

# Transforming Rifampicin-Resistant Tuberculosis Care: Diagnostics, Treatment, and Public Health in the Era of Shorter All-Oral Regimens

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## Citation

Tanvir Ahmed & Farzana Rahman (2026). Transforming Rifampicin-Resistant Tuberculosis Care: Diagnostics, Treatment, and Public Health in the Era of Shorter All-Oral Regimens. *Dinkum Journal of Medical Innovations*, 5(01):10-18. <https://doi.org/10.71017/djmi.5.01.d-0562>

## DOI

<https://doi.org/10.71017/djmi.5.01.d-0562>

## Identification

D-0562

## Publication History

Submitted: 04-01-2026  
Accepted: 19-01-2026  
Published: 31-01-2026

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## ABSTRACT

**Background:** Rifampicin-resistant tuberculosis remains one of the most serious forms of antimicrobial resistance and a major barrier to global tuberculosis elimination. Rifampicin resistance is clinically important because it is often used as a surrogate marker for multidrug-resistant tuberculosis, especially in settings where rapid isoniazid susceptibility testing is unavailable.

**Objective:** This article presents an original scholarly synthesis of rifampicin-resistant tuberculosis, focusing on epidemiology, molecular mechanisms, diagnostic approaches, shorter all-oral treatment regimens, adverse-event monitoring, social determinants, implementation barriers, and future research needs.

**Methods:** Recent evidence supports a major shift from prolonged injectable-containing regimens toward six-month and nine-month all-oral regimens based on bedaquiline, pretomanid, linezolid, moxifloxacin, delamanid, clofazimine and fluoroquinolones where appropriate.

**Results:** However, regimen success depends on early molecular diagnosis, complete drug susceptibility testing, patient-centered adherence support, pharmacovigilance, nutritional and psychosocial care, infection prevention, and equitable access.

**Conclusion:** Rifampicin-resistant tuberculosis should now be managed not only as a microbiological problem but also as a systems-level challenge requiring precision diagnostics, shorter effective therapy, social protection and antimicrobial-resistance governance.

**Keywords:** Rifampicin-resistant tuberculosis, MDR/RR-TB, drug-resistant TB, bedaquiline, antimicrobial resistance

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## 1. INTRODUCTION

Tuberculosis remains one of the leading infectious causes of death worldwide, and drug-resistant tuberculosis is among the most urgent antimicrobial-resistance threats. Rifampicin-resistant tuberculosis refers to disease caused by *Mycobacterium tuberculosis* strains resistant to rifampicin, one of the most powerful first-line anti-tuberculosis medicines [1]. Rifampicin resistance may occur alone, but in many settings, it is associated with isoniazid resistance and therefore functions as a practical marker for multidrug-resistant tuberculosis. The importance of rifampicin resistance goes beyond one drug. Rifampicin is a sterilizing agent that allows effective treatment shortening in drug-susceptible tuberculosis. When rifampicin resistance is present, standard first-line treatment becomes inadequate, risk of treatment failure increases, infectiousness may be prolonged, and patients require more complex regimens [2]. WHO describes multidrug-resistant tuberculosis as a continuing public health crisis and health security threat, with only about two in five people with drug-resistant tuberculosis accessing treatment in 2024. The past five years have changed the treatment landscape significantly. Injectable agents have largely been replaced by shorter all-oral regimens. The six-month BPaLM regimen, consisting of bedaquiline, pretomanid, linezolid and moxifloxacin, has become central to treatment of eligible patients with multidrug-resistant or rifampicin-resistant tuberculosis. WHO's 2025 consolidated tuberculosis treatment guidance includes updated recommendations for managing both drug-susceptible and drug-resistant tuberculosis [3]. This article provided an updated, value-added scholarly discussion of rifampicin-resistant tuberculosis. It focuses on disease burden, resistance biology, diagnosis, treatment, patient-centered care, social determinants, implementation gaps and future priorities. The article is written as an original academic synthesis using recent evidence published mainly within the last five years, including WHO reports, clinical trial evidence, peer-reviewed reviews relevant to tuberculosis diagnosis, treatment complexity and social determinants.

