Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol. 6 No. 3 (2025): March 2025 Issue
https://doi.org/10.51168/sjhrafrica.v6i3.1591
Original Article

GLOBAL TRENDS, RISK FACTORS, AND CHALLENGES IN DRUG-RESISTANT TUBERCULOSIS: A SYSTEMATIC REVIEW OF ANTIMICROBIAL RESISTANCE PATTERNS AND DETERMINANTS

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Abstract

Background

Drug-resistant tuberculosis (DR-TB) remains one of the greatest threats to global public health, with multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) posing significant challenges to TB control efforts. While scientific advancements have led to improved diagnostics and treatment options, the continued spread of resistant TB strains threatens to undo decades of progress. This systematic review synthesizes evidence on the global patterns of antimicrobial resistance (AMR) in TB, identifying key determinants, regional variations, and critical gaps in TB management.

Materials and Methods

A systematic review of published studies was conducted to examine the prevalence, risk factors, diagnostic and treatment challenges, and policy gaps contributing to AMR in TB. Studies were selected based on their focus on MDR-TB and XDR-TB, with a particular emphasis on regional differences, evolving resistance mechanisms, and healthcare system limitations.

Results

The review highlights significant regional variability in MDR-TB and XDR-TB prevalence, with the highest burden observed in sub-Saharan Africa, South Asia, and Eastern Europe. Increasing evidence suggests that primary MDR-TB transmission rather than treatment failure is driving resistance in high-burden regions, challenging traditional TB control strategies. Key risk factors include previous TB treatment, HIV co-infection, delayed diagnosis, and poor treatment adherence. Diagnostic challenges persist, with limited access to drug susceptibility testing (DST) and delayed MDR-TB detection contributing to prolonged infectious periods. Treatment barriers include adverse drug reactions, financial constraints, and the rising resistance to second-line drugs, particularly fluoroquinolones.

Conclusion

The growing burden of DR-TB underscores the urgent need for strengthened global TB control strategies, including expanded molecular diagnostics, enhanced adherence support, pharmacovigilance, and infection control measures. Without decisive action, MDR-TB and XDR-TB will continue to spread, increasing treatment failures and mortality rates. Urgent investment in TB research, new drug development, and healthcare infrastructure is critical to containing the global DR-TB epidemic.

Keywords: *Drug-resistant tuberculosis, Multidrug-Resistant Tuberculosis, Extensively Drug-Resistant Tuberculosis, Antimicrobial Resistance, Risk Factors, Treatment Challenges, Global Health*
Submitted: *2025-03-02* ***Accepted:*** *2025-03-16* ***Published:*** *2025-03-31*
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I. Introduction

a) Global Burden of Tuberculosis and Antimicrobial Resistance

Tuberculosis (TB) remains a significant global public health challenge, disproportionately affecting low- and middle-income countries, particularly in Africa. Despite being a preventable and treatable disease, the emergence of antimicrobial resistance (AMR) in TB has compounded the burden, undermining control efforts and threatening progress toward elimination goals. In 2021 alone, an estimated 465,000 cases of rifampicin-resistant TB (RR-TB) and multidrug-resistant TB (MDR-TB) were reported globally, with Africa accounting for a substantial proportion of these cases due to its high TB incidence and limited healthcare resources (Diriba *et al.,* 2023; WHO, 2021).

b) MDR-TB and XDR-TB: Diagnostic and Therapeutic Challenges

MDR-TB, characterized by resistance to both isoniazid and rifampicin, and extensively drug-resistant TB (XDR-TB), which involves additional resistance to fluoroquinolones and second-line injectable drugs, present significant diagnostic and therapeutic challenges

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(Calligaro *et al.* 2014). The prevalence of XDR-TB among MDR-TB cases has been estimated at approximately 9%, with a notable burden in African regions (Diriba *et al.,* 2023). Studies from Ethiopia, South Africa, and Tanzania have highlighted the role of inadequate diagnostic infrastructure, delayed treatment initiation, and high rates of HIV co-infection in driving the epidemic of drug-resistant TB in Africa (Duga, 2024; WHO, 2021).

c) Socio-Economic and Systemic Factors Exacerbating AMR in TB

Several socioeconomic and systemic factors exacerbate the AMR burden in TB patients in Africa. Poverty, overcrowded living conditions, and poor adherence to treatment regimens are pervasive, creating an environment conducive to the transmission of resistant strains (Duga, 2024; WHO, 2021). In Eswatini, for instance, adverse drug reactions (ADRs) to MDR-TB treatment have been reported to impact adherence, further complicating disease management (Duga, 2024). The interplay between HIV and TB also significantly contributes to poor outcomes, as seen in South African cohorts, where HIV co-infection is associated with increased mortality and resistance rates (WHO, 2021; Dlamini *et al.,* 2023).

d) Advances in Resistance Detection and Surveillance

Innovative solutions such as whole-genome sequencing (WGS) and wastewater-based epidemiology (WBE) have emerged as promising tools for understanding resistance patterns and guiding interventions. WGS has provided insights into genetic mutations conferring resistance, such as katG and rpoB mutations, in Ethiopian and South African MDR-TB strains, enabling targeted treatment strategies (Diriba *et al.,* 2023; WHO, 2021). WBE, on the other hand, has demonstrated the potential to detect antibiotic resistance genes (ARGs) in community settings, offering a cost-effective surveillance approach (Duga, 2024).

e) Study Rationale and Objective

Despite significant advancements in tuberculosis (TB) diagnosis and treatment, the increasing burden of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) continues to pose a major global health challenge. The spread of drug-resistant TB strains is primarily driven by delayed diagnosis, incomplete or ineffective treatment, poor infection control, and direct person-to-person transmission (Monde *et al.,* 2023). While some countries have made progress in reducing MDR-TB rates, high-burden regions, particularly in sub-Saharan Africa, South Asia, and Eastern Europe, continue to experience rising transmission rates and treatment failures (Nyasulu *et al.,* 2024). In addition, emerging resistance to fluoroquinolones and other second-line drugs further limits treatment options, increasing the risk of untreatable TB (Diriba *et al.,* 2023).

