EVALUATION OF TREATMENT OUTCOMES AND FACTORS ASSOCIATED WITH UNSUCCESSFUL OUTCOME AMONG DRUG RESISTANT TUBERCULOSIS PATIENTS AT PUNJAB, PAKISTAN

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by

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LIST OF ABBREVIATIONS

AFB	Acid Fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
ATCC	American Type Culture Collection
Bdq	Bedaquiline
Am	Amikacin
Amx	Amoxicillin
ANOVA	Analysis of Variance
BMI	Body Mass Index
CI	Confidence Interval
Cfz	Clofazimine
Clr	Clarithromycin
Clv	Clavulanic acid
Cm	Capreomycin
Cs	Cycloserine
DOTS	Directly observed treatment-short course
DR-TB	Drug Resistance Tuberculosis
DST	Drug Susceptibility Testing
E	Ethambutol
EMRO	Eastern Mediterranean Region of World Health Organization
Eto	Ethionamide
FLDs	First line anti-TB drugs
FQs	Fluoroquinolones
HIV	Human Immunodeficiency Virus
H	Isoniazid
Km	Kanamycin
Lfx	Levofloxacin
LTR	Long Treatment Regimen
Lzd	Linezolid
MTB	Mycobacterium Tuberculosis
MDR-TB	Multidrug Resistant Tuberculosis
Mfx	Moxifloxacin

NTP	National Tuberculosis Control Program
Ofx	Ofloxacin
PSA	Para-amino Salicylic Acid
PDR-TB	Poly Drug Resistant TB
PMDT	Programmatic Management of Drug-Resistant Tuberculosis
Pto	Prothionamide
Pre-XDR-TB	Pre-Extensive Drug Resistant Tuberculosis
R	Rifampicin
RR	Rifampicin resistant
S	Streptomycin
SD	Standard deviation
SE	Standard Error
SLDs	Second-line anti-TB drugs
SCC	Sputum culture conversion
STR	Short treatment regimen
TB	Tuberculosis
UNICEF	United Nations Children's Emergency Fund
WHO	World Health Organization
XDR-TB	Extensive drug-resistant TB
Z	Pyrazinamide

LIST OF APPENDICES

PENILAIAN HASIL RAWATAN DAN FAKTOR YANG BERKAITAN DENGAN HASIL RAWATAN YANG TIDAK BERJAYA DI KALANGAN PESAKIT TUBERKULOSIS TAHAN UBAT DI PUNJAB, PAKISTAN

ABSTRAK

Pakistan berada di tangga keempat di dunia dalam beban *Drug-Resistant Tuberculosis* (DR-TB). Hasil rawatan sangat dipengaruhi oleh ciri-ciri epidemiologi pesakit seperti gaya hidup, kepadatan penduduk, parameter klinikal asas, corak ketahanan ubat dan mengendalikan komplikasi *Adverse Drug Reactions* (ADR). Sebagai negara dengan beban DR-TB yang tinggi, Pakistan kekurangan data prospektif mengenai impak epidemiologi tempatan, corak ketahanan, kegagalan rawatan, faktor risiko, dan pengurusan kesan sampingan ubat. Satu kajian prospektif terhadap 271 pesakit DR-TB yang didaftar dan dirawat di Hospital Universiti Perubatan Nishtar Multan telah dilakukan untuk menilai ketahanan ubat asas, hasil rawatan, dan sifat serta kekerapan tindak balas ADR. Semua pesakit DR-TB yang didaftar di lokasi kajian adalah layak kecuali wanita hamil, kanak-kanak dan pesakit kurang upaya intelektual. Pesakit-pesakit telah dipantau sehingga hasil rawatan diumumkan. Di antara semua yang didaftarkan, 210 (77.5%) pesakit berumur kurang dari 50 tahun, manakala 195 (72%) pesakit berkahwin. Pengangguran ditemui di kalangan 165 (60%) pesakit. Pesakit-pesakit yang sebelum ini mengalami kegagalan rawatan adalah 198 (73%) pesakit dalam kajian ini. 189 (69%) pesakit bertahap hemoglobin yang lebih rendah juga diperhatikan. Ketahanan *isoniazid* ditemui pada 134 (49.4%) pesakit berbanding dengan 78% yang dilaporkan secara global di kalangan pesakit-pesakit DR-TB, diikuti oleh *pyrazinamide* 64 (23.6%), *ethambutol* 45 (16.6%) dan *streptomycin* 22 (8.11%) masing-masing. Antara ubat *Second-Line*

