

# Drug resistance pattern, prevalence and risk factors for resistance to second line anti-tuberculosis drugs in Balochistan, Pakistan

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## Drug resistance pattern, prevalence and risk factors for resistance to second line anti-tuberculosis drugs in Balochistan, Pakistan

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## ABSTRACT

**Background.** Pakistan is high burden drug resistant tuberculosis (DR-TB) country. For devising a treatment regimen and optimizing empirical drug therapy, the local epidemiology and drug resistance patterns are needed to be considered.

**Objectives.** To evaluate the drug resistance pattern, prevalence and risk factors for resistance to second line anti-tuberculosis drugs (SLD) among DR-TB patients in Balochistan, Pakistan.

**Design and Setting.** This cross-sectional study was carried out at the Fatimah Jinnah Chest and General Hospital in Quetta's programmatic management unit of the DR-TB (PMDT).

**Methods.** This study included all DR-TB patients, regardless of their age, TB location, or medication resistance pattern. The sociodemographic, microbiological, and clinical data of the patients were gathered using a standard data collecting form. SPSS 20 was used to analyze the data. A statistically significant p-value was defined as less than 0.05.

**Results.** A total of 354 patients were included in the final analysis. Among them majority were females (61.7%), belonged to the age group 19-30 years(36.7%), were previously treated for TB (95.8%) at public sector hospital(42.7%) and did not suffer from any other comorbidity(88.7%). The study participants were resistant to a median of three anti-TB drugs (range 1-8). The most common type of DR-TB was multi DR-TB (77.1%), followed by mono DR-TB (18.1%), extensive DR-TB(3.1%) and poly-DR (1.7%). A total of 147 (41.5%) patients were resistant to any second line anti-TB drug (SLD). Among SLD, the resistance was high for fluoroquinolones (38.4%), followed by ethionamide (4.8%) and injectable SLD(4.2%). Upon multivariate binary logistic regression analysis previous treatment of cat-II regimen had statistical significant association with resistance to any SLD (OR=5.273, 95%CI=1.098-25.316).

**Conclusion.** It is concerning to see such a high level of SLD resistance, especially to fluoroquinolones. More stringent regulations are advised to regulate the non-prescription sale and indiscriminate use of fluoroquinolones, as well as testing for drug resistance in cat-I failures instead of placing patients on cat-II therapy.

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## Introduction

Drug resistant tuberculosis (DR-TB) is a major threat to the successful control of TB globally (Ahmad, Javaid et al. 2015). Anti-TB drugs resistance is not a recent event It developed soon after the invention of anti-TB drugs (Crofton and Mitchison 1948, Zhang and Yew 2009). Drug-resistant cases were classified as extensive drug resistance (XDR), multidrug resistance (MDR), resistance to rifampicin and isoniazid together, resistance to any fluoroquinolone, and resistance to one of the second line injectables in order to monitor drug sensitivity testing (DST) in clinical isolates of *M. tuberculosis* (Organization 2014) and rifampicin resistance (RR): the identification of rifampicin resistance, either phenotypically or genotypically, without the emergence of resistance to any further anti-tuberculosis medications. include MDR or XDR, poly-drug resistance, and mono-drug resistance (Falzon, Schünemann et al. 2017).

In recent years, there has been a fast spread of multidrug resistant tuberculosis (MDR-TB), which is defined as resistance to at least rifampicin and isoniazid together. According to estimates from throughout the world, the incidence of MDR-TB in 2012 was 3.6% and the caseload was 20%, with clear regional variations in prevalence (Organization 2013). "Resistance that develops in a person with no history of anti-tuberculosis treatment in the past" is the term used to describe primary drug resistance (Javaid, Hasan et al. 2008).

Unfortunately, Pakistan has a high rate of drug-resistant tuberculosis (DR-TB) and ranks fifth in the world for the prevalence of multi-drug resistant tuberculosis (MDR-TB). 61% of the TB cases in the WHO's Eastern Mediterranean Region are in Pakistan (Atif, Anwar et al. 2018). In 2016, 356,390 new and relapsed cases of TB were notified in the country, presenting an increase in the number of notified cases as compared with 2015 (323,856 cases) (Global 2016, Organization 2017). Programmatic management of DR-TB (PMDT) in Pakistan was initiated in 2010. At present, there are 31 centers all around the country where DR-TB patients are treated. Out of these 31 PMDT units, one is located in the Balochistan province of Pakistan (Ahmad, Javaid et al. 2016). Being the single PMDT unit of the province, DR-TB patients from all across the province and nearby Afghanistan are referred to the center. For devising a treatment regimen and optimizing empirical drug therapy for DR-TB patients, the consideration of local epidemiology and drug resistance patterns are of utmost importance. Unfortunately, no published information is available regarding the drug resistance pattern of DR-TB patients referred to the

sole PMDT Unit of the province. Over successful treatment of MDR-TB Studies conducted in the last several years have revealed that MDR-TB relapse following effective therapy is a frequent occurrence. Following that, the recurrence rates range from 3.2% to 4.4% (Ennassiri, Jaouhari et al. 2017, Batool, Khan et al. 2019).