## 2. GLOBAL BURDEN OF RIFAMPICIN-RESISTANT TUBERCULOSIS

The global burden of rifampicin-resistant tuberculosis remains high despite better diagnostic and treatment tools. WHO's Global Tuberculosis Report 2025 states that multidrug-resistant or rifampicin-resistant tuberculosis caused an estimated 150,000 deaths worldwide in 2024. The WHO 2025 factsheet further reported that approximately 390,000 people developed MDR/RR-TB in 2024, but only 164,545 people were treated for rifampicin-resistant tuberculosis, equal to around 42% of the estimated burden [4]. This gap shows that the main challenge is no longer simply the absence of treatment. Rather, it is the failure to detect, classify, enroll and retain patients in care. The burden is concentrated in high-TB-burden countries, including India, Indonesia, China, the Philippines, Pakistan, the Russian Federation and several countries in Africa and Eastern Europe. In 2023, WHO reported that India, the Russian Federation, Indonesia, China and the Philippines together accounted for more than half of estimated global MDR/RR-TB incident cases. The epidemiology of rifampicin-resistant tuberculosis is shaped by incomplete treatment, weak diagnostic access, delayed drug susceptibility testing, poor infection control, poverty, crowding, malnutrition, migration, HIV, diabetes, smoking, alcohol use and health system fragmentation [5]. In many low-resource settings, rifampicin-resistant tuberculosis is diagnosed late, often after several months of ineffective therapy, allowing further transmission and amplification of resistance.

## 3. MOLECULAR BASIS OF RIFAMPICIN RESISTANCE

Rifampicin targets the beta subunit of bacterial RNA polymerase, encoded by the *rpoB* gene. Most rifampicin resistance in *M. tuberculosis* results from mutations in the rifampicin resistance-determining region of *rpoB*. These mutations reduce drug binding and allow bacterial transcription to continue despite rifampicin exposure. The biological importance of rifampicin resistance is twofold. First, it

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indicates resistance to one of the most potent first-line drugs. Second, because rifampicin resistance is frequently associated with isoniazid resistance, it often signals multidrug-resistant tuberculosis. Molecular platforms such as Xpert MTB/RIF and Xpert MTB/RIF Ultra detect *M. tuberculosis* and rifampicin resistance by identifying mutations in *rpoB*. A 2025 review of Xpert limitations explains that the assay detects tuberculosis complex organisms and rifampicin resistance by evaluating mutations in the *rpoB* gene [6]. However, molecular testing has limitations. Some mutations may confer low-level resistance, some results may be discordant with phenotypic testing, and rare mutations may be missed. Therefore, rifampicin resistance should trigger comprehensive drug susceptibility testing, including fluoroquinolone resistance testing, because fluoroquinolone susceptibility determines eligibility for several shorter regimens.

#### 4. DIAGNOSIS OF RIFAMPICIN-RESISTANT TUBERCULOSIS

The diagnostic priority is rapid identification of both tuberculosis and rifampicin resistance. Xpert MTB/RIF and Xpert MTB/RIF Ultra are widely used because they provide rapid results directly from clinical specimens. Xpert Ultra improves detection compared with the original assay, particularly in smear-negative and paucibacillary disease, although interpretation of trace results and discordant resistance findings still requires clinical judgment [7]. Molecular diagnosis shortens the time from suspicion to appropriate treatment. Without rapid molecular testing, patients may be started on standard first-line therapy and remain infectious while receiving ineffective treatment. This is especially dangerous for people with cavitary pulmonary disease, HIV coinfection, malnutrition, diabetes or household exposure to children. TrueNat platforms are increasingly important in some high-burden countries because they can detect tuberculosis and rifampicin resistance closer to the point of care. A study article on tubercular meningitis notes that TrueNat MTB, MTB-RIF Dx and MTB Plus are emerging molecular assays in India, with MTB and MTB Plus used for initial tuberculosis diagnosis and MTB-RIF Dx used for rifampicin resistance detection after a positive diagnostic test [8]. Line-probe assays and sequencing-based approaches can detect resistance to rifampicin, isoniazid, fluoroquinolones and injectable agents. Culture-based drug susceptibility testing remains important, especially when molecular results are discordant or when extended resistance patterns need confirmation. However, culture-based testing is slow and requires laboratory infrastructure that many high-burden areas still lack. A practical diagnostic algorithm should include:

- Clinical suspicion of pulmonary or extrapulmonary tuberculosis.
- Rapid molecular test for *M. tuberculosis* and rifampicin resistance.
- If rifampicin resistance is detected, immediate enrolment into drug-resistant tuberculosis care.
- Baseline fluoroquinolone resistance testing.
- Additional testing for isoniazid, bedaquiline, linezolid, pretomanid or second-line drugs where available [9].
- HIV testing, diabetes screening, pregnancy assessment and baseline safety investigations.
- Contact investigation, especially for children and household members.