This systematic review aims to synthesize global evidence on antimicrobial resistance (AMR) patterns in tuberculosis, focusing on prevalence trends, key risk factors, and challenges in diagnosis and treatment. Studies have highlighted previous TB treatment, inadequate access to drug susceptibility testing (DST), co-infection with HIV, and healthcare system limitations as significant determinants of MDR-TB transmission (Diriba *et al.,* 2023). By analyzing research from diverse geographic regions, this review identifies common risk factors, regional variations in MDR-TB and XDR-TB prevalence, and gaps in existing TB control strategies (Mumena, 2023). Furthermore, it explores innovative interventions such as molecular diagnostics, shorter treatment regimens, and adherence support programs that could help mitigate the spread of drug-resistant TB (Reta *et al.,* 2024) .

The findings of this review aim to inform global public health policies and guide future research efforts, ensuring a more effective and coordinated response to the MDR-TB and XDR-TB crisis. As drug-resistant TB continues to evolve, strengthening health systems, expanding access to rapid molecular diagnostics, and promoting patient-centered treatment approaches will be critical to controlling MDR-TB and XDR-TB worldwide.

II. Material And Methods

a) Study Design

This systematic review was conducted to synthesize available evidence on the patterns and determinants of antimicrobial resistance (AMR) in tuberculosis (TB) patients in Africa. The review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework.

b) Search Strategy

A comprehensive search was performed across electronic databases, including PubMed and Google Scholar, to identify relevant peer-reviewed articles. The search included studies published between 2023 and 28 January 2025. Search terms were combined using Boolean operators to optimize retrieval and included the following:

- "Antimicrobial resistance" OR "AMR"
- "Tuberculosis" OR "TB"
- "Multidrug-resistant tuberculosis" OR "MDR-TB"
- "Extensively drug-resistant tuberculosis" OR "XDR-TB"
- "Determinants"
- "Resistance patterns"

Language restrictions were applied to English, but studies had to be available in full text.

c) Eligibility Criteria

The inclusion and exclusion criteria were as follows:

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i. Inclusion Criteria:

- Studies focusing on AMR in TB patients globally.
- Research addressing MDR-TB or XDR-TB.
- Articles analyzing resistance patterns, determinants, or interventions.
- Empirical studies, systematic reviews, and meta-analyses providing quantitative or qualitative data.

ii. Exclusion Criteria:

- Studies with insufficient methodological detail or lacking original data (e.g., editorials, letters to the editor, opinion pieces)
- Studies focused exclusively on drug-susceptible TB without reference to drug resistance
- Research that explored antimicrobial resistance in non-tuberculosis pathogens

d) Study Selection

All identified articles were imported into Mendeley for citation management and duplicate removal. Titles and abstracts were screened independently by two reviewers to identify potentially relevant studies. Full texts of the selected articles were then assessed for eligibility based on the inclusion and exclusion criteria. Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer.

e) Data Extraction

Data were extracted using a standardized form developed for this review. The following information was collected:

- Study characteristics: author(s), year, study location, study design, and population.
- Resistance patterns: prevalence of MDR-TB and XDR-TB and specific drug resistance mutations (e.g., katG, rpoB).
- Determinants of AMR: socio-economic factors, healthcare system issues, treatment adherence, and co-morbidities such as HIV.
- Interventions: diagnostic tools, treatment regimens, and innovative surveillance strategies (e.g., wastewater-based epidemiology, whole-genome sequencing).

f) Data Synthesis

A qualitative synthesis was conducted to analyze the patterns and determinants of antimicrobial resistance (AMR) in tuberculosis (TB) patients across a global context. Given the variability in study designs, data availability, and reporting formats, a meta-analysis was not feasible. Instead, a systematic review approach was employed to identify common trends, regional differences, and key risk factors contributing to MDR-TB and XDR-TB prevalence. The findings were synthesized to highlight the most pressing challenges in diagnosis, treatment, and TB control policies, providing a comprehensive narrative on the global burden of drug-resistant TB.

III. Results and Discussion

The initial review process began with 52 studies, all related to antimicrobial resistance (AMR) in tuberculosis (TB). To ensure that only the most relevant studies were included, the documents were systematically screened based on language, relevance, focus on MDR-TB/XDR-TB, and data availability.

The first step involved language screening, where 2 studies were excluded because they were not in English. Next, during the title and abstract screening, 6 additional studies were removed as they were rendered ineligible based on their scope, meaning they did not align with the study's focus on drug-resistant TB, prevalence trends, or treatment challenges. Following this, full-text accessibility was assessed, as studies without full access could not be thoroughly reviewed. At this stage, 8 studies were excluded due to restricted access to the full text, leaving 36 studies for full-text screening.

In the full-text review, each study was assessed for methodological rigor, relevance to MDR-TB/XDR-TB, and inclusion of meaningful findings related to resistance patterns and treatment challenges. Several studies were found to be too broad or lacking sufficient data on MDR-TB and XDR-TB. Specifically, 3 studies were excluded because they focused only on TB treatment innovations without addressing AMR. Two (2) studies did not differentiate MDR-TB from drug-susceptible TB, making them unsuitable for the review. Two (2) documents were removed as they were opinion pieces rather than primary research. Twenty-three (23) more studies lacked sufficient data on MDR-TB or XDR-TB prevalence, making them ineligible for inclusion. After applying these eligibility criteria, only 6 studies met the inclusion criteria and were retained for qualitative synthesis. Given the heterogeneity in study designs and the absence of standardized prevalence data, conducting a meta-analysis was not feasible. Many studies lacked quantitative prevalence estimates, used inconsistent methodologies, or applied varied definitions for MDR-TB and XDR-TB, making pooled statistical analysis unreliable.

