EVALUATION OF MANAGEMENT, TREATMENT OUTCOMES, AND IN-DEPTH ANALYSIS OF PEDIATRIC DRUG-RESISTANT TUBERCULOSIS PATIENTS IN PUNJAB AND KHYBER PAKHTUNKHWA, PAKISTAN

MUHAMMAD SOAIB SAID

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by

MUHAMMAD SOAIB SAID

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DEDICATION

My Unpretentious Effort I Dedicated to My Beloved Parents Especially My Mother Who Is Always a Source of Motivation, Encouragement, and Inspiration and Whose Wishes Motivate Me to Strive for Higher Education. To My Beloved Family Especially Ayesha & Maryum and My Wife For Her Constant Support Throughout This Journey.

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I feel the utmost obligate to offer my best gratitude to ALMIGHTY ALLAH, the Compassionate, and Beneficent to the entire creature. All the praise and the glory is to Him. Countless salutations to the Holy Prophet (P.B.U.H), the city of knowledge and blessing for entire creatures, Who has guided humanity to seek understanding from the cradle to the grave, and enabled me to win this honor of life. I want to express my deepest gratitude to my main supervisor Dr. Amer Hayat Khan who was abundantly helpful and offered invaluable assistance, support, and guidance in completing this PhD research thesis and counselling at each step of the research work. Thanks are extended to my Co-Supervisor Dr. Razia Fatima, Dr. Ooi Guat See and Dr. Amjad Khan for helping and guiding me. My deepest thanks to Dr. Rabbiya Ahmad for her sincere support, and encouragement, and for always praying for me and believing in me. Thanks to my friends Dr. Izharullah Khan, Dr. Asif Mehmood Hashmi, Dr. Khurshid Alam, Dr.Usman Ahmed, Dr. Faiza Naeem, and other lab colleagues. Last, but not least, I would like to pay my heartiest compliments to my Mother and Father whose great love, care, and prayers enabled me to achieve this goal, and my brothers especially my elder brother, Muhammad Yasir Khan who supported and appreciated me at every step during my whole studies. Also thanks to all others Naseer Khan, Sajid Said, Tauseef Raja, Ahsan Said, and my sisters for being helpful and available for me all the time during my whole life as well as studies and for their encouragement in achieving this goal.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AFB	Acid Fast Bacilli
Am	Amikacin
AOR	Adjusted odd ratio
ATT	Anti-Tuberculosis Treatment
Bdq	Bedaquiline
BHU	Basic health unit
BMI	Body mass index
CDC	Communicable disease control
Cfz	Clofazimine
CI	Confidence interval
Cm	Capreomycin
CMU	Common Management Unit
Cs	Cycloserine
DOTS	Directly Observed Therapy Short Course
DR-TB	Drug-resistant tuberculosis
DST	Drug susceptibility testing
EMRO	Eastern Mediterranean Region
EPI	Expanded Programme on Immunization
Eto	Ethionamide
FLD	First Line Drug
FP	Family planning
gm/dl	gram/deciliter
HIV	Human Immunodeficiency Virus
HPF	High Power Field

Km	Kanamycin
Lfx	Levofloxacin
LHV	Lady health visitors
LHW	Lay health workers
LMIC	Low-middle-income country
LOS	Length of stay
LTR	Long Treatment Regimen
Lzd	Linezolid
MDR	Multidrug-resistant tuberculosis
MDR	Multi-drug-resistant
Mfx	Moxifloxacin
mg/dl	milligram/deciliter
MTB	*Mycobacterium* Tuberculosis
NR	Non-replicating
NTP	National TB Program
Ofx	Ofloxacin
OR	Odds ratio
PMDT	Programmatic Management Drug Resistance Tuberculosis
PZA	Pyrazinamide
SD	Standard Deviation
SDGs	Sustainable Development Goals
SDR	Single drug-resistant
SLD	Second Line Drug
SNPs	Single nucleotide polymorphisms
STR	Short Treatment Regimen
TB	Tuberculosis
TDR	Totally drug-resistant

UHC	Universal health coverage
UL	units/liter
UNICEF	United Nations International Children's Emergency Fund
WHO	World Health Organization
XDR	Extensively drug-resistant

LIST OF APPENDICES

PENILAIAN PENGURUSAN, HASIL RAWATAN, DAN ANALISIS MENDALAM PESAKIT TUBERKULOSIS KANAK-KANAK DAN RINTANGAN UBAT DI PUNJAB DAN KHYBER PAKHTUNKHWA, PAKISTAN

ABSTRAK

Tuberkulosis rintang ubat (DR-TB), terutamanya tuberkulosis rintang pelbagai ubat (MDR-TB) dan tuberkulosis rintang ubat secara meluas (XDR-TB), merupakan cabaran kesihatan awam yang besar, khususnya di negara-negara dengan beban penyakit yang tinggi seperti Pakistan. Pengurusan DR-TB dalam kalangan kanak-kanak adalah kompleks dan memerlukan pemahaman mendalam mengenai hasil rawatan, corak kerintangan ubat, reaksi buruk terhadap ubat (ADR), serta kadar pertukaran kultur kahak. Kajian ini bertujuan untuk menilai faktor risiko yang dikaitkan dengan kerintangan terhadap ubat barisan kedua (SLD) dalam kalangan pesakit pediatrik DR-TB, menilai hasil rawatan dan faktor peramal kegagalan rawatan, serta menganalisis kejadian dan kesan ADR. Selain itu, kajian ini juga meneliti kadar dan faktor peramal pertukaran kultur kahak dalam kalangan pesakit MDR-TB. Kajian ini dijalankan dalam dua fasa, dengan fasa retrospektif (2015–2021) menganalisis data dari lokasi Programmatic Management of Drug-Resistant TB (PMDT) untuk mengenal pasti ciri sosiodemografi dan klinikal utama. Dalam kalangan 491 pesakit DR-TB, 52.5% adalah perempuan, 60.5% berumur antara 5–14 tahun, dan 51.9% tinggal di kawasan bandar. Sebanyak 90.4% pesakit mengalami kurang berat badan, dan 99.4% adalah HIV-negatif. Kes rawatan semula merangkumi 74.3% daripada jumlah pesakit, dengan 70.3% didiagnosis sebagai MDR-TB dan 95.1% mengalami TB pulmonari. Hasil makmal menunjukkan kadar kerintangan yang tinggi terhadap