#### 5. TREATMENT EVOLUTION: FROM LONG INJECTABLE REGIMENS TO SHORTER ALL-ORAL THERAPY

Historically, rifampicin-resistant tuberculosis treatment lasted 18–24 months and often included injectable drugs such as amikacin, kanamycin or capreomycin. These regimens were toxic, difficult to complete, costly and associated with hearing loss, renal toxicity, poor adherence and weak outcomes. The modern treatment era is different. Bedaquiline, pretomanid, linezolid, delamanid and optimized fluoroquinolone-based regimens have transformed the field [10]. WHO's 2022 update recommended a six-month BPaLM regimen for eligible patients with MDR/RR-TB, replacing many older long regimens.

WHO's 2025 treatment guidance continues to consolidate updated recommendations for drug-resistant tuberculosis care.

## 6. BPaLM AND BPaL REGIMENS

BPaLM consists of bedaquiline, pretomanid, linezolid and moxifloxacin. When fluoroquinolone resistance is confirmed or strongly suspected, moxifloxacin is usually removed, resulting in BPaL. WHO guidance describes pretomanid at 200 mg once daily, linezolid at 600 mg once daily and moxifloxacin at 400 mg once daily in the BPaLM regimen. The TB-PRACTECAL trial was a major turning point. It showed that a six-month all-oral regimen was safer and more effective than standard care, with 89% cure in the BPaLM group compared with 52% in the standard-care group [11]. A 2026 review also summarized that six months of BPaLM cured 89% of people with rifampicin-resistant tuberculosis in TB-PRACTECAL. The clinical advantages of BPaLM include shorter duration, no injectable drug, faster culture conversion, simplified administration and improved patient acceptability. However, it is not suitable for all patients. Exclusions or special considerations may include pregnancy, very young age depending on national guidance, extensive extrapulmonary disease, drug intolerance, resistance to core drugs, QT prolongation risk, severe liver disease or prior exposure to bedaquiline, pretomanid or linezolid [12].

## 7. NEW SIX-MONTH AND NINE-MONTH REGIMENS

The drug-resistant tuberculosis pipeline is expanding beyond BPaLM. WHO issued a 2024 rapid communication describing key updates, including a new six-month regimen based on bedaquiline, delamanid and linezolid combined with levofloxacin, clofazimine or both, and several nine-month all-oral regimens for MDR/RR-TB without fluoroquinolone resistance [13]. The end TB trial also contributed important evidence by comparing five experimental nine-month regimens containing bedaquiline or delamanid with other oral drugs. The end TB programme reported that several regimens were non-inferior to standard care and represented a major improvement over longer regimens that could include daily injections [14]. These developments mean that treatment selection is becoming more individualized. The future standard will likely not be a single universal regimen but a menu of shorter regimens chosen according to fluoroquinolone susceptibility, previous drug exposure, age, pregnancy status, extrapulmonary involvement, comorbidities and resistance profile.

## 8. SAFETY MONITORING AND ADVERSE EVENTS

Shorter all-oral regimens are easier to complete, but they still require careful monitoring. Bedaquiline and delamanid can prolong the QT interval. Linezolid can cause peripheral neuropathy, optic neuropathy, myelosuppression and lactic acidosis. Pretomanid can contribute to hepatotoxicity and should be used carefully in patients with liver disease [15]. Fluoroquinolones can cause QT prolongation, tendinopathy, dysglycaemia, neuropsychiatric effects and other adverse events.