Anti-Tuberculosis (SLD), ketahanan tertinggi adalah terhadap *ofloxacin* 67 (24.72%), diikuti oleh *kanamycin* 8 (2.9%), *amikacin* 5 (1.8%), *capreomycin* 4 (1.4%) dan *ethionamide* 2 (0.7%). Majoriti, 204 (82.9%) pesakit, mencapai konversi kultur sputum pada akhir permulaan rawatan selama dua bulan. Keberhasilan hasil rawatan (69%) berada di bawah kriteria minimum WHO (> 75%). Hasil rawatan yang tidak berjaya termasuk kematian (17.7%), pesakit susulan (12.5%), dan kegagalan rawatan (0.73%). Penggunaan SLD sebelum ini didapati mempunyai hubungan yang signifikan (OR 3.071(1.112- 8.475, p-value 0.03) dengan ketahanan terhadap *fluoroquinolone* . Hubungan yang signifikan secara statistik (OR 7.637(3.819 - 15.296, p-value < 0.001) didapati antara kavitas paru-paru asas semasa umur >50 tahun (OR 3.877(1.68-8.8.95), (p-value 0.001), berat badan asas < 40 kg (OR 3.183(1.364-7.428), (p-value 0.007) dan kavitas paru-paru asas (OR 5.26 (2.103-13.156), (p-value < 0.001) merupakan faktor risiko yang signifikan dalam kalangan pesakit yang meninggal dunia. Pesakit susulan memiliki hubungan yang signifikan dengan kavitas paru-paru asas (OR 4.643 (1.462-14.747), (p-value 0.009) Daripada 718 ADR, gangguan *gastrointestinal* (GIT) (66.7%), gangguan sistem saraf (59.4%), gangguan elektrolit (55.7%), dan *arthralgia* adalah ADR tertinggi yang dilaporkan, diikuti oleh ototoksisitas (24%), tindak balas gatal/ruam (12.9%), *Dyspnea* (12.5%) dan *tinnitus* (8.8%). Rawatan telah diubah suai kepada 23% pesakit kehilangan pendengaran akibat amikacin. Kavitasi paru-paru asas (OR 3.419 (1.694 - 6.902), (p-value 0.001) telah diakui sebagai faktor risiko untuk terjadinya ADR. Corak kegagalan rawatan tempatan adalah faktor penting dalam merancang regimen yang disesuaikan secara individu. Penggunaan *fluoroquinolone* yang tidak rasional sebelum ini di kalangan orang awam boleh meningkatkan risiko hasil terapi di kalangan pesakit DR-TB. Kadar kejayaan hasil rawatan boleh dipertingkatkan dengan melibatkan pesakit susulan. ADR adalah tinggi tetapi

diuruskan dengan cekap. Pengenalpastian faktor risiko membantu profesional penjagaan kesihatan membuat keputusan awal dan meningkatkan hasil rawatan

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ABSTRACT

Pakistan ranks fourth globally in terms of drug-resistant Tuberculosis (DR-TB) burden. Treatment outcomes are greatly affected by patients' epidemiological characteristics such as lifestyle, population density, baseline clinical parameters, drug resistance patterns and clinical practices to manage adverse drug reactions (ADRs) complications. Being a high-burden DR-TB country, Pakistan lacks prospective data about the impact of local epidemiology, resistance pattern, unsuccessful treatment outcomes, risk factors, and management of adverse drug reactions. A prospective study of 271 DR-TB patients enrolled and treated at Nishtar Medical University Hospital Multan was carried out to assess the baseline drug resistance, treatment outcomes and nature and frequency of ADRs. All DR-TB patients enrolled at the study site were eligible except pregnant women, children, and intellectually disabled patients. Patients were followed until the treatment outcome was declared. Among all the enrolled, 210 (77.5%) patients were aged less than 50 years, while 195 (72%) were married. Unemployment was found among 165 (60%) patients. Previously treatment failure patients were 198 (73%) in the study. Lower hemoglobin levels were observed among 189 (69%) patients. Isoniazid resistance was found to be in 134 (49.4%) patients as compared to globally reported 78% among DR-TB patients, followed by pyrazinamide 64 (23.6%), ethambutol 45 (16.6%) and streptomycin 22 (8.11%) respectively. Among second-line anti-tuberculosis drugs (SLDs), resistance was highest for ofloxacin 67 (24.72%), followed by kanamycin 8 (2.9%), amikacin 5 (1.8%), capreomycin 4 (1.4%)

and ethionamide 2 (0.7%). The majority, 204 (82.9%) patients, got their Sputum culture conversion at the end of the two-month treatment initiation. Successful treatment outcome (69 %) was below the WHO minimum criteria (> 75%). Unsuccessful outcomes included died (17.7%), loss to follow-up (12.5%), and treatment failure (0.73%). Previous use of SLDs was found to have a significant association (OR 3.071(1.112- 8.475, p-value 0.03) with fluoroquinolone resistance. Statistically significant association (OR 7.637(3.819 - 15.296, p-value < 0.001) was found between baseline lung cavitation while age >50 years (OR 3.877(1.68-8.8.95), (p-value 0.001), baseline weight < 40 kg (OR 3.183(1.364-7.428), (p-value 0.007) and baseline lung cavitation (OR 5.26 (2.103-13.156), (p-value < 0.001) were significant risk factors among died patients. Loss to follow-up patients had a significant association with baseline lung cavitation (OR 4.643 (1.462-14.747), (p-value 0.009). Out of 718 ADRs, gastrointestinal (GIT) disturbances (66.7%), nervous system disorders (59.4%), electrolyte disturbances (55.7%), and arthralgia were the highest reported ADRs, followed by ototoxicity (24%), pruritic reactions/rash (12.9%), Dyspnoea (12.5%) and tinnitus (8.8%). Treatment was modified among 23 % of the patients due to amikacin-induced hearing loss. Lung cavitation at the baseline (OR 3.419 (1.694 - 6.902), (p-value 0.001) was recognized as the risk factor for the ADRs occurrence. The local resistant pattern is an essential factor when designing individualized regimens. Previous irrational fluoroquinolone use among the public may risk therapeutic outcomes among DR-TB patients. Successful treatment outcomes rate can be enhanced by engaging loss to follow-up patients. ADRs were high but were managed efficiently. Risk factors identification helps healthcare professionals make early decisions and improve treatment outcomes.

CHAPTER 1

INTRODUCTION

1.1 Microbes and Drug Resistance

Earth harbours versatile forms of intricate life which all began billions of years ago in the form of simplest microorganisms. Similarly, humans, the most intelligent but recently evolved creatures as compared to microbes, they dock many folds of microbial genetic material in themselves than their own (Sender et al., 2016). Humans are extremely vulnerable to disease causing variants of microbes. Nonetheless, the pathogens only account for less than 1% of all the microorganisms (Asghar et al., 2021).