ubat barisan pertama, termasuk isoniazid (68.4%), rifampicin (61.7%, p=0.026), pyrazinamide (76.2%), dan ethambutol (84.1%). Analisis multivariat mengenal pasti gred smear AFB yang lebih tinggi (AFB+3: OR 2.8, 95% CI: 1.5–3.6, p<0.001) serta kumpulan umur 5–14 tahun (OR 5.1, 95% CI: 1.37–19.65, p=0.0015) dan 15–24 tahun (OR 1.5, 95% CI: 1.04–2.40, p=0.031) sebagai faktor peramal utama bagi kerintangan ubat barisan kedua. Kejayaan rawatan dicapai dalam 77.6% kes, dengan 73.5% pesakit sembuh, manakala kadar kegagalan rawatan adalah 22.4%, termasuk kadar kematian sebanyak 6.9% dan kegagalan rawatan sebanyak 3.3%. Penggunaan kanamycin (OR 1.9, 95% CI: 1.02–3.82, p=0.041) dan levofloxacin (OR 2.6, 95% CI: 1.14–5.94, p=0.023) dikaitkan dengan hasil rawatan yang lebih baik, manakala rifampicin dikaitkan dengan hasil rawatan yang lebih buruk (OR 0.56, 95% CI: 0.35–0.89, p=0.015). Fasa prospektif (Januari 2023–Jun 2024) menilai kadar pertukaran kultur kahak, kejadian ADR, dan faktor yang berkaitan. ADR dikesan dalam 46.2% pesakit, dengan anemia (42.9%), hepatotoksisiti (42.2%), dan loya/muntah (29.1%) sebagai kesan sampingan yang paling kerap berlaku. Sejarah TB sebelumnya meningkatkan risiko ADR (OR 1.98, p=0.003), manakala rejimen rawatan jangka pendek (OR 0.61, p=0.006) dan ketiadaan kavitasi pada imbasan X-ray dada (OR 0.56, p=0.01) menunjukkan kesan perlindungan. Penemuan ini menekankan kepentingan strategi rawatan yang disesuaikan, serta keperluan untuk ujian kerintangan yang kukuh dan pemantauan ADR bagi meningkatkan kepatuhan pesakit dan kejayaan rawatan. Kajian ini menyimpulkan bahawa walaupun faktor demografi seperti umur dan jantina mungkin tidak memberikan kesan yang signifikan terhadap hasil rawatan secara keseluruhan, ciri klinikal seperti profil kerintangan ubat memainkan peranan penting, khususnya dalam persekitaran DR-TB dengan beban penyakit yang tinggi.

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ABSTRACT

Drug-resistant tuberculosis (DR-TB), particularly multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, presents a significant public health challenge, especially in high-burden countries like Pakistan. Managing pediatric DR-TB is complex, requiring a thorough understanding of treatment outcomes, drug resistance patterns, adverse drug reactions (ADRs), and sputum culture conversion. This study aimed to assess risk factors associated with second-line drug (SLD) resistance in pediatric DR-TB patients, evaluate treatment outcomes and unsuccessful treatment predictors, and analyze ADR incidence and impact. Additionally, the study examined the rate and predictors of sputum culture conversion in MDR-TB patients. Conducted in two phases, the retrospective phase (2015–2021) analyzed data from Programmatic Management of Drug-Resistant TB (PMDT) sites, identifying key socio-demographic and clinical characteristics. Among 491 DR-TB patients, 52.5% were female, 60.5% were aged 5–14 years, and 51.9% resided in urban areas. Notably, 90.4% were underweight, and 99.4% were HIV-negative. Retreatment cases comprised 74.3%, and 70.3% had MDR-TB, with pulmonary involvement in 95.1%. Laboratory findings indicated high resistance to first-line drugs, including isoniazid (68.4%), rifampicin (61.7%, p=0.026), pyrazinamide (76.2%), and ethambutol (84.1%). Multivariate analysis identified higher AFB smear grades (AFB+3: OR 2.8, 95% CI: 1.5–3.6, p<0.001) and age groups 5–14 years (OR 5.1, 95% CI: 1.37–19.65, p=0.0015) and 15–24 years (OR 1.5, 95% CI: 1.04–2.40, p=0.031) as significant

predictors of second-line drug resistance. Treatment success was observed in 77.6% of cases, with 73.5% cured, while unsuccessful outcomes reached 22.4%, including a 6.9% mortality rate and 3.3% treatment failure. Kanamycin (OR 1.9, 95% CI: 1.02–3.82, p=0.041) and Levofloxacin (OR 2.6, 95% CI: 1.14–5.94, p=0.023) were associated with improved outcomes, whereas Rifampicin was linked to poorer outcomes (OR 0.56, 95% CI: 0.35–0.89, p=0.015). The prospective phase (January 2023–June 2024) evaluated sputum culture conversion rates, ADR prevalence, and associated factors. ADRs were prevalent in 46.2% of patients, with anemia (42.9%), hepatotoxicity (42.2%), and nausea/vomiting (29.1%) being the most common. Previous TB history increased ADR risk (OR 1.98, p=0.003), while short treatment regimens (OR 0.61, p=0.006) and non-cavitation on chest X-rays (OR 0.56, p=0.01) were protective. These findings emphasize the importance of tailored treatment strategies, highlighting the need for robust resistance testing and ADR monitoring to improve patient adherence and treatment success. The study concludes that while demographic factors such as age and gender may not significantly impact overall treatment outcomes, clinical characteristics like drug resistance profiles play a crucial role, particularly in high-burden DR-TB settings.

CHAPTER 1

INTRODUCTION

1.1 Background

Tuberculosis (TB) is a serious infectious disease primarily affecting the lungs, caused by *Mycobacterium tuberculosis* (Allué-Guardia et al., 2021; Devi, 2023). It remains one of the leading causes of death worldwide, accounting for significant global morbidity and mortality (Curtin et al., 2023). Approximately one-third of the worldwide population is infected with TB, with 10.4 million new cases and 1.8 million deaths reported in 2022 (Deka et al., 2022). Of these deaths, 0.4 million occurred among individuals co-infected with Human Immunodeficiency Virus (HIV). Countries such as India, Indonesia, China, Nigeria, Pakistan, and South Africa bear 60% of the total TB burden (Abdullah et al., 2022), with nearly 95% of deaths occurring in low- and middle-income countries (LMICs) (Abdullah et al., 2022; Foo et al., 2022).

Two main strains of *Mycobacterium* i-e *M. tuberculosis* and *M. africanum* are responsible for TB infections (Mancuso et al., 2023). While *M. tuberculosis* is widely distributed, *M. africanum* is prevalent in West Africa, where it continues to contribute to TB-related mortality (Mancuso et al., 2023; Sahal et al., 2023). People with weakened immune systems, including those with HIV, diabetes, malnutrition, or smoking habits, are particularly vulnerable (Real et al., 2021).

Global prevalence of Tuberculosis

The burden of TB continues to rise, with 10.6 million new cases and 1.6 million deaths reported in 2021, an increase from 2020 (World Health Organization (WHO), 2022a). The incidence rate of TB also increased by 3.6%, reversing the trend of a

nearly 2% annual decrease seen over the past two decades (Ding et al., 2022). Drug-resistant tuberculosis (DR-TB) poses a major challenge, with a 3% rise in case

between 2020 and 2021. Approximately 450,000 cases of rifampicin-resistant TB (RR-TB) were reported in 2021, with Eastern Europe and Central Asia showing the highest proportions of multidrug-resistant TB (MDR-TB) (Zhdanova et al., 2023). Despite these challenges, treatment access remains limited, with fewer patients receiving necessary care in 2021 than in previous years (Bagcchi, 2023).

Pediatric tuberculosis constitutes almost 1.2 million cases per year, resulting in nearly 240,000 fatalities among children, predominantly in high-burden nations (Verkuijl et al., 2022). Pediatric tuberculosis is frequently underdiagnosed owing to non-specific symptoms and diagnostic difficulties, especially in children under five years of age (Joshi, 2023). Tuberculosis (TB) is categorized into pulmonary TB (PTB), affecting the lungs and accounting for 85% of cases, and extrapulmonary TB (EPTB), which infects other organs such as lymph nodes, bones, and the central nervous system (Gopalaswamy et al., 2021). Drug-resistant tuberculosis (DR-TB), encompassing multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB), is a substantial worldwide health challenge, with 500,000 cases of MDR-TB documented each year (Duga, 2024). Pediatric multidrug-resistant tuberculosis is especially alarming due to restricted therapeutic alternatives and elevated fatality rates (Maphalle et al., 2022). Mitigating the worldwide tuberculosis burden necessitates the advancement of diagnostic methodologies, the enhancement of vaccine development, and the fortification of treatment adherence initiatives to fulfil the WHO End TB Strategy targets (Oluwatamilore, 2022).

