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Cost impact of culture reversion in extensively drug-resistant tuberculosis in Pakistan: a multi-center retrospective study

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Contributions: Muhammad Abubakar, Matti Ullah: study concept and design. Rimsha Mukhtar, Mahnoor Irfan: data collection. Rimsha Mukhtar, Matti Ullah, Muhammad Abubakar: data analysis. Rimsha Mukhtar: manuscript writing, formatting, and finalization. Muhammad Abubakar, Mahnoor Irfan: writing – draft of specific sections. Muhammad Abubakar: supervision of the overall study. All authors critically reviewed and approved the final manuscript.

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Abstract

Culture reversion among extensively drug-resistant tuberculosis (XDR-TB) patients leads to treatment prolongation and imposes a substantial economic burden on national tuberculosis programs; however, evidence quantifying this burden in high-burden countries such as Pakistan remains limited. This study aimed to quantify the additional treatment costs attributable to culture reversion and reconversion among XDR-TB patients managed under Pakistan's Programmatic Management of Drug-Resistant Tuberculosis (PMDT) program. This retrospective multicenter observational study used routinely collected data from 30 PMDT treatment centers across Pakistan. Culture-confirmed XDR-TB patients registered between May 2010 and June 2019 with complete clinical, microbiological, and treatment records were included.

Culture conversion, reversion, and reconversion were defined according to World Health Organization criteria. Treatment costs were calculated using actual drug regimens received by patients and national procurement prices, adjusted to 2024 USD using official exchange rates and inflation indices. Additional costs were estimated for patients whose treatment duration exceeded the standard 24-month regimen due to reversion.

Of 404 eligible XDR-TB patients, 309 (76.5%) achieved initial culture conversion. Among these, 155 (38.3% of total; 50.2% of converters) experienced culture reversion, and 82 (20.3% of total) subsequently achieved reconversion. Forty-six reconverted patients required treatment beyond 24 months. The cumulative additional drug cost attributable to reconversion-related treatment prolongation was USD 28,295.54, fully borne by the national TB program.

Culture reversion among XDR-TB patients results in significant additional treatment costs for Pakistan’s TB control program. Strengthening early treatment monitoring, adherence support, and individualized regimen optimization is essential to reduce reversion, limit unnecessary treatment extension, and mitigate economic burden.

Key words: XDR-TB, reversion, reconversion, economic burden, programmatic management of drug-resistant TB.

Introduction

Extensively drug-resistant tuberculosis (XDR-TB) is the most challenging type of tuberculosis (TB) to treat. It is defined as TB caused by Mycobacterium tuberculosis (MTB) concurrently resistant to isoniazid (INH), rifampicin (RIF), any fluoroquinolones (FQs), and at least one second-line injectable (SLI) drugs. However, the definition has now evolved to include resistance to linezolid (LZD), bedaquiline (BDQ), or both, in addition to the standard criteria [1].

XDR-TB is especially difficult to treat because it is resistant to the most potent first- and second-line anti-TB medications (SLDs) [2]. Over a million people die each year of TB, and the prevalence of XDR-TB is rising globally. Treatment involves prolonged use of multiple first- and second-line anti-TB drugs, many of which have questionable effectiveness or lower efficacy. Consequently, the global treatment success rate for XDR-TB patients is only 59%, lower than the 64% success rate seen in MDR-TB patients [2].

This disparity in success rates is in line with countries like Pakistan and India, where the burden of drug-resistant TB is particularly high and a substantial proportion of MDR-TB patients are female. In Pakistan, cultural stigma surrounding TB and entrenched gender inequality contribute to delays in treatment-seeking behavior among women. This results in misdiagnosis, inconsistent treatment practices, poor adherence to the recommended course of treatment, and ultimately the development and spread of drug-resistant TB strains [3].

Treatment regimens for XDR-TB are more prolonged and complex than those for drug-susceptible TB, often lasting up to 20-24 months or longer. These regimens require expensive antibiotics, specialized medications, extended hospital stays, and intensive monitoring—all contributing to significantly higher treatment costs [4]. If the treatment is not managed effectively, these costs can escalate further.