To cure infections, the importance of developing effective antimicrobial medications is irrefutable. The development of antibiotics can be undoubtedly regarded as one of the greatest biomedical discoveries that revolutionized the healthcare industry. In the hindsight, the availability of antibiotics has also changed the community practices, such as irrational and unnecessary prescription of these drugs, self-medication, and laxed behavior toward microbial containment. Which, in turn, has allowed the microorganism to adopt and have headed to the advent of evolved pathogens resistant to the antibiotics and resulted in a huge surge in the nosocomial infections and pandemics (Beloin & McDougald, 2021; Bowler et al., 2020; Horton & Nett, 2020; Lawal et al., 2021; Ma et al., 2020; Sharma et al., 2019).

Antibiotics kill the microbes or restrain them from growing by interrupting their key physiological functions. If antibiotics are given in subtherapeutic doses or there is a medication error, pathogens may make alteration in those drug attachment sites and become non-responsive to that or similar class of medications in the future

(Nadeem et al., 2020; Radecka et al., 2014). This phenomenon is known as drug resistance. A plenty of factors contribute to the growing threat of antibiotic resistance, including but not limited to uncontrolled and unethical use of antibiotics in farming and agriculture that contaminate the natural reservoirs, poor protocols for prescribing and medication errors in clinical settings, alarming self-medication behavior in communities, and the enormous ease in worldwide transportation (Alghadeer et al., 2018; Cabrera-Aguas et al., 2020; Covvey et al., 2015; Karakonstantis & Kalemaki, 2019; Kumar & Saleem, 2020; Levy & Marshall, 2004; Luu et al., 2021; Parish, 2019; Tebug et al., 2021; Ukuhor, 2021).

Resistant microbes related infections have led to a surge in deaths around the globe, almost 35000 deaths were accounted for 2.8 million drug resistant infections in 2019 in US only (Kadri, 2020), that amounts for huge economic burden to the healthcare setup (annual expenditure of 4.6 billion dollars) (Nelson et al., 2021). There have been humongous consumption of antibiotics during the current COVID 19 pandemic, which could result alarming increase in the antimicrobial resistance (Dunachie et al., 2020).

1.2 Tuberculosis

Mycobacterium tuberculosis (MTB), an airborne-infectious bacillus bacteria, is responsible for causing tuberculosis (TB). which has triggered deaths more than any other infectious disease throughout known human civilization (Daniel, 2006). Despite the effectiveness of the current strategies to treat TB, it is still an important health problem worldwide. Approximately 1.3 million people perished to the TB worldwide in 2020 as quoted in a latest global tuberculosis report by World Health organization (WHO), which makes it the leading cause for mortality among the infectious diseases

after Covid-19. More or less 9.9 million TB cases were reported internationally during 2020 with an average incident rate of 127 cases per 100, 000 individuals (WHO, 2021b).

From 1990 up to 2013, global mortality rate regarding TB has declined by 47% (WHO, 2013c). During the last few decades, effective interventions in the diagnosis and management of TB have demonstrated to save about nearly 43 million lives globally (WHO, 2015a), but these gains are being undermined by the spread of drug resistance. Emergence of resistance to anti-TB drugs has been studied and documented as early as 1940s (Wolinsky et al., 1948), but it was only during the 1990s, upon discovery of the resistant strains of MTB against two most potent anti-TB drugs, Isoniazid (H) and Rifampicin (R), which alarmed the scientific community about the birth of drug resistant tuberculosis (DR-TB) (Espinal, 2003; Frieden et al., 1995; Kim et al., 2003). Treating the Rifampicin resistant (RR) or multidrug resistant (MDR), which includes resistant to both H and R collectively termed as RR/MDR-TB, is a challenging task because this type of TB is impervious to isoniazid and rifampicin, leaving behind the only way out to be replaced by less potent, prolonged use, more expensive, and much more toxic therapeutic choices, the second-line anti-TB drugs (SLDs) (Caminero, 2006; WHO, 2014a). The use of SLDs is also linked to certain limitations such as collection and reporting of the treatment outcomes (Mitnick et al., 2007), owing to the insufficient evidenced based randomized control trials, lesser testing laboratories, and fewer skillful clinicians for its accurate diagnosis (Nathanson et al., 2010) and more toxic and less effectiveness of these agents (Bloss et al., 2010; Caminero, 2006). In 2020, the success rate of treatment against DR-TB (59%) was less than that of new and relapsed MTB patients (86%). Moreover, due to lapses in data collection approach, approximately 14% of DR-TB patients were said to be lost to

follow up, whereas almost 4% of the cohort was not evaluated in the 2018 (WHO, 2021b).

The wide range of adverse drug reactions (ADRs), encountered during the management therapy because of the use of multiple SLDs, is yet another challenge of DR-TB treatment alongside the poor outcomes (Avong et al., 2015; Bloss et al., 2010; Sagwa et al., 2012; Sturdy et al., 2011; Wu et al., 2016). These ADRs can be lethal like renal failure or disabling effects such as hearing or visual impairment or the gastrointestinal (GI) disruptions, compromising the standard of life of the patients (Avong et al., 2015), which lead to the discuntinouation of therapy (Al-Sadi et al., 2015; Bloss et al., 2010; Furin J et al., 2001; Törün et al., 2005). These undesirable effects are reason for decreased patient compliance, increased hospitalization, and higher morbidities and mortalities (Leimane et al., 2005; Nathanson et al., 2004a; Törün et al., 2005).

Pakistan is one of the high-burdened countries with respect to DR-TB disease numbers, as it stands fourth as per WHO (WHO, 2021b). Programmatic management of drug resistant TB (PMDT) plan for management of DR-TB in Pakistan was launched as a pilot project in the year 2010, which led to establishment of 34 PMDT functional sites (NTP, 2019) till 2019. Nonetheless, when considering execution of PMDT plan, management of TB and treatment outcomes of patients, there is scarcity of the information or the availability of the reliable data about DR-TB. The impact of DR-TB treatment remains an ignored topic even though SLDs in this treatment have serious negative effects on interpersonal, mental, and physical wellbeing of individuals.

