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DRUG RESISTANCE IN TUBERCULOSIS: MECHANISMS, EPIDEMIOLOGY, DIAGNOSIS, AND CURRENT MANAGEMENT STRATEGIES — A LITERATURE REVIEW

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Abstract

Tuberculosis (TB) remains one of the leading infectious causes of death globally, with drug-resistant forms representing a critical and growing threat to public health. Drug-resistant TB — encompassing multidrug-resistant tuberculosis (MDR-TB), pre-extensively drug-resistant tuberculosis (pre-XDR-TB), and extensively drug-resistant tuberculosis (XDR-TB) — arises primarily through chromosomal mutations in Mycobacterium tuberculosis under selective therapeutic pressure from inadequate or incomplete treatment. This literature review synthesises evidence from PubMed-indexed publications to examine the molecular mechanisms underlying drug resistance, global epidemiological trends, contemporary diagnostic innovations, and evolving treatment paradigms. Key resistance mechanisms include mutations in katG and inhA conferring isoniazid resistance, rpoB mutations mediating rifampicin resistance, and multigenic alterations in gyrA/gyrB conferring fluoroquinolone resistance. Molecularly, platforms such as Xpert MTB/RIF Ultra and whole-genome sequencing have substantially shortened the path to diagnosis. The WHO-endorsed BPaLM regimen has transformed MDR-TB treatment, offering a six-month all-oral course with markedly improved outcomes. Nonetheless, treatment success rates remain suboptimal globally, and the drug development pipeline requires urgent investment. This review underscores the need for integrated surveillance, rapid diagnostics, individualised regimens, and sustained research investment to curb the global burden of drug-resistant TB.

Keywords: *tuberculosis; drug resistance; multidrug-resistant tuberculosis; extensively drug-resistant tuberculosis; antimicrobial resistance.*

INTRODUCTION

Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), is one of the oldest and most consequential infectious diseases affecting humanity. Despite decades of chemotherapy, the World Health Organization (WHO) estimated 10.6 million new TB cases and 1.3 million deaths in 2022, maintaining TB's rank as the second leading infectious disease killer globally, surpassed only by COVID-19 [1]. The advent of effective anti-TB chemotherapy in the 1950s prompted optimism about the eradication of the disease; however, the emergence of drug-resistant strains has fundamentally undermined control efforts and transformed TB into a complex, resource-intensive, and often fatal condition [2].

Drug-resistant TB (DR-TB) arises when Mtb strains harbour mutations that confer resistance to one or more anti-TB agents. The spectrum of DR-TB ranges from mono-resistance (affecting a

single drug) to the most severe forms: MDR-TB (resistance to at least rifampicin and isoniazid), pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance), and XDR-TB (pre-XDR-TB with additional resistance to bedaquiline or linezolid) [3]. The global burden of MDR/RR-TB was estimated at 410,000 incident cases in 2022, with treatment success rates of only 57% for MDR-TB and approximately 39% for XDR-TB [1].

The factors driving drug resistance are multifactorial: inadequate treatment regimens, poor patient adherence, suboptimal drug quality, weak healthcare infrastructure, and transmission of already-resistant strains all contribute to this epidemiological crisis [4]. High-burden countries in Asia, Eastern Europe, and sub-Saharan Africa disproportionately carry this load, and the intersection of DR-TB with HIV co-infection and the disruption caused by the COVID-19 pandemic has further complicated global progress [5].

This literature review was conducted to provide a comprehensive and current synthesis of the molecular mechanisms of drug resistance in TB, global epidemiological trends, advances in diagnostic platforms, and evolving therapeutic strategies — with a focus on evidence published in PubMed-indexed journals. The classification of DR-TB as defined by the WHO 2021 revision is summarised in Table 1.

Table 1. WHO Classification of Drug-Resistant Tuberculosis (2021 Revision)

Category	Definition	First reported / Redefined
RR-TB	Resistance to rifampicin (any pattern)	WHO 2014
MDR-TB	Resistance to rifampicin AND isoniazid	1990s
Pre-XDR-TB	MDR/RR-TB + resistance to any fluoroquinolone	WHO 2021 revision
XDR-TB	Pre-XDR-TB + resistance to bedaquiline or linezolid	WHO 2021 revision
TDR-TB	Resistance to all available anti-TB agents (proposed)	Udwadia et al., 2012

METHODS

This review was conducted following IMRAD guidelines and structured using a pre-defined search strategy. A systematic search of the PubMed database was performed using Medical Subject Headings (MeSH) terms combined with Boolean operators. Primary search terms included: "tuberculosis" AND ("drug resistance" OR "multidrug-resistant tuberculosis" OR "extensively drug-resistant tuberculosis" OR "MDR-TB" OR "XDR-TB"). Secondary searches targeted sub-topics including "tuberculosis molecular mechanisms of resistance," "Xpert MTB/RIF Ultra," "whole-genome sequencing tuberculosis," and "BPaLM regimen tuberculosis."