In terms of both patient-borne and health system expenses, MDR-TB and XDR-TB treatments are substantially costlier than treatments for drug-susceptible TB. Research from India has shown that decentralized, home-based treatments for MDR-TB are more cost-effective than centralized, hospital-based models. Centralized treatment (hospital-based model) costs an estimated US$3390, whereas decentralized care costs US$1724, with an ICER of US$2383 per QALY gained. This implies a potential savings of nearly US$1666 per case using the decentralized model [5].

Pakistan ranks fifth globally in terms of drug-resistant TB burden [6]. According to the World Health Organization's 2022 TB country profile for the Eastern Mediterranean Region (EMRO), Pakistan has an incidence rate exceeding 265 cases per 100,000 people [7]. To combat this, the

National TB Control Program (NTP) in Pakistan employs the Directly Observed Therapy Short-course (DOTS) strategy. This strategy provides free or subsidized testing, no administrative fees, and access to first-line anti-TB medications at no cost. Despite these provisions, patients still face considerable out-of-pocket expenses, including costs for transportation to treatment centers, lost income, pre-diagnostic testing due to delayed or incorrect diagnoses, hospital accommodation and meals, and the cost of treating drug-resistant or extra-pulmonary TB [8]. Reconversion of patients with XDR-TB adds another layer of financial and logistical burden. Reconverted patients are those who initially converted to a negative culture during treatment but later reverted to a positive culture, indicating treatment failure or relapse. Since these patients require extended or repeated treatment regimens—fully funded by the national health system—the urgency to reduce reconversion rates becomes even more critical.

Therefore, effective strategies must be developed to prevent initial conversion failures and manage reverted cases efficiently. To date, there has been limited research assessing the frequency of reversion following initial culture conversion and the subsequent impact on treatment costs. Thus, this study aims to fill this gap by evaluating the financial burden associated with reconversion due to treatment reversion, specifically within the context of Pakistan's healthcare system.

Materials and Methods

Study design and setting

This retrospective, multi-center observational study was conducted across 30 PMDT treatment centers in Pakistan. These centers operate under the National TB Control Program and provide standardized diagnosis and treatment for drug-resistant TB.

Study population

All culture-confirmed XDR-TB patients registered for treatment between 1 May 2010 and 30 June 2019 were screened. Patients were included if they had complete demographic, clinical, microbiological, and treatment outcome data from treatment initiation to final outcome. Patients with incomplete drug susceptibility or treatment records were excluded.

Figure 1 shows a STROBE-conformant flow diagram that identifies patient identification, eligibility evaluation, and causes of exclusion at any point of the study.

Diagnostic procedures

TB and drug resistance diagnosis was conducted according to national PMDT guidelines that prevailed at the time of the study. The diagnosis was done initially by sputum smear microscopy and GeneXpert MTB/RIF (CBNAAT). Confirmation of culture was done in the MGIT 960 liquid culture system and solid culture in some cases. Line probe assays and phenotypic DST of first- and second-line anti-TB drugs were used to test drug susceptibility.

Treatment regimens

Patients were managed as per national PMDT guidelines at the start of treatment. The combination of fluoroquinolones, second-line injectable agents, ethionamide, cycloserine, clofazimine, and para-aminosalicylic acid characterized the treatment regimens, which were mostly injectable-based during most of the study period (2010-2016). The introduction of newer drugs like bedaquiline was only programmed in later years of the study period and were administered to few eligible patients. Only drugs received by each patient were used to calculate costs.

Definitions of outcomes

- Culture conversion: Two negative sputum cultures on two separate occasions separated by at least 30 days since initiation of treatment.
- Culture reversion: One positive sputum culture following reported conversion.
- Reconversion: Two negative sputum cultures after being reverted.

Data collection

Electronic Nominal Recording and Reporting System (ENRS) was used to retrieve retrospective data, which was checked with patient medical records at treatment sites. Variables were socio-demographic factors, medical history, micro biology, treatment schedules, length of therapy and end results.