1.3 Emergence of drug-resistant tuberculosis (DR-TB)

Reporting of resistance for anti-TB drugs was noticed soon after the breakthrough of first line anti-TB drugs (FLDs)(Crofton & Mitchison, 1948). Drug resistant phenomenon, encountered during the management of microbial infection, is found against nearly all chemotherapeutics drugs. Microbial drug resistance could be of two types; primary, where there is appearance of resistant strains in patients who don't have previous drug history (Telenti & Iseman, 2000). The non-chromosomal heritable genetics called "episomes" are believed to be involved in this type of resistance. On the other hand, when resistance is developed through antimicrobial treatment, it is called secondary drug resistance, which is also called acquired medication resistance (Telenti & Iseman, 2000). While in case of secondary or acquired drug resistance, bacterial strains develop resistance during the course of therapy against those medications whom microbial strains showed sensitivity at the beginning of treatment (Telenti & Iseman, 2000).

1.4 Drug resistance mechanism in MTB

A general phenomenon of chromosomal mutation in a bacterial strain has been found to occur approximately every million reproduction cycles, which might need thousands of years to develop resistance against a medicine. However, in reality, the process of horizontal gene transfer among different bacterial strains exponentially increases the probability of development of drug resistance(Telenti & Iseman, 2000).

In case of resistance development in MTB, if only chromosomal mutations occur, it would take more than 5000 years to yield only 1 % bacterial population resistant against INH (David & Newman, 1971), Hence, it makes it nearly impossible for the MTB to acquire resistance against the use of at least 3 effective anti-TB drugs.

Nevertheless , conditions such as suboptimal treatment regimen, drugs not taken timely, use of single medicine, low drug distribution in the infected organ due to empyema and cavitation lead to selective adoption of drug evasion in bacteria (Zhang & Yew, 2009). At the beginning, such a selective pressure would allow survival of the mutant bacterial species only, whereas all other drug-sensitive bacterial are killed, leading to the emergence of mono-therapy resistant TB (Mitchison, 1954). These genetically favorable microbes, when encounter a drug from another class of antibacterial, they have the greater tendency to avoid death by enforcing further mutations, thus creating multi-resistant strains such as DR-TB strains (Zhang & Yew, 2009).

The management of TB, during earlier and present days, has high impact on drug resistance in DR-TB patients (Caminero, 2010). This level of resistance can be prevented by rational use of drug susceptible TB. In case of countries, with higher rates of drug resistance, TB occurrence and prevalence are the outcome of poor TB management (WHO, 2009). There are many factors which lead to DR-TB, to name, previously ineffective TB treatment (Caminero, 2010), poor implementation of directly observed treatment short-course (DOTS) (Aguilar et al., 2005),), low quality anti-TB products (Lambregts-van Weezenbeek & Veen, 1995), poorly managed supply chain for anti-TB drugs (Lambregts-van Weezenbeek & Veen, 1995) compromised adherence to the treatment guideline (Achanta et al., 2013), non-adherence by patients (Ejaz et al., 2010), co-morbidity with HIV (Faustini et al., 2006), diabetes mellitus (Gomes et al., 2014), age of patients (Atre et al., 2011), gender of the patients (Ejaz et al., 2010), close contacts with DR-TB (Martínez et al., 2010), and living in congested settings placements such as camps, hospitals and prisons (Habeenzu et al., 2007).

1.5 Drug Resistant Tuberculosis Epidemiology and Management

1.5.1 Epidemiology (Global)

As indicated by the 2021 Global tuberculosis report of WHO, nearly 9.9 million people got ill from TB with eight countries counting for two third overall burden of TB disease. Among ill TB patients 1.3 million died. It was estimated that half of the population who fell ill were men > 15 years of age. Approximately 3 million people were provided with TB treatment in 2020 which was a 21% reduction as compared to 2019 when 3.6 million ill population were treated for disease (WHO, 2021b). Around 1 in 3 those in need, were treated for DR-TB, which also fell 15% from the previous year. Globally, in 2019, an estimated 3.3% (95% confidence interval (CI): 2.3 – 4.3%) of new cases and 18% (95% CI: 9.7 – 27%) of previously treated cases had DR-TB. Among all the RR-TB cases nearly 78% were MDR-TB cases. The incidence of cases with H resistance but not with R needs modified regimen. It was estimated that during the 2019 incidence of DR cases counted for nearly 465,000 (range 400,000-535,000). The incidence of mortality due to DR-TB was 182,000 (range 113,000-250,000)(WHO, 2020). The COVID-19 had a reverse association towards TB and has caused a sufficient damage to the global efforts to eradicate TB and it's all forms. The global health community has lost progress, they had achieved during last few years in combat against TB and first time since 2005, it was witnessed a year-on-year increase in deaths due to TB in 2020. Top 20 countries in terms of DR-TB contributes to 86 % of the global DR-TB burden with India leading in this category with the maximum absolute numbers (WHO, 2020).

1.5.2 Epidemiology in Pakistan

TB, a highly prevalent infectious disease in Pakistan, accounts for one of the major health burdens of the country that has been overlooked in the past. As early as in 1962, Pakistan collaborated with WHO and United Nations International Children Emergency Fund (UNICEF) for the management of TB. This collaboration targeted establishing of the TB treatment centers in district headquarter hospitals (De Muynck et al., 2001; Javaid, 2011). The program came to a halt in 1985 due to lack of funding from UNICEF. Nonetheless, WHO declared TB as worldwide emergency, which led Pakistan to initiate the (DOTS) policy to attain better treatment outcomes. Five sites were allocated, merely one was functional. Despite the revised national guidelines and TB control policy in Pakistan to manage TB, Pakistan was announced as a nonfunctional country in TB management in1998 (De Muynck et al., 2001). Back in 2000, the estimated case notification rate for new and relapsed smear-positive cases (a vital gauge for a successful TB control program) was merely 2. 8%, which was far beneath the 70% target set by WHO (WHO, 2009). Before the launch of countrywide TB Control Program in 2001, there did not exist any coherent strategy to counter the TB malice.