Ultimately, this review includes 6 studies, providing valuable insights into the global patterns of AMR in TB, the key risk factors driving resistance, diagnostic and treatment challenges, and critical gaps in TB control policies. While a quantitative synthesis could not be performed, the qualitative findings offer a comprehensive understanding of the evolving MDR-TB and XDR-TB crisis and its implications for public health interventions worldwide.

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Original Article

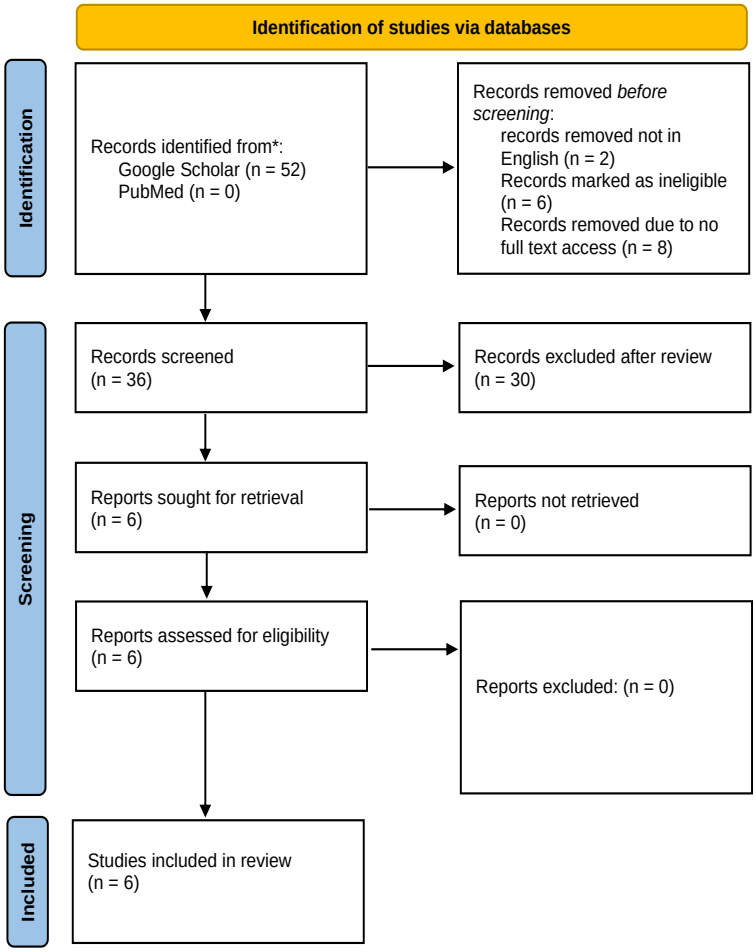

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Figure 1: PRISMA Diagram

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Table 1: Studies Included in the Review

S/N	Authors	Title	Region	Year	Inclusion Criteria	Findings
1	Peter S. Nyasulu, Cheick Oumar Doumbia, Veranyuy Ngah, Antieme Combo Georges Togoc, Bassirou Diarra, Gershom Chongwe	Multidrug-resistant tuberculosis: latest opinions on epidemiology, rapid diagnosis and management	Sub-Saharan Africa	2024	Latest epidemiology and management strategies for MDR-TB	Increasing MDR-TB burden linked to delayed diagnosis, treatment defaulting, and HIV co-infection.
2	Vulika Nangombe, Mondjila Amkongo, Brian Godman, Dan Kibuule	Drug-resistant tuberculosis treatment success predictors in Namibia	Namibia	2024	Analysis of treatment success factors for DR-TB	Treatment success rate improved but remains below global targets; gender and age influence success.
3	Ngula Monde, Musso Munyeme, Gershom Chongwe, Jonas Johansson Wensman, Mildred Zulu, Seter Siziya, Rabecca Tembo, Kabengele K. Siame, Obi Shambaba, Sydney Malama	First and Second-Line Anti-Tuberculosis Drug-Resistance Patterns in Pulmonary Tuberculosis Patients in Zambia	Zambia	2023	Study on resistance patterns in first-line and second-line TB drugs in Zambia	High prevalence of MDR-TB with some cases of pre-XDR and XDR-TB detected.
4	Alaa Alibrahim, Homoud Alqahtani, Ashokkumar Thirunavukkarasu, Ibtisam Qazi	Prevalence, patterns, and determinants of drug-resistant tuberculosis in Gulf Cooperation Council countries: An updated systematic review	GCC Countries	2024	Systematic review on DR-TB prevalence, risk factors, and resistance patterns	Isoniazid monoresistance most common; MDR-TB correlated with previous TB treatment and expatriate status.
5	David Kajoba Mumena, Nyerere Andrew Kimangâ€™a, Ngugi Caroline Wangari, Kwenda Geoffrey	Genotypic Characterization of Drug-Resistant Mycobacterium Tuberculosis among New and Previously Treated Tuberculosis Cases in Zambia	Zambia	2023	Genotypic analysis of MDR-TB resistance genes in Zambian cases	High diversity in resistance mutations with evidence of transmission between new and previously treated cases.
6	Basha Chekesa, Harinder Singh, Norberto Gonzalez-Juarbe, Sanjay Vashee, Rosana Wiscovitch-Russo, Christopher L. Dupont, Musse Girma, Oudessa Kerro, Balako	Whole-genome sequencing-based genetic diversity, transmission dynamics, and drug-resistant mutations in Mycobacterium tuberculosis isolated from extrapulmonary tuberculosis patients in western Ethiopia.	Ethiopia	2024	WGS-based study of drug resistance mutations and transmission	Lineage 4 strains are dominant, high clustering rate indicates recent transmission, with some resistance mutations undetected by standard assays.