## Methods

This study, which was done at the PMDT unit of the Fatimah Jinnah Chest and General Hospital in Quetta, Pakistan, was retrospective and cross-sectional in nature. The study comprised all DR-TB patients who were enrolled in therapy at the study site. The study included all DR-TB patients, regardless of their age, TB location, or medication resistance pattern. The sociodemographic, microbiological, and clinical data of the patients were gathered using a standard data collecting form. We analyzed the data using SPSS 20. For continuous values, mean and standard deviations were computed, while frequencies and percentages were displayed for categorical variables. Categorical factors were observed to be associated using univariate analysis. Factors linked to SLD resistance were identified through the use of multivariate binary logistic regression analysis. P-values less than 0.05 were regarded as statistically significant.

## Results

A total of 354 patients were included in the final analysis. Among them majority were females (61.7%), belonged to the age group 19-30 years (36.7%), were previously treated for TB (95.8%) at public sector hospital (42.7%) and did not suffer from any other comorbidity (88.7%). The study participants were resistant to a median of three anti-TB drugs (range 1-8). The most common type of DR-TB was multi DR-TB (77.1%), followed by mono DR-TB (18.1%), extensive DR-TB (3.1%) and poly-DR (1.7%). A total of 147 (41.5%) patients were resistant to any second line anti-TB drug (SLD). Among SLD the resistant was high against fluoroquinolones (FQ) (38.4%), followed by ethionamide (4.8%) and injectable SLD (4.2%). Upon multivariate binary logistic regression analysis previous treatment of cat-II regimen had statistical significant association with resistance to any SLD (OR=5.273, 95%CI=1.098-25.316).

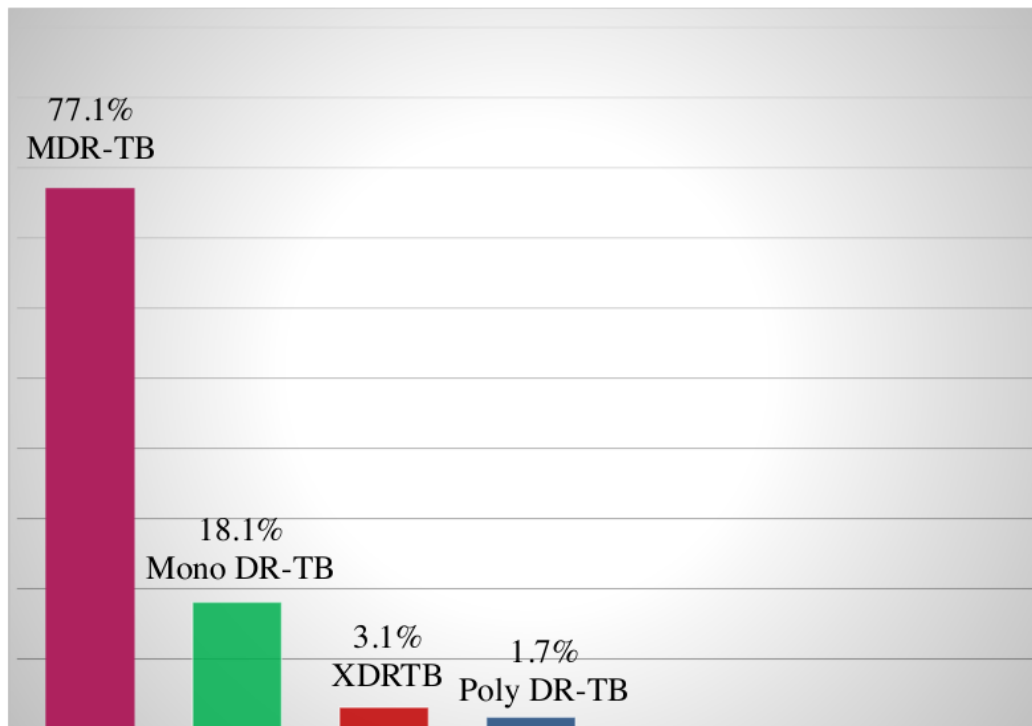
**Table 1 Sociodemographic features of respondents**

