Prevalence of Primary Drug Resistance to Tuberculosis Drugs at a Tertiary Center in Saudi Arabia and Associated Risk Factors" conducted by Mohammed S. Al Shahrani and his team examines the occurrence of mono TB and MDR-TB at King Fahd Armed Forces Hospital in Jeddah. Published in the Saudi Medical Journal in July 2021 this study looks at cases spanning from 2000 to 2018. Identifies risk factors such as age, gender, and various health conditions. The research reveals that pyrazinamide had a resistance rate of 33.4% followed by isoniazid at 26.7% and streptomycin at 20.6%. Ethambutol showed a resistance rate at 7.1% (Alshahrani et al., 2021).

Additionally, Ahmad M Al Hayani study focuses on evaluating drug TB prevalence and influencing factors in Makkah, Saudi Arabia as part of the National Tuberculosis Prevention Program during January 2016 to September 2020. The study looked into 472 confirmed cases of TB. The study results confirmed the presence of MDR-TB cases with a prevalence rate of 1.5%. Moreover, the prevalence of TB resistant to a drug ranged from 2.1% to 3.4%. Especially resistance to isoniazid and streptomycin was the highest at 3.4% while resistance to pyrazinamide was the lowest at 2.1%. One important finding from the research was that males had higher rates of MDR-TB indicating a potential gender influence on developing resistant forms of TB. (Al Hayani et al. 2021).

In an investigation by Habous and his teammates analyzed DR-TB patterns and associated risk factors among 1116 newly diagnosed tuberculosis patients in Dubai between January 2016 and November 2019. This retrospective study conducted at Dubai Health Authority assessed DR-TB against both first line and second line TB medications. The findings revealed that 17.3% of patients

showed resistance to one or more first line drugs. Resistance rates, for TB drugs were reported as follows; INH at 3.6% streptomycin at 2.95% pyrazinamide at 2.59%. Rifampicin at 0.3%. The study also found that 4.5% of patients had MDR-TB. Diabetes mellitus was identified as a risk factor for TB drug resistance while no strong link was observed between HIV co infection and drug resistance (Habous et al., 2020).

Researchers investigated drug resistance patterns in MTB patients in Basra. The study considered a set of 2,296 TB patients who have been diagnosed and 246 more patients who were treated again from January 2016 to December 2020. The researchers found that DR-TB showed among cases when compared with newly diagnosed cases and retreated cases, it is 2.4% against 20.3% respectively. The highest rates of resistance to first-line TB drugs such as isoniazid and rifampicin were found in the patients who received retreatment. The rate of MDR-TB also experienced an increase during the period of study, for example, it was only 0.17% in cases and got to 1.6% by the end of the research timeframe. Furthermore, the research also pointed out a progressive trend for strains resistant to multiple drugs specifically isoniazid. (Mohammed et al., 2022).

In the study of Alfaham and his colleagues, they Explored DR-TB and MDR-TB among previously treated patients at Wad Madani Tuberculosis Center in Sudan. This survey conducted between 2018 and 2019 involved 300 TB patients. Through the GeneXpert test scientists identified MTB DNA and the *rpoB* gene linked with DR-TB. Findings revealed that 34% (103/300) of participants were diagnosed with TB. Of these 9.7% (10/103) had MDR-TB with half of the MDR cases found in treated patients who experienced a relapse. The study features the prevalence of MDR-TB among relapsed

patients which highlights the necessity for enhanced treatment and management strategies. The existence of MDR-TB in some treated individuals implies challenges in initial treatment effectiveness and the potential dissemination of resistant strains (Alfaham et al., 2022).

In a study by Noha S. Soliman and team they thoroughly examined the prevalence and patterns of MDR-TB and non-tuberculous mycobacteria (NTM) in Egypt using various diagnostic methods. This study is vital for understanding how MDR-TB spreads and the challenges posed by NTM in that region. Out of 1,019 MTB isolates analyzed NTM was found in 38.37% of cases while multidrug resistance was seen in 7.16% of isolates. Specifically, MDR-TB was identified in 4.2% of cases and 8.05% of treated cases showing a significant difference, between the two groups (P value <0.05). It's interesting that all the drug resistant tuberculosis isolates from sources were MDR-TB while the extrapulmonary MTB isolates had resistance patterns without rifampicin. The MDR-TB isolates showed combinations of resistance, to isoniazid, rifampicin, streptomycin and ethambutol. The common combination was isoniazid, rifampicin, streptomycin and ethambutol (46.5%) followed by isoniazid and rifampicin (24.6%). This detailed analysis helps in understanding how resistance evolves and in planning public health responses to tackle TB in Egypt.

A study conducted by the public health sector in Bahrain utilized an observational method to examine the occurrence and resistance profiles of MDR-TB between 2014 and 2018. The study focused on patients clinically diagnosed with TB including those with MTB cultures for evaluation. Testing involved drug susceptibility for anti-tuberculosis medications and molecular testing for MTB PCR and rifampicin resistance genes. The findings indicated

a decrease in TB cases from 17 per 100,000 individuals in 2014 to 11 per 100,000 in 2018. Among the 946 reported patients 588 had confirmed MTB cultures with 15 isolates (3%) identified as MDR-TB. Notably isoniazid monoresistance was prevalent at a rate of 9% among tested isolates while streptomycin showed a resistance rate of 6% rifampicin at 3% and ethambutol at 1%. Most MDR cases were observed in Bahraini males, with pulmonary complications. The research findings, based on data gathered from the TB surveillance database and analyzed at a public health lab offer valuable insights into the epidemiology and resistance trends of tuberculosis in the region. These trends align with those observed in Gulf countries (Alkhawaja, 2020).

Comparative Analysis of MDR-TB Prevalence and Management Challenges in the Middle East and North Africa Regions

MDR-TB prevalence and patterns vary throughout the Middle East and North Africa. Each country distinct epidemiological profile provides insights into challenges and the effectiveness of public health measures. Egypt stands out with a prevalence of MDR-TB among previously treated cases. In Egypt 8.05% of treated cases were found to have MDR-TB, a rate than that observed in countries like Bahrain and Saudi Arabia where lower prevalence was noted through mono resistant strains. Sudan also reported a 9.7% MDR-TB rate among diagnosed TB patients highlighting the significant challenge, in managing re treatment cases.

In Saudi Arabia research indicates a pattern of resistance showing rates for drugs such, as pyrazinamide (33.4%) and isoniazid (26.7%). This implies that resistance to medications can be considerably high potentially complicating treatment approaches. Conversely in UAE, a region within the United Arab

Emirates resistance levels is lower with isoniazid resistance at 3.6%. Rifampicin at 0.3%. The diminished rates of drug resistance in UAE may signify effective tuberculosis control strategies or variances in population dynamics and healthcare systems.

In Iraq and Sudan cases of patients who have undergone retreatment pose a challenge. Iraq exhibited a prevalence of drug resistance among retreated cases compared to diagnosed ones with resistance rates standing at 20.3% versus 2.4%, respectively. Similarly in Sudan half of the instances of MDR-TB arose in retreated individuals emphasizing concerns regarding treatment compliance, efficacy and potentially the transmission of resistant strains, within these communities.

2.1.4 Global Analysis of Multi Drug-Resistant Tuberculosis

The rise of MDR-TB represents a significant global health challenge, especially in regions where TB is prevalent. Following our regional analysis, this study expands its focus to examine the prevalence and resistance patterns of MDR-TB worldwide, incorporating insights from a broad range of international studies especially countries with high MDR-TB prevalence rate according to the WHO yearly report (WHO,2023).

Table (3): Global Epidemiological Patterns, Methodologies, and Key Findings of Multi-Drug-Resistant Tuberculosis (MDR-TB) Studies Across the World.

Researcher(s)/Year	Title	Country	Methodological Approach	Research Tools and Methods	Main Results
(Zhou et al., 2022)	Drug resistance patterns and dynamics of tuberculosis in Zhejiang Province, China: Results from five periodic longitudinal surveys	China	Longitudinal study	Data from five structured surveys; Standardized testing for TB drug resistance, statistical analysis	A decline in rifampicin-resistant TB (RR-TB) prevalence was observed, alongside notable resistance to fluoroquinolones in new cases (3.8%), suggesting emerging challenges in TB management. MDR-TB remains prevalent especially in previously treated cases, highlighting persistent issues in treatment adherence.
(Zhang et al., 2022)	Characteristics and Trend of Drug-Resistant Tuberculosis at a major specialized hospital in Chongqing, China: 2016 versus 2019	China	Retrospective cohort study	Phenotypic and molecular diagnostic methods, drug sensitivity testing, statistical analysis	Findings indicate a significant increase in drug resistance and culture positivity rates, particularly among previously treated TB cases. The rise in MDR-TB and pre-XDR-TB cases suggests worsening resistance patterns.

(Seema et al., 2023).	A Retrospective Study on Multi-Drug Resistant Tuberculosis in a Tertiary Care Hospital: An Alarming Threat of Concern	India	Retrospective study	Phenotypic and molecular diagnostic methods, drug sensitivity testing, statistical analysis	Persistent high resistance rates to first-line TB drugs were noted, with MDR-TB rates being slightly lower than national averages, indicating local variations in resistance patterns.
(Verma et al., 2021)	Prevalence of multi-drug resistant tuberculosis and factors associated with treatment outcome in three districts of Himachal Pradesh, India	India	Cross-sectional study	Questionnaires, interviews, review of medical records, statistical analysis	The study reported a low default rate in treatment adherence and significant socio-demographic factors influencing MDR-TB prevalence, with 31% of MDR-TB patients having a history of previous treatment.
(Sharma et al., 2020).	Trends & treatment outcomes of multidrug-resistant tuberculosis in Delhi, India (2009-2014): A retrospective record-based study	India	Retrospective study	Reviews of patient records, treatment cards, and laboratory registers, statistical analysis	A decrease in favorable treatment outcomes was documented, from 58.13% in 2009 to 38.74% in 2014. Factors such as being male and undernourished at treatment onset were linked to poor outcomes, stressing the need for enhanced healthcare strategies.

(Kostyukova et al., 2023)	Epidemiology and Drug Resistance Patterns of Mycobacterium tuberculosis in High-Burden Area in Western Siberia, Russia.	Russia	Retrospective study	Phenotypic and molecular diagnostic methods, drug sensitivity testing, statistical analysis	A decline in overall TB incidence was noted, but MDR-TB cases rose, with 67.9% of isolates showing multidrug resistance. This highlights severe resistance challenges and the need for ongoing surveillance and adapted treatment strategies.
(Velasco et al., 2020)	Multidrug Resistant Mycobacterium Tuberculosis Among Military and Civilian Personnel seen at a Tertiary Military Hospital, Manila, Philippines (2015–2018)	Philippine	Cross-sectional study	Phenotypic and molecular diagnostic methods, drug sensitivity testing, statistical analysis	Higher TB and rifampin resistance rates were observed among military personnel compared to civilians, likely due to close living quarters and elevated exposure risks.
(Glasauer et al., 2019)	First-line tuberculosis drug resistance patterns and associated risk factors in Germany, 2008-2017	Germany	Retrospective study	National surveillance data, a decade of tuberculosis case reports, statistical analysis	Out of 26,228 cases with complete drug susceptibility testing results, 12.7% showed resistance to at least one drug. MDR-TB prevalence stood at 2.1%, with significant resistance

					seen among foreign-born individuals and those with prior TB history.
(Ali et al., 2020)	Prevalence of multi-drug resistant Mycobacterium tuberculosis in Khyber Pakhtunkhwa – a high tuberculosis endemic area of Pakistan	Pakistan	Cross-sectional study	Phenotypic and molecular diagnostic methods, drug sensitivity testing, statistical analysis	Among the confirmed TB cases, 4.9% were diagnosed with MDR-TB. There was a higher incidence of TB among females and a notable rate of 10.4% MDR-TB among previously treated patients, highlighting regional challenges.
(Chen et al., 2020)	Multidrug-resistant tuberculosis in the United States, 2011–2016: patient characteristics and risk factors	USA	Retrospective study	US National Tuberculosis Surveillance and Genotyping Service, statistical analysis	Of the TB cases studied, 1.4% were confirmed as MDR-TB. Most MDR-TB cases were due to reactivation of latent

In a study conducted in Zhejiang Province, China researchers, Zhou and his teammates looked at the evolution of DR-TB in the span of 20 years. They looked at data from surveys on DR-TB, and the results were based on the 2018 survey involving 996 patients showed that the prevalence of rifampin TB stood at 2.5% for cases and 4.3% for relapsed cases. Particularly, a significant portion (81.8%) of RR-TB cases were categorized as MDR-TB indicating resistance to both rifampin and isoniazid. The MDR-TB rates were 2.04% for new cases and 3.51% for previously treated cases. Moreover, it was highlighted that a second-line drug fluoroquinolone resistance rate of 3.8% in TB cases was superior to the resistance rates observed for rifampicin. These trends point towards a decreasing prevalence of rifampin TB over time aligning with surveillance data and underscoring the importance of continuous monitoring and widespread testing to combat DR-TB effectively (Zhou et al., 2022).

In another study in China by Huizheng Zhang and team researchers aimed to outline the trends in DR-TB at a hospital in Chongqing by comparing data, between the years 2016 and 2019. The research included 985 TB patients, with confirmed culture results in 2016 and 835 in 2019, all of the patients underwent testing for DR-TB. The overall rates of DR-TB increased from 40.2% in 2016 to 43.1% in 2019. Particularly concerning was the increase in rates of MDR-TB from 25% to 33.4% between the two years and pre-XDR TB rates rose from 7.1% to 12.8%. These results highlight a concerning trend of drug TB emphasizing the need for prompt diagnosis and effective treatment to control the spread of resistant strains of TB, in Chongqing (Zhang et al., 2022).

A study was carried out by researchers in India, at the Rajendra Institute of Medical Sciences to review the patterns and occurrence of MDR-TB between 2017 and 2019. They investigated 549 cases studying samples of pulmonary TB and extra-pulmonary cases. The results showed that the resistance levels to TB remained consistently high throughout the three-year period ranging from 49.1% to 52.1%. The study also found that the rate of MDR-TB in cases was 2.7% while in treated cases it was higher at 11.2% which is lower than average. This research underscores the battle against TB resistance. Stresses the crucial measures required to combat MDR-TB effectively (Seema et al., 2023).

