

Incidence of Extensively Drug-Resistant Tuberculosis Resistance Pattern in Multidrug-Resistant Tuberculosis Isolates of Private versus Public Sector

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Abstract: Tuberculosis is an ongoing dilemma in Pakistan and the Southern part of Asia. It has become a main part and parcel of research and further management in Pulmonology and Chest Medicine. Newer researches are focused on newer drugs and their efficacy on different strains of tuberculosis. Different resistance patterns and need of newer class of anti-tuberculosis drugs are talk of the town and need vigilant attention for further better management of this disease. To evaluate incidence of Extensively Drug-Resistant (XDR) resistance pattern in Multidrug-Resistant Tuberculosis (MDR-TB) isolates of private versus public sector. The study is comparative and retrospective cohort study; eighty patients were recruited for the study and split into two groups: group 1, which included forty MDR-TB stock cultures from the Laboratory of Microbiology, BMSI, and group 2, which included forty culture-positive specimens from JPMC and the Ojha Institute of Chest Diseases, Karachi. The XDR resistance pattern of these samples was examined. In accordance with WHO standards from 2021, the indirect percentage technique was employed for medication susceptibility. Results revealed that total 3.75% of patients showed extensively drug resistant resistance pattern among the MDR isolates, out of 80 patients. In group 1, none of the patients showed XDR resistance pattern while the 3 patients showing XDR pattern were from group 2, which were from Public Sector. Hence it is concluded, the XDR resistance pattern among isolates of MDR TB was higher in public sector hospital as compared to the private sector.

Keywords: Extensively Drug-Resistant, Multidrug-Resistant, Tuberculosis, Private versus Public Sector

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Introduction

Tuberculosis is a global health enigma with mortality rates of 1-2 million per year, with an incidence rate of 9 million new cases every year. Transmission is mainly air-borne via droplet transmission through infected people. Disease progresses if the patient is compromised in terms of immunity, and the disease has a resistant strain [1]. Extensively drug-resistant tuberculosis (XDR-TB), according to the revised WHO 2020/2021 definition, is tuberculosis caused by *Mycobacterium tuberculosis* that



fulfills the criteria for multidrug-resistant TB (resistance to at least isoniazid and rifampicin) and shows additional resistance to any fluoroquinolone, along with resistance to at least one Group A drug, specifically bedaquiline or linezolid [2].

The incidence and treatment of extensively drug-resistant tuberculosis (XDR-TB) in Pakistan pose a serious and intricate public health concern. The advent of XDR-TB, which exhibits resistance to a broad range of first-line and important second-line anti-tuberculous medications, further exacerbates Pakistan's high tuberculosis burden [3]. Here are some specific factors to think about:

Epidemiological Concerns: Pakistan's battle with TB, including both regular strains and the more daunting XDR-TB, highlights a critical health crisis. XDR-TB is especially concerning due to its resistance to multiple drug regimens, rendering it much more difficult to treat and control. This resistance also leads to higher mortality rates and poses a significant threat to public health [4].

Diagnostic Challenges: A major hindrance in the fight against TB in Pakistan is the difficulty in accurately detecting resistance, particularly to second-line drugs (SLDs). The diagnostic tests for SLD resistance are not as well-developed, standardized, or reliable as those for first-line drugs. This diagnostic gap results in challenges in correctly identifying the nature of the TB strain, which is crucial for effective treatment [5].

Research and Data Shortcomings: There is a notable scarcity of comprehensive research and widespread, community-based data on TB in Pakistan. Most of the existing data emanates from hospital-based studies, which may not fully capture the broader epidemiological trends. This paucity of data limits the ability to understand the full scope of the TB problem and hampers the development of effective public health strategies [6].

Increasing Drug Resistance Trends: Although limited, available studies, primarily from hospital settings, indicate an alarming upward trend in drug resistance. This trend not only complicates the treatment landscape but also suggests potential shortcomings in existing TB control measures. These could include issues related to treatment adherence, drug availability, and overall management of TB cases [7].

Broader Public Health Implications: Addressing TB and XDR-TB in Pakistan requires a comprehensive public health response. This includes enhancing diagnostic capabilities, standardizing tests for detecting SLD resistance, improving TB surveillance systems, and ensuring the availability and accessibility of effective treatment regimens. Moreover, there is a need for preventive strategies focusing on halting the spread of TB and increasing public awareness about the disease and its management [8].