In 2001, with the revival of national TB program (NTP) and implementation of DOTS, Pakistan witnessed enormous progress in DOTS coverage, case notifications, and treatment outcomes. A period of 4 years was spent to broaden the DOTS coverage to all healthcare units in the country (Javaid, 2011; Vermund et al., 2009). More than a decade ago, only 8% population of Pakistan had DOTS policy which was uplifted to 100% in 2005 (WHO, 2009). A massive surge (62%) in case detection rate of new and relapsed cases had been noticed in 2014, much greater than the meager 3.9% in 1995 (WHO, 2015b). On top of that, TB treatment success has

been increased from 70% in 800 treated patients in 1995 to 93% in 326455 treated cases in 2020 across the nation(NTP, 2020b; WHO, 2020).

Currently, Pakistan ranks 5th among 30 high burden countries, even though outstanding advancement has been done regarding DOTS coverage, TB case notification, and TB success rate. Pakistan contributes to whooping 61% TB burden throughout Eastern Mediterranean Region of WHO (EMRO) with estimated likelihood of 573000 (95% CI: 409 000-764000) incidence. People who have age class >15 years were typically the most affected age group with incidence 531000 cases (95% CI: 354000-707000) in Pakistan, like the different developing countries. Currently TB incidence in Pakistan is estimated to be 611000 cases (95% CI: 445000-803000). In 2020, 44000 deaths were documented due to TB (WHO, 2021b). During the last two decades, a sharp increase in the prevalence of DR-TB in Pakistan (Naz et al., 2021) has been observed. It was estimated that proportion of TB cases with new cases of DR-TB were 2.5% (2.4 - 2.7) while proportion of previously treated cases of TB had DR-TB 4.9 % (4.5 - 5.4) and unfortunately, estimated incidence of DR-TB cases in Pakistan was 28000 according to WHO (WHO, 2020). The prevalence rate of drug-resistant TB is alarming, because NTP did not consider the management of the drug-resistant cases in the early 2000s and restricted its resources to the management of MTB cases only. Moreover, due to absence of aggressive case identification designs for DR-TB patients, most of the DR-TB cases referred were of treatment failure or complicated nature.

Marked improvement in reporting of DR-TB cases have been noted due to adoption of PMDT and increased productivity of NTP. The target was to establish 45 PMDT unit sites throughout the country till 2019, but the efforts lagged and only 73%

target was achieved (NTP, 2019). Nevertheless, this step itself had a huge impact on the detection and enrollment of DR-TB patients. Unlike in 2010, where only 444 cases were notified, during 2020, a total of 2689 DR-TB were notified (WHO, 2011a, 2021b). It is estimated that Pakistan contributes nearly 25000 DR-TB patients to global burden of the disease (WHO, 2020). During 2000-2018, data shows that after the implementation of PMDT model approach, there had been a marked decrease in mortality rate per 100,000 population per year. The estimated cumulative incidence of DR-TB in both new and previously treated TB patients remained around 20 % in 2016 (WHO, 2016). Although, the number with bacteriologically confirmed cases has been grown during the span of last two decades along with increase in detection and treatment enrollment, the actual number of DR-TB patients always remained lower than the total detected cases, leaving an open window of possible infectious hubs in the community which pose serious threat to the efforts being carried out to end all forms of TB (WHO, 2020). This poses a huge financial burden to the country as well as the global economy. Such cases increase the chances of prevalence of DR-TB, and a noteworthy proportion of patients remain undocumented in DOTS program. Notified forms of all TB cases (both MTB and DR) along with certain important indicators have been mentioned in the table 1.1(WHO, 2022).

Table 1.1 Documented TB profile of Pakistan (2008-2020)

Year	Notified TB cases	New TB cases with DST results (%)	Previously Treated TB cases with DST results (%)	RR tested cases (% of TB cases)	RR Tested cases (% of previously treated TB cases)	Notified DR/RR-TB cases	Patients started on DR-TB treatment	DR/RR-TB cases in treatment outcome cohort
2010	269 290	-	3	4	7	444	424	195
2011	270 394	-	-	5	7	432	344	427
2012	273 097	0	1	6	10	2 501	1 045	858
2013	298 446	5	22	9	18	2 596	1 495	1 484
2014	316 577	0	72	12	58	3 243	2 662	2 565
2015	331 809	3	84	25	53	3 059	2 553	2 544
2016	366 061	9	50	34	60	3 331	2 813	2 804
2017	368 897	29	47	50	72	3 475	3 016	2 813
2018	369 548	45	79	47	72	3 824	3 102	3 076
2019	334 754	59	89	59	80	3 820	3 004	-
2020	276 736	71	76	69	87	2 689	2 372	-

TB, Tuberculosis; RR-TB, Rifampicin resistant Tuberculosis; DR-TB, drug resistant Tuberculosis; DST, Drug susceptibility testing (WHO, 2022)

Treatment outcomes both successful and unsuccessful (failed, died and loss to follow up) among the drug resistant tuberculosis patients in Pakistan during the last decade (WHO, 2022) have been presented as a function of percentage in table 1.2.