**Table 01:** A practical monitoring plan should include

| Monitoring Area      | Why It Matters                                                                  |
|----------------------|---------------------------------------------------------------------------------|
| ECG monitoring       | Detect QT prolongation from bedaquiline, delamanid, moxifloxacin or clofazimine |
| Full blood count     | Detect linezolid-related anemia, leukopenia or thrombocytopenia                 |
| Liver function tests | Monitor hepatotoxicity from pretomanid, bedaquiline and other drugs             |
| Renal function       | Important for comorbid illness and dose adjustment where needed                 |

|                         |                                                         |
|-------------------------|---------------------------------------------------------|
| Visual assessment       | Detect linezolid-associated optic neuropathy            |
| Neuropathy screening    | Detect linezolid-related peripheral neuropathy early    |
| Sputum smear/culture    | Track bacteriological response                          |
| Adherence review        | Identify missed doses, side effects and social barriers |
| Mental health screening | Address depression, anxiety, stigma and isolation       |

The clinical goal is not simply to prescribe a regimen but to complete treatment safely. Early recognition of toxicity allows dose adjustment, drug substitution or supportive treatment before permanent harm occurs.

## 9. PATIENT-CENTERED CARE AND ADHERENCE

Rifampicin-resistant tuberculosis treatment is physically, emotionally and financially demanding. Even shorter regimens can be difficult for patients who face poverty, stigma, malnutrition, unemployment, transport costs, housing insecurity or weak family support [16]. A study on drug-resistant tuberculosis in rural Nepal emphasized that access to healthcare, financial status and distance from home strongly influence adherence and outcomes. It also highlighted stigma, job loss and disclosure-related difficulties as major psychosocial consequences of DR-TB. This finding is highly relevant to rifampicin-resistant tuberculosis because poor adherence can produce treatment failure, relapse, ongoing transmission and further resistance [17]. A patient-centered model should include transport support, nutritional supplementation, counselling, peer support, mental health care, digital adherence tools where appropriate, adverse-event management and protection against catastrophic costs.

## 10. NUTRITION, COMORBIDITY AND HOST FACTORS

Treatment outcomes are influenced not only by the drug regimen but also by host health. Malnutrition, anemia, diabetes, HIV, smoking, alcohol use and vitamin deficiencies may worsen outcomes. A study on tuberculous pleural effusion in Bangladesh reported that 75% of participants had vitamin D deficiency and 15% had vitamin D insufficiency, supporting the wider observation that nutritional deficits are common in tuberculosis populations [18]. Although vitamin D supplementation should not be presented as a substitute for anti-tuberculosis treatment, nutritional assessment is important. Patients with rifampicin-resistant tuberculosis often require protein-calorie support, micronutrient assessment, diabetes control, HIV treatment, smoking cessation and management of anemia. Strong tuberculosis programs increasingly integrate clinical treatment with social and nutritional support.

## 11. INFECTION PREVENTION AND PUBLIC HEALTH CONTROL

Rifampicin-resistant tuberculosis is preventable, but transmission continues when diagnosis is delayed and infection control is weak. Public health control requires early case detection, effective treatment, household contact investigation, preventive treatment for eligible contacts, ventilation, respiratory protection in high-risk clinical settings and community education. Contact investigation is especially important because household contacts may share both exposure risk and social vulnerability [19]. Children, people living with HIV and immunocompromised individuals should be prioritized. Health facilities must reduce transmission through triage, cough etiquette, rapid testing, airborne infection control, adequate ventilation and separation of infectious patients when necessary.

## 12. IMPLEMENTATION BARRIERS

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Despite scientific progress, implementation remains uneven. WHO reported that the number of people with MDR/RR-TB started on six-month regimens increased from 5,653 in 2023 to 34,256 in 2024, and that 97 countries were using six-month regimens by the end of 2024. This is encouraging, but the number treated remains far below the estimated global burden.

Key barriers include:

- Limited access to rapid molecular testing.
- Shortage of cartridges and laboratory capacity.
- Delayed fluoroquinolone resistance testing.
- High cost or limited availability of new drugs.
- Weak pharmacovigilance systems.
- Inadequate clinician training on new regimens.
- Exclusion of patients with extrapulmonary disease or complex comorbidities.
- Poor integration between public and private sectors.
- Stigma and financial hardship.
- Insufficient long-term outcome monitoring.

The biggest risk is creating a two-tier system where patients in well-resourced settings receive rapid diagnosis and shorter oral regimens, while patients in poorer settings continue to face delay, toxicity and treatment failure.