International Context and Collaboration: The issue of TB, particularly drug-resistant strains, is not confined to national borders but is a matter of global health concern. International cooperation in terms of technical assistance, research collaboration, and funding is essential for countries like Pakistan to effectively tackle the TB crisis [9].

Future Strategies: To address the TB challenge more effectively, there is a need for increased investment in research, particularly in understanding drug resistance patterns and developing more accurate and rapid diagnostic tests for SLD resistance. Moreover, incorporating community-based approaches in TB control programs, enhancing the health system's capacity to manage TB, and addressing the social determinants that contribute to TB transmission are critical for long-term success [2, 3, 4].

A strain that exhibits resistance to two or more main first-line medicines is known as multidrug resistance (MDR). A rare form of multidrug-resistant tuberculosis (MDR TB) known as extensively drug-resistant TB (XDR TB) is resistant to either Isoniazid, Rifampin, a fluoroquinolone, and either



Bedaquiline or Linezolid in addition to a second-line injectable consisting of Amikacin, Kanamycin, and Capreomycin. Since tuberculosis is a disease that mostly affects underdeveloped nations, more study is still needed to fully understand medication mechanisms of action and resistance patterns.⁵⁻⁶

Third line of treatment including Macrolides, Arginine, Linezolid and Rifabutin has also been documented but not fully evidence based [7, 8].

The difference between private and public sector hospitals are evident in the population reaching out to them. Patients exposed to public sector hospitals are prone to more TB contacts and lack of awareness causes them to receive inappropriate or inadequate treatment. Taking ATT for lesser duration of time than the recommended duration causes resistance and tend to cause more severe symptoms in the next flare [9].

Also, lack of availability of medicines and decreased supply of the resources lead to a vicious cycle of inadequately managed TB cases that further become contact to the surrounding people making them prone to catch TB and suffer until diagnosed [10].

Methods

This study was conducted in institute of Basic Medical Sciences Institute (BMSI), Microbiology Department with collaboration of Ojha Institute of Chest Diseases (OICD) and Jinnah Postgraduate Medical Centre (JPMC), Karachi. It was a cross-sectional retrospective study, and 40 stock cultures were obtained from BMSI, as well as combined JPMC and OICD, and were respectively grouped into two named groups: Group 1, representing the private sector, and Group 2, representing the public sector.

The inclusion criteria included isolates that were resistant to INH and RIF, and sputum smears with >10 AFB/HPF from patients already diagnosed with MDR TB. Patients responding to INH, RIF or having very few organisms in sputum samples were excluded from the study. Drug susceptibility testing was carried out using standard anti-tuberculosis drug concentrations added to Lowenstein–Jensen medium for rifampicin and isoniazid, using the traditional indirect proportion method; however, the study protocol did not specify specific critical concentrations. The Microbiology Department of the Institute of Basic Medical Sciences employed normal laboratory techniques to assure the quality control of culture and drug susceptibility tests. Stock cultures were kept under standard conditions, and no particular reference strain was mentioned.

The predicted percentage of XDR-TB among MDR-TB cases in the public sector was estimated to be 5% based on existing regional literature and surveillance data, whereas the expected percentage in the private sector was estimated to be 0.5–1%. The minimal necessary sample size was determined using a 95% confidence level, 80% power, and a 1:1 allocation ratio between the two groups. A minimal sample size of around 36–40 MDR-TB isolates per group was determined. To provide sufficient statistical power, a total of 80 MDR-TB isolates—40 from the public sector and 40 from the private sector—were included in the study.

Isolates were cultured on Lowenstein-Jensen medium and an Antibiotic Susceptibility Test was carried out. Drug susceptibility test was carried out by the indirect proportion method. Using the indirect proportion approach, resistance was defined as the growth of *Mycobacterium tuberculosis* isolates on drug-containing Lowenstein-Jensen medium; isolates exhibiting resistance to both isoniazid and rifampicin were categorized as multidrug-resistant tuberculosis (MDR-TB). The stocks were assessed and reassessed at 2 weeks and 4 weeks and final readings were recorded after 40 days. The Statistical Package for Social Sciences (SPSS) version 23.0 was used to input, code, and analyze the collected data. The study variables were summarized using descriptive statistics. Frequencies and



percentages were used to express categorical factors such as gender, culture medium, public or private stock culture institute, and MDR resistance patterns. Age and days to culture positive were examples of continuous variables that were shown as means with standard deviations or, when applicable, medians with interquartile ranges. The resistance patterns of isolates from the public and private sectors were compared using stratified analysis. Tables and graphs were used to display the data, and all analyses were carried out in line with the goals of the study.