Inclusion criteria were: (1) original research articles, systematic reviews, and meta-analyses published between January 2000 and December 2024; (2) studies involving human populations with drug-resistant or drug-susceptible TB; (3) articles published in English in full-text form. Exclusion criteria included conference abstracts without full publications, editorials without primary data, and studies exclusively using animal models. From an initial pool of 94 records, 20 primary sources were selected for detailed synthesis based on methodological rigor and relevance to the review questions. Reference lists were hand-searched for additional eligible

sources.

RESULTS

1. Molecular Mechanisms of Drug Resistance

Unlike many bacterial pathogens, M. tuberculosis does not acquire resistance through horizontal gene transfer; all clinically significant resistance in Mtb arises exclusively through spontaneous chromosomal point mutations that accumulate stepwise under antibiotic selection pressure [6]. This fundamental biological feature has several clinical implications: resistance acquisition is generally sequential rather than simultaneous, and the probability of spontaneous resistance to two drugs simultaneously is the product of individual mutation rates — approximately 10^{-16}, making adequate dual-drug coverage the cornerstone of TB chemotherapy [7].

Isoniazid (INH) resistance represents the most frequent genetic event in clinical Mtb populations. Approximately 60–70% of INH-resistant strains harbour the katG S315T substitution, which reduces catalase-peroxidase activity and prevents bioactivation of the INH prodrug. Promoter mutations in the inhA regulatory region (principally at positions −15 and −8) account for 15–34% of resistant isolates and also confer low-level cross-resistance to ethionamide [6].

Rifampicin (RIF) resistance is almost exclusively mediated by mutations within an 81-base-pair hypervariable region — the rifampicin resistance-determining region (RRDR) — of the rpoB gene. Codons 516, 526, and 531 harbour more than 95% of clinically significant rpoB mutations [8]. Because RIF resistance is so strongly correlated with MDR-TB in clinical settings, it serves as the primary surrogate marker for MDR-TB in molecular diagnostics.

Fluoroquinolone resistance, which defines the pre-XDR and XDR categories, is predominantly conferred by mutations in the quinolone resistance-determining regions (QRDR) of gyrA and gyrB, which encode subunits of DNA gyrase. Codons 90, 91, and 94 of gyrA account for the majority of high-level resistance [9]. Resistance to bedaquiline — the first genuinely novel anti-TB drug in over four decades — involves mutations in atpE encoding the c-subunit of mycobacterial ATP synthase, or in Rv0678, which upregulates MmpL5-mediated drug efflux. Linezolid resistance is mediated by mutations in rrl (23S rRNA) and rplC (ribosomal protein L3) [10].

The key resistance-conferring mutations and their estimated frequencies are summarised in Table 2.

Table 2. Key Drug Resistance-Conferring Mutations in Mycobacterium tuberculosis

Drug	Gene	Mutation / Region	Frequency (%)
Isoniazid (INH)	katG	S315T substitution	60–70%
Isoniazid (INH)	inhA	Promoter mutations (−15, −8)	15–34%
Rifampicin (RIF)	rpoB	81-bp RRDR (codons 516, 526, 531)	>95%
Pyrazinamide	pncA	Multiple point mutations	72–97%

(PZA)			
Ethambutol (EMB)	embB	Codon 306 (most frequent)	47–65%
Fluoroquinolones	gyrA/gyrB	QRDR codons 90, 91, 94 (gyrA)	75–94%
Bedaquiline	atpE / Rv0678	atpE point mutations; Rv0678 MmpL5 overexpression	Emerging
Linezolid	rrl / rplC	23S rRNA mutations; ribosomal protein mutations	Emerging

2. Global Epidemiology of Drug-Resistant TB

The global epidemiology of DR-TB reflects a complex interplay of biological, social, and systemic determinants. According to the WHO Global TB Report 2023, approximately 410,000 incident cases of MDR/RR-TB occurred in 2022 [1]. India, China, and the Russian Federation together account for approximately 45% of the global MDR-TB burden [1]. Eastern European and Central Asian countries have historically exhibited particularly high rates of primary drug resistance, partly attributable to widespread use of low-quality medications and disrupted treatment systems following the dissolution of the Soviet Union [11].