Variables	Mean $\pm$ SD	No. (%)
<b>Gender</b>		
Female		217(61.3)
Male		137(38.7)
<b>Age (years)</b>	38.20 $\pm$ 17.11	
<18		27(7.6)
19-30		130(36.7)
31-45		84(23.7)
46-60		69(19.5)
>60		44(12.4)
<b>Residence</b>		
Rural		279(78.8)
Urban		75(21.2)
<b>Weight(kg)</b>	2.36 $\pm$ 1.204	
1-20		6(1.7)
21-40		121(34.2)
41-60		192(54.2)

>60		35(9.9)
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**Table 2 Multivariate analysis of factors associated with SLD resistance**

24 Variable	B	OR (95%CI)	P-value
<b>Age (years)</b>	0.020	Referent	0.967
≤18	0.679	1.020 (0.403-2.579)	0.164
19-30	0.262	1.972 (0.757-5.134)	0.602
31-45	-0.082	1.299 (0.486-3.474)	0.881
46-60		0.921 (0.315-2.697)	
>60			
<b>Previous TB treatment</b>	1.146	Referent	0.144
No	<b>1.663</b>	3.146 (0.676-14.636)	<b>0.038</b>
cat I	0.700	<b>5.273 (1.098-25.316)</b>	0.431
cat II		2.015 (0.352-11.525)	
others			
<b>Residence</b>	-0.313	Referent	0.278
Rural		0.731 (0.416-1.286)	
Urban			

**Fig. 1 Drug resistance pattern of the study participants**

## Discussion

This analysis aims to determine Drug resistance pattern, prevalence and risk factors for resistance to second line anti-tuberculosis drugs in a high TB Burden Country. The high proportion of female patients in the current study is against the global epidemiology of male predominance in TB patients, but is line with the previous reports from Pakistan (Ahmad, Javaid et al. 2015, Ahmad, Javaid et al. 2016, Javaid, Hasan et al. 2017). This high proportion of females patients can be due to the fact that females take care of the infected patients exposing them to infections more than male individuals (Lomtadze, Aspindzelashvili et al. 2009, Codlin,



Khowaja et al. 2011). Another possible reason can be the male dominant society where females are deprived of healthcare facilities where they receive health care very late in case of chronic diseases. The predominance of MDR-TB in the current cohort augments the previous finding that in >90% cases rifampicin resistance is accompanied by resistance to isoniazid comparable with studies reported from Gujrat India (Trivedi and Desai 1988) and Pakistan (Javaid, Hasan et al. 2017). The high resistance against SLD, particularly against FQ, which make the backbone of MDR-TB treatment, is a threatening issue and in line with previously reported high FQ resistance among DR-TB patients from Pakistan (Ahmad, Javaid et al. 2015, Ahmad, Javaid et al. 2016, Javaid, Hasan et al. 2017), a meta-analysis from 26 centers (Falzon, Gandhi et al. 2013) a review by Amy Sarah Ginsburg et al (Ginsburg, Grosset et al. 2003). This high ratio of resistance can be due to poor management of Tuberculosis treatment in country and compromised anti TB medicines (Shah, Sadiq et al. 2003, Wells, Ge et al. 2011, Ahmad, Javaid et al. 2016). FQs resistance most probably can be due to irresponsible use of these medications by healthcare practitioners and paramedics before referral of patients to TB treatment centers due to poor knowledge of health practitioners and inadequate facilities of diagnosis. In the present study, the emergence of previous TB treatment with cat-II regimen as the only risk factor for SLD resistance advocates for testing cat-I failures for drug resistance rather than putting them on cat-II regimen (Javaid, Hasan et al. 2017).

## Conclusion

The high prevalence of acquired drug resistance in this study demonstrates the ineffectiveness of the national tuberculosis control program. Additionally, incorrect or irregular use of antituberculosis medications in recent years has resulted in the proliferation and accumulation of drug-resistant strains of tuberculosis. MDR-TB is a complicating issue for the management of tuberculosis (TB) illness. Since MDR-TB is a man-created illness, efforts should be made to prescribe the right course of action for the recommended amount of time. Drug resistance patterns vary over time and across different locations, making them crucial to understand when creating a successful regimen. This suggests that setting up cutting-edge diagnostic facilities is necessary for the early identification of MDR-TB. Periodic surveys should be used to improve drug-resistance monitoring in order to identify trends and take appropriate action as needed. To

manage FQ resistance, more stringent regulations governing the non-prescription sale and careless use of FQ are advised.

### **Ethical Approval**

<sup>21</sup> The University of Balochistan, Quetta's Faculty of Pharmacy and Health Sciences' Research and Ethics Committee gave its approval to this work.

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