Result

50% patients in group 1 were males while rest was female. 56.7% of the total patients were male while 43.3% patients were females in group 2 (Figure 1). Age groups were made to better assess and analyze the data. 43.4% patients were in the age group of 15 to 25 years. 50% were in the age group of 26 to 35 years. While only 6.6% patients fell in the age group of 36-45 years indicating the likelihood of the disease to infect the youth and adolescents. Group 1 (private sector) had no XDR-TB cases, whereas Group 2 (public sector) had an incidence of 3.75% (Figure 2). Ten patients in Group 2 reported contact exposure, whereas only two patients in Group 1 had a history of positive TB contact. 23.3% of patients in Group 2 had a primary TB diagnosis, 43.3% had an initial MDR-TB diagnosis, and 33.3% had a subsequent MDR-TB diagnosis. Three isolates showed resistance to ofloxacin, one isolate showed resistance to amikacin, and four isolates showed resistance to kanamycin, according to an analysis of drug susceptibility patterns across all 80 samples. 100% of the isolates showed capreomycin sensitivity. Amikacin and capreomycin were effective against all 40 isolates (100%) in Group 1. One isolate (3.75%) each showed resistance to kanamycin and ofloxacin. Ofloxacin resistance was found in two isolates (4.6%), kanamycin resistance in four isolates (10%), and amikacin resistance in one isolate (2.5%) in Group 2, although capreomycin sensitivity was maintained in all isolates (100%). Interestingly, there was no evidence of amikacin and kanamycin cross-resistance (Figure 3).