1.1.1 Prevalence of Tuberculosis in Pakistan

Pakistan, one of the countries with a high burden of TB, reported 570,000 new cases in 2019, contributing to 43,900 TB-related deaths (Hafeez et al., 2023). A major barrier to controlling TB in Pakistan is the underdiagnosis and under-reporting of cases, due to stigma and social misconceptions, inadequate healthcare infrastructure, socioeconomic barriers, gender disparities, cultural and social barriers and engagement with private healthcare providers, which operates outside the National TB Program (NTP) (World Health Organization (WHO), 2022a). Effective TB control is a key health goal outlined in the United Nations Sustainable Development Goals (SDGs), to end the global TB epidemic by 2030 (Silva et al., 2021). Even with the availability of very effective medication, TB (TB) continues to be a significant global public health issue (Weldemhret, 2023).

1.2 Tuberculosis in Children

Children, especially those under the age of 15, are particularly vulnerable to TB. According to the World Health Organization (WHO), over 1 million children develop TB each year, yet two-thirds of these cases go undiagnosed and unreported (World Health Organization (WHO), 2022d). The diagnosis of TB in children is challenging due to low detection rates due to the paucibacillary nature of pediatric TB, difficulty in obtaining diagnostic samples, atypical and non-specific clinical presentation, limited use of advanced diagnostic tools, and lack of awareness and screening Programs which contribute to underreporting and hinder effective treatment (Reuter et al., 2020). Immunological deficiencies, both acquired and genetic, increase the risk of developing TB in children (Xu & Yamada, 2023). Each day, TB claims the lives of over 600 children worldwide (Organization, 2022d). Of the estimated 1 million

pediatric cases in 2019, 70% were either misdiagnosed or unreported (Kiziltaş & Babalik, 2023). The limited capacity to obtain sputum samples from children, along with diagnostic challenges, further complicates the situation (Wobudeya et al., 2022).

Pediatric tuberculosis (TB) is an increasing public health concern in Pakistan, contributing significantly to the national TB burden (Ahmed et al., 2023). Children, particularly those under 15 years of age, account for an estimated 20-25% of all TB cases, while true prevalence is likely underreported due to diagnostic problems, limited case discovery, and non-specific symptoms (Khurana & Dhingra, 2023). Pulmonary TB (PTB) remains the primary form, but extrapulmonary TB (EPTB)—including tuberculous lymphadenitis, meningitis, and bone/joint TB—is frequently documented, particularly in younger children (Maphalle et al., 2022). The incidence of drug-resistant tuberculosis (DR-TB) in paediatric populations is increasing, with multidrug-resistant tuberculosis (MDR-TB) cases associated with inadequate treatment adherence, protracted diagnosis, and transmission from untreated adult cases (Enane & Christenson, 2021). Malnutrition, poverty, and insufficient BCG vaccine coverage exacerbate paediatric vulnerability (Tousey-Pfarrer). Not withstanding the endeavours of the National TB Control Program (NTP), obstacles remain due to inadequate access to child-appropriate TB diagnostics, a deficiency of skilled paediatric TB specialists, and insufficient integration of TB services into standard child healthcare (Tshivhase, 2023). Enhancing active case detection, preventative therapy for high-risk children, and optimising treatment adherence measures is crucial to diminish paediatric TB morbidity and death in Pakistan (Malik, 2020).

1.3 Drug-Resistant Tuberculosis: A challenge

Drug-resistant TB, particularly MDR-TB, is one of the most formidable challenges in TB control (Stephanie et al., 2021). Unlike many other bacterial pathogens that acquire resistance through horizontal gene transfer, resistance in *Mycobacterium tuberculosis* primarily arises from chromosomal mutations (Xia, 2023). These mutations affect drug activation, target binding, or drug permeability, leading to various forms of resistance (Wu, 2020).

The WHO categorizes drug-resistant TB into several types, including single drug-resistant TB (SDR-TB), MDR-TB (resistant to at least isoniazid and rifampicin), extensively drug-resistant TB (XDR-TB), and total drug-resistant TB (TDR-TB). MDR-TB often arises from inadequate treatment and mismanagement of drug regimens (Gautam & Gautam, 2020). Phenotypic drug susceptibility testing (DST) remains the gold standard for diagnosing MDR-TB, though it may take up to 12 weeks to yield results (Iacobino et al., 2020; Singh & Chibale, 2021). Significantly, the WHO has not yet recognized TDR-TB, likely because of constraints in testing second-line treatments for resistance through drug susceptibility testing (Singh et al., 2023).

The two reasons why MDR/RR-TB continues to emerge and spread are mismanagement of TB treatment and person-to-person transmission (Islam, 2022). Most people with TB are cured by a 6-month treatment regimen that is provided to patients with adequate support (Gautam & Gautam).

The gold standard for diagnosing MDR/XDR-TB is phenotypic DST (Sanchini et al., 2024). Still, the delay in starting therapy can take up to 12 weeks to get results that directly affect effective treatment (Gill et al., 2022). To address this, the most effective way would be a single diagnostic test that looks for all potential mutations in

the resistance genes' profile (Nandlal et al., 2022). This quick and accurate diagnosis should lead to effective treatment and a decrease in the development of resistance (Avershina et al., 2021).

Treatment failure must be prevented to avoid the spread of MDR/XDR infections (Chowdhury et al., 2023). However, DR-TB can also spread when a new infection arises with a resistant *Mycobacterium tuberculosis* strain (Emane et al., 2021). The WHO has published recommendations on the duration of treatment, the drug combinations to be utilized, and the methods for monitoring patient response to treat DR-TB effectively (Dookie et al., 2022). The MDR/RR-TB regimens are available in two lengths: (i) a normal shorter regimen lasting nine to twelve months, or (ii) extended regimens lasting up to twenty months (Abidi et al., 2020).

1.4 Health care system in Pakistan

Due to the expanding requirements of the global population, the emergence of new public health issues regularly, and the diversity of population demographics, it is impossible to declare any healthcare system to be flawless (Kreindler et al., 2022). Every system requires ongoing pruning to analyze its strengths and weaknesses and meet the needs of its constituents (Saba Raoof & Durai, 2022). This also applies to the healthcare system in Pakistan. The healthcare system in Pakistan serves a vast population of over 220 million people by combining the public and private sectors (Malik, 2022).

Pakistan's healthcare system is divided into three levels: primary, secondary, and tertiary (Hashami, 2020). There are 671 maternity and child health facilities, 1,142 hospitals, 5,499 dispensaries, 5,438 basic health units, and 5,438 dispensaries in Pakistan (CHAUDHRY). A basic health unit (BHU) is a comprehensive outreach

program that consists of midwives, lady health visitors (LHV), and communicable disease control (CDC) (Bashir & Ahmad, 2022). BHUs offer family planning (FP), skilled birth attendants during delivery, nutritional counseling, prenatal and postnatal care, and preventive treatments such as the Expanded Programme on Immunization EPI vaccination and management of sexually transmitted infections and reproductive tract infections (Quist-Nelson, 2022).