Cost estimation

The cost of treatments was determined by using national prices of procurement of anti-TB drugs available through the National TB Control Program. The expenditures were initially entered in Pakistani Rupees (PKR) and changed into United States Dollars (USD) based on the official exchange rate of 2024 (1 USD = 278.21 PKR). The Consumer Price Index adjusted the inflation

with 2024 as a base year. Other expenses were also added to reconverted patients who took a longer treatment regimen, which was above the usual regimen of 24 months.

Supplementary Table 1 gives unit price in USD of all anti TB drugs used among XDR TB patient and the individual level cost breakdown for the 46 reconverted patients is provided in *supplementary Table 2.*

Statistical analysis

The data were analyzed with Microsoft Excel 2016 and SPSS 26.0. The characteristics and outcomes of the patients were summarized using descriptive statistics. Means ± standard deviations or medians with interquartile ranges were used to express continuous variables whereas frequencies and percentages were used to represent categorical variables.

Results

Baseline clinical and microbiological characteristics

The research involved 404 patients of XDR-TB. The average age was 32.9 ±14.3 years, and 55 percent of them were males. The majority of patients (93.6%) had a prior history of treatment of tuberculosis. A subset of the patients had comorbidities, diabetes mellitus being the most prevalent, and immunodeficiency states such as HIV infection were uncommon. A small percentage of cases found concomitant extrapulmonary tuberculosis. Pulmonary TB radiologic assessment demonstrated that the disease was mostly bilateral, and baseline cavitary lesions were present in a significant number of patients. Baseline microbiological diagnosis was determined after the use of CBNAAT and culture-based DST that verified XDR-TB based on WHO definitions. Table 1 provides the summary of the baseline demographic, clinical, radiologic, and microbiologic features of XDR-TB patients (n= 404).

Treatment monitoring and outcomes

The microscopy and culture of the sputum were conducted monthly during the treatment as per the PMDT guidelines. Out of 404 patients, 309 (76.5%), obtained initial culture conversion. Among these 155 (50.2%) were reverted to culture and 82 later reconverted. A total of forty-six of the reconverted patients needed care beyond the normal time frame of 24 months.

The cumulative incremental cost of the drug of these 46 patients because of the extension of treatment was USD 28,295.54. Microbiologic and programmatic treatment outcomes of XDR-TB patients is given in Table 2.

Discussion

The study points out the high programmatic and economic consequences of culture reversion in the XDR-TB patients treated within the PMDT framework in Pakistan. The demographic profile of the patients, with a predominant number of males and young-middle adulthood individuals, is aligned with the global epidemiological trends of tuberculosis and drug-resistant TB. Past research has indicated that TB is more susceptible in males and economically productive age groups because of the delayed health-seeking behavior, work-related factors, and difficulties in adherence to treatment, which can lead to drug resistance. [9,10].

The incidence of drug resistance among this cohort is very high, which may be explained by the high percentage of patients who have undergone previous TB treatment. The chronic use of anti-tuberculosis medications, late diagnosis, non-rational use of antibiotics, poor-quality medications, and lack of adherence have been largely recorded as some of the major contributors to the amplification of resistance in DR-TB. Other high-burden settings have also described similar patterns of resistance, with extensive resistance to first-line drugs, highlighting the global character of the problem [11,12].

One of the significant results of this research is that culture reversion occurs often after the initial conversion. Culture reversion is a loss of ability to maintain bacteriological response and has significant clinical and economic implications. Extended periods of treatment following reversion and reconversion directly raise the cost of care and burden national tuberculosis control programs. This strain is a particular cause of concern in low- and middle-income nations, where the management of XDR-TB already appears to take a disproportionate share of resources relative to those needed to manage drug-susceptible TB [13].

According to prior literature, factors such as extensive pulmonary disease, having had exposure to second-line anti-tuberculosis medications, comorbidity, low body mass index, and difficulty with adherence have been identified as factors that may predispose patients to culture reversion. Though the current study was not aimed at formally assessing predictors of reconversion, the high rate of reversion witnessed underlines the necessity of close bacteriological surveillance, timely regimen optimization, and effective adherence support during treatment [14].