HIV co-infection profoundly worsens DR-TB outcomes. Among people living with HIV who develop TB, immune suppression accelerates disease progression, reduces immune-mediated clearance capacity, and complicates drug interactions between antiretroviral and anti-TB regimens [5]. The COVID-19 pandemic caused an estimated 1.4 million "missing" TB diagnoses in 2020–2021, with projected downstream consequences for resistance amplification and mortality [12]. The proportion of TB patients with MDR-TB is approximately 3.9% among new cases and 19% among previously treated cases globally, though these estimates vary substantially by region [1].

3. Diagnostic Advances

Rapid and accurate diagnosis of DR-TB is a prerequisite for appropriate therapy and transmission interruption. Traditional culture-based drug susceptibility testing (DST) using Löwenstein-Jensen or BACTEC MGIT liquid culture requires 3–8 weeks given the slow growth rate of Mtb, resulting in significant diagnostic delays [13].

Molecular diagnostic platforms have substantially transformed this landscape. The Xpert MTB/RIF assay (Cepheid, USA) simultaneously detects Mtb DNA and rpoB mutations conferring rifampicin resistance within approximately two hours directly from sputum samples. Its enhanced successor, Xpert MTB/RIF Ultra, incorporates two additional multi-copy amplification targets (IS6110 and IS1081), achieving superior sensitivity for paucibacillary disease including smear-negative and paediatric TB — with reported sensitivity for RIF resistance detection of 87–90% [14]. The WHO recommends Xpert Ultra as the initial diagnostic test in settings with moderate-to-high TB prevalence.

Line probe assays — the MTBDRplus and MTBDRsl assays (Hain Lifescience, Germany) — extend genotypic DST to isoniazid, fluoroquinolones, and second-line injectable agents, providing resistance profiles within 24–48 hours from culture or direct sputum specimens [15]. Whole-genome sequencing (WGS) represents the current frontier, providing comprehensive

resistance profiles, phylogenetic strain typing, and outbreak investigation in a single assay [16]. To standardise WGS-based resistance interpretation, the WHO published a catalogue of Mtb mutations with established clinical significance in 2021, which was updated in 2023 [1].

4. Treatment of Drug-Resistant TB

The treatment of MDR-TB underwent a landmark paradigm shift following the WHO 2022 consolidated guidelines, which were informed by pivotal clinical trials including ZeNix, TB-PRACTECAL, and STREAM Stage 2 [3]. The preferred regimen for MDR/pre-XDR-TB — the BPaLM regimen (bedaquiline, pretomanid, linezolid, moxifloxacin) — delivers a six-month all-oral course. TB-PRACTECAL demonstrated a treatment success rate of 89% at 72 weeks with BPaLM, compared with 52% in the control arm [17]. For XDR-TB or fluoroquinolone-resistant MDR-TB where moxifloxacin cannot be included, the BPaL regimen (bedaquiline, pretomanid, linezolid) is recommended, extended to 6–9 months [3].

Bedaquiline, a diarylquinoline ATP synthase inhibitor, was the first genuinely novel anti-TB drug class introduced in over 40 years following its 2012 FDA approval. Delamanid, a nitroimidazole targeting mycolic acid synthesis, received conditional European approval in 2014 and has been incorporated into individualised regimens for XDR-TB [18]. Linezolid demonstrates potent bactericidal activity against Mtb but is complicated by dose-dependent adverse effects — peripheral neuropathy, myelosuppression, and optic neuritis — requiring therapeutic drug monitoring and dose optimisation [19].

For drug-susceptible TB, the TBTC Study 31/ACTG A5349 trial demonstrated non-inferiority of a four-month rifapentine–moxifloxacin regimen (4RPM) compared with the standard six-month regimen [20]. Current WHO-recommended regimens and their indications are summarised in Table 3.