Patients are referred by a Lady health worker (LHW) to BHU or, if necessary, to the next higher level of care RHC (Shah & Jariko, 2021). Health systems typically lack clear borders, but developing nations with low incomes have a protracted process of building their health systems (Cho, 2022).

The healthcare system in Pakistan faces numerous obstacles, such as insufficient finance, restricted infrastructure, the exodus of medical personnel, a dearth of emphasis on preventative healthcare (PHC), and unequal resource distribution (Nwakamma et al., 2024). The most notable accomplishment of the healthcare system in Pakistan among these concerns is the Sehat Sahulat Program (SSP), Pakistan's first comprehensive universal health coverage (UHC) effort (Khan et al., 2023).

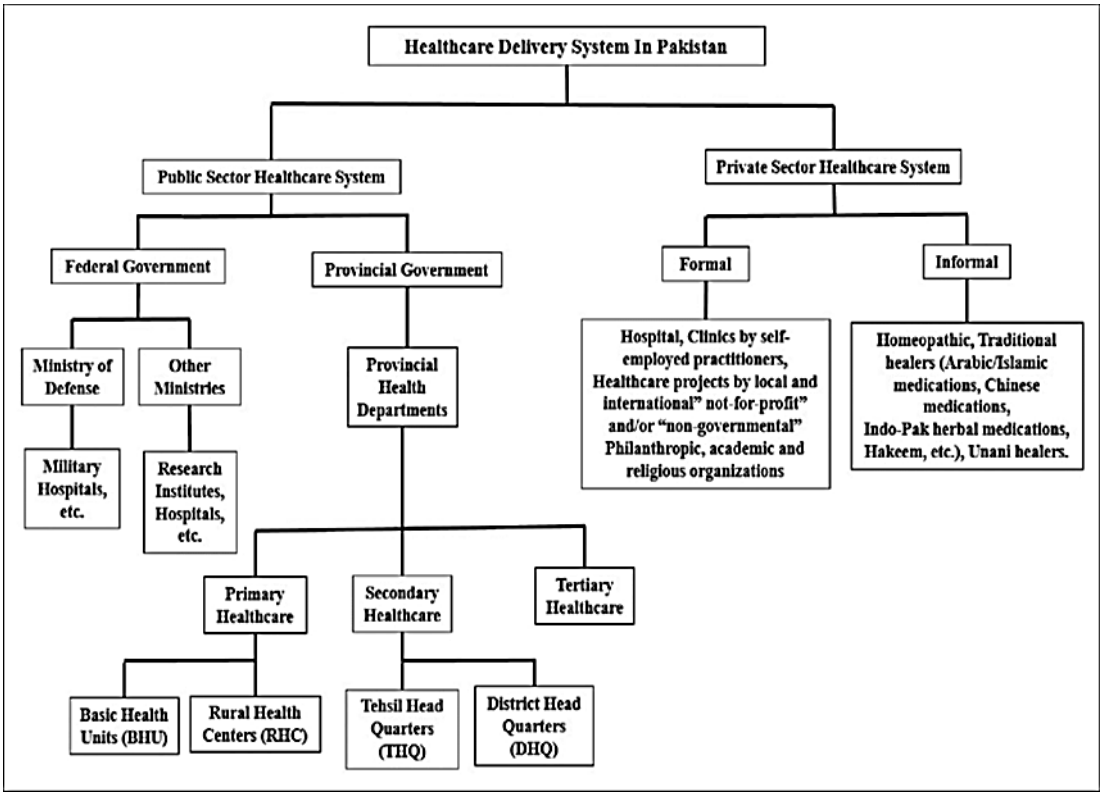

Figure 1.1 Healthcare system of Pakistan (Qidwai, 2016)

1.5 Prevalence of Multidrug-resistant Tuberculosis globally

Multidrug-resistant tuberculosis (MDR-TB) remains a major global health challenge, with nearly 500,000 new cases reported annually, making it one of the leading causes of death (Wubu et al., 2023). It is the second most common infectious disease-related cause of mortality globally, after HIV/AIDS (Liu et al., 2024). Studies consistently show that MDR-TB rates are significantly higher in patients who have previously undergone TB treatment compared to newly diagnosed cases (Koirala et al., 2021).

Low- and middle-income countries (LMICs), particularly in East Africa, experience the highest rates of TB-related morbidity and mortality (Sanders, 2023). Countries like Ethiopia, Rwanda, Kenya, Tanzania, and Uganda report high incidences of MDR-TB, with Ethiopia bearing a heavy burden due to high rates of HIV co-

infection and MDR-TB, HIV-positive patients with TB face a significantly higher risk of mortality (Lelisho et al., 2022). Globally, 30 countries account for the majority of MDR-TB cases, with a disproportionate number of LMICs (Akalu et al., 2023). Approximately 75% of the global MDR-TB caseload is in middle-income countries, while low-income countries account for 4%, and high-income countries such as the Republic of Korea and the Russian Federation represent 19% of cases (Huria, 2023).

MDR-TB, characterized by resistance to at least isoniazid and rifampicin, was found in 3.6% of newly diagnosed cases and 18% of previously treated cases (Monde et al., 2023). Treating MDR-TB requires prolonged use of second-line medications such as bedaquiline, linezolid, and moxifloxacin (Vanino et al., 2023). These drugs are less effective, more expensive, and carry a higher risk of side effects compared to first-line therapies (Espinosa-Pereiro et al., 2022).

1.5.1 Prevalence of Multidrug-resistant Tuberculosis in Pakistan

Multidrug-resistant tuberculosis (MDR-TB) and other drug-resistant strains have increasingly become a major public health challenge in Pakistan, which ranks fourth among the 30 countries with the highest TB burden (M. A. Khan et al., 2022). The country reported approximately 518,000 TB cases in recent years, including 15,000 cases of MDR-TB (Jahangir et al., 2023). Provincial data indicates that Punjab has the highest proportion of MDR-TB cases, accounting for 51%, followed by Sindh (23%), Khyber Pakhtunkhwa (15%), and Baluchistan (3.5%) (Rafique, 2023). The growing number of MDR-TB cases is largely attributed to factors such as treatment failure, relapse, co-existing medical conditions, and increased mortality (Wakjira et al., 2022).

Drug resistance in TB emerges due to several factors, including inadequate or inappropriate medication regimens, delayed diagnoses, insufficient follow-up, and a lack of social support systems (Beauchamp et al., 2021). Recent data also revealed that 4.2% of newly diagnosed TB cases are rifampicin-resistant, with much higher rates among previously treated patients, where the resistance rate is nearly four times higher (Ren et al., 2022). To address this growing challenge, Pakistan must prioritize early disease control, strengthen TB awareness and management programs, and implement rigorous infection control protocols. Adherence to WHO guidelines for MDR-TB treatment and expanded screening efforts are essential to curbing the spread of MDR-TB in the country (Espinosa-Pereiro et al., 2022). Susceptibility pattern of strains to investigate a relationship between *M. tuberculosis* strain prevalence and drug resistance. Figure 1.2 describes the geographical distribution of different genotypes in the Sindh, Punjab, NWFP, and Baluchistan provinces.