In a research study the focus was, on understanding the prevalence of MDR-TB and the factors influencing treatment outcomes across three districts in Himachal Pradesh, India. The study took place over one year from January to December 2019 involving a total of 3756 TB patients identified, with 118 cases diagnosed with MDR-TB. The results showed an MDR-TB prevalence of 3.14% within the study group. Specifically, the occurrence of MDR-TB was 2.42% among TB cases and 9% among those who had been treated before. The research also looked into how MDR-TB was distributed, with pulmonary cases making up the majority (98.3% of MDR-TB instances). Interestingly a significant number of MDR-TB patients (69%) had no history of treatment indicating primary transmission within the community. Besides the findings, the research also considered the elements connected to the results of MDR-TB. The study particularly emphasized the importance of the following factors, diagnosing methods, and overall control of the plan's effectiveness with a strong monitoring and support system, in dealing with and thus decreasing the impact of MDR-TB (Verma et al., 2021).

A recent, in-depth research study by Sharma and colleagues (2020) delved into the analysis of MDR-TB in Delhi, India spanning the years from 2009 to 2014. They examined the data of 2,958 MDR-TB patients across three DR-TB treatment hospitals, revealing patterns and demographic impacts on treatment outcomes. The findings revealed a concerning trend in positive treatment outcomes over the 6-year period with 53.28% of patients achieving favorable results by the end of the study. The study also emphasized the prevalence of MDR-TB cases with rates at 3.4% among new TB cases and 18%, among relapsing individuals highlighting the serious challenges faced in effectively managing MDR-TB in this region (Sharma et al., 2020).

In a research study, by Kostyukova and teammates (2023) they looked at the spread of TB and resistance to antitubercular drugs in the Omsk region of Western Siberia, an area known for its high disease burden. The study, carried out in 2021 focused on 851 patients newly diagnosed with TB to investigate the trends in DR-TB, MDR-TB and XDR-TB. The results highlighted a concerning prevalence of MDR-TB indicating that 67.9% of resistant positive cases were resistant to both isoniazid and rifampicin which are of the most important antitubercular drugs. Notably, 40.4% were categorized as pre-XDR TB and 19.2%, as XDR strains. These findings emphasize the challenges faced in controlling TB within this region (Kostyukova et al., 2023).

In a study conducted in 2020 Velasco and coworkers observed the trend of MTB and MDR-TB in a hospital located in Manila, the Philippines covering the period from 2015, to 2018. The investigation involved a total of 795 participants comprising both former military personnel well as civilians. It offered an evaluation of tuberculosis infection rates among these demographics. The results highlighted a contrast in infection rates; members

of the military exhibited a higher prevalence of MTB at 18% in comparison to civilians, at 8%. Moreover, rifampicin resistance was identified in 17% of individuals who tested positive for TB (Velasco et al., 2020).

From 2008, to 2017 in Germany a study delved into the analysis of resistance to tuberculosis drugs. The research relied on surveillance data to explore resistance patterns in Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin. Out of 26,228 cases with drug susceptibility test results 12.7% (3,324 cases) exhibited resistance to at one of the drugs studied. Notably monoresistance to Streptomycin was prevalent despite its reduced use as a drug during the study period. Within the MDR-TB cases (556 instances) 39.2% displayed resistance to all five drugs—raising concerns about extensively drug resistant TB within this group. The research also highlighted varying levels of drug resistance among demographics; foreign born individuals showed rates of any drug resistance (16.0%) compared to German born individuals (8.3%). Moreover, MDR-TB prevalence was substantially higher in the foreign-born population (3.3%) than, in German-born adults (0.6%), according to Kostyukova et al. (2023).

Sajid Ali and his team thoroughly examined the MDR-TB rates in Khyber Pakhtunkhwa, Pakistan a region heavily affected by TB. Using an approach they looked into the occurrence. Spread of drug resistant TB variants. The study involved studying 1,969 TB patients revealing that 97 individuals (4.9%) had MDR-TB. The research also highlighted resistance, to Streptomycin and Isoniazid found in 9% and 6% of cases respectively. An interesting discovery was the prevalence of TB among females compared to males and a concerning 10.4% rate of MDR-TB among patients who had undergone TB treatment. These findings emphasize the necessity, for

enhanced public health strategies. Improved diagnostic services to effectively combat TB in regions grappling with high levels of drug resistance (Ali et al., 2020).

A recent research paper delved into the issue of MDR-TB, in the United States between 2011 and 2016. By examining surveillance data, the study aimed to identify characteristics and risk factors associated with MDR-TB specifically looking at the impact of past TB infections recent transmissions of MDR-TB and the reactivation of dormant MDR-TB cases. Out of a total of 45,209 TB cases reviewed 615 cases (1.4%) were classified as MDR-TB. Interestingly 41 cases (6.7%) were linked to transmissions highlighting the rarity of MDR-TB spreading through recent close contact. The majority of cases (449 cases or 73%) were attributed to reactivated latent infections. The study also emphasized risk factors for individuals born outside the U.S. those with a history of previous TB treatment showing that their likelihood of contracting MDR-TB was significantly increased if they had been in contact, with MDR-TB patients (Chen et al., 2020).

2.3.1. Comparative Analysis of MDR-TB Prevalence and Management Challenges Across Different Regions

Russia is notable, for its prevalence of MDR-TB as highlighted in a study conducted in Western Siberia where 67.9% of TB cases resistant to isoniazid and rifampicin were identified. A significant portion of these cases were classified as pre-XDR and XDR-TB indicating a serious challenge in managing tuberculosis within the region.

In China two studies shed light on aspects of the TB situation. In Zhejiang Province there has been a decline in resistance over time suggesting

interventions and monitoring practices. However, Chongqing has seen an increase in MDR-TB rates from 25% to 33.4% over three years, underscoring disparities in disease management at the level.

India consistently reports rates of MDR-TB among retreated cases across studies with rates reaching 11.2% in one study and 9% in another conducted in Himachal Pradesh. This points to challenges related to treatment adherence and effectiveness along with issues concerning primary transmission given the high prevalence of MDR-TB among patients without a history of prior treatment.

In the Philippines a significant number of TB individuals were found to have a resistance, to rifampicin indicating the unique challenges of dealing with TB in crowded urban areas. Germany on the other hand has reported levels of drug resistance notably streptomycin monoresistance being common and significant resistance rates to all five drugs studied among MDR TB cases especially in foreign born individuals.

The United States has a prevalence of MDR TB at 1.4% with most cases attributed to reactivated latent infections rather, than recent transmissions. This highlights the importance of screening and managing latent TB infections in high-risk populations.

Chapter 3

Methods and procedures

3.1 Study Area/Setting

This study was conducted in the Kingdom of Bahrain through two main institutions: The University of Bahrain (UoB) and the Public Health Directorate (PHD). The PHD laboratories has been chosen as the primary site for data collection because they serve as the national reference laboratory for TB testing. This ensures that the data collected is comprehensive and representative of the nation's TB burden, due to the PHD's central role in TB diagnosis and monitoring throughout Bahrain. The laboratory follows very strict testing protocols; hence it is a reliable source of data for this retrospective study.

UoB was selected for data analysis based on the availability of technological resources, including advanced statistical software such as IBM SPSS and high-performance computing facilities. These resources support the accurate and efficient processing and analysis of large datasets.

These two institutions combined offered a convenient location for this study to be carried out and they assisted in ensuring that the data and its analysis were reliable and valid.

3.2 Study Design

The study adopted a retrospective design to identify all cases of TB that were diagnosed in Bahrain from 2013 to 2024 with the exception of 2021 when data was incomplete. Retrospective studies are popular because they enable researchers to utilize existing data and thus do not require the time and resources that would be involved in collecting data in the field over time. This research strategy was particularly suitable for this study as a large number of

TB cases have been documented in Bahrain during the study period, thus enabling the researcher to make long-term comparisons.

This study does not require direct patient interaction and so the ethical requirements are rather straightforward. However, this design has the major limitation that analysis is confined to the data that is available; data may be incomplete or there may be variables that are not included in the analysis. Additionally, retrospective studies can establish associations but not causes, which is a restriction on the generation of conclusions.

However, this design was chosen because it met the study's objectives of identifying the trends in drug resistant TB and examining demographic factors associated with the incidence of TB.

3.3 Study Subjects

The study population consisted of all patients who have ever been tested for TB at the Public Health Directorate laboratories between 2013 and 2024. After initial data extraction, a total of 1,158 TB positive samples were included in the dataset, both Bahraini citizens and non-Bahraini residents.

The number of cases of drug resistant TB analyzed was 310, having reduced from an initial pool of 340 cases because of the exclusion of duplicate samples. These exclusions were necessary to make the data accurate and to avoid the overrepresentation of specific patients in the analysis. Repeat samples from the same patient within a two-month period were excluded, as TB cultures take 6-8 weeks to grow, making later samples redundant. These exclusions were only applied if the repeated sample was of the same type (pulmonary or extra-pulmonary).

3.4 Data Collection Methods

This study utilized secondary data that was obtained from PHD's TB database which contains complete information of all the patients who were diagnosed with TB within the study period. No direct patient contact was involved and therefore informed consent was not needed. All the data collected were anonymized with regard to demographic variables and clinical information to protect the patient's privacy and confidentiality.

The dataset contained the following key variables:

- **Demographic Data:** Nationality, age, and gender.
- **Drug Resistance:** Resistance profiles for five key TB drugs: Streptomycin, Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide.
- **Sample Type:** Pulmonary and non-pulmonary samples.

This dataset provided a robust foundation for analyzing both the prevalence and trends of drug-resistant TB in Bahrain over an 11-year period.

3.5 Laboratory Procedures

3.5.1 Primary Drug Susceptibility Testing (SIRE)

Antimicrobial susceptibility testing (AST) helps in the effective handling of TB patients. It should be mentioned that not only is it the way to identify the most effective drug regimen for a particular patient; it also analyzes the particular cases when the patients resist the therapy even after the antimicrobial treatment. The BACTEC MGIT 960 system, primarily used for AST, gives accurate results for the first-line anti-TB drugs: Streptomycin (S), Isoniazid (I), Rifampin (R) and Ethambutol (E), all together called SIRE. This method allows the laboratory for a relatively fast and qualitative test to decide

on the resistance of MTB isolates to the above major drugs by the use of defined test concentrations.

The principle of the test involves a growing MTB culture in the existence of a known concentration of a drug while at the same time keeping control culture without the drug. An isolate is considered susceptible to the drug if it does not grow in the presence of the drug but does so in the control medium. If, however, growth is detected in both media, the isolate is said to be resistant. Susceptibility testing mostly employs the proportion method, where the bacterial resistance to the drug is decided if there is 1% or more of the bacteria the drug does not affect.

The BACTEC MGIT 960 system follows a broth-based method for MTB detection and AST. Unlike its predecessor, which used radiometric detection, the MGIT 960 system uses fluorescence-based oxygen consumption to monitor bacterial growth. The liquid culture medium containing mycobacteria respiring actively and consuming oxygen is detected by the system according to the reduction of oxygen and the corresponding increase in fluorescence. The system is designed in such a way that the detection of mycobacterial growth and drug susceptibility becomes both rapid and automated, thus, significantly lowering its turnaround time associated with this method compared to others. The increase in the fluorescence of the oxygen sensor is the automatically registered parameter from which the growth value is evaluated. Thus, drug susceptibility can be evaluated in real time.

The MGIT 960 SIRE susceptibility testing kit constitutes the lyophilized forms of the four drugs, each of them with a pre-defined concentration. The system confirms its accuracy in testing susceptibility by having concentrations that are slightly lower than those are used in the conventional solid media

method, thus minimizing the risk of false susceptibility results. The kit further comes with the MGIT SIRE growth supplement, which increases the amount of bacteria in the medium. The drugs and supplements have to be stored properly, where reconstituted drug solutions have to be kept at -20°C or lower and discarded after six months or upon expiration.

The test procedure is initiated with the reconstitution of lyophilized drugs that require the use of sterile distilled water. A particular volume of the drug solution is then introduced into the designated MGIT tubes, which are labeled, in order to achieve the critical concentration in the medium. The preparation of the bacterial inoculum is carried out utilizing liquid cultures that are grown in the MGIT tubes. The inoculum is subsequently added to every tube that has the drug and a growth control tube, then the tubes are incubated in the MGIT 960 system. For the purpose of susceptibility testing, the bacterial suspension is brought to the McFarland 0.5 standard and it is used undiluted if it is processed on day 1 or 2. In the case of samples processed on days 3-5, a 1:5 dilution is done by adding 1.0 ml of positive broth to 4.0 ml sterile saline.

While the test in incubation the system machine is actively taking readings for monitoring bacterial growth. The test usually takes from 4 to 13 days, depending on the growth rate of the bacteria. Results of the test are interpreted based on the growth unit (GU) values, a drug tube with GU below 100 shows susceptibility, while a GU of 100 or higher shows resistance. When indeterminate result happens, due to a lot of reasons including contamination, non-viable bacterial growth, or slow-growing resistant strains. Under this condition, retesting is recommended using a sub-culture of the original sample.

Immediately after the testing is finished, the results should be directly reported and also it should be mentioned the method used for the test, the type of drug, and the concentration level. In case of resistance, it is advisable to do a visual confirmation of the medium to rule out contamination. AST are very important for TB treatment plans, and it is used to choose the effective drugs and also it is used to prevent further development (Siddiqi & Rüsç-Gerdes, 2006).

3.5.2 Pyrazinamide Susceptibility Testing

Distinct from the other primary anti-TB medications (SIRE), PZA is the only one that is effective in an acidic environment. As a result, PZA susceptibility testing needs acidic conditions (pH 5.9) to imitate its intracellular activity. Two standard protocols are followed: the agar proportion technique using pH 5.9 acidified Middlebrook 7H10 medium and the BACTEC MGIT 960 system. The last method has been favored recently for its non-radiometric feature despite earlier issues like the inhibited mycobacterial growth at low pH during the conventional method used.

The BACTEC MGIT 960 PZA susceptibility test is a qualitative, liquid media dependent procedure designed to evaluate the susceptibility of MTBC to PZA. The MGIT 960 medium is a modified 7H9 broth with an adjusted pH of 5.9 to support bacterial growth while preserving PZA activity. The system similar to SIRE as both uses the same incubator machine system BACTET MGIT 960, utilizes fluorescence-based oxygen sensing technology to monitor bacterial growth in real-time. The test establishes resistance based on bacterial growth in the presence of the drug compared to growth control.