The economic cost of XDR-TB treatment is still immense. The cost of drug-resistant TB treatment has been estimated to be many times higher than that of drug-susceptible disease, and XDR-TB regimens have been associated with a long duration, increased toxicity and reduced success rates. In this research, the prolonged treatment was considered beyond the normal time constraint,

which led to a calculable incremental drug cost burden imposed solely on the national program, meaning the value of averting reversion to minimize unwarranted spending [15].

Compliance is a feature of effective TB treatment. The lack of adherence has continuously been associated with the failure of treatment, relapse, the rise of mortality rates, and the further spread of resistant strains. Various socioeconomic, psychological, and health-system related issues are associated with non-adherence in DR-TB patients, such as adverse effects of treatment, long-term therapy, financial barriers, stigma, and inaccessibility to care. The experience of other settings indicates that psychosocial support, patient education, care decentralization, and better communication between the provider and the patient could significantly enhance adherence and treatment outcomes [13-15].

Loss to follow-up in DR-TB and XDR-TB patients is a major health issue. Community-based and decentralized care models have been more widely embraced based on WHO guidance, and have demonstrated potential in enhancing access, decreasing delays in treatment access, and lowering patient expenditures. Decentralized care reinforcement and sufficient training, supervision, and inter-level communication can contribute to better retention in care and overall treatment success. On the whole, the results of the present research emphasize the need to maintain bacteriological surveillance, detect patients at risk of reversion in an early stage, and implement programmatic measures designed to enhance adherence and care persistence. A decrease in culture reversion can not only enhance patient outcomes but can also significantly reduce the cost of XDR-TB management in high-burden environments [16].

Limitations

This research has a number of limitations. First, since routinely collected programmatic data were retrospectively used, complete World Health Organization-defined final treatment outcomes (cure, treatment completion, treatment failure, death, and loss to follow-up) were not consistently available across all patients and thus could not be analyzed comprehensively. Second, a number of clinical variables, especially comorbidities, radiologic findings, and concomitant extrapulmonary tuberculosis, were not consistently put into the database. Consequently, these parameters were characterized in a descriptive manner and could not be analyzed in a quantitative or inferential manner and some of the pre-existing clinical and microbiological variables were not fully recorded, and the occurrence of culture reconversion was minimal. Consequently, univariate and multivariate analyses to determine independent risk factors of reconversion were not conducted because this would have yielded unstable and perhaps

inaccurate estimates. Thirdly, the database consists of the preBDQ era or pre2020 data. These cost impact may be significantly affected with newer shorter regimens as and when available in the region. Lastly, the economic analysis only covered direct drug costs, but not indirect costs and the expenses incurred by the patient.

Conclusions

The reversion of culture among patients with XDR-TB creates significant extra treatment expenses because of extended therapy. Specific interventions to enhance treatment adherence and early detection are needed to decrease reversion and maximize the use of resources in the high-burden environment like Pakistan.

Abbreviations

TB: Tuberculosis, DR-TB: Drug Resistance TB, XDR-TB: Extensively DR-TB, WHO: World Health Organization, LTFU: Loss to follow up, MDR TB: Multidrug Resistance TB, HIV: Human Immunodeficiency Virus, BMI: Body Mass Index, FLDS: First-line drugs, RHZE: Rifampicin, isoniazid, pyrazinamide, Ethionamide, EXTRA PTB: Extrapulmonary tuberculosis, SLD: Second line anti-TB drugs, PMDT: Programmatic Management of Drug-resistant Tuberculosis, DST: Drug Susceptibility Testing, LPA: Line-probe assay, MTB: Mycobacterium tuberculosis, RIF: Rifampicin, INH: Isoniazid, FQS: Fluoroquinolones, BDQ: Bedaquiline, LZD: Linezolid, NTP: National TB Control Program, ENRS: Electronic nominal recording and reporting system, DOTS: Directly observed treatment, EMRO: Emergency Management and Response Office, ICER: Incremental Cost-effectiveness Ratio, QALY: Quality-adjusted life year, SCC: Sputum Culture Conversion, AM: Amikacin, BDQ: Bedaquiline, CM: Capreomycin, SLIs: Second-line injectable.