Table 1.2 Treatment outcomes of Drug-Resistant TB Patients in Pakistan

Year	Successful (%)	Failed (%)	Died (%)	Lost to follow up (%)	Not evaluated (%)
2009	60	8.1	21.62	6.76	2.7
2010	70	2.05	14.6	9.23	4.1
2011	70	1.69	11.48	5.62	10.77
2012	71	2.68	15.15	4.46	6.41
2013	69	3.71	16.98	5.59	4.65
2014	65	3.31	17.7	9.86	3.7
2015	64	5.27	17.57	10.69	2.4
2016	63	4.39	17.51	9.59	4.96
2017	63	4.23	18.13	10.52	3.52
2018	70	4.29	14.17	9.53	1.63

TB, Tuberculosis

1.5.3 DR-TB management in Pakistan

The guidelines for the PMDT program launched in 2010 and were updated in 2012 and 2019. These guidelines are used countrywide for the management of DR-TB (NTP, 2014b; NTP, 2020a). Treatment plans with various combinations of drugs has been presented in table 1.3.

Table 1.3 Treatment Plans for DR-TB treatment as recommended by National Tuberculosis Program, Pakistan guidelines.

Treatment Plan	Duration	Drugs combination
Conventional/ LTR(NTP, 2014a)	8-Month (Intensive Phase)	Am/Km/Cm + FQs (Ofx/Lfx/Mfx) + Eto + Cs + Z
	12- Month (Extensive Phase),	Lfx + Eto + Cs +Z
	While patient with SLDs use history will have PSA addition	Lfx + Eto + Cs +Z + PSA
STR(NTP, 2017b)	9-11 Month (Total)	
	4-6 Month (Initial)	Km + Mfx + Pto + Cfz + Z + E + H (High dose)
	5 Months (Trailed by)	Mfx + Cfz + E + Z
All Oral Bdq regimen(NTP, 2019)	4 – 6 Month (Initial)	Bdq + E + Z + Cfz + Mfx/Lfx + H (High dose)
	5 – Month (Trailed by)	Mfx/Lfx + E + Z + Cfz
LTR regimens along with Bdq		
Bedaquine, Linezolid and Thioamide derivatives containing regimen		

DR-TB, drug resistant Tuberculosis; LTR, longer treatment regimen; STR, shorter treatment regimen; Am, Amikacin; Km, Kanamycin; Cm, Capreomycin; FQs, fluoroquinolones; Ofx, Ofloxacin; Lfx, Levofloxacin; Mfx, Moxifloxacin; Eto, ethionamide; Cs, Cycloserine; Z, Pyrazinamide; SLDs, Second line drugs; PSA, Para-amino salicylic acid; Pto, Prothionamide; Cfz, Clofazimine, E, Ethambutol; H, Isoniazid; Bdq, Bedaquine (Falzon et al., 2011; NTP, 2017b)

Unfortunately, Pakistan stands 4th in terms of global DR-TB burden. It implemented the PMDT protocol for DR-TB in 2010.Currently there are 33 operational PMDT sites throughout the country. WHO and its partner agencies devised the DOTS-Plus protocols in 1998 to obtain optimum therapy outcomes against DR-TB (Bastian et al., 2000).

Fundamental principles of this protocols are:

i) Continued political dedication.

ii) Unambiguous and early diagnosis of the disease through quality guaranteed culture and DST

iii) Seamless provision and proper utilization of quality medicine (FLDs and SLDs)

iv) DOTS

v) Standardized documentation procedure

Later on, Green Light Committee (GLC) was founded by the collaboration of WHO with worldwide partners to supervise the proper execution of the DOTS-Plus protocols and to formulate "Models of Good Practices" for DR-TB treatment (Gupta et al., 2002). This committee offers specialized support for applying the DOTS-Plus protocol and ensures satisfaction of all standards before the commencement of the program in any region. Furthermore, by working together with pharmaceutical organizations, GLC ensures a reliable supply of superior quality SLDs at minimal pricing (Cobelens et al., 2008). On the basis of encouraging results (59%-83%) in DR-TB patients at 5 low-resource settings through implementation of DOTS-Plus protocols (Nathanson et al., 2006). WHO came up with idea of establishing PMDT approach (WHO, 2008a). Since then, the PMDT guidelines have been continuously updated (WHO, 2011a, 2014b). DOTS-Plus strategy (Bastian et al., 2000) is a feasible

and cost efficient approach that markedly influences the DR-TB patient mortality, especially in high-burden areas with limited resources (Sterling et al., 2003). Table 1.4 provides information about anti-TB drugs utilized for the treatment of drug resistant TB within Pakistan during the study period with recommended doses.

Table 1.4 Management of DR-TB as recommended by National Tuberculosis Program, Pakistan guidelines.

Group	Drugs	Recommended dose per day (mg/kg of body weight)	Recommended maximum dose per day(mg)	Common adverse effects
Group 1 FLDs	E	25	1600 to 2000	Visual impairment
	PZA	30 to 40	2000 to 2500	Gastrointestinal problems, photosensitivity, jaundice, liver damage, arthralgia
Group 2 Injectable anti-TB drugs	Km	15 to 20	1000	Ototoxicity and nephrotoxicity
	Am	15 to 20	1000	
	Cm	15 to 20	1000	
Group 3 Fluoroquinolones	Lfx	7.5 to 10	750 to1000	GIT problems, sleeplessness, headache, allergies, depression, tremors
	Mfx	7.5 to 10	400	
Group 4 Oral bacteriostatic SLDs	Eto	15 to 20	750 to 1000	GIT problems, metallic taste, Increase saliva, liver damage and peripheral neuropathy
	Pto	15 to 20	750 to 1000	
	Cs	15 to 20	750 to 1000	Dizziness, headache, depression, loss of memory and psychosis
	PAS	150	8000 to 12000	GIT problems, pyrexia, cutaneous Reactions
Group 5 Anti-TB drugs with limited data available on efficacy	Amx/ Clv	No established dosage regimen for RR/DR-TB. Generally recommended daily dose for adults 875/125 mg BID or 500/125 mg TID.		GIT problems, cutaneous reactions, and Headache
	(Clr)	Recommended daily dose for adults is 50 mg BID.		-