Similar to SIRE the testing process begins with the reconstitution of the PZA drug. Each PZA drug vial is reconstituted with 2.5 ml of sterile distilled water to get a final concentration of 8000 µg/ml. For inoculum preparation, the test

culture must be a verified pure isolate of MTBC. For susceptibility testing, the bacterial suspension is adjusted to McFarland 0.5 standard and used undiluted if processed on day 1 or 2. For samples processed on days 3-5, a 1:5 dilution is prepared by adding 1.0 ml of positive broth to 4.0 ml sterile saline.

Inoculation and incubation involve labeling two MGIT PZA tubes: one as the growth control and the other as the PZA drug-containing tube. A volume of 0.8 ml of PZA growth supplement is added to both tubes. Then, 0.1 ml (100 μ L) of the reconstituted PZA drug is added to the PZA tube only. A bacterial suspension of 0.5 ml is inoculated into both tubes, with the GC tube obtaining an additional 1:10 dilution step. Tubes are mixed and placed in the MGIT 960 system for automated processing.

The BACTEC MGIT 960 instrument monitors growth and provides results between 4 and 21 days. A GC reaching a GU of 400 or more indicates a valid test. Results are reported as sensitive if growth is inhibited in the presence of PZA and resistant if bacterial growth occurs despite the presence of PZA. If the GC tube shows positive growth in less than 4 days or remains negative for 21 days, an error message X will appear, requiring a repeat test (Siddiqi & Rüscher-Gerdes, 2006).

3.6 Data Cleaning

To ensure the accuracy of analysis, a thorough data cleaning process was carried out. Any duplicate samples were identified and removed, particularly in cases of more than one sample from a patient in a two month period. This was because TB cultures take 6-8 weeks to grow, so any sample taken in that time is very likely to be a repeat of the original.

In addition, These exclusions were only applied if the repeated sample was of the same type (pulmonary or extra-pulmonary).

Very little data was missing, only one gender entry and six age entries. For analyses involving these specific variables, the missing cases were excluded. However, these cases were still included in other parts of the analysis where demographic information wasn't needed.

3.7 Statistical Methods

All statistical analyses were performed at IBM SPSS Statistics software. The descriptive statistics were first used to summarize and explore the dataset.

Descriptive Statistics:

- Frequency distributions were calculated for categorical variables such as gender, age group, and nationality.
- Measures of central tendency (mean, median) were calculated for continuous variables where applicable, such as age.
- Percentage breakdowns were provided for the different age groups, genders, and drug resistance profiles, giving a clear picture of the demographics and clinical characteristics of the TB-positive patients.

Data Visualization:

- Pie charts will be used to represent the distribution of gender within different age groups and sample types (pulmonary vs. non-pulmonary). This will provide a clear visual representation of the demographic distribution of TB cases.
- Bar charts will be utilized to show the breakdown of nationalities, with nationalities grouped into categories for ease of comparison. This will

help illustrate the prevalence of TB among different population groups in Bahrain.

- Tables will be included to present the frequency and percentage of drug resistance to each of the five key drugs (Streptomycin, Isoniazid, Rifampicin, Ethambutol, Pyrazinamide).

These visual aids will complement the descriptive statistics and provide a more intuitive understanding of the dataset.

3.8 Ethical Considerations

Although this study did not include direct patient contact, several ethical considerations were involved. The data for this research was from an authorized database of the PHD, making sure that it was well sorted and checked and met the national healthcare standards.

All patient data was fully anonymized before analysis to ensure privacy and confidentiality. No personally identifiable information (PII) was utilized in the study and the dataset was processed securely to prevent unauthorized access. Moreover, the study met all the ethical requirements on both the UOB and the PHD sides, and the necessary institutional review boards' approval for the use of this data was obtained.

3.9 Significance of the Public Health Directorate

The Public Health Directorate (PHD) is a central pillar of Bahrain's healthcare system, particularly in the surveillance, diagnosis, and management of infectious diseases such as tuberculosis. As the nation's only reference laboratory, the PHD receives all suspected and confirmed TB cases for further testing. Advanced methods such as PCR-based diagnostics and

drug resistance profiling are routinely applied to confirm cases and guide treatment strategies.

The existence of a single reference laboratory offers clear advantages: it ensures standardized diagnostic procedures, consistent quality control, and centralized expertise, which contribute to reliable and comparable results across the country. However, this centralization also presents challenges. Reliance on a single facility may create bottlenecks, especially during surges in testing demand, potentially delaying results. Additionally, workload pressure on the laboratory could impact turnaround times and strain resources.

Acknowledging both its strengths and limitations highlights the PHD's critical role in national TB control while also pointing to the need for strategies that safeguard against over-reliance on a single facility. Including supporting evidence from Ministry of Health reports or WHO assessments of Bahrain's TB services would strengthen the section and add credibility. The PHD data is well-founded, providing a rational TB prevalence picture in Bahrain. Public health research values the PHD data to the most as it contains the information about both the Bahraini nationals and the residents, which gives the researchers the possibility to track the TB transmission and DR-TB patterns in the population. This data can be utilized for the implementation of national healthcare policies and strategies to prevent and control TB.

Chapter 4

Results, Discussion, and Recommendations

4.1 Results

In my thesis, the total study population consisted of 310 TB-positive cases, with a predominance of male participants. Among these, 216 (69.7%) were male, 93 (30.0%) were female, and 1 case (0.3%) had gender not mentioned, giving a male-to-female ratio of approximately 2.3:1.

The distribution of DR-TB cases shows substantial regional variation. The largest proportion originates from the South Asian region (Bangladesh, India, Nepal, Pakistan, and Sri Lanka), with 123 cases (39.68%). West Asia, represented mainly by Bahraini nationals (58 cases) and a single Saudi Arabian national, contributes 59 cases (19.03%). Southeast Asia (Philippines, Indonesia, and Thailand) accounts for 48 cases (15.48%), while the African region (Ethiopia, Guinea, Kenya, Somalia, Sudan, and Uganda) reports 22 cases (7.10%).

The “Other” category (25 cases, 8.06%) includes both specified but less common countries (e.g., Russia, Bhutan) and cases explicitly classified in the system as “Other countries.” Meanwhile, 31 cases (10.65%) were registered as “Unknown,” meaning the nationality was not recorded.

Nationality-specific analysis highlights Indian nationals as the largest group (19.03%), followed closely by Bahraini nationals (18.71%). Filipino (13.55%) and Bangladeshi (13.23%) nationals also contribute significantly. The “Unknown” group accounts for 10.65%, “Other” for 6.77%, while Ethiopian (5.48%), Pakistani (4.52%), and Nepalese (2.58%) nationals represent smaller proportions.

Although smaller in number, African and “Other” groups illustrate the diversity of Bahrain’s expatriate workforce and global migration patterns,

which are consistent with known labor and TB trends in the region (WHO, 2024; LMRA, 2023). Overall, non-Bahraini individuals constitute the majority, with 252 out of 310 cases (81.29%), reflecting the heavy influence of migrant populations on TB epidemiology in Bahrain.

Further interpretation of these demographic patterns, including their association with risk factors and public health implications, will be presented in the Discussion chapter.

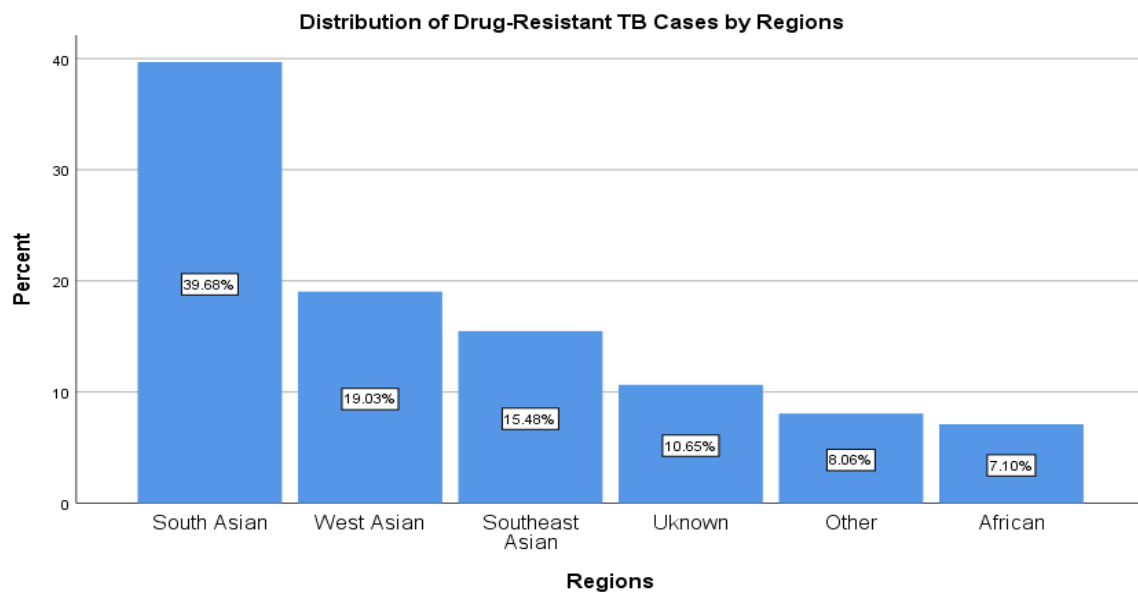


Figure 2 Bar chart Showing the Distribution of Drug-Resistant TB Cases by Region. This figure visualizes the geographic distribution of drug-resistant TB cases across different regions during the study period (2013–2023).

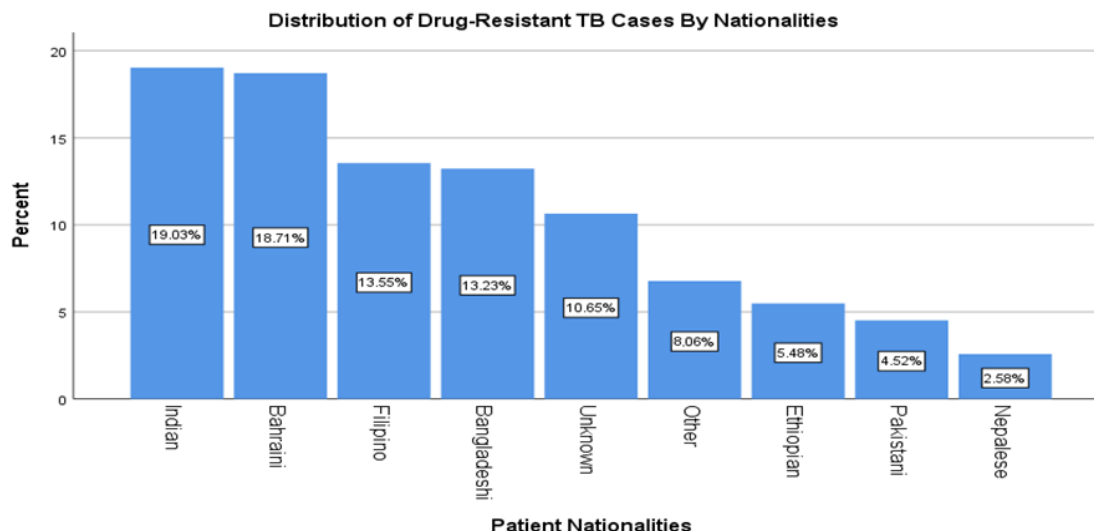


Figure 3 Bar Chart Showing the Distribution of Drug-Resistant TB Cases by Nationalities. This figure presents the percentage distribution of drug-resistant TB cases across different nationalities during the study period (2013–2023).

The distribution of drug-resistant TB by age is shown in Figure 4. The 21–40 age group accounts for the largest proportion of cases (60.2%), highlighting the need for targeted prevention and treatment efforts. The second highest number of cases is in the 41–60 years age group with 28.95%, which also represents a considerable proportion that should not be overlooked in TB control measures. The over 60 years group accounts for 7.57%, and the least is in the under 20 years with 3.29%.

The mean age of the people with drug resistant TB is 38.23 years, and the median age is 35 years. This means that the majority of the cases are from middle aged people. These statistics indicate that drug resistant TB mainly occurs in the working population especially those between 21 and 40 years. Since the majority is in this group it becomes vital to channel the TB prevention, control and treatment efforts to this group of young adults.

Combating the disease at this central population will help in the reduction of the disease incidence and its complications.

This information supports the importance of the public health measures that are focused on early identification, regular treatment and education on the prevention of TB especially among the at-risk groups. Further interpretation of these findings is provided in the Discussion chapter.

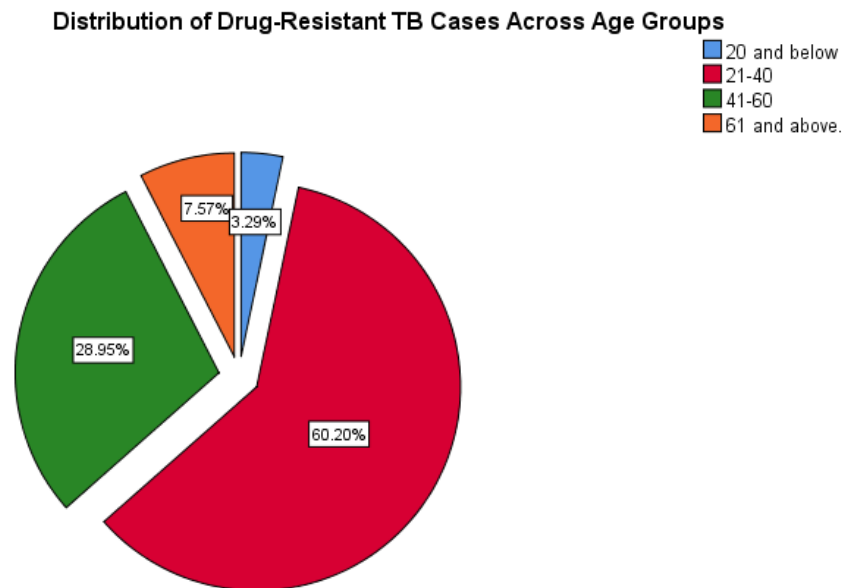


Figure 4 Pie Chart Showing the Distribution of Drug-Resistant TB Cases Across Age Groups. This figure illustrates the percentage distribution of drug-resistant TB cases among different age groups (20 and below, 21-40, 41-60, and 61 and above) during the study per

This bar chart in Figure 5 shows the percentage distribution of population by age group (0-20, 21-40, 41-60 and 61 and over) across six regions: West Asian, South Asian, African, Southeast Asian, Unknown and Other. The largest percentage in the 0-20 age group is from the West Asian region which includes all Bahrainis and only one Saudi, with 60%, followed by South Asian region with 20%, and African region with 10%. The other regions are not represented in this age group, and the Unknown region has 10%. In the 21-40

age group, the South Asian region (mainly Indian and Bangladeshi individuals) has a very high frequency of 44.81%, followed by the Southeast Asian region (16.39%), and the Unknown region (11.48%). The African region has 10.93%, and the West Asian and Other regions each have 8.2%. In the 41-60 age group, the South Asian region has the highest frequency of 35.23%, followed by the West Asian region (primarily Bahraini) with 25%, and the Southeast Asian region with 17.05%, the Other region has 10.23%, the Unknown region 11.36%, and the African region 1.14%. In the 61 and above age group, the West Asian has the highest share of 65.22%, and the South Asian region (Indians and Bangladeshi) follows with 21.74%. The Other region has 4.35%, the Southeast Asian region 8.7%, and the African and Unknown regions have no representation. Further interpretation of these regional age-distribution patterns, including their relation to population demographics and risk factors, will be provided in the Discussion chapter.