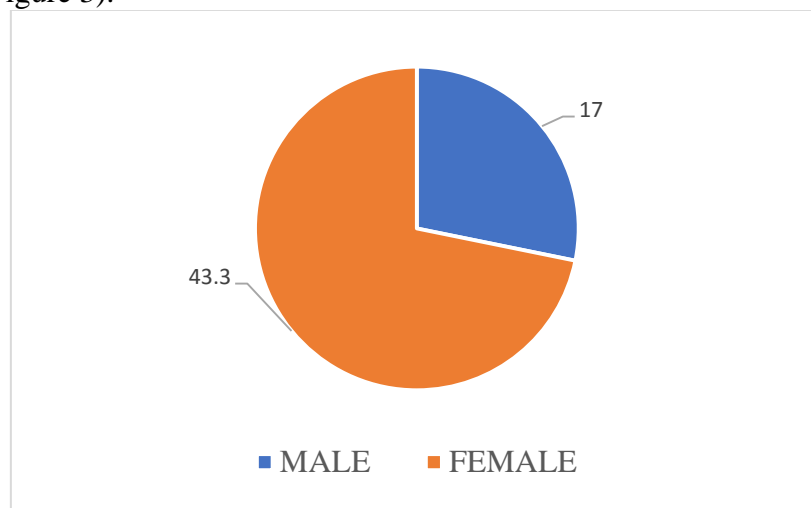


Figure 1: Sex Distribution of Group 2



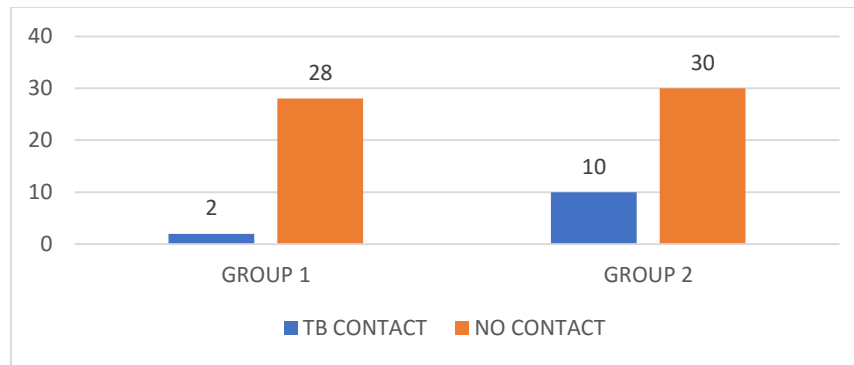


Figure 2: TB Contact

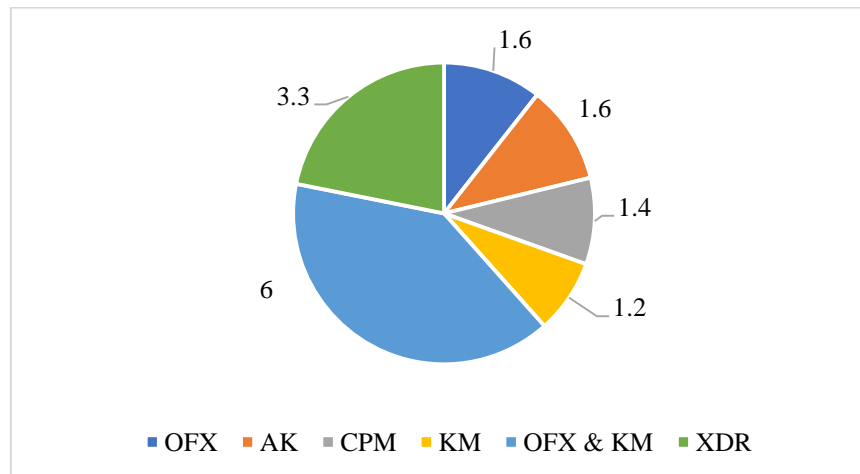


Figure 3: Resistance Pattern

Discussion

In HBC, various socio-economic and biological factors, such as poverty, place of residence, consultation locations, education levels, and wait times for healthcare facilities, contribute to the evolving trends in chemotherapy application for TB [11]. The global community, guided by the Sustainable Development Goals (SDGs), is committed to ending TB by 2035 [12]. Notably, advancements in diagnostic tools, such as the PCR-based Geno Type MTBD plus assay, reveal mutations at position G944C with S315T amino acid changes in MDR cases [13].

Recent research has identified the development of microRNAs targeting various transcriptional factors as a promising avenue [14]. Specifically, miRNA-204 has demonstrated effects on signaling pathways influencing the activities of pulmonary arterial smooth muscle cells. These findings highlight the multifaceted approach required to address the complex challenges posed by TB, including antibiotic resistance, socio-economic factors, and promising developments in molecular research and therapeutic strategies [15]. The global community's commitment to achieving SDGs offers a framework for concerted efforts to combat TB and reduce its impact on public health by the target year of 2035 [16].

Saifullah et al quoted risk factors regarding DR and XDR-TB in their cohort study. In this retrospective analysis conducted at a tertiary care hospital from 2014 to 2019, authors aimed to understand factors associated with drug-resistant tuberculosis (DR-TB) among patients [17]. Out of 580 individuals, 34.1% were diagnosed with drug-susceptible TB (DS-TB), while 382 had DR-TB,



including cases of rifampicin-resistant TB (RR-TB), multidrug-resistant TB (MDR-TB), and extensively drug-resistant TB (XDR-TB) [18]. Notable differences in demographics and clinical characteristics emerged between DS-TB and DR-TB patients [17]. Logistic regression analysis identified independent risk factors for MDR-TB, XDR-TB, and RR-TB, including age, marital status, tobacco use, previous treatment, treatment failure, and chest X-ray findings [19]. The study highlighted the substantial prevalence of DR-TB cases and underscored the significance of timely identification of high-risk patients for informed decision-making in prevention, treatment, and disease control strategies. The predictive accuracy of the models was considered excellent, offering insights for targeted interventions and improved patient outcomes [20, 21].

Another retrospective observational study focused on extensively drug-resistant tuberculosis (XDR-TB), a significant global health concern. The research aimed to analyze treatment outcomes and identify factors associated with unfavorable results among XDR-TB patients [22]. Data from 184 eligible patients registered between March 2012 and August 2018 in 10 Programmatic Management Units of Pakistan's National Tuberculosis Control Program was examined [23]. The findings revealed that only 32.1% successfully completed treatment, while 45.1% succumbed to mortality, 13% experienced treatment failure, and 6% were lost to follow-up [24]. Factors significantly linked to unfavorable outcomes included the use of bedaquiline in conventional therapy, unfavorable interim treatment outcomes, and the occurrence of adverse drug events (with a negative association) [25]. The study highlights a sub-optimal treatment success rate, emphasizing the need for immediate attention from program managers and clinicians to address the high mortality and poor success rates observed in this cohort [26]. As recommended by Ahmed S et al, contact tracing and precautions are mandatory to stop prevalence of TB in high risk areas and greater contact burden. They have exemplified the COVID era to reduce the disease burden [25].