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	Gumi, Gobena Ameni					

a) Prevalence and Geographic Distribution of Drug-Resistant Tuberculosis

The prevalence of MDR-TB and XDR-TB varied significantly across regions, reflecting disparities in healthcare infrastructure, diagnostic capabilities, and public health interventions. A systematic review in the GCC countries (Alibrahim *et al.,* 2024) found that isoniazid monoresistance was the most commonly detected form of drug resistance, with MDR-TB primarily associated with prior TB treatment and expatriate populations. In contrast, a study conducted in Zambia (Monde *et al.,* 2023) reported alarmingly high rates of MDR-TB, with 9.8% of patients exhibiting resistance to isoniazid and rifampicin and a subset progressing to pre-XDR and XDR-TB. Similarly, in Ethiopia, whole-genome sequencing (WGS) studies (Chekesa *et al.,* 2024) revealed that 7.87% of extrapulmonary TB isolates showed resistance to at least one anti-TB drug, though full-fledged MDR-TB was detected in only a small proportion of cases.

Across the studies, there was consensus that sub-Saharan Africa remains one of the hardest-hit regions for drug-resistant TB. In Namibia, treatment success rates for MDR-TB remained below the global target of 85%, with age, gender, and pulmonary disease severity emerging as key determinants of treatment outcomes (Nangombe *et al.,* 2024). The prevalence of rifampicin-resistant TB (RR-TB) was particularly concerning, with some studies suggesting that underdosing of rifampicin and self-medication contributed to rising resistance rates (Mumena *et al.,* 2023).

b) Patterns of Antimicrobial Resistance in Tuberculosis: A Global Perspective

The patterns of antimicrobial resistance (AMR) in tuberculosis (TB) vary significantly across different regions, shaped by factors such as healthcare infrastructure, socioeconomic conditions, disease transmission dynamics, and the effectiveness of national TB control programs (Liebenberg *et al.,* 2022). While multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) have been traditionally concentrated in high-burden regions like Africa, South Asia, and Eastern Europe, emerging trends suggest that resistant TB strains are increasingly spreading to other parts of the world, including Latin America and the Middle East (Bainomugisa *et al.,* 2019; Gao *et al.,* 2024).

Additionally, the mechanisms of resistance are evolving, with increasing evidence that TB is no longer becoming drug-resistant solely due to treatment failures but also due to direct transmission of already-resistant strains. Recent whole-genome sequencing (WGS) studies have shown that a significant proportion of MDR-TB cases arise from primary transmission rather than acquired resistance through improper treatment, particularly in high-burden regions like China and Southeast Asia (Che *et al.,* 2024; Nonghanphithak *et al.,* 2021). This shift from acquired to primary MDR-TB transmission has profound implications for global TB control efforts, as it underscores the urgent need for stronger infection control measures, rapid diagnostics, and more effective drug regimens (Liebenberg et al., 2022). The identification of genomic clusters of MDR-TB and XDR-TB strains suggests that transmission is playing a greater role in the ongoing AMR crisis than previously assumed, necessitating improved contact tracing, surveillance, and preventative strategies (Che *et al.,* 2024; Gao *et al.,* 2024).

1. Regional Variability in Drug-Resistant TB Prevalence

The burden of MDR-TB is unevenly distributed across different regions, with some areas experiencing high rates of primary transmission while others struggle primarily with poor treatment adherence, leading to acquired resistance. Sub-Saharan Africa remains one of the most severely affected regions, with South Africa, Zambia, Namibia, and Ethiopia reporting alarming MDR-TB rates. In Namibia, studies indicate that treatment success rates for MDR-TB remain below 70%, largely due to delayed diagnosis, high HIV-TB co-infection rates, and inadequate access to second-line treatment options (Nangombe *et al.,* 2024). In Ethiopia, whole-genome sequencing (WGS) studies reveal that resistant TB strains are clustering within communities, indicating that person-to-person transmission is a significant driver of MDR-TB rather than poor treatment adherence alone (Chekesa *et al.,* 2024).

South Asia, particularly India, Nepal, Pakistan, and Bangladesh, also faces a severe MDR-TB crisis. India alone accounts for 27% of the world's MDR-TB cases, the highest globally (Bagcchi, 2023). A case-control study in Nepal (Acharya *et al.,* 2024) found that previous TB treatment and incomplete medication adherence were the strongest predictors of MDR-TB, but new evidence suggests that inadequate regulatory control over antibiotic use is also fueling resistance in the region. The unregulated sale of antibiotics, particularly fluoroquinolones, has led to widespread resistance to these critical second-line TB treatments. Similarly, in Pakistan and Bangladesh, poor infection control measures and overcrowding in urban slums have been linked to higher rates of primary MDR-TB transmission.

In Eastern Europe and Central Asia, particularly Russia, Ukraine, Kazakhstan, and Uzbekistan, MDR-TB rates are among the highest in the world, with 30 50% of MDR-TB cases progressing to XDR-TB (Bagcchi, 2023). The breakdown of public health infrastructure, lack of adherence support programs, and high incarceration rates contribute significantly to MDR-TB persistence. Studies

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have shown that prisons in Russia and Ukraine serve as hotspots for MDR-TB transmission, where poor ventilation, inadequate screening, and overcrowding allow resistant strains to spread rapidly. Additionally, the prevalence of Beijing lineage TB strains, which have been genetically linked to higher drug resistance, further exacerbates the problem in these regions.