As can be seen from Figure 5, there are clear trends in the distribution of the population by age group, with the West Asian region (comprising Bahraini individuals), leading in the population of young (0-20) and old (>60) people; the South Asian region, heavily influenced by Indian and Bangladeshi individuals, having a high representation in the working age groups (21-40 and 41-60 years). The middle age groups of the Southeast Asian and Unknown regions have moderate contributions but have a negligible representation in the young and old populations. The African region has a limited representation overall; the highest percentage (10.93%) is in the 21-40 year age group, while the Other region has low percentages in all age groups, with a peak of 10.23% in the 41-60 year age group. This distribution of population by age group and region shows that there is a difference in the contribution of regions, with the

West Asian and South Asian regions making a significant contribution, especially in the young and middle-aged population and illustrates varying demographic and regional patterns.

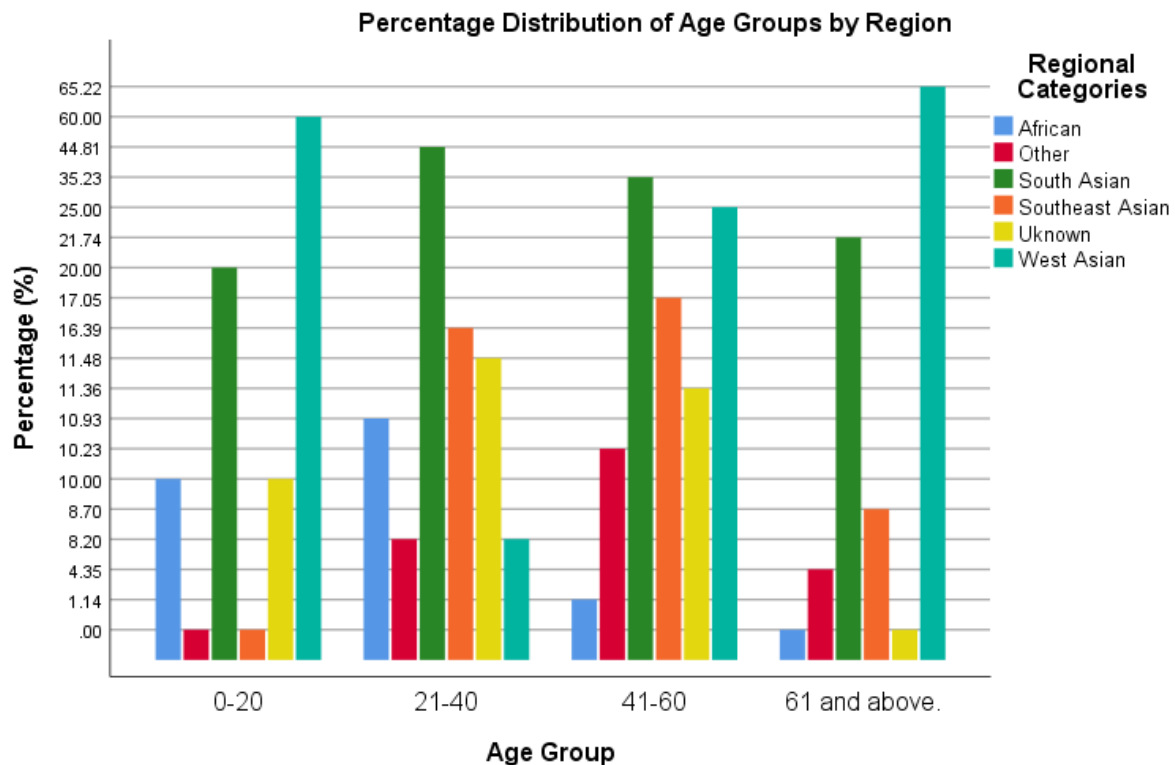


Figure 5 Bar Chart Showing the Percentage Distribution of Age Groups by Region. This figure illustrates the percentage breakdown of different age groups (e.g., 20 and below, 21–40, 41–60, 61 and above) across various regions during the study period (2013–2023).

The distribution of specimen types in DR-TB cases is represented in Figure 6. The largest category is "Sputum," accounting for 60.32% of all samples, highlighting its prominence in TB diagnostics. Other notable specimen types include "Bronchial Wash" (8.1%), "DTA" (5.8%), and "Tissue" (5.5%), indicating that while sputum remains the primary diagnostic specimen, other types of specimens are also used for diagnosis in a smaller proportion of cases. Further analysis of the data shows that out of a total of 310 samples, 232 (approximately 74.8%) were pulmonary, while 78 (approximately 25.2%) were extra-pulmonary. This breakdown suggests that pulmonary specimens

are predominantly used in the detection of drug-resistant TB, which aligns with global patterns, since pulmonary TB is the most common form and the main source of transmission (WHO, 2022). However, extra-pulmonary TB, although less common, is still clinically important because it can be more difficult to diagnose and may occur in individuals with underlying vulnerabilities such as immunosuppression or HIV co-infection (Zumla et al., 2013).

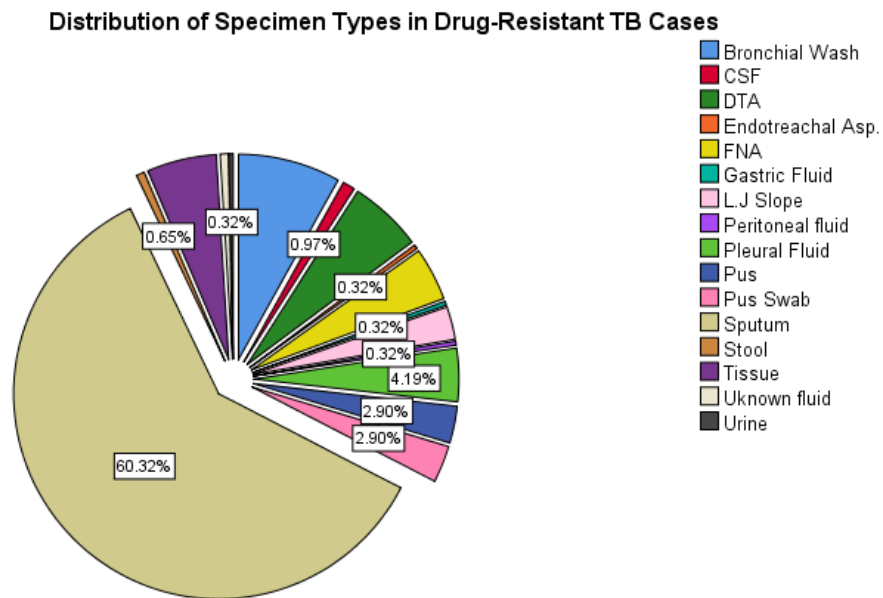


Figure 6 Pie Chart Showing the Distribution of Specimen Types in Drug-Resistant TB Cases. This figure illustrates the proportion of specimen types (e.g., sputum, bronchial lavage, lymph node aspirate, etc.) associated with drug-resistant TB cases during the study period (2013–2023).

Figure 7 shows a pie chart that represents the distribution of drug resistance and sensitivity in 1,158 TB-positive cases across six categories of tuberculosis drugs. The largest section, making up 64% of the pie and shown in yellow, indicates that the majority of cases are sensitive to all tested drugs, meaning these cases show no drug resistance. The second-largest section, colored green and comprising 15.92% of the chart, represents cases that are resistant to

Pyrazinamide, one of the primary first-line drugs used in TB treatment. Following that, the red section, accounting for 8.88%, illustrates resistance to Isoniazid, another essential anti-TB drug. The light blue segment, which represents 5.92% of the cases, corresponds to resistance to streptomycin. The chart also shows two smaller segments: an orange section representing 2.64% of the cases that are resistant to rifampicin, and a cyan section, also covering 2.64%, indicating resistance to ethambutol. Overall, while most TB cases are drug-sensitive, a significant proportion exhibit resistance, particularly to isoniazid and pyrazinamide.

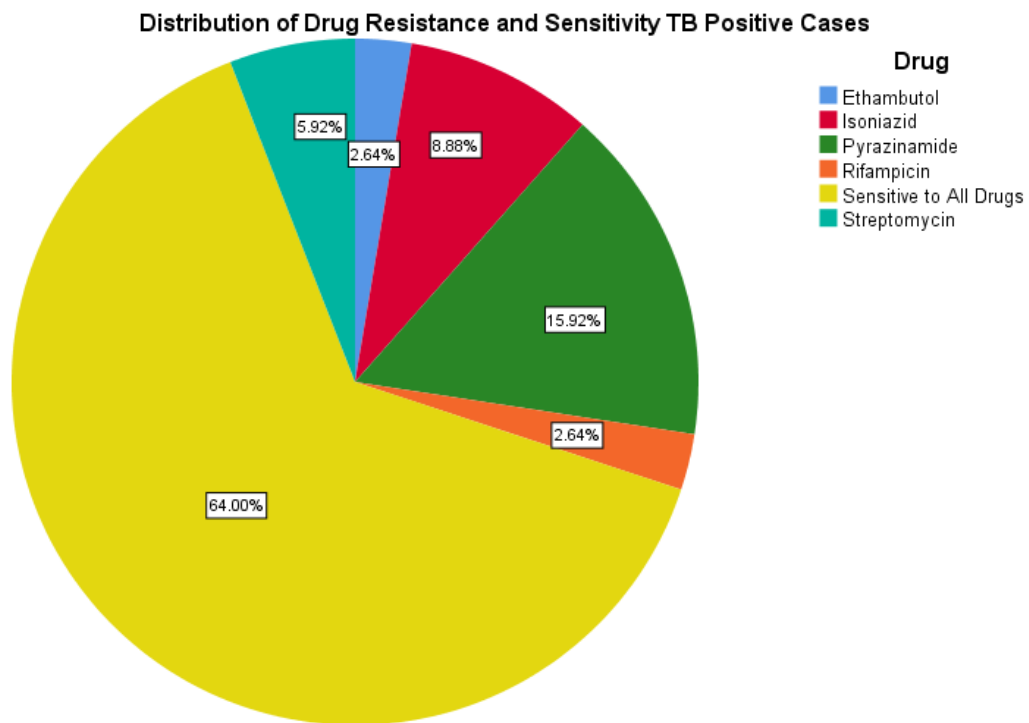


Figure 7 Pie Chart Showing the Distribution of Drug-Resistant and Drug-Sensitive TB Positive Cases. This figure depicts the proportion of TB positive cases resistant to specific drugs (Ethambutol, Isoniazid, Pyrazinamide, Rifampicin, and Streptomycin) compared to cases sensitive to all drugs. The visualization highlights the dominance of drug sensitivity and the varying prevalence of resistance to individual drugs during the study period (2013–2023).

The study reveals a concerning rise in DR-TB over the decade as shown in table 4 and figure 8, with notable peaks in 2015, 2018, and 2023. These fluctuations indicate shifts in resistance patterns, highlighting the evolving

challenge in TB management. A significant peak in MDR-TB cases occurred in 2018, reaching 4 out of 73 total TB cases (5.48%). This marked the highest proportion recorded in the study, a sharp increase from 1.42% (2/141 cases) in 2015 and 1.96% (3/153 cases) in 2013. However, by 2023, MDR-TB slightly declined to 2.02% (2/99 cases), yet it remained a critical concern for TB control.

Resistance to Pyrazinamide surged in 2018, reaching 32.88% (24/73 cases), up from 24.63% (33/134 cases) in 2015. This represented the second highest peak during the study period. By 2023, resistance levels remained alarmingly high at 32.65% (32/98 cases). A sharp increase in resistance to any of the five tested drugs was observed in 2015, rising to 37.31% (50/134 cases) from 17.65% (27/153 cases) in 2013. However, an unexpected drop to 9.60% (12/125 cases) in 2020. By 2023, resistance surged to 48.96% (47/96 cases), the highest recorded level, emphasizing the worsening trend.

In 2015, resistance to any drug spiked to 37.31% (50/134 cases), largely driven by Pyrazinamide resistance (24.63%). The year 2018 saw the highest MDR-TB proportion (5.48%) and a Pyrazinamide resistance peak (32.88%), with 41.10% (30/73 cases) of cases showing resistance to at least one drug. By 2023, the situation had deteriorated further, with resistance to any drug reaching 48.96% (47/96 cases), while Pyrazinamide resistance (32.65%) remained near its 2018 peak.

Over the study period, the number of cases sensitive to all five drugs declined significantly. In 2013, 82.35% (126/153 cases) of TB cases were fully susceptible, but by 2023, this figure had dropped to 51.04% (49/96 cases).

Further interpretation of these peaks will be discussed later on the discussion section.