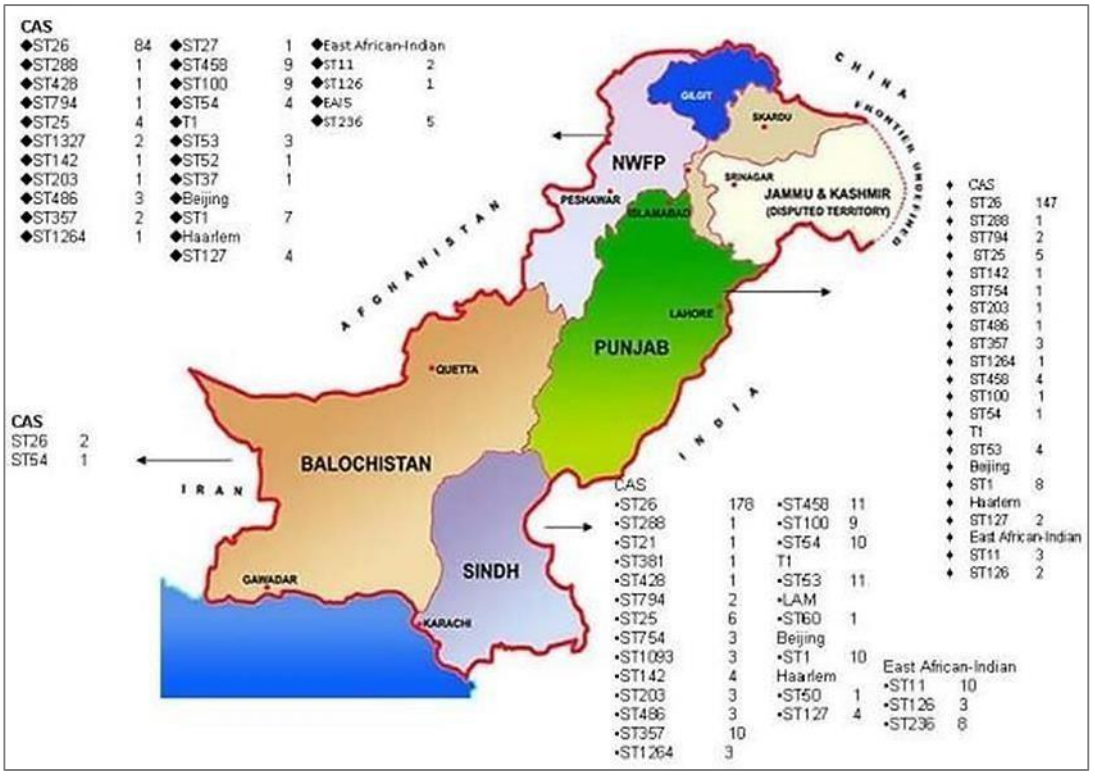

Figure 1.2 Genotyping and drug resistance patterns of *M. tuberculosis* strains in Pakistan (Tanveer et al., 2008)

1.6 Global Burden of Pediatric Multidrug-resistant Tuberculosis

Tuberculosis (TB) remains a significant global health issue, affecting an estimated 1 million children annually (Yerramsetti et al., 2022). However, many children do not receive timely diagnosis or treatment (Organization, 2021c). In 2019, approximately 208,000 children died from TB, and by 2021, this number rose to 239,000, with children under five accounting for 80% of these deaths (Ergenekon et al., 2023; Sharrow et al., 2022).

Despite the growing concern, limited research has examined the patterns of drug resistance in children, including MDR-TB (Zhang et al., 2023). One of the primary challenges in diagnosing drug-resistant TB in children is the difficulty in obtaining sufficient samples for testing, as pediatric TB tends to be paucibacillary and extrapulmonary, and young children often cannot produce adequate sputum (Schaaf & Seddon, 2021).

Additionally, sputum collection in children is complicated by the tendency to swallow sputum, leading to sample contamination (Calderaro et al., 2022). This, combined with the limitations of current diagnostic tools, makes confirming TB in children particularly difficult, even with advanced techniques like nucleic acid amplification testing (Dubale et al., 2022). Only about 40% of pediatric pulmonary TB cases receive microbiological confirmation, and this percentage is even lower for extrapulmonary TB (Sharma et al., 2021). Consequently, drug susceptibility testing (DST) data for pediatric cases are often sparse, with genotypic methods like Xpert MTB/RIF commonly used but still inadequate for accurate drug resistance profiling (Pillay et al., 2023).

The lack of comprehensive data on pediatric MDR-TB complicates efforts to implement effective control strategies, particularly within the framework of the WHO's End TB Strategy (du Preez et al., 2022). The global distribution of pediatric MDR-TB cases varies significantly across regions (Ou et al., 2021). In 2019, 30 high-burden countries accounted for nearly 87% of all MDR-TB cases worldwide (du Preez et al., 2022). Additionally, the incidence and mortality of pediatric TB are closely linked to a country's socioeconomic status, particularly health spending (Liu et al., 2023).

Efforts to model TB trends across countries have struggled to incorporate economic factors as predictors of drug resistance, leaving gaps in understanding the true burden of pediatric MDR-TB (Trajman et al., 2022). Although all age groups are susceptible to MDR-TB, there is limited data on the extent of this issue among children (Maphalle et al., 2022). Treatment for children with MDR-TB mirrors that for adults, but children often require empirical treatment due to challenges in obtaining confirmed DST results (Anyansi, 2021). While data on pediatric treatment outcomes are limited, available evidence suggests that outcomes can be as good as those seen in adults (Pecora et al., 2021). However, the treatment of pediatric MDR-TB is complicated by factors such as the rapid metabolism of medications in young children and the paucibacillary nature of their disease, making standard adult treatment protocols potentially less effective (Whittaker et al., 2021).