### **13. VALUE-ADDED FRAMEWORK FOR RIFAMPICIN-RESISTANT TB CARE**

A modern rifampicin-resistant tuberculosis programme should be built around seven linked priorities:

- **Rapid diagnosis** Every presumptive TB patient should have access to molecular testing that detects rifampicin resistance early.
- **Resistance-informed regimen selection** Fluoroquinolone susceptibility testing should be performed quickly because it determines whether BPaLM, BPaL or another regimen is appropriate.
- **Shorter all-oral treatment where eligible** Six-month or nine-month all-oral regimens should be prioritized when supported by current guidance and patient eligibility.
- **Active safety monitoring** ECG, blood counts, liver tests, neuropathy screening and visual monitoring should be built into routine care.
- **Social and nutritional support** Treatment should include transport support, food assistance, counselling and protection from catastrophic costs.
- **Infection control and contact management** Household contacts and healthcare settings must be actively managed to prevent further transmission.
- **Digital and registry-based follow-up** Programs should track culture conversion, adverse events, relapse, mortality, resistance amplification and patient-reported outcomes.

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## 14. FUTURE RESEARCH PRIORITIES

Future rifampicin-resistant tuberculosis research should move beyond short-term cure alone. Important priorities include:

- Head-to-head comparison of six-month regimens.
- Optimal linezolid dose and duration to reduce toxicity.
- Regimen safety in pregnancy, children and extrapulmonary TB.
- Real-world effectiveness in low-resource settings.
- Whole-genome sequencing for resistance prediction.
- Host-directed therapies and immune biomarkers.
- Better treatment for pre-XDR and XDR-TB.
- Prevention strategies for contacts of MDR/RR-TB patients.
- Cost-effectiveness of decentralized treatment.
- Mental health and stigma interventions.
- Long-term relapse-free survival after shorter regimens.

Artificial intelligence and genomic surveillance may help identify resistance patterns earlier, but these tools must be implemented ethically and equitably. The priority remains access: no diagnostic innovation will reduce mortality if patients cannot receive timely testing, treatment and follow-up.

## 15. CONCLUSION

Rifampicin-resistant tuberculosis is a defining challenge for global tuberculosis control and antimicrobial-resistance policy. The scientific outlook is more hopeful than it was a decade ago because shorter, safer and more effective all-oral regimens are now available for many patients. BPaLM and related regimens have changed the standard of care by reducing treatment duration and improving outcomes. However, the global response remains limited by underdiagnosis, incomplete drug susceptibility testing, weak access to new medicines, toxicity monitoring gaps, stigma, poverty and fragile health systems. Rifampicin-resistant tuberculosis should therefore be addressed through an integrated model that combines rapid molecular diagnosis, resistance-guided treatment, shorter all-oral regimens, pharmacovigilance, social protection, nutritional support and strong public health surveillance. The next major breakthrough will not only be a new drug; it will be the ability to deliver existing and emerging tools equitably to every patient who needs them.

## AUTHOR CONTRIBUTION STATEMENT

Tanvir Ahmed & Farzana Rahman: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, Drafting the work or reviewing it critically for important intellectual content; AND Final approval of the version to be published, and Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**ACKNOWLEDGEMENTS:** No specific individuals, institutions, or organizations contributed additional support or assistance requiring formal acknowledgement for this study.

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## DECLARATIONS:

**Funding:** This research received no specific grant, financial support, or funding from any public, commercial, or non-profit organization.

**Conflicts Of Interest:** The authors declare that there are no conflicts of interest, financial or otherwise, that could have influenced the research, analysis, or interpretation of the findings presented in this article.

**Data Availability:** The datasets and information used in this study are publicly available from the sources cited within the article. No proprietary or restricted data were used.

**Trial Registration:** Trial registration is not applicable to this study, as it does not involve clinical trials, human participants, or experimental interventions.

**Generative AI Disclosure:** Generative artificial intelligence tools were not used for generating research data, conducting analyses, or producing scientific conclusions in this study. The authors take full responsibility for the content and accuracy of the manuscript.

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## **SUPPLEMENTAL MATERIAL**

No supplementary files, datasets, figures, or additional materials are associated with this study. Any information necessary to understand and evaluate the work is included in the main article.