Table (4): Trends in Drug Resistance Among TB Patients from 2013 to 2023. The table presents the number and percentage of TB cases resistant to Isoniazid, Rifampicin, Ethambutol, Pyrazinamide, Streptomycin, and MDR (Multidrug-resistant TB: resistance to Isoniazid and Rifampicin at the same time).

Year	Isoniazid Resistant	Rifampicin Resistant	Ethambutol Resistant	Pyrazinamide Resistant	Streptomycin Resistant	MDR	Resistant to any of the five tested anti-TB drugs	Sensitive to all five tested drugs
2013	14/153 (9.15%)	3/153 (1.96%)	3/153 (1.96%)	27/153 (17.65%)	6/153 (3.92%)	3/153 (1.96%)	27/153 (17.65%)	126/153 (82.35%)
2014	13/147 (8.84%)	5/147 (3.40%)	5/147 (3.40%)	24/144 (16.67%)	8/147 (5.44%)	5/147 (3.40%)	36/144 (25.00%)	108/144 (75.00%)
2015	14/141 (9.93%)	4/141 (2.84%)	4/141 (2.84%)	33/134 (24.63%)	8/141 (5.67%)	2/141 (1.42%)	50/134 (37.31%)	84/134 (62.69%)
2016	15/106 (14.15%)	5/106 (4.72%)	5/106 (4.72%)	NO REAGENT: 0/84 (0.00%)	16/106 (15.09%)	5/106 (4.72%)	22/84 (26.19%)	62/84 (73.81%)
2017	3/79 (3.80%)	1/79 (1.27%)	1/79 (1.27%)	7/76 (9.21%)	7/79 (8.86%)	1/79 (1.27%)	14/76 (18.42%)	65/76 (85.53%)
2018	8/73 (10.96%)	4/73 (5.48%)	4/73 (5.48%)	24/73 (32.88%)	4/73 (5.48%)	4/73 (5.48%)	30/73 (41.10%)	43/73 (58.90%)

2019	12/109 (11.01%)	4/109 (3.67%)	1/109 (0.92%)	17/109 (15.60%)	3/109 (2.75%)	4/109 (3.67%)	27/109 (24.77%)	82/109 (75.23%)
2020	6/129 (4.65%)	2/131 (1.53%)	2/129 (1.55%)	4/127 (3.15%)	5/129 (3.88%)	0/131 (0.00%)	12/125 (9.60%)	113/125 (90.40%)
2022	14/119 (11.76%)	3/119 (2.52%)	4/119 (3.36%)	31/120 (25.83%)	10/117 (8.55%)	3/120 (2.50%)	47/117 (40.17%)	68/117 (58.12%)
2023	12/99 (12.12%)	2/99 (2.02%)	4/99 (4.04%)	32/98 (32.65%)	7/97 (7.22%)	2/99 (2.02%)	47/96 (48.96%)	49/96 (51.04%)

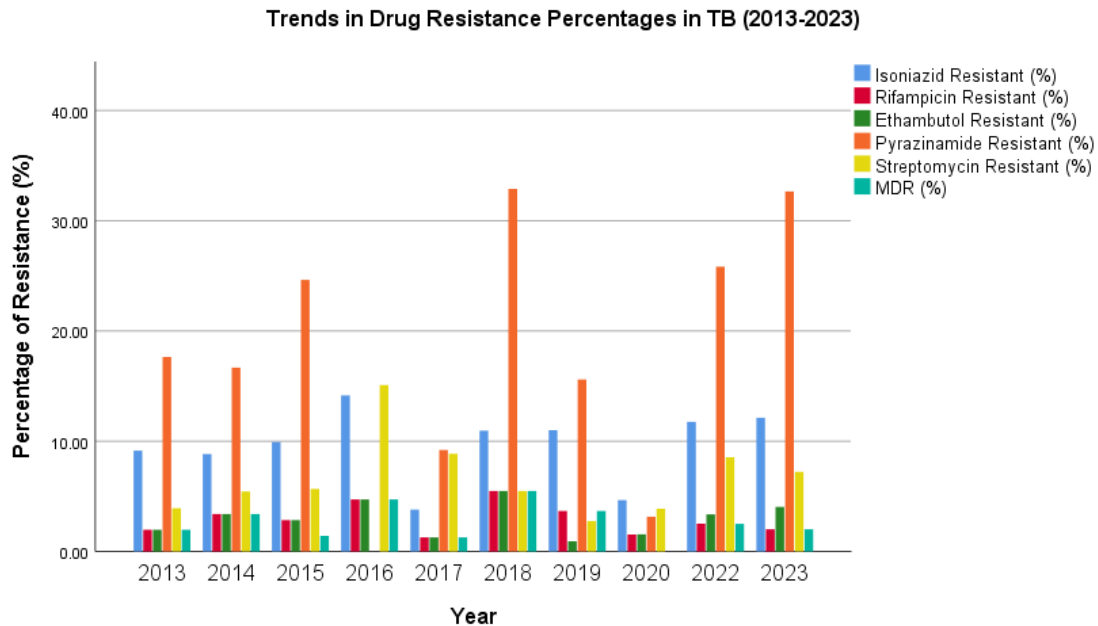


Figure 8 Bar Chart Showing the Trend in Drug Resistance Percentages in TB (2013–2023). MDR refers to multidrug-resistant TB, defined as resistance to at least Isoniazid and Rifampicin. This visualization highlights the percentage of TB cases resistant to five major drugs (Streptomycin, Isoniazid, Rifampicin, Ethambutol, Pyrazinamide) and MDR over the 10-year period, emphasizing trends and variations.

This study is based on demographic and clinical categories of TB patients and uses Table 5 to analyze drug resistance. The drugs are Streptomycin, Isoniazid, Rifampicin, Ethambutol and Pyrazinamide. The resistance of each drug is described among TB patients by sex, age categories, forms of TB and region of origin. The chi-square values and linked p-values are presented to help with the statistical significance, where the probability of the demographic variable and drug resistance association is $p \leq 0.05$. We denote significant results as ‘S’ in the ‘Significance’ column, and ‘N/S’ for the non-significant results.

For Streptomycin, the analysis reveals no significant association between resistance and sex, with a p-value of 0.733. Similarly, age categories show no significant association, as the p-value is 0.562. However, an important result

is observed in the form of TB, where pulmonary TB shows a statistically significant association with Streptomycin resistance ($p = 0.004$). This suggests that resistance to Streptomycin may be more obvious in pulmonary TB cases. Regional analysis, did not yield a statistically significant association, (p -value 0.346.)

Isoniazid has different patterns of resistance. There is no significant association with sex ($p = 0.165$) but there is a difference in the resistance between pulmonary and extra-pulmonary TB ($p = 0.011$). This correlation means that pulmonary TB patients are likely to be resistant to Isoniazid. Moreover, there is a significant association with region ($p = 0.002$), especially among South Asian and African populations. This means that the likelihood of Isoniazid resistance is high and is dependent on the geographic location of the patients, which may be due to differences in TB strains or treatment regimens in these regions.

Rifampicin, analyzed across the same variables, shows no significant associations with any demographic or clinical factors. Neither sex ($p = 0.881$), age ($p = 0.573$), form of TB ($p = 0.112$), nor regional classification ($p = 0.965$) appears to significantly influence resistance to Rifampicin in this sample. These findings suggest that Rifampicin resistance may be more uniformly distributed across demographics and clinical categories, lacking a strong association with specific patient characteristics.

There is a statistically significant association between drug resistance and form of TB for Ethambutol as well as Isoniazid. This implies that pulmonary TB cases may have higher rates of resistance to Ethambutol than extra-pulmonary TB cases, although other demographic factors such as sex ($p = 0.773$), age ($p = 0.777$), and region ($p = 0.093$) are not significant. Thus, the

determinative factor of Ethambutol resistance is the form of the TB, and other demographics are not. One plausible explanation is that pulmonary TB lesions typically harbor a higher bacterial burden, which means the drug penetrates those sites more and imposes greater selection pressure, favoring survival of resistant mutants (Allué-Guardia et al., 2021). In other words, the more the bacteria are exposed to antimicrobials under lung conditions, the greater the chance that resistance-conferring mutations will be selected (Godfroid et al., 2020).

From the above table it is important to note that, Pyrazinamide resistance, though mentioned in the table, has to be explained with caution as phenotypic tests for this drug are known to produce false resistant results at times. The literature has extensively discussed that the phenotypic assessment of Pyrazinamide resistance is notorious for providing accurate information that has led to the exaggeration of the levels of resistance to this drug. We found no significant relationships between the resistance to Pyrazinamide and most of the demographic characteristics examined. However, there is a significant association by regional classification ($p = 0.007$), particularly in South Asia, which may have a greater incidence of Pyrazinamide resistance. Because of the biases in the phenotypic testing, these results should be treated with caution, keeping in mind the probability of inaccurate resistance results in phenotypic tests, which may distort actual Pyrazinamide resistance.

The table shows notable resistance patterns across different drugs and demographic factors. Pulmonary TB is closely associated with Streptomycin and Isoniazid, which means that the resistance to these drugs may be more common in pulmonary TB. Isoniazid and Pyrazinamide regional associations further suggest that geography may play a role in the patterns of resistance,

which may be genetic, or a result of variation in treatment practices around different areas. The case of Pyrazinamide is also unique in that the problem of phenotypic testing is the highest rate of resistant strains, which may not truly reflect the resistance because of technical reasons. This will be discussed in greater detail in the limitation section, concerning the accuracy of Pyrazinamide resistance detection in TB diagnostics. These findings thus open up possibilities of how demographic and clinical factors may influence drug resistance in TB, and how treatment plans can be tailored to the patient and how TB control strategies can be enhanced based on patient characteristics.

Table (5): Analysis of Drug Resistance Patterns in TB Patients Across Demographic and Clinical Categories. This table summarizes resistance patterns for five major TB drugs (Streptomycin, Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide) based on sex, age, form of TB and region categories.

Drug	Category	Demographic	Sensitive	Resistant	Chi-Square Value	P-Value	Significance
Streptomycin	Sex	Female	67	163	2.014	0.733	N/S
		Male	25	47			
	Age Categories	20 and below	6	4	4.863	0.562	N/S
		21-40	131	48			
		41-60	70	16			
		61 and above	19	4			
	Forms of TB	Pulmonary TB	181	49	11.234	0.004	S
		Extra-Pulmonary TB	50	23			
	Region Categories	South Asian	90	29	11.144	0.346	N/S
		West Asian	44	13			

		Southeast Asian	42	6			
		African	13	9			
		Other	17	7			
		Unknown	25	8			
Isoniazid	Sex	Female	51	42	6.489	0.165	N/S
		Male	144	69			
	Age Categories	20 and below	7	3	3.483	0.746	N/S
		21-40	108	73			
		41-60	59	28			
		61 and above	17	6			
	Forms of TB	Pulmonary TB	148	84	9.011	0.011	S
		Extra-Pulmonary TB	48	27			
	Region Categories	South Asian	85	37	27.15	0.002	S
		West Asian	43	14			

		Southeast Asian	28	20			
		African	5	17			
		Other	15	10			
		Unknown	20	13			
Rifampicin	Sex	Female	85	8	1.181	0.881	N/S
		Male	190	25			
	Age Categories	20 and below	9	1	4.773	0.573	N/S
		21-40	158	24			
		41-60	80	8			
		61 and above	23	0			
	Forms of TB	Pulmonary TB	210	22	4.373	0.112	N/S
		Extra-Pulmonary TB	66	11			
	Region Categories	South Asian	108	14	3.574	0.965	N/S
		West Asian	52	7			

		Southeast Asian	45	3			
		African	20	2			
		Other	21	4			
		Unknown	30	3			
Ethambutol	Sex	Female	85	8	1.8	0.773	N/S
		Male	199	14			
	Age Categories	20 and below	9	1	3.248	0.777	N/S
		21-40	165	16			
		41-60	82	5			
		61 and above	23	0			
	Forms of TB	Pulmonary TB	216	16	9.112	0.011	S
		Extra-Pulmonary TB	69	6			
	Region Categories	South Asian	115	7	16.229	0.093	N/S
		West Asian	52	5			

		Southeast Asian	45	3			
		African	17	5			
		Other	23	2			
		Unknown	33	0			
Pyrazinamide	Sex	Female	25	59	2.59	0.858	N/S
		Male	53	132			
	Age Categories	20 and below	5	4	7.121	0.625	N/S
		21-40	53	103	2.597	0.458	N/S
		41-60	20	58			
		61 and above	6	16			
	Forms of TB	Pulmonary TB	61	144			
		Extra-Pulmonary TB	23	42			
	Region Categories	South Asian	29	77	31.569	0.007	S
		West Asian	10	42			

		Southeast Asian	10	30			
		African	12	5			
		Other	5	13			
		Unknown	8	23			

Table Keys:

- **S:** Statistically significant association ($p\text{-value} \leq 0.05$)
- **N/S:** Not statistically significant association ($p\text{-value} > 0.05$)

4.2. Discussion

This thesis tracks MDR-TB in Bahrain over the last 11 years, on resistance to first-line anti-tubercular drugs and the emergence of MDR-TB. From the findings, there were significant fluctuations in the resistance rates since the peaks were noted in Pyrazinamide resistance (24.63%) in the year 2015 and in MDR TB prevalence (5.48%) in the year 2018. By the year 2023 almost 50% of the tested cases showed resistance to at least on the 5 primary drugs tested, which causes complications in the already difficult problem of DR-TB management.

MDR-TB is considered a major public health problem around the globe, because it complicates protocols, prolongs patient recovery, increases the cost of healthcare (Dheda et al., 2017). The increasing prevalence of DR-TB could turn into major public health crises such as the rise in death rates, raising the expenses for healthcare, and a growing burden on vulnerable populations. The situation underlines the immediate necessity for a longer-term commitment to TB control strategies. (WHO, 2022). Resistance to first-line drugs, especially Rifampicin and Isoniazid which reduces the effectiveness of conventional treatment protocols, and ultimately requiring a more toxic and expensive second-line drugs (Bereda, 2022). There is a global concern where there is rising in the MDR-TB cases, especially in regions with high TB burdens like India, China, and Russia (WHO, 2022). The prevalence of MDR-TB in Bahrain, even though it is lower than that in high-burden countries, is still an issue of concern.

The discussion ahead will relate these findings to the findings of the world trends, examine the demography effect of DR-TB in Bahrain. Alongside that, we also plan to touch on the limitations of the existing diagnostic techniques

and suggest methods to fortify the TB control actions.