Latin America, particularly Peru, Brazil, Mexico, and Argentina, has a lower burden of MDR-TB compared to Africa and Asia, but recent studies indicate that primary MDR-TB transmission is increasing in urban slums and prison populations (Alibrahim *et al.,* 2024). Unlike in other regions where MDR-TB is mainly due to treatment failure, in Latin America, resistant strains are now spreading directly within communities, raising concerns about long-term TB control strategies.

The Middle East and Gulf Cooperation Council (GCC) countries currently have lower MDR-TB rates compared to Africa and Asia, but migration patterns from high-burden TB countries have introduced resistant strains into these regions. A systematic review (Alibrahim *et al.,* 2024) found that expatriate populations from South Asia and East Africa accounted for a significant portion of MDR-TB cases in the GCC, indicating that international travel and labor migration play a role in MDR-TB dissemination. Even in high-income countries like Western Europe and North America, MDR-TB cases have been reported, largely linked to immigrant populations from high-burden countries. Although MDR-TB prevalence in these regions remains relatively low, sporadic outbreaks have demonstrated the importance of strong surveillance systems and border health screenings.

2. Primary MDR-TB Transmission vs. Acquired Resistance: A Changing Dynamic

Historically, drug-resistant TB was thought to emerge primarily as a result of incomplete or inadequate treatment regimens, leading to acquired resistance. However, recent evidence suggests that primary MDR-TB transmission where individuals contract a drug-resistant TB strain despite never having been treated before is becoming more common (Chekesa *et al.,* 2024). This shift has major implications for TB control strategies, as it suggests that ensuring treatment adherence alone is not sufficient to curb the spread of MDR-TB.

In South Africa and Ethiopia, WGS data indicate that resistant TB strains are clustering within communities, meaning that new cases are arising from recent person-to-person spread rather than from treatment failures (Chekesa *et al.,* 2024). In India and Nepal, researchers have found high MDR-TB rates even among newly diagnosed TB patients with no prior history of TB treatment, further supporting the notion that primary MDR-TB transmission is now a major driver of the epidemic (Acharya *et al.,* 2024). The situation is even more concerning in Russia and Ukraine, where primary MDR-TB rates exceed 25% of new cases, the highest globally (Bagcchi, 2023). This trend underscores the critical need for infection control measures, active case detection, and expanded access to rapid molecular diagnostics, as relying solely on treatment adherence programs will no longer be sufficient to contain MDR-TB transmission.

3. Expanding Resistance to Second-Line Drugs: The Rise of Pre-XDR and XDR-TB

Another alarming trend is the increasing resistance to second-line TB drugs, leading to more cases of pre-XDR and XDR-TB. While MDR-TB is already difficult to treat, a growing number of patients are now developing resistance to fluoroquinolones and second-line injectables, further limiting treatment options.

In Eswatini, up to 44% of MDR-TB patients have developed resistance to fluoroquinolones, significantly reducing their treatment success rates (Duga *et al.,* 2024). Similarly, in Russia and Eastern Europe, nearly 50% of MDR-TB cases exhibit fluoroquinolone resistance, pushing these cases into pre-XDR or XDR-TB categories (Bagcchi, 2023). In Namibia and Peru, resistance to injectable second-line drugs such as amikacin, capreomycin, and kanamycin has also increased, complicating treatment regimens further (Nangombe *et al.,* 2024). This pattern highlights the urgency of scaling up newer TB treatment options such as bedaquiline and delamanid, as well as improving pharmacovigilance to ensure that second-line drugs are used appropriately to prevent further resistance development.

c) Risk Factors for Drug-Resistant Tuberculosis

Several common risk factors for MDR-TB emerged across studies. The most frequently cited risk factor was a history of previous TB treatment. Studies in Zambia (Monde *et al.,* 2023) and Nepal (Acharya *et al.,* 2024) showed that patients with a prior history of TB were 40 times more likely to develop MDR-TB than those with no prior TB treatment. Incomplete or inadequate TB treatment regimens, poor adherence due to long treatment durations, and improper drug administration were significant contributors to resistance.

A systematic review in the GCC countries (Alibrahim *et al.,* 2024) identified younger age, female gender, diabetes mellitus, renal failure, and expatriate status as additional risk factors for MDR-TB. In Ethiopia (Chekesa *et al.,* 2024), high clustering rates of Lineage 4 (L4) Mycobacterium tuberculosis strains suggested that recent transmission was a major factor in the persistence of drug-resistant TB rather than acquired resistance alone.

Another emerging risk factor was TB/HIV coinfection, which complicated treatment regimens and increased mortality rates among MDR-TB patients. In Namibia, HIV-positive patients had significantly lower treatment success rates compared to HIV-negative patients, suggesting that immune suppression may accelerate drug resistance development (Nangombe *et al.,* 2024).

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d) Diagnostic Advancements and Challenges in Drug-Resistant TB Detection

Several studies underscored the importance of rapid and accurate diagnostics for containing the spread of drug-resistant TB. The adoption of whole-genome sequencing (WGS) in studies from Ethiopia (Chekesa *et al.,* 2024) and Zambia (Mumena *et al.,* 2023) provided valuable insights into genetic mutations associated with resistance. These studies revealed that some resistance mutations went undetected by conventional tests such as GeneXpert MTB/RIF and line-probe assays (LPA), underscoring the need for more comprehensive molecular diagnostics.

