# Shorter Drug-Tuberculosis Regimen: Implications with High Fluoroquinolone Resistant Tuberculosis and Weak Healthcare Systems

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A**bstract:**
The prevalence of drug-resistant pulmonary tuberculosis (DR-TB) in India, particularly Multidrug-resistant and Rifampicin-resistant TB (MDR-TB and RR-TB), poses a significant challenge to the country's efforts in controlling and eliminating the disease. The high incidence of FLQ-R in MDR-TB cases further complicates management and leads to poor outcomes. The implementation of Shorter Course Chemotherapy (SCC) for MDR-TB, including all-oral regimens, faces uncertainties in the Indian context due to the high prevalence of FLQ-R, limited healthcare system capacities, and challenges in detecting resistance. The BPaLM regimen recommended by the WHO for MDR/RR-TB cases, including those with FLQ-R, may be a more suitable option for India. However, the feasibility and appropriateness of newer regimens in the Indian setting require careful evaluation, along with the development of tailored strategies and guidelines to optimize treatment outcomes and prevent the development of further drug resistance. Addressing these complexities is crucial for the success of India's National Tuberculosis Eradication Program and the overall management of DR-TB in the country.

I**ntroduction:**
Drug-resistant pulmonary tuberculosis (DR-TB) poses a significant challenge to India's efforts to control and eliminate this longstanding disease, placing a substantial burden on the country's ongoing initiatives. In 2022, the World Health Organization (WHO) estimated 410,000 cases of Multidrug-resistant and Rifampicin-resistant TB (MDR-TB and RR-TB) worldwide, with India accounting for approximately 26% of these cases. Some important forms of drug resistance include Hr-TB, RR-TB, MDR-TB, Pre-XDR-TB, and XDR-TB. Prognosis in MDR and XDR TB cases is notably poor, ranging from 17–24% and 23–61%, respectively. The Pre-XDR-TB is new addition which includes MDR-TB with additional fluoroquinolone resistance (FLQ-R). The pivotal role of FLQ-R in all these cases is a major factor contributing to their bleak prognosis. [1]

The prevalence of MDR-TB in India varies from 2.4% to 5.6% in newly diagnosed cases and 11.6% to 35.8% in previously treated cases of tuberculosis [2-6]. Managing these cases is crucial, not only because they are challenging to treat, but also because they pose a significant infectious risk to their contacts, often leading to primary MDR-TB. These cases also remain infectious for longer periods. In the current era, diagnosing DR-TB is not enough; identifying resistance patterns through drug susceptibility testing (DST) and tailoring specific treatments are equally essential. This approach yields better results and prevents the progression or acceleration of drug resistance. However, treating these cases requires extended regimens with challenges of increased toxicity, difficulty in tolerance, high costs, and poor therapy outcomes. Addressing these complexities is vital in India for the success of the ambitious National Tuberculosis Eradication Program (NTEP), aiming to make the country TB-free by 2025.

**Challenges and Uncertainties Surrounding FLQ-R Management:**
In the past decade, significant transformations have reshaped the approach to tackling tuberculosis, particularly with the introduction of Shorter Course Chemotherapy (SCC) for MDR-TB. However, in the Indian context, uncertainties surround this therapy. Challenges arise from the high prevalence of MDR-TB, issues related to FLQ-R, and the current limitations of the healthcare system in dealing with these intricate cases. Despite advancements, addressing these concerns remains pivotal to the successful implementation of SCC, ensuring its optimal impact on MDR-TB management in India.

Fluoroquinolones (FLQs), particularly newer ones like Levofloxacin (LFX) and Moxifloxacin (MFX), exhibit remarkable efficacy against Mycobacterium tuberculosis (MTB) in both drug-sensitive (DS-TB) and DR-TB cases. They demonstrate an early bactericidal activity (EBA) comparable to Isoniazid (INH) and are considered safe for long-term use as anti-tuberculous (Anti-TB) agents without cross-resistance to other companion drugs. Treatment regimens incorporating FLQs, where organisms are sensitive to it, result in higher treatment success rates with lower mortality, and have better safety profiles. For over two decades, FLQs have held a core position in MDR-TB treatment, as indicated by the WHO guidelines. Despite numerous changes, additions, and deletions in drug recommendations, FLQs persist as indispensable Group A agents for both short and long-term MDR-TB regimens, whether in the form of all-oral or injection-containing therapies. [7-9] Fluoroquinolone resistance significantly impacts outcomes in MDR-TB cases, complicating management and leading to poor results. Identifying resistance to this crucial drug is essential for improving prognosis and devising treatment strategies that enhance survival rates.
Regrettably, the prevalence of FLQ-R in India among MDR-TB cases has reached alarming levels, standing at 24.14% in newly diagnosed and 20.91% in treated cases [3]. Reports from NTEP in 2021 and 2022 using second-line Line Probe Assays (SL LPAs) indicate FLQ-R rates of 28.4% and 29.8% in RR/MDR-TB cases [10]. Various other studies have consistently shown FLQ-R in RR/MDR-TB cases ranging from 36% to 69.2%, employing diverse methodologies. [11-15]

The widespread misuse of FLQs in India, both as an antibiotic, even in suspected tuberculosis cases, and as an Anti-TB drug, is a significant concern contributing to the high incidence of FLQ-R. The attractiveness of FLQs lies in their efficacy, easy availability, low cost, excellent tolerability, and a favourable safety profile, leading to their frequent misuse as antibiotics. In the context of DS-TB, FLQs are often misused as an additional drug to enhance therapy, replacing rifampicin or pyrazinamide to improve overall tolerance, or as an add-on drug to failing regimens. These practices contribute significantly to the development of high FLQ-R in MTB.