The prevalence of extensively drug-resistant tuberculosis (XDR) and pre-extensively drug-resistant tuberculosis (Pre-XDR) among MDR-TB patients was assessed in another investigation. Among MDR TB patients, the prevalence rates of Pre-XDR and XDR-TB were 171/531 (32.2%) and 18/531 (3.4%), respectively. Ten of the eighteen XDR-TB patients had resistance to fluoroquinolone (FQ), amikacin (Am), kanamycin (Km), and capreomycin (Cm). 05 showed resistance to Km+FQ. One patient was resistant to Cm+FQ, while two were resistant to Am+Km+FQ. All 171 PRE-XDR TB patients were found to be resistant to FQ, and none of them were resistant to second-line injectibles (Am, Km, and Cm) [27].

Conclusion

The results of this study show that MDR-TB isolates from the public sector were more likely than those from the private sector to exhibit XDR-TB resistance patterns. Furthermore, a higher percentage of patients from the public sector stated that they had a positive history of tuberculosis contact. However, because of the study's single-center design and small sample size, these findings should be taken cautiously. To confirm these findings and get a better understanding of sector-specific variations in drug resistance patterns, larger, multicenter studies with a wider geographic representation are necessary.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS



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No animals were used in this study. The study on humans was conducted in accordance with the ethical rules of the Helsinki Declaration and Good Clinical Practice.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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References

1. Mohan K, Alam A, Patnaik R. Prevalence and patterns of drug-resistant tuberculosis in India: evidence from the last 2.5 decades. *Ann Rom Soc Cell Biol.* 2021;25(4):754–778.
2. Thomsen J, Abdulrazzaq NM, Nyasulu PS, Al Hosani F, Habous M, Weber S, et al. Epidemiology and antimicrobial resistance of *Mycobacterium* spp. in the United Arab Emirates: a retrospective analysis of 12 years of national antimicrobial resistance surveillance data. *Front Public Health.* 2024;12:1244353.
3. Faye LM, Hosu MC, Apalata T. Drug-resistant tuberculosis in rural Eastern Cape, South Africa: a study of patients' characteristics in selected healthcare facilities. *Int J Environ Res Public Health.* 2024;21(12):1594.
4. Bhanushali A, Atre S, Nair P, Thandaseery GA, Shah S, Kuruwa S, et al. Whole-genome sequencing of clinical isolates from tuberculosis patients in India: real-world data indicates a high proportion of pre-XDR cases. *Microbiol Spectr.* 2024;12(5):e02770-23.
5. Kamolwat P, Nateniyom S, Chairasert A, Disratthakit A, Mahasirimongkol S, Yamada N, et al. Prevalence and associated risk factors of drug-resistant tuberculosis in Thailand: results from the fifth national anti-tuberculosis drug resistance survey. *Trop Med Int Health.* 2021;26(1):45–53.
6. Ullah H, Ahmed H, Salman A, Iqbal R, Hussaini SJ, Malikzai A. The rising tide of tuberculosis in Pakistan: Factors, impact, and multifaceted approaches for prevention and control. *Health Science Reports.* 2024 Oct;7(10):e70130. Farhat M, Cox H, Ghanem M, Denkinger CM, Rodrigues C, Abd El Aziz MS, et al. Drug-resistant tuberculosis: a persistent global health concern. *Nat Rev Microbiol.* 2024;22(10):617–635.
7. Olabiyi OE, Okiki PA, Adarabioyo MI, Adebisi OE, Adegoke OE, Esan OE, et al. Distribution of multidrug-resistant tuberculosis in Ekiti and Ondo States, Nigeria. *New Microbes New Infect.* 2023;55:101192.