In addition to WGS, machine-learning approaches have been explored as a predictive tool for drug resistance mutations. A study in India applied structure-based machine-learning models to predict pyrazinamide resistance, demonstrating the potential for AI-driven diagnostics in MDR-TB detection (Moreno *et al.,* 2023). However, diagnostic challenges persist in low-resource settings, where access to WGS and rapid molecular diagnostics remains limited. Many studies emphasized that the delayed detection of MDR-TB often led to prolonged transmission periods, increasing the burden of resistant TB strains in the community.

e) Treatment Success and Challenges

Despite advances in treatment regimens, MDR-TB and XDR-TB continue to present significant treatment challenges. In Namibia (Nangombe *et al.,* 2024), treatment success rates for MDR-TB patients stood at 66.5%, well below the global target. Younger patients and those with bilateral pulmonary disease had particularly poor treatment outcomes. Several studies highlighted adverse drug reactions (ADRs) as a barrier to treatment adherence. In Eswatini, 44% of MDR-TB patients experienced at least one ADR, with bedaquiline being the most frequently associated drug (Duga *et al.,* 2024). In Ethiopia, studies on drug-resistant TB in extrapulmonary patients found that some resistance mutations were linked to increased treatment failure due to inadequate drug penetration into affected tissues (Chekesa *et al.,* 2024). A key recommendation across studies was the need for patient-centered care approaches, including community-based adherence support programs, shorter drug regimens, and improved pharmacovigilance for TB medications.

f) Evolutionary and Genomic Insights into Drug-Resistant TB

Advancements in genomics have significantly enhanced our understanding of how Mycobacterium tuberculosis evolves resistance. In a study analyzing the evolution of drug resistance in different TB lineages (Hlanze *et al.,* 2024), researchers found that epistatic interactions among resistance mutations played a crucial role in the emergence of multidrug resistance. A key discovery from WGS studies was the role of pre-requisite mutations that serve as stepping stones for the development of high-level resistance. These findings suggest that routine surveillance of genetic markers could help predict future resistance patterns and inform targeted treatment strategies.

g) Strategies for Controlling Drug-Resistant Tuberculosis

The findings from this meta-analysis highlight the pressing need for a comprehensive and multi-pronged approach to tackle drug-resistant tuberculosis (DR-TB). While scientific advancements have led to better diagnostic tools and treatment options, the persistent gaps in healthcare infrastructure, patient adherence, and surveillance systems continue to fuel the spread of multidrug-resistant (MDR) and extensively drug-resistant tuberculosis (XDR-TB). To address these challenges, the following recommendations should be prioritized:

1. Scaling Up Rapid Molecular Diagnostics

One of the biggest barriers to effective TB control is the delay in diagnosing drug resistance. Many resource-limited countries still rely on sputum smear microscopy, which cannot detect resistance, leading to prolonged infectious periods and increased community transmission (Bagcchi, 2023). To combat this, the widespread implementation of Whole-Genome Sequencing (WGS) and AI-driven predictive models is crucial. WGS allows for early and precise detection of resistance mutations, enabling clinicians to tailor drug regimens before standard treatments fail (Chekesa *et al.,* 2024). AI-based predictive models have been developed to analyze large datasets and predict resistance patterns, potentially detecting emerging drug-resistant TB strains before they become clinically apparent (Moreno *et al.,* 2023).

However, access to these technologies remains a challenge in low-resource settings. The WHO Global TB Report (2023) stresses the need for increased funding to scale up next-generation sequencing platforms in high-burden TB regions. Portable GeneXpert Ultra and Truenat MTB tests have shown promise in detecting rifampicin resistance within hours (Alibrahim *et al.,* 2024), but further decentralization of these tools is needed to bridge the gap between laboratory capabilities and real-world patient access.

2. Implementing Community-Based Adherence Support Programs

Non-adherence to TB treatment is a major driver of resistance. Treatment durations range from six months for drug-susceptible TB to up to 24 months for MDR-TB, often involving toxic and difficult-to-tolerate medications (Duga *et al.*, 2024). Studies have shown that poor adherence rates are often linked to financial hardship, transportation barriers, medication side effects, and social stigma (Monde *et al.,* 2023). Community-based interventions have

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https://doi.org/10.51168/sjhrafrica.v6i3.1591
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proven to be effective in improving adherence and reducing treatment default rates (Nangombe *et al.*, 2024). Key strategies include:

- Home-based Directly Observed Therapy (DOT): In-person monitoring by community health workers (Bagcchi, 2023).
- Digital adherence technologies: SMS reminders and video DOT (v-DOT) have improved adherence rates by over 70% in rural settings (Alibrahim *et al.*, 2024).
- Financial and nutritional support: Providing food rations and transportation subsidies has significantly improved treatment success (Mumena *et al.*, 2023).
- Patient peer support groups: Studies in Namibia and Zambia found that peer-led counseling sessions improved psychological resilience and treatment completion rates (Nangombe *et al.*, 2024).

3. Enhancing Pharmacovigilance to Monitor Adverse Drug Reactions (ADRs)

MDR-TB regimens are associated with high rates of severe ADRs, including liver toxicity, kidney impairment, hearing loss, and psychiatric disorders (Duga *et al.*, 2024). Studies in Eswatini found that 44% of MDR-TB patients experienced at least one ADR, with bedaquiline and linezolid being the most frequently implicated drugs (Chekesa *et al.*, 2024). To improve patient safety and adherence, robust pharmacovigilance systems must be strengthened by:

- Expanding real-time ADR monitoring systems to capture data across multiple healthcare settings (Bagcchi, 2023).
- Training healthcare workers to recognize and intervene early in ADR cases before they lead to treatment discontinuation (Moreno *et al.*, 2023).
- Developing alternative treatment strategies, such as dose modifications or adjunct therapies to minimize toxicity (Alibrahim *et al.*, 2024).