E, Ethambutol; PZA, Pyrazinamide; Km, Kanamycin; Am, Amikacin; Cm, Capreomycin; Lfx, Levofloxacin; Mfx; Moxifloxacin; Eto, Ethionamide; Pto, Prothionamide; Cs, Cycloserine; PAS, Para-aminosalicylic acid; Amx, Amoxicillin; Clv, Clavulanate; Clr, Clarithromycin; BID, twice daily; TID, thrice daily(NTP, 2014a)

1.6 Statement of Problem

Pakistan stands 4th in DR-TB global burden and harbors the highest number of DR-TB patients within EMRO region. PMDT protocols has been implemented in Pakistan since 2010, however, management of DR-TB patients and the associated outcomes have not been well documented as large amount of clinical data particularly about the delayed DST results, patient's sociodemographic variables, drug regimen modification, frequency, and nature of ADRs and their management is not updated in NTP repository, so it remains unreported. Before the implementation of PMDT protocols, the management of DR-TB patients were carried out with varied therapy regimens, and the associated findings were monitored using random criteria.

Due to non-availability of sputum culture facilities during the pre-PMDT implementation period, sputum smear microscopy at random time points during therapy was considered sole criteria for the conclusion of treatment outcomes. Sputum smear microscopy is a relatively less accurate tool as compared to sputum culture for measurement of treatment outcome (WHO, 2011a, 2014b, 2018, 2021b). Moreover, the diagnostic identification of disease and the co-morbidities, and reporting and management of therapy associated untoward reactions were not appropriately handled. Therefore, the degree of bias in these findings could erroneously impact the clinical practices in Pakistan. In the initial years, after the implementation of PMDT protocols, substantial improvement was noticed in the management of the TB.

However, in the last few years, there has been lack of effort or resource allocation to enhance the treatment outcomes as witnessed in the initial years after the implementation of PMDT protocols. The studies conducted after 2010 were mostly retrospective and cross-sectional which lacked the inherent shortcomings of the study

designs, such as lesser control over required data, bias in data collection, data not representative of general population, and absence of link between the therapy management and outcome. Some studies, due to lesser control over data, lacked key laboratory data, chest imaging for cavitary disease, absence of documentation of imaging studies, limited resistance pattern profile and missing of treatment adherence status which were needed to analyze the unsuccessful treatment outcome (Baluku et al., 2021; Bogale et al., 2021; Tola et al., 2021). One of the retrospective study used a modified treatment regimen that cannot be generalized for local study population and treatment outcome cannot be compared to the other study cohort with different epidemiological variables (Koirala et al., 2021). Drug susceptibility testing data against limited number of drugs also cause study bias and hinders the result generalization (Baluku et al., 2021).

Studies that mentioned interruption, did not mentioned the reason for interruption and reason for regimen modification (Dhakulkar et al., 2021). Missing of adverse drug reaction documentation, absence of important parameter such as BMI, co-morbidities, HIV infection status, lack of monthly sputum sampling from patients, deficient demographic data, lack of DST results, and without smoking and alcohol consumption information were the limitations among already conducted studies (Li et al., 2020; Van et al., 2020). Some of the studies were of extremely smaller sample size while other lacked data on ADR monitoring, time dependent adherence to therapy, absence of treatment outcome, disease state, missing laboratory reports, and absence of DST results (Aibana et al., 2017; Akshata & Chakrabarthy, 2016; Parmar et al., 2018; Singh et al., 2019).

Retrospective studies only include the routine monitoring variables which may lack the duration of illness prior the initiation of therapy (Van der Walt et al., 2016) . Even if the prospective studies were conducted, there was a lack of focus on the predictors and risk factors of the adverse events associated with therapy and the management of these adverse events in DR-TB patients. To identify the impact of local clinical practices and improve the management of DR-TB in Pakistan, there is a definite need to conduct prospective studies to evaluate the treatment outcome, ADRs management, and predictors and risk factors for therapy failure and ADRs.

1.7 Study Rationale

Evaluation of management and therapeutic outcomes of a study cohort is an efficacious way to scrutinize the program efficacy (Leimane et al., 2005). In the absence of prospective studies, retrospective do provide initial point for understanding but lesser control on data and absence of key demographic and clinical parameter, bias in exclusion and inclusion criteria with respect to disease and age and absence of TB drugs information to the patients in these studies raise concerns on the validity of these studies. Therefore, the current study, due to its prospective nature, will assess the program efficacy by evaluating the treatment management and outcomes. Thus, enabling the program coordinators to better identify complications and risks that will lead to improvement of overall program.

With rapidly growing population, financial constraints, poor hygiene, and dietary practices, severely hit by environmental pollution and despite all the governmental efforts to contain TB disease, active TB cases are on the rise. Currently it is estimated that Pakistan harbors around 25000 DR-TB cases(WHO, 2020). It was observed that around 51% of all the DR-TB cases were reported from Punjab, which

is the most populated province of country.(Sheikh et al., 2018). So, a study was conducted in the southern part of Punjab province which roughly contributes to the 40% of province population at a tertiary care, Nishtar Medical University, Hospital, Multan.

In current study, evaluation of baseline drug resistance pattern will lead to better understanding of local epidemiological characteristics and will help the policy makers and clinicians to design highly individualized regimens based on local needs and allocation of specified resources for a particular area. As it is highly important for optimization of empirical therapy. This will help to assess the suitability of standard guidelines for treatment initiation.

Fluoroquinolones have remained the backbone of DR-TB treatment until now. Unfortunately, irrational fluoroquinolones use is highly prevalent in society for general respiratory tract ailments by prescriber either as unnecessary prescribing or failure to compliance with guidelines(Chang et al., 2019; Sergiu & Adalgiza, 2018; Werner et al., 2011). Furthermore, fluoroquinolones are among the most common self-medication along with macrolides and cephalosporins(Nepal & Bhatta, 2018). Assessment of risk factors for fluoroquinolones resistance will facilitate clinicians to identify the risk groups and selection of more appropriate drug.