8. Nnanna J, Ikegbunam M, Nnanna P, Okoye E, Esimone C. Serotypes and antibiotic susceptibility patterns of optochin-resistant *Streptococcus pneumoniae* from adults in Nigeria. *Int J Infect Dis.* 2023;134(Suppl 1):S3–S4.
9. Sylverken AA, Kwarteng A, Twumasi-Ankrah S, Owusu M, Arthur RA, Dumevi RM, et al. The burden of drug-resistant tuberculosis in Ghana: results of the first national survey. *PLoS One.* 2021;16(6):e0252819.
10. Migliori GB, Tiberi S, Zumla A, Petersen E, Chakaya JM, Wejse C, et al. MDR/XDR-TB management of patients and contacts: challenges facing the new decade. *Int J Infect Dis.* 2020;92(Suppl):S15–S25.
11. Dheda K, Cox H, Esmail A, Wasserman S, Chang KC, Lange C. Recent controversies about MDR and XDR-TB: global implementation of the WHO shorter MDR-TB regimen and bedaquiline for all with MDR-TB. *Respirology.* 2018;23(1):36–45.
12. Faksri K, Kaewprasert O, Ong RT, Suriyaphol P, Prammananan T, Teo YY, et al. Comparison of whole-genome sequencing and phenotypic drug susceptibility testing for MDR-TB and XDR-TB. *Int J Antimicrob Agents.* 2019;54(2):109–116.
13. Tasnim T, Tarafder S, Alam FM, Sattar H, Kamal SM. Pre-extensively drug-resistant tuberculosis among pulmonary MDR-TB patients in Bangladesh. *J Tuberc Res.* 2018;6(3):199–206.
14. Bhering M, Duarte R, Kritski A. Predictive factors for unfavourable treatment outcomes in MDR-TB and XDR-TB patients in Rio de Janeiro State, Brazil, 2000–2016. *PLoS One.* 2019;14(11):e0218299.
15. Siddiqui S, Brooks MB, Malik AA, Fuad J, Nazish A, Bano S, et al. Evaluation of GenoType MTBDRplus for detection of drug-resistant *Mycobacterium tuberculosis* isolates from Karachi, Pakistan. *PLoS One.* 2019;14(8):e0221485.
16. Khan FU, Khan A, Khan FU, Hayat K, Chang J, Khalid W, et al. Assessment of adverse drug events and associated risk factors among patients treated for multidrug-resistant tuberculosis in Pakistan. *Front Pharmacol.* 2022;13:876955.
17. Massud A, Khan AH, Syed Sulaiman SA, Ahmad N, Shafqat M, Ming LC. Unsuccessful treatment outcomes and associated risk factors among DR-TB patients in Pakistan. *PLoS One.* 2023;18(8):e0287966.
18. Tasnim T, Tarafder S, Alam FM, Sattar H, Kamal SM. Pre-extensively drug-resistant tuberculosis among pulmonary MDR-TB patients in Bangladesh. *J Tuberc Res.* 2018;6(3):199–206.
19. Abubakar M, Ahmad N, Atif M, Khan AH, Ghafoor A. Treatment outcomes among childhood extensively drug-resistant tuberculosis patients in Pakistan. *ERJ Open Res.* 2022;8(1):00290-2021.
20. Saifullah A, Mallhi TH, Khan YH, Iqbal MS, Alotaibi NH, Alzarea AI, et al. Risk factors associated with the development of MDR- and XDR-TB: a retrospective cohort study. *PeerJ.* 2021;9:e10826.
21. Munir MK, Rehman S, Iqbal R. Meeting the challenge, making a difference: multidrug-resistant tuberculosis in Pakistan. *Pak J Med Res.* 2018;57(1):1–2.
22. Ul Manan MA, Naqvi S, Mushtaq A, Shafqat M. Prevalence of pre-XDR-TB and XDR-TB among MDR-TB patients. *Pak J Chest Med.* 2018;24(4):208–211.
23. Sheikh AS, Aziz M, Ayaz M. Rising trends of multidrug-resistant tuberculosis in Pakistan. *Biomed J.* 2018;1:4.



24. Ahmed S, Lotia-Farrukh I, Khan PY, Adnan S, Sodho JS, Bano S, et al. High prevalence of multidrug-resistant tuberculosis among household contacts in a high-burden setting. *Int J Tuberc Lung Dis.* 2023;27(8):646–652.
25. Naidoo K, Perumal R, Cox H, Mathema B, Loveday M, Ismail N, et al. Epidemiology, transmission, diagnosis, and management of drug-resistant tuberculosis: lessons from South Africa. *Lancet Infect Dis.* 2024;24(4):e85–e97.
26. Dixit A, Freschi L, Vargas R, Gröschel MI, Nakhoul M, Tahseen S, et al. Estimation of country-specific tuberculosis resistance antibiograms using pathogen genomics and machine learning. *BMJ Glob Health.* 2024;9(3):e013532.
27. Magnesium sulphate- first line anticonvulsant in the treatment of eclampsia. Tayyaba Majeed, Yasmin Sattar, Fatima Waheed, Naeem Majeed, Sadaf Zahra, Irum Chaudry, Zahid Mahmood, Numan Majeed, *Journal of Fatima Jinnah Medical College*, Vol 4, Issue 3.