4. Strengthening TB/HIV Integration to Address Co-Infection Challenges

TB remains the leading cause of death among HIV-positive individuals, and MDR-TB in HIV patients is associated with worse treatment outcomes (WHO, 2021). Studies in Namibia and Zambia found that HIV-positive MDR-TB patients had significantly lower treatment success rates than HIV-negative individuals (Nangombe *et al.*, 2024; Mumena *et al.*, 2023). To improve outcomes, the following strategies should be scaled up:

- Routine TB screening for all HIV patients and vice versa (Alibrahim *et al.*, 2024).
- Integrated HIV-TB treatment programs to ensure simultaneous administration of antiretroviral therapy (ART) and TB medication (Bagcchi, 2023).
- Decentralization of TB/HIV clinics to reduce patient burden and improve retention (Duga *et al.*, 2024).

5. Improving Infection Control Measures in High-Burden Regions

MDR-TB transmission in hospitals, prisons, and urban slums remains a major challenge (Chekesa *et al.*, 2024). Studies show that many MDR-TB cases arise from direct person-to-person transmission rather than acquired resistance (Alibrahim *et al.*, 2024). Key strategies to reduce MDR-TB transmission include:

- Improving ventilation in healthcare settings (Bagcchi, 2023).
- Mandatory N95 respirators for healthcare workers (Mumena *et al.*, 2023).
- Expanding preventive therapy (short-course rifapentine regimens) for high-risk populations (Moreno *et al.*, 2023).

Tackling drug-resistant TB requires global collaboration, increased funding, and sustainable policy reforms. The integration of molecular diagnostics, adherence support, pharmacovigilance, TB/HIV coordination, and infection control measures can significantly reduce MDR-TB prevalence and improve patient outcomes. Failure to act swiftly risks undoing decades of progress in TB control.

IV. Conclusion

Drug-resistant tuberculosis (DR-TB) represents one of the most urgent and complex global health challenges of our time. While medical advancements have led to improved diagnostics and treatment regimens, the continued spread of multidrug-resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) threatens to undermine decades of progress in TB control. This review highlights how regional disparities in healthcare infrastructure, socioeconomic conditions, and public health responses are shaping the evolving patterns of antimicrobial resistance (AMR) in TB, with resistance now being driven not only by treatment failure but also by direct person-to-person transmission of resistant strains.

Across different regions, the burden of drug-resistant TB varies significantly. Countries in sub-Saharan Africa, South Asia, and Eastern Europe bear the highest MDR-TB rates, driven by treatment interruptions, weak infection control, and the high prevalence of co-existing conditions like HIV. Meanwhile, in Latin America and the Middle East, MDR-TB rates are increasing, fuelled by gaps in early detection and international migration. In some areas, primary transmission of drug-resistant strains now surpasses acquired resistance, signaling a dangerous new phase of the epidemic where individuals are infected with MDR-TB strains even before receiving any TB treatment. This shift challenges the traditional understanding of TB resistance and necessitates a rethinking of global TB control strategies.

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol. 6 No. 3 (2025): March 2025 Issue
https://doi.org/10.51168/sjhrafrica.v6i3.1591
Original Article

One of the most pressing issues is the growing resistance to second-line TB medications, including fluoroquinolones and injectable agents, leading to an increase in pre-XDR and XDR-TB cases. The emergence of untreatable TB strains is no longer a distant threat; it is a real and present danger, especially in regions with limited access to newer TB drugs like bedaquiline and delamanid. Without urgent intervention, we risk entering an era where TB is no longer curable with existing treatment regimens, reversing the progress made over the last two decades. To combat this crisis, multifaceted global strategies must be urgently implemented. First, expanding access to rapid molecular diagnostics such as whole-genome sequencing (WGS) and AI-driven predictive models will be crucial for detecting resistance earlier and guiding appropriate treatment decisions. Many high-burden countries still rely on outdated diagnostic tools that fail to detect emerging drug-resistant mutations, leading to delays in appropriate treatment initiation and prolonged transmission periods. Investment in affordable, decentralized diagnostic platforms will be essential to closing this gap. Secondly, treatment adherence support programs must be strengthened, especially in low-resource settings where patients face financial, logistical, and social barriers to completing TB therapy. Community-based interventions, such as home-based Directly Observed Therapy (DOT), digital adherence monitoring tools, and financial incentives, have proven successful in reducing treatment default rates and should be scaled up globally. Additionally, enhancing pharmacovigilance systems to monitor adverse drug reactions (ADRs) can help mitigate side effects that often lead to treatment discontinuation. Thirdly, infection control measures must be reinforced, particularly in high-transmission settings such as hospitals, prisons, and urban slums. As evidence increasingly points toward person-to-person transmission of MDR-TB, strategies must go beyond focusing solely on treatment adherence to include preventive therapy for high-risk individuals, improved ventilation in healthcare settings, and stronger TB screening policies for vulnerable populations. Finally, the global response to TB drug resistance must be coordinated and well-funded. Historically, TB research and treatment have been underfunded compared to other infectious diseases like HIV/AIDS and malaria. To effectively address MDR-TB and XDR-TB, there must be sustained investment in TB drug development, vaccine research, and health system strengthening. Countries must also prioritize equitable access to new TB medications, ensuring that patients in low- and middle-income countries are not left behind in the fight against DR-TB.

The rise of drug-resistant TB is not just a problem for high-burden countries, it is a global crisis that demands urgent and coordinated action. If we fail to strengthen diagnostic capabilities, expand treatment options, and implement robust infection control measures, the world risks facing a new era of untreatable tuberculosis. However, with political will, financial commitment, and scientific innovation, the tide can still be turned. TB elimination is within reach, but only if we act decisively, collectively, and immediately.

a) Recommendations

The findings from this review strongly suggest that addressing drug-resistant tuberculosis (DR-TB), particularly multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), requires a shift in how health systems approach diagnosis, treatment, and prevention. The priority should be expanding access to timely and accurate diagnostic tools. Many patients in high-burden regions are still diagnosed too late, often after transmitting the disease or developing further resistance. Rapid molecular diagnostics such as GeneXpert and whole-genome sequencing have proven effective in detecting resistance earlier. These tools should be made available not just in major hospitals but also in peripheral health centers where most people first seek care.