4.3 Prevalence and Trends in MDR-TB

The prevalence and trends of DR-TB in Bahrain over the span of the years from 2013 to 2023, shows the challenges posed by DR-TB in the country. This section of the thesis gives an analysis of annual trends, emphasizing the notable years with significant peaks in DR-TB were seen. The impact of these ups and downs on public health was evaluated, with Table 1 summarizing the main data and Figure 1 picturing them. These two allow us to have a complete view of the changing burden of MDR-TB in this decade.

4.3.1 General Overview of Resistance Trends

From 2013 to 2023 DR-TB showed considerable variation. While the overall trend points towards an increase in drug resistance, specific years recorded remarkable peaks or shifts in resistance patterns. Among the key antitubercular drugs studied, isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin. Pyrazinamide resistance demonstrated the most pronounced and notable fluctuations observed among all the tested drugs, peaking at 24.6% in 2015 and reaching 32.65% in 2023, emphasizing significant variability throughout the years. The reasons contributing to this variation will be explained later.

The findings of the thesis correspond closely with results reported in other Gulf Cooperation Council (GCC) countries. For example, in Saudi Arabia, MDR-TB rates were reported to range from 1.5% to 8% in various studies (Al-Hayani et al., 2021; Al-Shahrani et al., 2021; Ammari et al., 2018; Sambas et al., 2020). Similarly, in 2018 it peaked MDR-TB resistance rate of 5.48% falls within this range, reflecting the GCC region's effective control of drug resistance compared to global trends. The alignment is additional evidence of

the region's successful efforts to keep down the resistance rates and further is the very manifestation of the strong public health interventions in TB management in the region.

4.3.2 Key Years and Significant Trends

2013-2015: Early Resistance Trends

At the start of the study years, spanning from 2013 to 2015, it set the base for understanding the prevalence and patterns of DR-TB in Bahrain. In 2013, the data showed that 1.96% of TB cases were resistant to rifampicin, which is considered one of the most important antitubercular drugs for TB treatment. Also, 9.15% of cases showed resistance to isoniazid, ultimately leading to an overall MDR-TB prevalence of 1.96%. These Initial data numbers give us an important starting point for understanding the DR-TB situation throughout the study timeframe.

In 2015 a concerning trend occurred, as the pyrazinamide resistance rates increased to 24.63% compared to 17.65% in 2013. In the same period, the resistance to streptomycin which was a first-line drug but due to its toxicity it became a second-line drug (Padma and Muralidhara Reddy, 2023)., but it is an important drug for relapsing cases, reached 5.67%. When compared to global data on DR-TB cases, Bahrain's resistance rates during this early phase were relatively low. For example, countries with higher TB burdens, such as India and Russia, reported significantly higher resistance rates to streptomycin, Isoniazid, rifampicin and ethambutol (Seema et al., 2023; Kostyukova et al., 2023; Zhang et al., 2022). However, the rise of this trend in Bahrain was consistent with the central regional trends identified in Saudi Arabia. Alshahrani et al. (2021) reported a pyrazinamide resistance rate of 33.4% among TB cases in Saudi Arabia, proposing problems in the Gulf region.

2016-2018: The Peak Years

The years 2016 to 2018 was a key phase in the fight DR-TB in Bahrain. Resistance to isoniazid increased to its highest level during the whole study time, climbing to 14.15% in 2016. Streptomycin resistance also reached its peak at 15.09%, this is a significant increase in streptomycin resistance, and it raises a problem about the effectiveness of retreatment regimens.

Streptomycin, historically used as a an important second-line agent, has limited modern alternatives in cases where MDR-TB continues (Padda & Muralidhara Reddy, 2023). By 2018, MDR-TB prevalence reached its peak at 5.48%, corresponding with alarming resistance rates to isoniazid and, rifampicin.

Compared to other countries like Philippines who reported rifampicin resistance rates as high as 17% (Velasco et al., 2020). In the other hand, Bahrain's RR-TB peaked 5.48% during the same year, reflecting significantly lower rates even at its highest. Bahrain also performed ways better compared to countries like Russia, where over 67.9% of resistant cases were classified as MDR-TB (Kostyukova et al., 2023), and China, where MDR-TB prevalence reached 25% (Zhang et al., 2022). This comparison clearly shows Bahrain's fairly good situation in handling TB drug resistance, although it still has to deal with raised amount in disease control.

2019-2020: A Temporary Decline

Following the peaks observed in 2018, resistance rates showed a temporary decrease in 2019 and 2020. Resistance to pyrazinamide decreased to 15.60% in 2019, also MDR-TB cases decreased to 3.67%. The most notable improvement occurred in 2020, with isoniazid resistance dropping significantly to 4.65%. Moreover, during that year, absolutely no newly

diagnosed MDR-TB cases were seen, indicating a critical stage in the improvement of TB control measures.

The temporary development in this is mainly credited to the improved public health measures put in place and to the enhanced adherence to the treatment protocols. Moreover, Also, no AST was performed during 2021 which is attributed to the impact of the COVID-19 pandemic, which disrupted medical services and healthcare systems globally, may have also played a role in these changes but it can be seen the number of samples was not affected by COVID-19 pandemic in contrast to other parts of the world, the research conducted in South Gujarat (Maniya et al., 2024) and Cape Town (Li et al., 2024) has demonstrated this. The studies show that the significant drop in TB case notifications was the major cause to the reduced accessibility to the healthcare and the avoidance of the resources to fight cancer COVID-19 that was pandemic time.

2022-2023: Resurgence of Resistance

After the years of COVID-19 pandemic, Bahrain experienced a resurgence in DR-TB cases. In 2022 resistance to isoniazid had increased to 11.76%, and by the year 2023, it did not change a lot and remained stable at 12.12%. Pyrazinamide resistance rate has increased to 32.65% in 2023, Aligning with the peak levels of 2018. Also, in 2023 almost half of TB cases were resistant to at least one anti-TB drug, highlighting a severe public health concern and MDR-TB prevalence was at 2.02%.

Resistance trends showing this rebound are similar with the global trends seen as the TB treatment and diagnostic services returned to normal after the pandemic. Zhang et al. (2022) in China reported a type of MDR-TB

Challenges in Chongqing which again brought the significance of the watchful eye and the strong health care systems to the forefront.

The resurgence emphasizes the importance of continuous funding in the TB control programs. Up-to-date diagnosis and treatment methods, and strict adherence to the intervention along with the public health measures are the most important weapons needed in this fight against DR-TB in Bahrain and beyond. These steps are the only way to prevent earlier years' successes in the fight against DR-TB from being undermined, and the healthcare system from being exposed to new challenges in the future.

Implications of Missing Data

In 2016, the lack of pyrazinamide resistance data due to reagent unavailability was a notable hindrance to carrying out a full trend analysis over the years. This unavailability of data on a crucial year means we have less ability to judge properly the variability or the trends and to do it without bias. Besides, the lack of data for the year 2021 aggravates this difficulty, thus putting in place an extra gap that breaks the chain of resistance trend analysis. These data interruptions are the reason why it is difficult to spot long-term features or to make precise statements about the progress of DR-TB over the years. The impacts of these data gaps and their consequences on the entire analysis are to be elaborated upon in the significant part of the discourse, as well as offering some strategies to alleviate such limitations.

4.4 Age, Gender and Regional Distribution of Drug-Resistant TB Cases

This part of the thesis will discuss and look into the effect of age, gender, and nationality on DR-TB trends in Bahrain, as identified in the study.

Observing these demographics, the chapter will shed light on the populations that are most affected. The distribution of DR-TB cases in Bahrain indicates distinct demographic and regional trends, which can guide effective public health strategies. Figures 3, 4, 5, and 7 show how age, nationality, and regional factors overlap to shape the epidemiology of DR-TB in Bahrain.

4.4.1 Regional Distribution Patterns

As illustrated in Figure 3, the South Asian region accounts for the largest share of drug-resistant TB cases, contributing 39.68% of the total. Nationalities from India, Bangladesh, Nepal, Pakistan, and Sri Lanka dominate this group, with Indian nationals alone contributing 19.03% of all cases (Figure 4). This mirrors global trends where India contributes 28% of all TB cases worldwide (WHO, 2022). reflecting their significant presence in Bahrain's workforce, particularly in labor-intensive sectors such as construction, domestic work, and hospitality, younger and middle-aged males (21–40 years) constitute the largest share of TB cases. These industries are often characterized by overcrowded living conditions and poor ventilation, which facilitate TB transmission and increase the risk of progression to drug-resistant forms. Similar challenges are observed in neighboring countries like Saudi Arabia, where large migrant populations from TB-endemic regions, particularly South Asia, face comparable socioeconomic and healthcare barriers. A recent review by Al Bati (2024) shows that migrant worker in Saudi Arabia, especially in labor-intensive sectors, are disproportionately affected by TB due to overcrowded housing, stress-induced immunosuppression, and fears related to immigration status, which delay timely diagnosis and treatment efforts (Al Bati, 2024). This mirrored scenario underscores the importance of region-

wide public health strategies targeting high-risk migrant communities to mitigate TB transmission.

The West Asian region, dominated by Bahraini nationals, accounts for 19.03% of cases, with Bahraini individuals contributing the majority (58 out of 59 cases). The high prevalence among Bahraini citizens is attributed to two main things the first thing is that they are the citizens of the country, and the second reason is due to extensive TB screening programs and better access to healthcare, which increase case detection rates compared to expatriates. A study conducted by AlKhawaja et al. (2018) has suggested that besides the mandatory TB surveillance; the pre-employment screening program of Bahrain also contributed to the detection of TB cases especially in the case of Bahraini nationals. Despite the fact that a large number of the TB patients in Bahrain are non-Bahrainis who come from high TB-burden countries, the effective healthcare system and intervention strategies have led to the early diagnosis and treatment of TB in citizens and expertise (AlKhawaja et al., 2018). 15.48% of cases have been infected in Southeast Asia led by Filipinos, Indonesians, and Thais. Like South Asians, Southeast Asians often work in high-risk environments with limited resources, making them vulnerable to TB transmission and resistance development.

In contrast, the African region contributes the smallest share at 7.10%, encompassing individuals from Ethiopia, Guinea, Kenya, Somalia, Sudan, and Uganda. While this group's representation is lower, it highlights the need to address unique challenges faced by African expatriate. The "Other" and "Unknown" categories, accounting for 8.06% and 10.65% respectively, reflect the diversity of Bahrain's expatriate population and underscore gaps in data collection that must be addressed for more accurate epidemiological analysis.

4.4.2 Age and Gender Distribution Patterns

Age is an important factor influencing the prevalence of drug-resistant TB, as shown in Figures 5 and 7. The 21–40 age group accounts for the largest proportion of cases at 60.20%, followed by the 41–60 age group (28.95%). This trend aligns with global findings, where the highest TB burden is observed among adult males aged 25–54, particularly in the 35–44 age group (WHO, 2022). The older age group (over 60) accounts for 7.57%, while the under-20 group represents only 3.29% of cases. These findings underscore the concentration of TB cases among younger and middle-aged adults, particularly those within the economically active population.

Gender differences are obvious in this thesis, with males composing 69.7% of cases in this study. This pattern of male predominance aligns with global TB trends, where males account for 56.6% of the cases worldwide (WHO, 2022), and this can be highly attributed to the fact that males have a higher risk of exposure in occupational and social settings. A study conducted in India by Seema et al. (2023) also similarly established a male-to-female ratio of 2.18:1, which in turn draws attention to the fact that the greatest burden of TB is by males who are economically active. Further, the gender disparity observed in Bahrain corresponds to the one found in the Makkah study, in Saudi Arabia, where 66.5% of the infected were males, who had a mean age of 43.4 years (Sambas et al., 2020). This is a clear demonstration of the continuing global tendency of higher TB burden among adult males, especially in the Working-age population, thus highlighting the need for gender- and age-specific interventions.

DR-TB is highly prevalent in younger and middle-aged adults especially male migrant workers, because they are engaged in social and economic activities,

often working in industries like construction, and domestic work. The settings and the occupations are mostly male workers, and most of the time they work in overcrowded, poorly ventilated spaces, which causes regular interaction, and this is the way of getting TB transmission. Research shows that the problem of mobility is also coupled with financial challenges thus making it hard to get medical care and also making it more challenging for a patient to stick to the prophylaxis. Shrivastava (et al. 2024) state that migrants face some formidable challenges to the control of TB, such as stigma, socio-economic disadvantages, and the lack of information about TB which ultimately leads to starting treatment late and incomplete treatment.

The 41–60 age group, accounting for 28.95% of cases, highlights a significant trend. While South Asians remain the largest contributors (35.23%), primarily driven by Indian and Bangladeshi workers in labor-intensive, high-risk occupations, the West Asian group, predominantly Bahraini nationals, follows closely at 25%. This increase among Bahrainis may reflect long-term exposure to TB, facilitated by occupational history, alongside the effectiveness of national screening programs that improve detection rates in this demographic.

Findings from Table 2 align with these observations. For instance, Isoniazid resistance demonstrates a significant association with the pulmonary TB ($p = 0.011$) and region of origin ($p = 0.002$), with higher resistance rates observed among pulmonary TB cases and South Asian populations. The significant association between isoniazid resistance and pulmonary TB highlights the higher burden of resistance among patients with pulmonary infections, a key issue in middle-aged expatriate worker

The over 60 age group, predominantly composed of Bahraini nationals (65.22%), emphasizes a diverse trend. This can be explained by older individuals who are more likely to have acquired TB infections earlier in life, which may reactivate as their immune systems weaken with age, a condition known as LTBI. As individuals age, their immune function deteriorates, a process known as immunosenescence. This leads to a diminished capacity to control latent *Mycobacterium tuberculosis* and increases the risk of reactivation. This risk is further heightened by inflammaging, a persistent, low-grade pro-inflammatory state characteristic of aging, which impairs immune regulation and lung homeostasis. Consequently, the elderly population serves as a significant reservoir for LTBI, particularly in regions with historical TB burden. Addressing this issue requires targeted strategies for screening, diagnosing, and managing LTBI in older adults to prevent progression to active TB disease (Olmo-Fontánez & Turner, 2022).