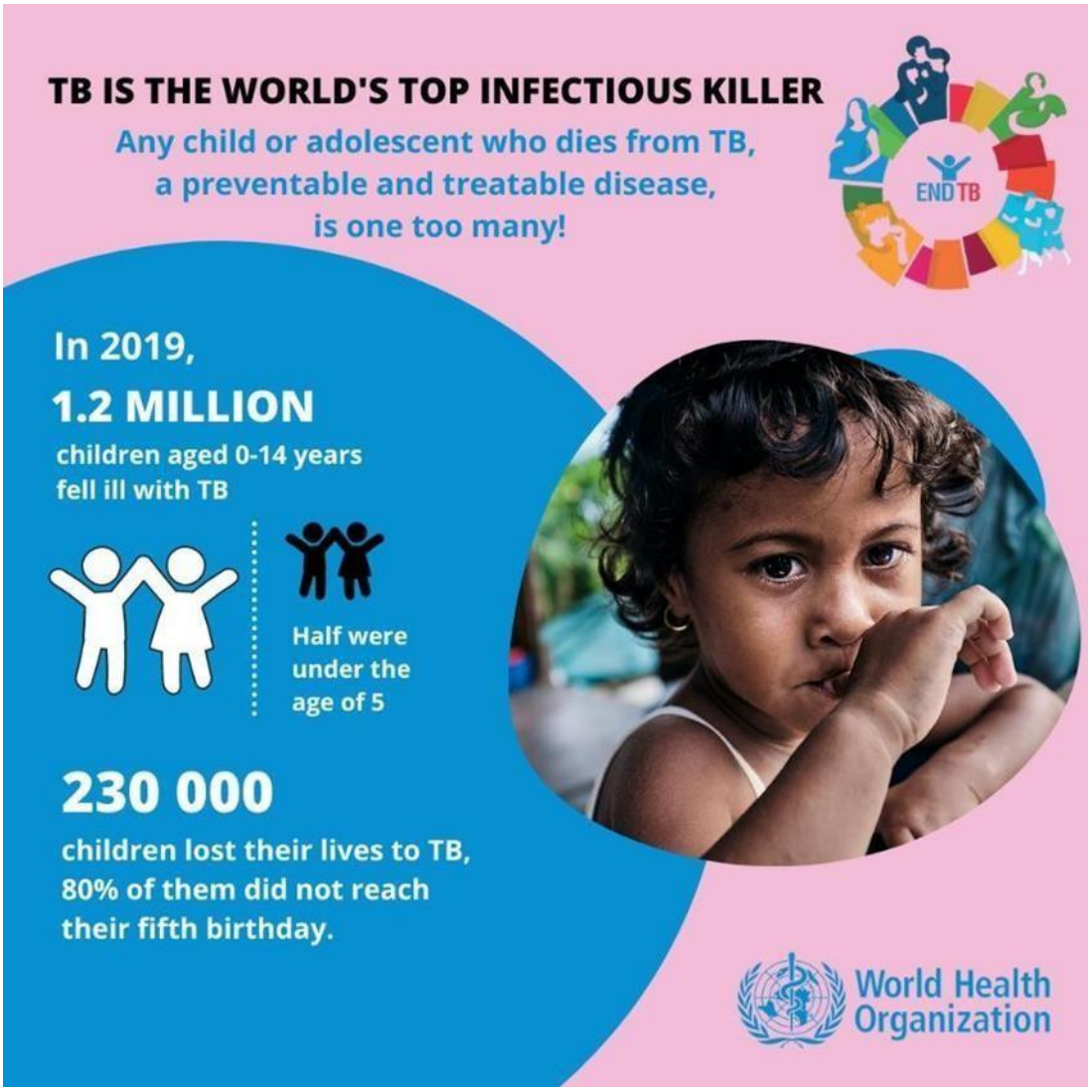

Figure 1.3 Prevalence of MDR TB in children globally (Organization, 2021d)

1.6.1 Multidrug-resistant Tuberculosis in Children in Pakistan

The programmatic management of drug-resistant tuberculosis (PMDT) was initiated in Pakistan in 2010, and currently, 33 PMDT units are operational across the country (Naz et al., 2021). Monitoring patient management and treatment outcomes has proven to be an effective way to assess the success of the program (Di Maio et al., 2022). Reported treatment success rates for MDR-TB patients in Pakistan vary, ranging from 40.5% to 83.7%, according to several cohort studies (Khan et al., 2022). Despite progress in managing adult MDR-TB, little is known about the

sociodemographic characteristics, treatment outcomes, drug resistance patterns, and risk factors specific to pediatric RR/MDR-TB patients in Pakistan (Hameto & Mamo, 2024). Among the provinces, Punjab has the highest proportion of RR/MDR-TB cases (46%), followed by Sindh (39%), Khyber Pakhtunkhwa (10%), and Baluchistan (2.7%) (Malik et al., 2022). In 2019, 73% of RR/MDR-TB patients who began treatment achieved successful outcomes, while 67% of pre-XDR/XDR-TB patients completed treatment successfully (Jassat, 2022). In 2019, 73% of RR/MDR-TB patients who began treatment achieved successful outcomes, while 67% of pre-XDR/XDR-TB patients completed treatment successfully (Madzgharashvili et al., 2021).

Table 1.1 Prevalence of MDR-TB in provinces of Pakistan (Ali et al., 2020)

Province	**Reported MDR- TB Cases**	**Percentage of Total**	**Treatment Success Rate**
Punjab	265,000	51%	67%
Sindh	120,000	23%	65%
Khyber Pakhtunkhwa	75,000	15%	63%
Baluchistan	18,000	3.5%	60%

1.7 Problem statement

Clinicians commonly use sputum smear and culture conversion to monitor the progress of MDR-TB treatment, but it remains uncertain how long patients stay contagious after initiating successful therapy (Meshesha, 2022). This uncertainty, coupled with the urgent need for better prevention and care among children, highlights significant gaps in managing MDR-TB (Seddon et al., 2021). A major challenge in resource-constrained settings is the lack of scalable and practical diagnostic tools across the spectrum of TB care (Olatunji et al., 2024).

Pediatric MDR-TB is particularly concerning, as rising resistance in children further complicates treatment availability and success (Alzarea, Khan, et al., 2024).

While MDR-TB remains the focus of TB control efforts due to its high morbidity and mortality, recent drug resistance surveys indicate that mono- and poly-resistant TB strains are more prevalent, with a global incidence of 3.5% in new MDR-TB cases and 17% in mono- and poly-resistant strains (Thakur et al., 2021).

Pakistan bears 61% of the TB burden in the WHO Eastern Mediterranean Region and ranks fifth globally in TB prevalence (Massud et al., 2023). Although the National TB Program (NTP) has made progress, the emergence and management of drug-resistant TB (DR-TB) remain pressing concerns, with Pakistan having the fourth-highest global prevalence of MDR-TB (U. Khan et al., 2022).

Recent studies indicate alarming levels of drug resistance in Pakistan, with 10.2% of TB cases showing rifampicin resistance, 9.9% resistant to isoniazid, and varying resistance to other first-line drugs like streptomycin, ethambutol, and pyrazinamide (Lempens, 2023). In Karachi, MDR-TB was detected in 5% of the sample population, with the prevalence of XDR-TB rising from 1.5% in 2006 to 4.5%

(Saifullah et al., 2021). A WHO study also found that Pakistan had the highest levels of ofloxacin resistance among the five countries surveyed (Adhikari, 2022). As per the findings of a WHO study evaluating fluoroquinolone and pyrazinamide resistance, Pakistan exhibited the highest levels of ofloxacin resistance among the five countries surveyed (Tahseen et al., 2020). While the NTP provides free anti-TB medications, treatment default rates are increasing, raising significant concerns about treatment adherence and disease control (Konka, 2019). While adult TB patients have shown fluctuating trends in treatment compliance, evidence suggests that pediatric

patients are also experiencing an increasing rate of treatment default (Maphalle et al., 2022). Several key factors contribute to this phenomenon are caregiver-dependent treatment adherence, lengthy and complex TB treatment regimens, high incidence of adverse drug reactions, socioeconomic and accessibility barriers, social stigma and misconceptions and weak follow-up and retention strategies, now estimated at 11%, up from earlier reports of 4% (Al-Darraji, 2020). This suggests that many default cases (a default case refers to a patient who interrupts treatment for at least two consecutive months (≥60 days) after being enrolled in TB treatment) go unreported, raising critical concerns about the factors driving these defaults. A thorough investigation is needed to identify the causes and risk factors for patient non- compliance, especially in regions where default rates are disproportionately high (Baloyi, 2020). All these alarming problems emphasize the urgency of addressing MDR-TB in Pakistan, particularly among pediatric populations (Ahmed et al., 2023).