References

1. Abubakar M, Ahmad N, Ghafoor A, et al. Treatment outcomes of extensively drug-resistant tuberculosis in Pakistan: a countrywide retrospective record review. Front Pharmacol 2021;12:640555.
2. Abubakar M, Ahmad N, Atif M, et al. Prognostic accuracy of time to sputum culture conversion in predicting cure in extensively drug-resistant tuberculosis patients: a multicentre retrospective observational study. BMC Infect Dis 2022;22:204.
3. Bagcchi S. WHO's global tuberculosis report 2022. Lancet Microbe 2023;4:e20.

4. Naz F, Ahmad N, Wahid A, et al. High rate of successful treatment outcomes among childhood rifampicin/multidrug-resistant tuberculosis in Pakistan: a multicentre retrospective observational analysis. BMC Infect Dis 2021;21:1209.
5. Heyckendorf J, Olaru ID, Ruhwald M, Lange C. Getting personal perspectives on individualized treatment duration in multidrug-resistant and extensively drug-resistant tuberculosis. Am J Respir Crit Care Med 2014;190:374-83.
6. John D, Chatterjee P, Murthy S, et al. Cost effectiveness of the decentralised care model for managing MDR-TB in India. Indian J Tuberc 2018;65:208-17.
7. Canton H. World Health Organization—WHO. The Europa Directory of International Organizations 2021: Routledge; 2021. p. 370-84.
8. Europa Publications. The Europa Directory of International Organizations 2022. London, UK: Routledge; 2022. pp. 380-95.
9. Razzaq S, Zahidie A, Fatmi Z. Estimating the pre-and post-diagnosis costs of tuberculosis for adults in Pakistan: household economic impact and costs mitigating strategies. Glob Health Res Policy 2022;7:22.
10. Abubakar M, Ullah M, Shaheen MA, Abdullah O. Why do patients with DR-TB do not complete their treatment? Findings of a qualitative study from Pakistan. BMJ Open Respir Res 2024;11:e002186.
11. Laycock KM, Enane LA, Steenhoff AP. Tuberculosis in adolescents and young adults: emerging data on TB transmission and prevention among vulnerable young people. Trop Med Infect Dis 2021;6:148.
12. Rifat M, Milton AH, Hall J, et al. Development of multidrug resistant tuberculosis in Bangladesh: a case-control study on risk factors. PloS One 2014;9:e105214.
13. Whitfield MG, Soeters HM, Warren RM, et al. A global perspective on pyrazinamide resistance: systematic review and meta-analysis. PloS One 2015;10:e0133869.
14. Stephanie F, Saragih M, Tambunan USF. Recent progress and challenges for drug-resistant tuberculosis treatment. Pharmaceutics 2021;13:592.
15. Nezenega ZS, Perimal-Lewis L, Maeder AJ. Factors influencing patient adherence to tuberculosis treatment in Ethiopia: a literature review. Int J Environ Res Public Health 2020;17:5626.
15. Gebreweld FH, Kifle MM, Gebremicheal FE, et al. Factors influencing adherence to tuberculosis treatment in Asmara, Eritrea: a qualitative study. J Health Popul Nutr 2018;37:1.

16. Kho S, Seung KJ, Huerga H, et al. Sputum culture reversion in longer treatments with bedaquiline, delamanid, and repurposed drugs for drug-resistant tuberculosis. Nat Commun 2024;15:3927.

Online supplementary material

Supplementary Table 1. Unit price in USD$ of all anti-tuberculosis drugs used among extensively drug-resistant tuberculosis patients.

Supplementary Table 2. Cost of drugs above 24 months of treatment.