The under 20 age group shows the smallest representation, with Bahraini nationals contributing the largest share (60%, Figure 7). This disparity can be attributed to differences in testing practices. Bahraini children are more likely to undergo part of contact tracing program. In contrast, expatriate households, which typically do not include children, are less likely to contribute to TB case detection within this age group.

4.4.3 Interplay Between Age, Gender, and Region

While age alone reveals critical patterns, examining the interplay between age, gender, and region provides a deeper and more refined insight into resistance patterns. The intersection of age and region reveals significant resistance patterns. As seen in Table 2, Isoniazid and Pyrazinamide resistance show notable associations with regional origin ($p = 0.002$ and $p = 0.007$,

respectively), particularly among South Asian populations. This finding emphasizes the influence of regional TB strains, differing treatment practices, and socioeconomic factors in shaping resistance patterns among male expatriates.

The intersection of age and regional distribution highlights critical trends. The 21–40 age group is predominantly represented by individuals from the South Asian region, with Indian and Bangladeshi nationals contributing the largest shares. These findings emphasize the vulnerability of expatriate workers in this demographic due to their occupational risks and limited healthcare access.

In the 41–60 age group, the South Asian region continues to dominate, followed by the West Asian region, which is primarily composed of Bahraini nationals. The presence of Bahraini nationals in this age group reflects the impact of national screening programs, which facilitate case detection among middle-aged citizens. The over 60 age group, almost exclusively Bahraini, underscores the need for targeted interventions to address latent TB reactivation and age-related immune declines in this population. (Olmo-Fontáñez & Turner, 2022).

4.5 The Impact of COVID-19 on TB Diagnosis, Management, and Drug Resistance: A Global and Local Perspective

The COVID-19 pandemic has greatly disturbed the healthcare system of the entire world, and one of the most significant consequences was its impact on TB diagnosis and management. TB saw a global reduction in case reporting

and testing during the pandemic, taking away years of progress in treating and getting rid of the disease.

There are several studies with convincing evidence highlighting this decline, attributing it to the heavy pressure the pandemic put on healthcare systems and the shift of resources toward dealing with COVID-19. For example, a study conducted in South Gujarat, India, reported a 29% reduction in TB case notification in the first year for the pandemic compared to 2019, as well as significant disruptions to testing services and treatment outcomes (Maniya et al., 2024). Another study in Cape Town, South Africa, revealed that there was a 28% decrease in TB diagnoses during the pandemic, also there was a high rate of patients who never started treatment and or dropped treatment and never completed it, which makes the job of providing effective TB care more difficult (Li et al., 2024). The studies indeed contribute to the signing evidence of the worldwide pattern of decreased TB detection during the pandemic years, as been elaborated in the Global Burden of Disease study, which detected a global TB notification drop (Yang et al., 2024). The drop in reported cases is a direct result of the overall chaos in the functions of diagnostic and healthcare services, which brings to surface the lack of strength that TB control efforts have when it comes to the public health crises.

One of the key factors that contributed to the decline was the distribution of TB diagnostic services. Human and material resources were shifted from TB programs as healthcare systems across the globe focused on managing COVID-19 critically. Diagnostic kits like GeneXpert which are extensively used for TB were now associated with COVID-19 test in many regions, which implies these resources for TB testing were not accessible. (Zimmer et al., 2021). This issue has been discussed by research from Mozambique that has

mentioned the reduced TB diagnostic activity in 2020 and 2021 which was a significant change. The positivity rate remained stable, but the number of processed samples was less indicating that the number of undiagnosed cases was backlogged which probably could have increased the TB transmission within the community (Ciccacci et al., 2024). Similarly, in Shiraz, Southern Iran, the COVID-19 pandemic caused a shift in TB detection patterns, as there was a significant decline in classic symptoms such as sputum production and there was an increase in the non-specific symptoms including fatigue which ultimately complicated the detection and diagnosis of TB (Fallahi et al., 2024). All these findings together emphasize the coupled challenges or reduced diagnostic capacity and hard-to-interpret clinical presentations, which contribute to the decline of TB notifications.

The lockdowns and movement control regulations were substantial factors in the decrease of TB testing and diagnosis. These actions, though important to fight the COVID-19 pandemic, restricted the patients' access to healthcare particularly in low- and middle-income countries where TB is most common. Worry about COVID-19 exposure further discouraged people who had TB symptoms to visit hospitals for treatment, which cause the delays in diagnosis and treatment. The consequence was a huge underreporting of TB cases as indicated by the research from Cape Town, where the reduced healthcare access was directly related to lower TB detection rates (Li et al., 2024). Another problem caused by COVID-19 pandemic was the overlap in symptoms between the diseases which led to misdiagnoses, many TB cases were misclassified as COVID-19 and this was seen in multiple studies in different regions (Fallahi et al., 2024; Yang et al., 2024). This misclassification did not

only delayed the effective treatment of TB but also increased the TB transmission due to delayed isolation and treatment of infectious cases.

The public health sector will be greatly affected by the above disruptions. TB is still one of the main deadly infectious diseases in the world, and the pandemic impact on TB control programs makes it a risk to the decades of progress that have been made. The cases of TB that have been undiagnosed and untreated may lead to an increase in the transmission of TB and a new DR-TB, which is more labour-intensive and more costly to fight. The studies predict that the long-run consequences of the interrupted TB diagnosis and treatment will be an increased rate of deaths and new TB cases, notably in the regions of high burden that have already been stressed due to the healthcare systems (Ciccacci et al., 2024; Yang et al., 2024). Additionally, the economic effect of these disturbances is huge. TB impacts, especially in low-income countries the delay of diagnosis and treatment can cause a lot of harm including productivity as well as higher healthcare costs ultimately leading to poor people that does not have enough money to buy good food even poorer (Jennings et al., 2024; Yang et al., 2024).

The pandemic showed the strongly rooted differences in global healthcare systems, while the higher income countries were able to assign some of its budget toward some TB services at least the main diagnostic ones, low and middle-income countries, faced a very tough challenge. In these regions, the shift of resources and budgets toward COVID-19 response effort left TB programs badly short of funding, and this worsened the already existing inequalities in healthcare access and results. Illustrating this point, scientific research results from sub-Saharan Africa and South Asia, which are the geographical areas with the highest incidence of TB, have reported notable

reduction in the number of TB cases being reported and people's adherence to the treatment during the pandemic, thus, making visible the vulnerability of these communities to public health emergencies (Ciccacci et al., 2024; Li et al., 2024; Yang et al., 2024). This difference is a testament to the absolutely critical demand for proper actions and extra money for the development of TB programs taken up inspiration by the COVID-19 pandemic.

The COVID-19 pandemic has highlighted the importance of incorporating TB efforts to manage wider public health plans. Strengthening health systems toward allowing us to manage multiple health challenges at the same time is very important to ensure that infectious diseases like TB shouldn't be ignored during future crises. This includes putting some of the resources into training the healthcare providers to manage and handle both TB and any emerging new pandemics, as well as creating new strong surveillance programs to catch and track pandemics and outbreaks very early. The world reaction to COVID-19 showed just how powerful coordinated international efforts can be, similar efforts should be available for TB.

The disturbances from COVID-19 pandemic which affected many countries around the world but unlike many countries, Bahrain's TB diagnostic testing and AST remained stable in the first year of the pandemic 2020 as the total number of positive cases did not change that much actually it increased from 109 in 2019 to 125 in 2020 and the DR-TB cases were consistent with other years, all this shows how strong Bahrain could manage multiple infectious diseases at the same time. But this did not last long as the situation worsened in 2021 as a huge major gap in TB management was created since no AST testing was carried out at all during that time. This complete stopping of the AST testing is a direct outcome of the huge pressure on the Bahrain healthcare

system, with many workers and even more budget and resources being shifted toward COVID-19 pandemic. This align with the global reports discussed earlier, showed how everything was shifted toward the pandemic. The absence of AST in 2021 is similar to what happened in the entire world and the disruption in TB diagnostics but hit Bahrain harder, where steady AST is key to keeping DR-TB under control

The interruptions caused major problems. This was combined with the observed increase resistance to the first-line drugs isoniazid and pyrazinamide in later years, the data showed how the pandemic could worsen the burden of DT-TB in Bahrain. These finding of the thesis highlight how important it is to reinvest in TB diagnostics and treatment services to strengthening Bahrain healthcare system so we can fight the upcoming emergency especially pandemics similar to COVID-19.

4.6 TB Resistance Patterns in Bahrain Compared to the GCC and North Africa

Staying within GCC and nearby countries for TB research and management is justified due to shared climate, socioeconomic factors, migration patterns, and healthcare policies. The large migrant population in Gulf countries, especially those from regions with high TB prevalence, plays a significant role in shaping TB epidemiology, as evidenced by my data. Additionally, the challenges faced in combating drug-resistant TB mirrors those studied in neighboring regions. Additionally, the experiments faced in fighting DR-TB is alike those studied in regional countries that is near Bahrain which shares a lot of issues. By addressing the share challenge together can lead to better and more enhanced TB control efforts. Comparison of TB drug resistance studies of other GCC/nearby countries is summarized in Table 6.

The findings from my thesis on DR-TB trends from 2013 to 2023 are consistent with several regional studies while also focusing on specific problem in Bahrain health care system. Similar to studies conducted in Saudi Arabia and Oman, my data highlight a significant burden of resistance to first-line anti-TB drugs, particularly Isoniazid and Pyrazinamide, with notable peaks in resistance in specific years such as 2015, 2018, and 2023.

When comparing resistance patterns for drugs, Isoniazid resistance in my study (12.12% in 2023) aligns with rates reported in Makkah (11.1%; Sambas et al., 2020) and Saudi Arabia overall (10.2%; Al-Shahrani et al., 2021). However, my findings are different than Dubai (3.6%; Habous et al., 2020) and Qatar (3.1%; Ali et al., 2020), where resistance was remarkably lower. Rifampicin resistance in my study (2.02% in 2023) is significantly lower than in Egypt 66.2%; (Alfaham et al., 2022), Basra (15.8% in retreated cases; Mohammed et al., 2022), and Sudan (via GeneXpert; Alfaham et al., 2022). For Pyrazinamide, resistance in my study (32.65% in 2023) closely mirrors the rate reported in Saudi Arabia (33.4%; Al-Shahrani et al., 2021) but far exceeds rates in Oman (3.5%; Gaifer et al., 2017) and Dubai (2.59%; Habous et al., 2020), highlighting a potential overestimation due to phenotypic testing limitations. Conversely, resistance to Ethambutol in my study (4.04% in 2023) is comparable to Makkah (7.4%; Sambas et al., 2020) but higher than Qatar (0.15%; Ali et al., 2020) and absent as monoresistance in Dubai (Habous et al., 2020). Finally, Streptomycin resistance in my study (7.22% in 2023) aligns with Saudi Arabia (11%; Al-Shahrani et al., 2021) and Dubai (2.95%; Habous et al., 2020) but is markedly lower than Basra's 17.1% in retreated cases (Mohammed et al., 2022). These comparisons highlight both regional

similarities and differences, showing how each country diagnostic methods, treatment approaches, and local TB patterns all interact.

Demographically, my study corroborates the male predominance observed in Dubai 74.2% (Habous et al., 2020) and in Saudi Arabia (Al-Hayani et al., 2021), with a similarly male patients constitution of 62.7% of the cases. Age distribution aligns with findings from Dubai, Makkah, and other regional studies, which identified the 21–40 age group as the most affected demographic (Sambas et al., 2020; Al-Shahrani et al., 2021; Habous et al., 2020; Alfaham et al., 2022). While variations in age categorization exist, such as Dubai's 26–35 grouping (Habous et al., 2020), the overall conclusion remains consistent across all studies: TB disproportionately affects individuals in their prime working years. Similarly, my study identifies the 21–40 age group as the most affected, accounting for 60.20% of drug-resistant TB cases, which underscores this pattern.

However, Oman presents a slight variation, as emphasized in (Gaifer et al., 2017). While most regional studies emphasize the 21–40 age group, Oman reported a higher prevalence of resistance among younger individuals (<20 years), with this group being significantly associated with drug resistance. Additionally, Although males accounted for 64.7% of TB cases, females showed higher drug resistance rates (61.5% of resistant cases), contrasting with typical male-dominated resistance patterns in other regional studies. (Gaifer et al., 2017) found that females were at a higher risk for DR-TB. These characteristics show that differences between genders and age group in Oman differ from other countries regional patterns, potentially

This can be because of many things including healthcare-seeking behavior, sociocultural factors. This shows why it's so important to shape TB strategies based on the specific risks faced by different groups in different areas

My data underscores an important approach of showing how significant the representation of specific populations especially the south Asians among DR-TB cases, particularly Indians and Bengalis and this finding has also existed in Qatar where 64.1% of DR-TB cases were among expatriates from the Indian subcontinent (Ali et al., 2020). In contrast we can see in Dubai the DR-TB had a broader demographic mix as it was prevalent among more diverse expatriate populations (Habous et al., 2020).

Clinically, resistance patterns in my study mirrors similar trends reported in Dubai and Egypt, with Pulmonary TB is more regularly associated with DR-TB. For instance, my findings that 74.8% of cases were pulmonary mirror the 88.5% pulmonary TB prevalence in Dubai (Habous et al., 2020).and the 97% prevalence of pulmonary samples in Egypt (Soliman et al. 2021) as well as in Saudi Arabia (Sambas et al., 2020) found that 86.7% of TB cases were pulmonary. Unlike Oman study (Gaifer et al., 2017) that found no significant difference between pulmonary and extrapulmonary resistance, my data reveal a significant association between pulmonary TB and resistance to Streptomycin and Isoniazid.