1.8 Rationale of the study

TB remains a significant global health challenge, with drug-resistant strains posing severe threats, especially in high-burden countries like Pakistan. Among the provinces, Punjab and Khyber Pakhtunkhwa report substantial cases of pediatric drug-resistant TB (DR-TB), where treatment non-compliance exacerbates the issue. Non-compliance in pediatric patients can stem from various factors, such as adverse effects, stigma, lack of awareness, and financial barriers. Pediatric patients are particularly vulnerable due to their reliance on caregivers, making treatment adherence more challenging. Understanding the specific causes of non-compliance in children with DR-TB can lead to the development of more targeted and effective interventions. This study aims to evaluate current management practices, assess treatment outcomes, and

identify factors contributing to non-compliance among pediatric DR-TB patients in these regions. By addressing these gaps, the study seeks to contribute valuable insights that can inform policies and practices to improve treatment adherence, outcomes, and long-term TB control efforts in Pakistan.

1.9 Research Questions (RQ)

Pakistan's public health is at risk from DR-TB. It is crucial to assess the care of pediatric DR-TB patients that have been identified and enrolled, even though the scope of the issue is yet unknown. In high-burden DR TB nations such as Pakistan, numerous questions need to be addressed. Among these inquiries are:

RQ1. What are the key risk factors associated with drug-resistant tuberculosis (DR-TB) in pediatric patients, and how do these factors relate to the drug resistance patterns of second-line drugs (SLD)?

RQ2. How do specific risk factors influence treatment outcomes in pediatric DR-TB patients?

RQ3. What are the primary factors contributing to unsuccessful treatment outcomes in pediatric DR-TB cases, and how can these be addressed for better management?

RQ4. What is the rate of sputum culture conversion among multidrug-resistant tuberculosis (MDR-TB) patients, and what are the key predictors associated with successful conversion?

RQ5. What is the incidence of adverse drug reactions (ADRs) during DR-TB treatment, and how do these reactions contribute to resistance to second-line drugs?

1.9.1 Specific Research Objectives (RO)

RO1. To identify the key risk factors associated with DR-TB in pediatric patients, with a particular focus on the drug resistance patterns of second-line drugs (SLD).

RO2. To analyze treatment outcomes in pediatric DR-TB patients and examine how these outcomes are influenced by specific risk factors.

RO3. To investigate the factors contributing to unsuccessful treatment outcomes in pediatric DR-TB cases, providing insights into potential areas for intervention.

RO4. To assess the rate and key predictors of sputum culture conversion among MDR-TB patients, linking this to overall treatment success.

RO5. To evaluate the incidence of adverse drug reactions (ADRs) during DR-TB treatment and their role in resistance to second-line drugs, informing strategies for improving patient management.

CHAPTER 2

LITERATURE REVIEW

2.1 Epidemiology of Drug-resistant Tuberculosis

Children over the age of 15 account for about half of MDR-TB cases (Ammari et al., 2022; Organization, 2022a). In 2019, it was estimated that MDR/RR-TB affected 3.3% of new TB cases and 18% of previously treated cases globally (Sachdeva et al., 2021). Of all RR-TB cases, approximately 78% were classified as MDR-TB (Agbota et al., 2023).

Treatment coverage has declined in recent years, with nearly 3 million people receiving TB treatment in 2020, a 21% decrease compared to 2019, when 3.6 million people were treated (Agbota et al., 2023) due to impact of the COVID-19 pandemic, economic and socioeconomic barriers, disruptions in TB healthcare infrastructure, diagnostic and treatment challenges, behavioral and psychological factors, global funding and policy challenges (Osei-Kuffour, 2023). For drug-resistant TB (DR-TB), only one in three patients in need of treatment for rifampicin-resistant/multidrug-resistant TB (RR/MDR-TB) received it in 2020, a 15% drop from the previous year. In 2019, it was estimated that MDR/RR-TB affected 3.3% of new TB cases and 18% of previously treated cases globally (Sachdeva et al., 2021).

Of all RR-TB cases, around 78% were instances of MDR TB (Ngolele, 2023). A modified regimen is necessary in cases where there is INH resistance but not rifampicin resistance (Cox et al., 2020). According to WHO global TB report in 2020, there were approximately 465,000 RR/MDR cases in 2019 (with a range of 400,000–535,000) (Duvenhage et al., 2022; Jasani et al., 2022). The global attempts to eradicate

TB in all of its forms have been severely harmed by the COVID-19 virus, which has a reverse connection with the disease (Patra et al., 2022).

The fight against TB has regressed from the achievements made in recent years, and in 2020, there was an annual increase in related mortality for the first time since 2005 (Sachdeva et al., 2021). India leads the group with the highest absolute numbers in terms of DR-TB, accounting for 86% of the worldwide DR-TB burden among the top 20 nations (Clark, 2023).

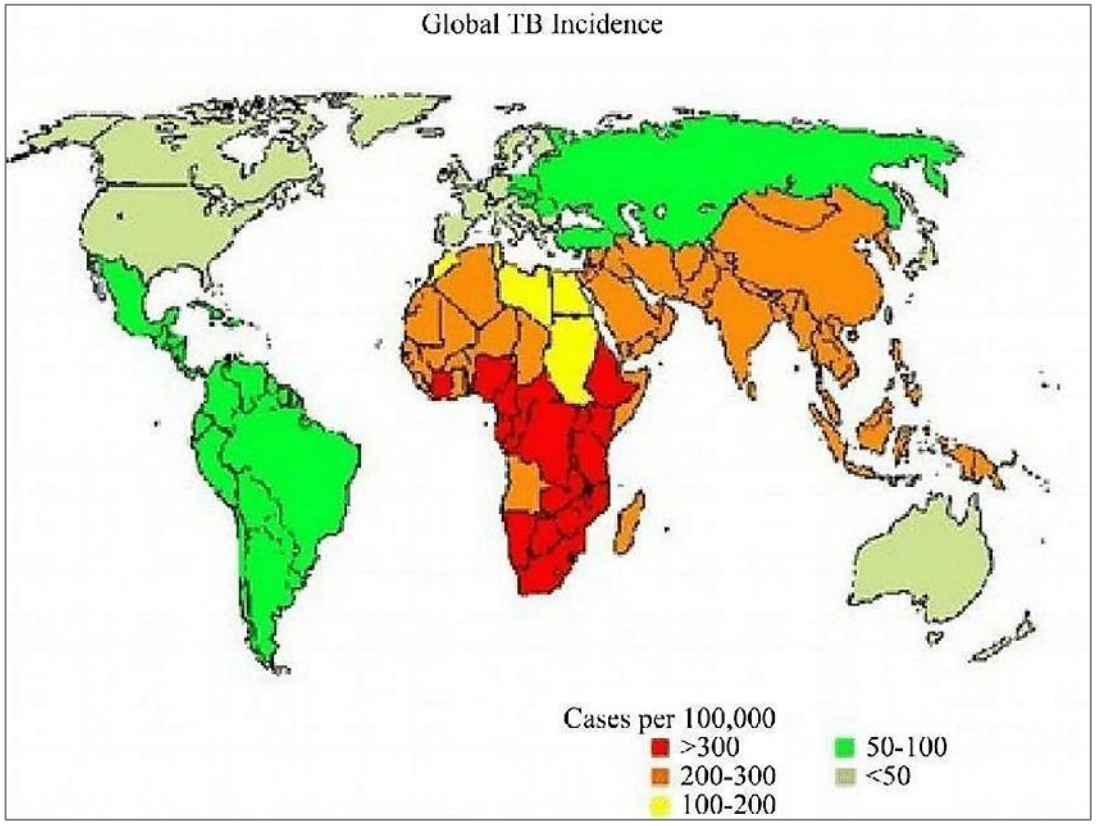

Figure 2.1 Global Distribution of MDR-TB (Clark, 2023)

2.2 WHO End TB Management

Ending the worldwide TB epidemic is the unifying aim of the SDGs, which UN Member States ratified in September 2015, and the WHO End TB Strategy, which

was approved by the WHO's 194 Member States in 2014 (Pradipta et al., 2021). It is also necessary to accomplish these targets so that no family affected would have to incur unmanageable expenses (Tshabalala, 2023).