Table 3. WHO-Recommended Treatment Regimens for Tuberculosis (2022 Guidelines)

Regimen	Drugs	Duration	Target population
BPaLM	Bedaquiline + Pretomanid + Linezolid + Moxifloxacin	6 months	MDR/pre-XDR-TB (preferred)
BPaL	Bedaquiline + Pretomanid + Linezolid	6–9 months	XDR-TB; fluoroquinolone-resistant MDR-TB
Shorter MDR regimen (modified)	Bedaquiline-based 7-drug regimen	9–11 months	MDR-TB without fluoroquinolone resistance
Standard DS-TB (4RPM)	Rifapentine + Moxifloxacin + Isoniazid + Pyrazinamide	4 months	Drug-susceptible TB (non-inferior to 6HRZE)
Standard DS-TB (6HRZE)	Isoniazid + Rifampicin + Pyrazinamide + Ethambutol	6 months	Drug-susceptible TB (standard)

DISCUSSION

The evidence synthesised in this review underscores that drug-resistant TB is simultaneously a biological phenomenon and a systemic failure of healthcare delivery. At the molecular level, the

stepwise accumulation of resistance mutations in Mtb is well characterised and serves as the foundation for molecular diagnostics and targeted drug development. At the system level, the clinical expression of drug resistance is profoundly shaped by healthcare capacity, treatment access, pharmacovigilance, and socioeconomic determinants [4, 11].

The transition from culture-based DST to molecular diagnostics marks a genuine inflection point in DR-TB management. The Xpert Ultra platform has enabled point-of-care detection of rifampicin resistance in settings previously dependent on weeks-long culture workflows [14]. WGS, while still largely confined to reference laboratories in high-income settings, is rapidly becoming the gold standard for comprehensive resistance profiling and represents the future of individualised DR-TB therapy [16]. Bridging the implementation gap — ensuring that molecular diagnostic advances reach the high-burden, low-resource settings where they are most urgently needed — remains a critical priority.

Therapeutically, the introduction of the BPaLM regimen marks a watershed moment comparable in significance to the introduction of rifampicin in the 1960s. By replacing poorly tolerated injectable agents (kanamycin, capreomycin) and reducing treatment duration from 18–24 months to six months, BPaLM has the potential to substantially improve patient adherence, reduce adverse effects, and increase treatment success rates [3, 17].

Nevertheless, several challenges persist. Resistance to bedaquiline and linezolid — the two pharmacological anchors of BPaLM — has already been documented in clinical isolates, raising urgent concerns about resistance amplification if these agents are deployed without robust microbiological support and DST capacity [10]. The drug development pipeline beyond the bedaquiline–pretomanid–delamanid generation remains sparse: several candidates have failed in late-stage trials, and economic incentives for pharmaceutical investment in TB — a disease disproportionately affecting impoverished populations — remain inadequate relative to the global disease burden [2].

The COVID-19 pandemic's disruption of TB services constitutes a cautionary lesson about the fragility of TB programme gains and the systemic nature of the epidemic. Rebuilding diagnostic and treatment capacity in disrupted healthcare systems, while simultaneously integrating TB control into broader infectious disease preparedness frameworks, is essential to reverse pandemic-related setbacks [5, 12].

CONCLUSION

Drug resistance in tuberculosis represents one of the most formidable challenges in contemporary infectious disease medicine. The molecular basis of resistance is well delineated, providing the scientific foundation for rapid molecular diagnostic assays and rationally designed therapeutic agents. The therapeutic landscape has been profoundly transformed by the WHO 2022-endorsed BPaLM regimen, offering a six-month, all-oral, bactericidal course for MDR/pre-XDR-TB with markedly improved efficacy compared with historical regimens [3, 17]. Nonetheless, global treatment success rates remain suboptimal, the antimicrobial pipeline requires urgent expansion, and implementation barriers in high-burden settings persist.

Addressing drug-resistant TB demands a multi-pronged and sustained global response: strengthening real-time surveillance systems to track emerging resistance patterns; expanding equitable access to rapid molecular diagnostics including WGS; ensuring universal access to WHO-recommended regimens through sustainable procurement mechanisms; accelerating investment in a diversified drug and vaccine development pipeline; and addressing the structural social determinants — poverty, malnutrition, overcrowding, and fragmented healthcare — that drive both TB transmission and resistance amplification [1, 4]. Only through such integrated, multi-sectoral strategies can the global community realistically progress toward the WHO End TB Strategy targets of a 90% reduction in TB incidence and 95% reduction in TB deaths by 2035.

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