The MDR-TB rates in my thesis show notable similarities and differences compared to regional studies. My data reveals an MDR-TB prevalence of 5.48% at its peak in 2018, which aligns closely with the rates reported in Makkah 5%; (Sambas et al., 2020) and Dubai 4.5%; (Habous et al., 2020). Similarly, studies in Qatar 1.2%; (Ali et al., 2020) and Oman 1.7%; (Gaifer et al., 2017) reported lower MDR-TB rates, even though their sample size was

much lower than the rest of the studies it indicates better control in those regions. In contrast, significantly higher MDR-TB rates were observed in Egypt 7.16% (Soliman et al. 2021), Basra, Iraq 14.2% among retreated cases; (Mohammed et al., 2022), and Sudan 9.7%; (Alfaham et al., 2022) reflecting greater challenges in TB management in these areas. The different results in MDR-TB prevalence across the region can be attributed to the healthcare system, people adherence to treatment and finally the diagnostic testing capabilities for example Egypt's and Iraq's higher rates of among relapsed patients shows how important to monitor treatment

Table (6): Comparative Analysis of DR-TB Epidemiology Across Gulf Cooperation Council (GCC) Countries: Demographic Trends, Resistance Patterns, and Clinical Profiles

Country/Region	Male %	Most Affected Age Group	Isoniazid Resistance %	Rifampicin Resistance %	Pyrazinamide Resistance %	Ethambutol Resistance %	Streptomycin Resistance %	MDR-TB %	Pulmonary TB %	Citation
Bahrain (2023)	62.70%	21–40	12.12%	2.02%	32.65%	4.04%	7.22%	5.48% (2018)	74.80%	<i>Current Study</i>
Saudi Arabia study 1	55.80%	21–40	10.20%	N/A	33.40%	7.10%	21%	8.30%	86.70%	Al-Shahrani et al., 2021
Saudi Arabia study 2	69.10%	21–40	10.20%	5.90%	5.40%	3.80%	11%	4.40%	90.60%	(Al Ammari et al., 2018)
Makkah, KSA	66.50%	25–44	11.10%	7.40%	N/A	7.40%	25.90%	5%	86.70%	Sambas et al., 2020
Dubai, UAE	74.20%	26–35	3.60%	0.30%	2.59%	0%	2.95%	4.50%	88.50%	Habous et al., 2020
Qatar	79.80%	21–40	3.10%	0.18%	N/A	0.15%	1.20%	1.20%	80%	Ali et al., 2020
Oman	64.70%	<20	1.70%	0.60%	3.50%	0.00%	N/A	1.70%	59.40%	Gaifer et al., 2017

Table Keys:

N/A: Data not available

4.7 Global TB Patterns: Focus on High-Burden and Representative Countries

The basis of selection for the global comparison was driven by two main factors: first, the nationalities of expatriates in Bahrain and the GCC. The second factor for choosing these countries was to reflect the different patterns of TB across various countries. High-burden countries such as India, Pakistan, and the Philippines were included because people of these countries are the major expatriate populations in the nations of Bahrain and GCC. Additionally, countries like China, with a significant TB burden, were chosen to reflect broader global trends. Although Germany and the United States are not considered high-burden countries, these countries are included to for the purpose of showing how strong surveillance programs and advanced healthcare systems can affect the incidence rate of these countries, which will offer insight into the experience of these countries and the best practices to be followed to reduce the TB around the world.

The findings from my study on DR-TB trends from 2013 to 2023 reveal patterns that agree with and move away from from global data, as emphasized in studies conducted worldwide. My study population, predominantly male (69.7%), parallels Germany, where males constituted 59.12% of cases (Glasauer et al., 2019), and Jharkhand, India, with males making up 68.6% of TB cases (Seema et al., 2023). This male predominance is consistent across most high-burden countries, including Russia (Kostyukova et al., 2023), the Philippines (Velasco et al., 2020), and the United States (Chen et al., 2020). However, in regions like Khyber Pakhtunkhwa, Pakistan, TB prevalence was higher among females (39%) than males (29%) (Ali et al., 2020), showing possible variations influenced by social or culture.

The age distribution in my thesis, with 60.2% of cases falling in the 21–40 age group, line up with global trends where TB mostly affects younger, and active people that goes to work every day. For instance, in Delhi, 56.18% of MDR-TB cases were in the 15–29 age group (Sharma et al., 2020), and in the Philippines, the highest prevalence was observed in the 30–39 age group (Velasco et al., 2020). Similarly, studies in Jharkhand, India, found that 41.23% of cases were in the 21–30 age group (Seema et al., 2023). Also, in Western Siberia, Russia, the burden of TB is shifting towards adult populations, with high rates of pre-XDR and XDR-TB (Kostyukova et al., 2023). This highlights the agreement on age-related TB distribution.

My thesis shows peaks, with MDR-TB prevalence reaching 5.48% in 2018. This aligns with data from Pakistan (4.9%) (Ali et al., 2020) and India, where MDR-TB rates ranged from 2.7% to 11.6%, depending on treatment history new cases or retreatment cases (Seema et al., 2023). However, our MDR-TB rates are significantly lower than regions like Western Siberia in Russia, where rates have risen to 33.4% (Kostyukova et al., 2023), and Chongqing, China, where MDR-TB prevalence increased from 25% in 2016 to 33.4% in 2019 (Zhang et al., 2022).

When comparing drug-specific resistance rates, my thesis recorded Isoniazid resistance at 12.12% in 2023, consistent with rates such as 6% in Pakistan (Ali et al., 2020), but lower than Jharkhand, India, where resistance reached 40.8% (Seema et al., 2023). Rifampicin resistance in my study was 2.02% in 2023, aligning with rates in Germany (2.5% among new cases) (Glasauer et al., 2019) but lower than the Philippines (17%) (Velasco et al., 2020) and Western Siberia, Russia (53.4%) (Kostyukova et al., 2023). Pyrazinamide resistance in my study was notably high at 32.65%, significantly more than the global

averages such as 3% in Pakistan (Ali et al., 2020) and 0% in Jharkhand (Seema et al., 2023). Streptomycin resistance, recorded at 7.22% in my study, was similar to Pakistan (9%) (Ali et al., 2020) and Jharkhand (2.24) (Seema et al., 2023).

The South Asian population are the largest group in my study. This finding parallels a global pattern for migrants from high-burden countries significantly increasing the spread of the disease including DR-TB. For example, in the USA non-US-born patients account for 1.8% of MDR-TB cases compared to only 0.5% among US-born patients which is almost 3 times more (Chen et al., 2020).

My study identified pulmonary TB as the most prevalent form of TB, comprising 74.8% of drug-resistant cases, consistent with findings from Delhi (86.7%) (Sharma et al., 2020), Pakistan (5.3% in pulmonary TB vs. 1.5% in extra-pulmonary TB) (Ali et al., 2020), and Jharkhand pulmonary TB significantly outnumbered extra-pulmonary cases (Seema et al., 2023). The significant association between pulmonary TB and DR-TB in my data highlights the need to focus on pulmonary cases for early detection and treatment.

the increasing prevalence of MDR-TB and pre-XDR-TB shows a challenge that should be noticed even though Bahrain still has low MDR-TB rates. For example, in Zhejiang Province, China, 81.8% of RR- TB cases were MDR-TB, and 37.5% were pre-XDR-TB (Zhou et al., 2022). In Western Siberia, XDR-TB cases increased sixteen-fold between 2012 and 2021 (Kostyukova et al., 2023).

4.8 Recommendations

1. Strengthen TB Control Measures:

Strengthen the TB control programs in Bahrain by creating and implementing in techniques for early detection and widening the access AST. These actions will contain the TB infection and also will improve the health of patients through the use of proper and quick treatments

2. Adopt Molecular Diagnostics:

Support the addition of molecular diagnostic testing for AST specifically the *pncA* gene which is responsible for the pyrazinamide resistance. This also enhances the accuracy and precision and the rate of efficiency of the DR-TB. These novel techniques are capable to give us better results than standard phenotypic assays.

3. Promote Public Health Education:

start broad public health campaigns to increase the knowledge of TB prevention and treatment adherence in high-risk groups like males and expatriates. Making a platform with multiple languages can help in deliverance of awareness.

4. Investigate Phenotypic Testing Limitations:

Further research should be conducted to assess the credibility and reliability of phenotypic testing for pyrazinamide resistance. More research should done to make a better protocol or improve the current one or molecular diagnostics should be used to mitigate false-resistant or false-susceptible results.

4.9 Limitations

1. Incomplete Data Coverage:

Certain years (e.g., 2021) were excluded due to missing data because of the pandemic, and reagents for specific drugs (e.g., Pyrazinamide in 2016) were unavailable. Additionally, this thesis was missing essential data points such as retreatment cases so we can compare if there is any resistance developed after the relapse and information on patients' countries of origin. These gaps will affect the accuracy of the trends and limit the ability to have a full picture of what is happening during a specific period.

2. Phenotypic Testing Reliability:

The phenotypic AST for pyrazinamide resistance can easily produce false results, this is potentially due to the high inoculation level which increases the medium's pH and impairing pyrazinamidase activity. Pyrazinamide drug resistance is caused by mutations in a gene called *pncA*, which makes pyrazinamidase. This enzyme makes pyrazinamide into its active form, pyrazinoic acid (Hadi et al., 2023).. Guidelines have special recommendations for using BACTEC MGIT 960 in liquid medium at pH 5.9 for AST (Siddiqi & Rüscher-Gerdes, 2006). There was cases around the world where there was false results of pyrazinamide testing which highlighted this limitation. In one study it was found that 21.1% (64 out of 304) of PZA AST results using the standard MGIT phenotypic method were falsely resistant, a discrepancy significantly reduced with diluted inoculum protocols (Morlock et al., 2017). Another study emphasized the fact that this phenotypic testing needs confirmatory testing. The study revealed that many isolates were classified as resistant at first but later on the

isolates were indeed susceptible, according to retesting with more accurate molecular techniques such as *pncA* gene sequencing and pyrazinamidase activity assays (Chedore et al., 2009). In a study conducted in Russia it was emphasized that BACTEC MGIT 960 pyrazinamide AST is unreliable according to authors the system could misclassify lower-leveled resistance as susceptible, and vice versa (Maslov et al., 2015). Another study found a solution for this issue by modifying the MGIT protocols to reduce the inoculum. By doing this the researchers got great results to lower the false resistant outcome (0.9%) one out of 106 tested isolates (Mustazzolu et al., 2017). these findings give us insight to what to do next, by using more reliable testing methods for pyrazinamide resistance especially the integration of molecular diagnostics such as *pncA* gene sequencing. These techniques are more reliable and overcome problems of old tests. Moving to molecular tests is really critical in TB testing. It promises a perfect way to find pyrazinamide resistance and helps with proper treatment plans..

3. **Lack of Molecular Testing:**

There were no molecular diagnostic methods used for AST except for GeneXpert which only gives rifampicin results. More molecular techniques should be used especially the whole bacterial genome to look for specific mutations causing the resistance. This will help us explore the genetic mechanism of resistance. Including these methods could provide a better understanding of resistance patterns and give us the chance to have better treatment strategies.

4.10 Conclusion

The study states that the MDR-TB has become now more of a challenge in Bahrain, particularly for adults and expatriate workers. The results of the study reflected the strong efforts of PHD reference laboratories, physicians, and healthcare workers responsible for early testing, isolation, and management of TB cases. The COVID-19 pandemic affected the entire world and disrupted the TB diagnostics including Bahrain this challenge highlights the importance of keeping a resilient healthcare service and learning from the pandemic. To address some of the problems faced in Bahrain, the primary need is improved public health strategies, such as the introduction of molecular diagnostics, a targeted program for the most affected groups, and enhanced healthcare collaboration. For the effective management of DR-TB, the first step is to have the proper monitoring systems, and then to focus on specific investigations that are aimed at seeking out the resistance patterns which must become an integral part of the public health strategy. These measures are very important, and they are essential to contain the resistant variants, and also for continuing the advancement of TB management. These efforts parallel with WHO goals to combat DR-TB and guarantee fair health results for all people.

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الملخص

يستعرض هذا البحث الاتجاهات وانتشار السل المقاوم للأدوية في مملكة البحرين بين عامي ٢٠١٣ و ٢٠٢٣، مع تركيز خاص على السل ذي المقاومة المتعددة للأدوية. يُعرّف السل المتعدد المقاومة بمقاومته للإيزونيازيد والريفامبيسين، ويُعدّ تحدياً كبيراً للأنظمة الصحية العامة على المستويين العالمي والمحلي. اعتمد البحث على تصميم رجعي، حيث جرى تحليل ١١٥٨ عينة إيجابية للسل، تم تحديد ٣١٠ منها كحالات مقاومة للأدوية. وقد أُجريت اختبارات فحص حساسية المضادات باستخدام نظام الزرع الآلي (إم جي أي تي ٩٦٠) على الأدوية الرئيسية: الستربتومايسين، الإيزونيازيد، الريفامبيسين، الإيثامبوتول، والبيرازيناميد.

أظهرت النتائج أن انتشار السل المتعدد المقاومة بلغ ذروته بنسبة ٥,٤٨٪ في عام ٢٠١٨، كما لوحظت مقاومة مرتفعة للبيرازيناميد حيث وصلت إلى ٣٢,٦٥٪ في عام ٢٠٢٣. يشير التحليل إلى ارتفاع معدل الإصابات بين الذكور (٦٩,٧٪) والأفراد الذين تتراوح أعمارهم بين ٢١-٤٠ عاماً (٦٠,٢٪)، مع تأثر غير البحرينيين، وخاصة الوافدين من جنوب آسيا، بشكل أكبر. وتُظهر المقارنات الإقليمية أن معدلات المقاومة في البحرين تتماشى مع تلك الخاصة بدول مجلس التعاون الخليجي، وتبقى أقل من المناطق العالمية ذات العبء العالي. علاوة على ذلك، فقد أدت جائحة كوفيد-١٩ إلى تعطيل كبير في تشخيص السل، مما تسبب في نقص الموارد لاختبارات فحص الحساسية في عام ٢٠٢١. وتؤكد هذه النتائج الحاجة الملحة إلى تعزيز طرق التشخيص الجزيئي، وتطوير أنظمة مراقبة فعالة، وتنفيذ تدخلات صحية عامة محددة، إلى جانب جهود إقليمية منسقة للسيطرة على انتشار السل المتعدد المقاومة والحدّ منه.

جامعة البحرين

قسم علوم الحياة

كلية العلوم



الاتجاهات في انتشار السل المقاوم المتعدد للأدوية في مملكة البحرين

(٢٠١٣-٢٠٢٣)

أطروحة مقدمة استكمالاً لبعض متطلبات الحصول على درجة الماجستير في العلوم البيولوجية

اعداد

الحسن المجتبى حميد الحمافي

الرقم الجامعي ٢٠١٧٦٩٠٤

اشراف

الدكتور علي سلمان بن ثاني (استاذ مشارك)

جامعة البحرين

مملكة البحرين

أكتوبر ٢٠٢٥