Assessment of treatment outcome and risk factors for unsuccessful outcomes will guide physician about the identification of probable risk groups during the early course of treatment and enable them to take necessary measure by providing enhanced and efficacious clinical management and care to avoid unsuccessful outcomes.

Loss to follow up patients largely contribute to unsuccessful outcome of a cohort. ADRs have been reported among important factors associated to loss to follow

up among DR-TB patients due to lengthy nature of treatment and occurrence of more frequent ADRs as compared drug susceptible TB. Assessment of nature and frequency of ADRs and their management and risk factors for occurrence of ADRs will facilitate clinician for early detection of risk groups and to design strategies for better ADRs management. The study site serves as a treatment hub to a densely populated geographic location, In the absence any prospective studies, there is lack of scientific data regarding local drug resistance trends, risk factors for fluoroquinolones resistance, risk factors for unsuccessful treatment outcomes, frequency and nature of ADRs, their management and associated risk factors. The determinations of objectives will facilitate the clinician to develop more updated and robust regimens for enhanced patient comfort and improved treatment outcomes.

1.8 Objectives

Our study was mainly focused to determine the baseline sociodemographic and clinical characteristics which largely impact the treatment outcomes and determination of various associated risk factors for early identification of risk groups among DR-TB outpatients. The specific study objectives include,

i. To identify the pattern of drug resistance among enrolled DR-TB patients and determination of associated risk factors for fluoroquinolones resistance
ii. To determine the sputum culture conversion rate at end of two-month treatment initiation and its associated predictors among DR-TB patients.
iii. To evaluate the treatment outcomes and risk factors linked to the treatment outcomes (unsuccessful).
iv. To assess the nature and frequency of treatment induced ADRs, laboratory confirmed, physician evaluated, or patient reported and their management.

v. To determine risk factors associated with the occurrence of DR-TB treatment induced ADRs among DR-TB patients.

CHAPTER 2

LITERATURE REVIEW

2.1 Drug resistance patterns and treatment outcomes among DR-TB patients

Globally, in 2019, nearly 0.2 million fatalities were reported due to DR-TB among a total of 1.4 million deaths due to TB patients (WHO, 2020). FLDs have the greatest efficacy, better tolerability, and comparatively lower incidence of adverse drug reactions (Bisson et al., 2020). However, the desired treatment benefits of DR-TB remedy are rarely obtained, owing to the fact that the drugs used as SLDs, because of the bacterial resistance shown against the FLDs, are less effective but comparatively more toxic due to their use for extended period of time (Caminero, 2006). This fact may be illustrated through the recent treatment success rate of medicine susceptible TB, which was 86% compared to the 50% treatment success of RR/DR-TB. The target success rate for the treatment of DR-TB patients for 2012 was set to be 70% by WHO, however, only 43 countries out of 127 nations were able to attain it (WHO, 2015).

Baez-Saldana et al (2016), between 1995 to 2010 with a total of 1243 Pulmonary TB patients (PTB) in Mexico which included both drug susceptible and isoniazid mono resistant TB patients. Standard treatment guidelines were followed, studied the impact of Isoniazid resistance on therapy outcome, and concluded that standardized treatment recommended by WHO with FLDs had a greater failure probability (adjusted hazard ratio (HR) 12.35, 95% CI 3.38–45.15) among isoniazid mono resistant TB patients when compared against drug susceptible TB patients. They suggested for the re-evaluation of optimal schedule for patients having isoniazid mono resistant -TB (Báez-Saldaña et al., 2016).

It was concluded that out of 6006 sputum samples of suspected TB patients in a cross sectional study conducted in Punjab, Pakistan, 2367 were culture positive MTB

cases, nearly 11.5% patients were at least resistant to one anti-TB while 9.3% showed MDR-TB with risk factors of early age and previously treated TB patients in Pakistan (Ullah et al., 2016).

FLDs anti-TB drug resistance study from Iran found the prevalence of H, R, S and E resistance 26% ,23%,22.5% and 16% respectively (Pourakbari et al., 2016). In another cross-sectional study of 240 patients conducted at PMDT site of high burden from Pakistan observed a high degree of resistance to all FLDs anti-TB (62%) and more than half were resistant to SLDs (55.1%) with a majority resistant to ofloxacin (52.7%). They recommended for more strict policies and protocol to counter the irrational use of fluoroquinolones among public (Ahmad et al., 2016)

In a letter to editor (2015), researchers high-lighted the high prevalence and consistent increase in fluoroquinolones resistance (17.4 % in 2005, 42.9 % in 2009 and 53.9 % in 2014) in Pakistan along questions being raised regarding the country's recommended standardized guidelines for the use of anti-TB drugs in Drug-resistant TB patients. It was also recommended that, in case of confirmed fluoroquinolones resistance in a nation-wide survey, WHO recommended guidelines should be opted for best possible treatment outcomes (Ahmad et al., 2015)

Ahmad N et al (2015) in an observational cohort study prospectively followed 196 MDR-TB patients and found high resistance to both Ofx and Z 54%. 74.6% patients were cured, 0.6% completed the treatment, 19.3 % died, 8% failed treatment with 1.1 % of default treatment. Patients having age more than 40 years (OR 3.412, p-value = 0.009), baseline body weight less than 40 Kg (OR 2.966, p-value = 0.02), presence of co-morbidities (OR 3.785, p-value = 0.023), resistance to ofloxacin (OR 2.777, P = 0.023), lung cavitation (OR 5.253, P < 0.001) and treatment modification due to occurrence of ADRs (OR 3.492, P = 0.037) had higher risk of unsuccessful