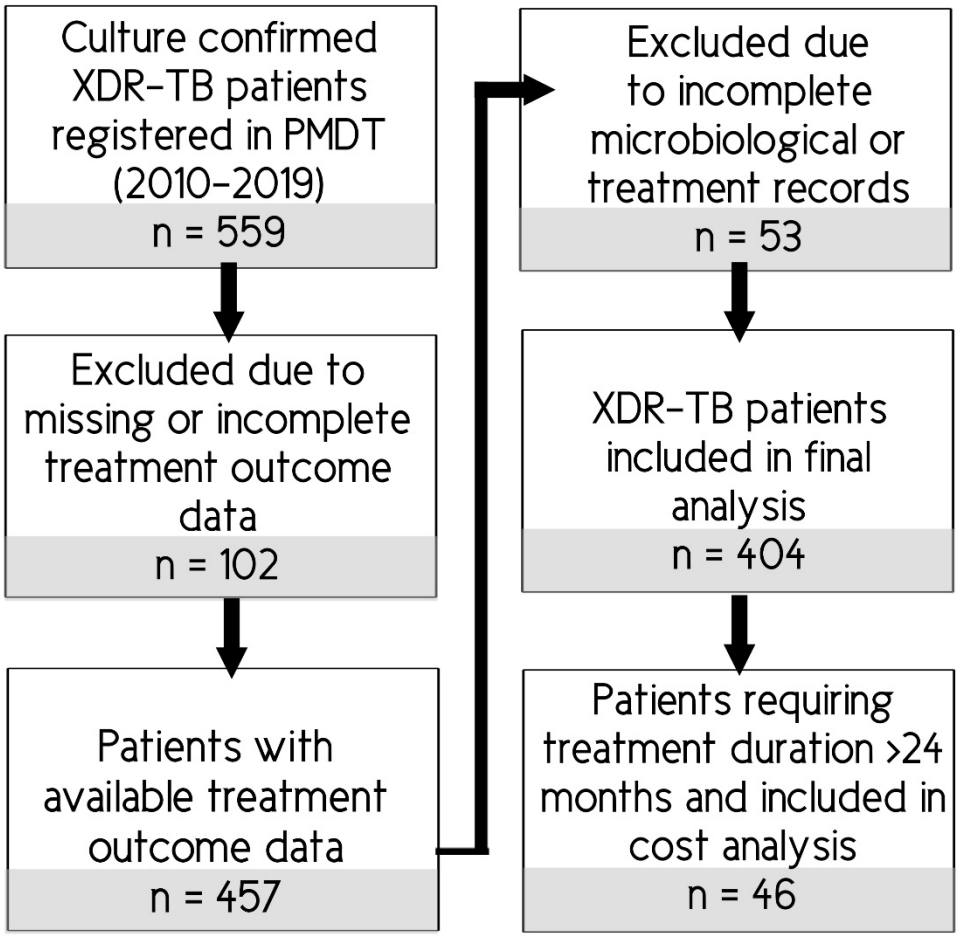

Figure 1. STROBE flow diagram of patient selection.

Table 1. Baseline demographic, clinical, radiologic, and microbiological characteristics of XDR-TB patients (n=404).

Characteristic	Value
Age, mean ± SD (years)	32.9±14.3
Male sex, n (%)	222 (55.0%)
Previous TB treatment, n (%)	378 (93.6%)
Baseline body weight 40 kg, n (%)	264 (65.3%)
Any comorbidity, n (%)	62 (15.3%)
Diabetes mellitus	Most frequent
Other chronic illnesses	Infrequent
HIV infection, n (%)	Rare
Concomitant extrapulmonary TB, n (%)	Infrequent
Pulmonary TB, n (%)	397 (98.3%)
Radiologic findings	
Bilateral lung disease	Common
Cavitary disease	Present in a subset
Baseline microbiologic diagnosis	
CBNAAT (Xpert MTB/RIF)	Positive for MTB
DST-confirmed XDR-TB	100%

Table 2. Microbiologic and programmatic treatment outcomes of XDR-TB patients (n=404).

Outcome	No of patients (%)
Converted patients	309 (76.5%)
Reverted patients	155(38.3%)
Reconverted patients	82(20.3%)
Required treatment >24 months	46 (11.4%)