Data from studies and meta-analyses indicate that the key determinants of treatment success in MDR-TB regimens include the baseline susceptibility to fluoroquinolones, pyrazinamide, and second-line injectables. The probability of successful treatment is highest among participants with MDR-TB susceptible to both fluoroquinolones and pyrazinamide, and lowest in those with resistance to both. Notably, individuals with pyrazinamide resistance but sensitivity to fluoroquinolones fare better than those resistant to fluoroquinolones but sensitive to pyrazinamide [16].

Detecting FLQ-R in all MDR-TB cases is imperative, not only to enhance outcomes but also to prevent the escalation of drug resistance. Despite the widespread implementation of shorter all-oral regimens in the public sector, efficient methods for detecting FLQ-R, such as Xpert MTB/XDR, Next-Generation Sequencing (NGS), or Whole Genome Sequencing (WGS), are yet to be integrated. While the latter requires proper validation and cannot be directly applied to clinical specimens, its potential in the present time remains limited. Reducing the turnaround time for SL-LPA and ensuring its availability for patients on newer regimens is crucial. Accelerating the reporting time of Xpert MTB is also essential for early MDR-TB diagnosis to prevent lesion aggravation and spread, making patients unsuitable for shorter regimens. These constraints pose challenges to FLQ-R detection, vital information required before initiating newer shorter regimens, as resistance to FLQ has become a pivotal factor in managing MDR/RR-TB cases.

The WHO implemented SCC for MDR-TB in 2016, initially with injectables, later transitioning to an all-oral regimen in 2019 by replacing injections with bedaquiline (BDQ). However, both all-oral and injection-containing regimens, as outlined in the guidelines, are not recommended in the presence of FLQ-R. This limitation narrows treatment options, or otherwise overall poor outcomes, if FLQ-R is not detected before start of therapy [17]. Furthermore, these regimens are only appropriate when the disease in the lungs is not extensive, and there is no severe extra-pulmonary tuberculosis (EXPTB). Additionally, the patient should not have received second-line drugs in the regimen for over one month. Unfortunately, in India, with a large number of MDR-TB cases, a high prevalence of FLQ-R, limited facilities for early detection in public sector, and validated facilities in the private sector, along with cases often presenting with extensive disease, this therapy option seems less applicable and is largely not indicated in most cases. Udwadia et al. (2019) reported at a tertiary care hospital in Mumbai that less than 5% of MDR-TB patients were considered suitable for the Short Injectable MDR regimen [18]. Similar observations have been made in other countries, with suitability ranging from 10% to 50% of their MDR/RR-TB cases [19]. Moreover, the WHO's recommendation for an all-oral bedaquiline-containing regimen comes with very low certainty. Addressing these shortcomings in the implementation of newer regimens requires strategic interventions, policy changes, and further upgrades and optimizations of diagnostic facilities for more effective management. It also demands consideration of alternative therapies based on prevailing drug resistance patterns, patient characteristics, and healthcare infrastructure.

For India, the new 6-month BPaLM regimen, a recent addition to the shorter regimens by WHO, which includes bedaquiline, pretomanid, linezolid, and moxifloxacin, recommended in 2022, appears well-suited to prevalent conditions. Specifically designed to address MDR/RR-TB and pre-XDR-TB (with additional FLQ-R) in individuals aged over 14 years, it covers extensive extrapulmonary TB cases, excluding those with central nervous system, osteoarticular, and disseminated tuberculosis. Notably, this therapy has been recommended even in cases with FLQ-R. Until the feasibility of this therapy is assessed in Indian conditions, it might be worthwhile to continue with conventional long-term regimens using all oral drugs. Although drug susceptibility testing for FLQ is encouraged with this regimen, it is mainly to guide decisions on whether moxifloxacin should be retained or dropped based on sensitivity to FLQs. This aims to prevent undue delays in initiating the BPaLM regimen. In cases of documented resistance to FLQ, the BPaL regimen without moxifloxacin is recommended [18].However, it's vital to emphasize that even these recommendations are conditional and come with very low certainty of evidence, as per WHO (2022).

Implementing a short course regimen for MDR/RR-TB necessitates a robust healthcare system, with careful consideration to avoid premature and hasty decisions in implementing these newer therapies. This highlights the ongoing need for research, monitoring, and further evidence generation to refine and strengthen treatment recommendations for MDR/RR-TB in Indian contexts. Unfortunately, social factors such as education, living conditions, nutritional status, alcohol abuse, and smoking habits also adversely impact overall therapy outcomes in our scenario. The healthcare infrastructure, first, must be well-equipped with trained professionals and facilities to ensure effective implementation and monitoring of the short course regimen, especially regarding its feasibility and managing adverse drug reactions. Cardiac monitoring is particularly essential for drugs known to prolong the QT interval, seen in many newer drugs, optimizing patient care and treatment outcomes.

Equally vital is preventing the development of resistance to the crucial drug FLQ, a core component in DR-TB management. Achieving this goal involves multifaceted interventions, encompassing strict regulations on over-the-counter sales, judicious antibiotic use, preserving FLQ for anti-TB purposes, robust surveillance to gauge drug resistance prevalence, and heightened awareness among both healthcare professionals and the public. Proactively preventing FLQ-R ensures its continued effectiveness in benefiting a growing number of MDR/RR-TB cases.

**Conclusion:**

Considering the prevalent FLQ resistance burden, compounded by India's substantial share of DR-TB cases, coupled with the existing challenges within healthcare services tailored for these cases, the adoption of shorter treatment regimens may not be the most fitting choice within the Indian context. As guidelines continue to evolve, it becomes imperative to judiciously evaluate their feasibility and appropriateness in our unique conditions, steering clear of potential harm. It is well within our capabilities to develop tailored strategies and guidelines that align with our unique setup, ensuring sustained benefits in the long run for our patients.

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