Significant efforts have been made to combat TB, which was previously dubbed "the captain of all these men of death," since the WHO made the unprecedented decision to declare the disease a "global emergency" (Schreiner, 2024). The WHO's 1995 "DOTS" strategy, which changed into the "Stop TB" strategy ten years later and the "End TB" strategy a year after that, offered a series of frameworks and goals for global and domestic control initiatives (Organization, 2021b). A TB-specific aim (6c) "to halt and reverse TB incidence" by 2015 was included in the Millennium Development Goals (the forerunner to the SDGs) in 2000 (Organization, 2023b). This target was supplemented by two Stop TB Partnership targets, which called for halving TB prevalence and death by 2015 compared with levels in 1990 (Taratara, 2022).

TB-related mortality (deaths per 100,000 populations annually) fell by 47% overall between 1990 and 2014, and by 2015, TB incidence had stopped. Between 2000 and 2015, treatment for TB prevented an estimated 49 million deaths worldwide (Marks et al., 2023). Controlling tuberculosis (TB) entails identifying and treating active disease as soon as it manifests and keeping latent TB infection from becoming entrenched or becoming an active illness (Lu et al., 2023). WHO has recognized the unique challenges in diagnosing and managing tuberculosis (TB) among children and has developed specific strategies to enhance pediatric TB management (Maphalle et

al., 2022). Key components of these strategies include Integrated Childhood TB Management, Directly Observed Treatment, Short-Course, Bacillus Calmette-Guérin (BCG) Vaccination, Development of Child-Friendly Drug Formulations, Development of Child-Friendly Drug Formulations (Jaganath et al., 2022).

Although the availability of TB preventative treatment is growing, the majority of people who should be receiving it are not (Bhargava & Bhargava, 2020). Just 6.3 million new cases of TB were recorded in 2016, which means that 4.1 million patients (or 40% of the projected disease burden) either had no diagnosis or had a diagnosis but were not informed of national programs (World Health Organization (WHO), 2022a). A multisector effort is needed to end the TB epidemic, emphasizing boosting socioeconomic development, creating a new TB vaccine, creating innovative diagnostic tools and treatment medications, and increasing health insurance coverage (Chopra et al., 2023). In the era of the SDGs, 2017 and 2018 marked significant milestones for international efforts to eradicate tuberculosis (Kanmani et al., 2024). The WHO organized the first global Ministerial Conference on TB in Moscow in November 2017 expediting expedite the WHO End TB Strategy's implementation (Citaristi, 2022). In September 2018, the United Nations General Assembly will hold its first-ever high-level meeting on tuberculosis (TB) (World Health Organization (WHO), 2022e). Heads of state will approve and accept an accountability framework and multi-sectoral approach during this conference (ul Eman et al., 2022).

Within this broad framework, NTP is accountable for providing efficient and high-quality diagnostic, treatment, and preventive services, and for stopping the spread of *Mycobacterium tuberculosis* from individuals who are infected to those who are not (World Health Organization (WHO), 2023c). To this purpose, the Stop TB Partnership announced 90-(90)-90 TB diagnostic and treatment targets as part of the Global Plan

to expedite the end of the TB pandemic (Marks et al., 2023). The UNAIDS 90-90-90 targets call for 90% of people living with HIV to know their status, 90% of people living with HIV who know their status to be on antiretroviral therapy, and 90% of people living with HIV on antiretroviral treatment to achieve viral suppression (Frescura et al., 2022).

2.3 Pakistan's Scenario/ Epidemiology of Drug-Resistant Tuberculosis

TB has been a longstanding health issue in Pakistan, yet it has historically received insufficient attention (Chaudhry & Khan, 2020). In 1962, Pakistan partnered with the World Health Organization (WHO) and UNICEF to manage TB by establishing treatment facilities in district hospitals (Behera et al., 2020). However, this initiative was discontinued in 1985 due to lack of funding from UNICEF (Organization et al., 2022). In response to the global TB emergency declared by WHO, Pakistan implemented the Directly Observed Therapy Short Course (DOTS) strategy to improve treatment outcomes (Zimmer et al., 2021). However, by 1998, Pakistan was deemed non-functional in TB management, despite updating national guidelines and TB control policies (Acharya, 2022).

By 2000, the case recognition rate for new and relapsing smear-positive TB cases was only 2.8%, far below the WHO target of 70% (Espinal & Raviglione, 2021). In 2001, the establishment of the National TB Control Program (NTP) marked a turning point, leading to improved DOTS coverage, case notification, and treatment outcomes (Sahal, 2023). By 2005, DOTS coverage had expanded to 100% of Pakistan's population, up from just 8% a decade earlier (WHO, 2009b). The case detection rate for new and relapsed TB cases increased significantly, from 3.9% in 1995 to 62% in 2014 (Shah et al., 2020)

Despite these improvements, Pakistan continues to bear a significant share of the global TB burden, contributing an estimated 573,000 cases to the WHO's Eastern Mediterranean Region, which accounts for 61% of the region's TB cases (NADEEM, 2023). In 2020, Pakistan reported 44,000 TB-related deaths (Rajeshwar, 2024).

Initially, the NTP did not prioritize drug-resistant TB (DR-TB), which led to concerning levels of resistance (Khanna et al., 2023). The passive case detection strategy contributed to missed or complex cases, resulting in treatment failures (Goroh et al., 2023). The introduction of the Programmatic Management of Drug-Resistant TB (PMDT) in the late 2000s marked a shift in addressing DR-TB (Lofranco et al., 2022). By 2019, efforts to expand PMDT units led to improved reporting, though only 73% of the goal to establish 45 units nationwide was achieved (Organization, 2020b). Nonetheless, the number of DR-TB cases notified grew significantly, from just 444 cases in 2010 to 2,689 cases in 2020 (Sachdeva et al., 2021). Pakistan is estimated to contribute approximately 25,000 DR-TB cases to the global TB burden (Massud et al., 2023). The death rate per 100,000 population significantly decreased from 2000 to 2018 following the adoption of the PMDT approach (Monedero-Recuero et al., 2021). Despite this progress, the actual number of treated DR-TB patients remains lower than the total number of diagnosed cases, creating potential infectious hubs within communities and posing a continued threat to TB elimination efforts (Dean et al., 2022). This has left an open window of potential infectious hubs in the community and poses a serious threat to the efforts being made to end all forms of TB (Jops et al., 2022). This gap in detection and treatment not only jeopardizes public health but also increases the economic burden on both the national and global economies (Pang & Amul, 2021). Many patients in the DOTS program remain unrecorded, contributing to