Improving treatment outcomes also depends heavily on supporting patients through their long and often difficult treatment journeys. Non-adherence continues to drive resistance, especially where financial hardship, drug side effects, and stigma interfere with a patient's ability to complete therapy. To counter this, health systems should implement community-based support programs that include home visits, digital reminders, nutritional support, and peer-led counselling. When patients feel supported and understood, they are far more likely to stay on treatment and recover fully. At the same time, efforts should focus on expanding access to safer and shorter treatment regimens. Current treatments for MDR-TB can last up to two years and often come with serious side effects. Newer medications such as bedaquiline and delamanid offer hope for more tolerable and effective regimens, but they remain inaccessible in many parts of the world. Governments and global health partners must invest in making these drugs available and affordable and support further research into even more patient-friendly treatment options. Infection control remains another critical area of focus. Transmission of DR-TB in healthcare settings, prisons, and densely populated communities continues to undermine progress. Basic but essential measures like improving ventilation, early isolation of suspected cases, and ensuring healthcare workers are adequately protected must be strengthened. These actions can significantly reduce the risk of person-to-person transmission.

The integration of TB and HIV services also needs urgent attention. Co-infection significantly worsens outcomes, and fragmented care contributes to late diagnoses and poor adherence. Offering TB and HIV services side by side in the same facilities would ensure that patients receive comprehensive care without the burden of navigating multiple systems. Such integration has been shown to improve early detection and reduce mortality. Additionally, there is a need to support more local research and surveillance efforts. Understanding local resistance patterns, transmission dynamics, and treatment barriers is essential for tailoring interventions that work.

Investments in national laboratories, training for local researchers, and improved reporting systems would help generate the high-quality data needed for effective TB control. Finally, drug-resistant TB should be treated as a global crisis requiring coordinated international action. Resistant strains cross borders, especially through migration and travel. Global health systems must collaborate on surveillance, data sharing, drug procurement, and funding. This collaboration should also include a commitment to equity, ensuring that low- and middle-income countries are not left behind in access to new tools and treatments.

b) Limitations

Despite the comprehensive nature of this systematic review, several limitations must be acknowledged. First, the variability in study methodologies, definitions, and data reporting across different regions posed challenges in making direct comparisons between findings. Some studies relied on whole-genome sequencing (WGS) for resistance detection, while others used traditional drug susceptibility testing (DST), which may not detect emerging resistance mutations. This inconsistency limits the generalizability of the findings.

The absence of sufficient standardized prevalence data prevented the inclusion of a meta-analysis. Many studies did not provide clear sample sizes, resistance rates, or demographic breakdowns, making it difficult to generate pooled estimates of MDR-TB and XDR-TB prevalence. As a result, this review is qualitative and focuses on narrative synthesis rather than statistical aggregation.

The geographic distribution of the included studies was uneven, with a concentration of research in high-burden regions like sub-Saharan Africa, South Asia, and Eastern Europe, while fewer studies examined emerging trends in Latin America, the Middle East, or remote areas with limited surveillance capacity. This may result in underrepresentation of drug-resistant TB trends in certain populations.

Finally, publication bias must be considered, as studies with significant or concerning findings on MDR-TB transmission and resistance trends may be more likely to be published, while reports showing stable or declining resistance rates may be underreported. Future research should aim to incorporate longitudinal studies with standardized methodologies to provide a clearer picture of MDR-TB and XDR-TB transmission dynamics worldwide.

b) Author Contributions

Ruth Chipampe Kafwanka conceptualized the study, led the development of the research framework, and was primarily responsible for writing the first draft of the manuscript. Rogers Chilyabanyama contributed to the literature search, data extraction, and critical analysis of the selected studies. Richard Chirwa provided guidance on the methodological approach, supervised the systematic review process, and reviewed the manuscript for intellectual content. Mubanga Lackson Chipimo assisted in synthesizing the findings, refining the discussion, and editing the final version of the manuscript. All authors contributed to the development of the final draft, reviewed the manuscript for accuracy and completeness, and approved the final version for publication.

c) Author Biography

Ruth Chipampe Kafwanka is a public health specialist and laboratory scientist with over 7 years of experience in infectious diseases, molecular diagnostics, and disease surveillance. She holds a Master of Public Health (MPH) and a Bachelor of Science in Biological Sciences. Her professional background includes expertise in ISO 15189-compliant laboratory management systems, PCR testing, gene sequencing, biosafety, and biosecurity. Ruth is an active researcher with published work focusing on epidemiology, health systems strengthening, and sustainable public health solutions.

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d) Competing Interests

The authors declare that they have no competing interests related to this study. This review was conducted independently and objectively, without any influence from pharmaceutical companies, government agencies, or private institutions that may have a vested interest in the findings. The analysis and interpretations presented in this article are based solely on the available scientific evidence.

c) Availability of Data

All data supporting the findings of this review are derived from publicly accessible, peer-reviewed journal articles

included in the reference list. No primary data were collected or generated by the authors.

d) Registration and Protocol

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Although the review was not prospectively registered in a public database such as PROSPERO, the review protocol was developed before the commencement of the study and guided the entire review process.

e) Acknowledgments

The authors would like to express their gratitude to the researchers, institutions, and organizations whose work provided the foundation for this review. Special thanks go to public health professionals, epidemiologists, and clinicians working on the frontlines of tuberculosis prevention and treatment. Their contributions to global TB surveillance and AMR research are invaluable in the fight against drug-resistant tuberculosis. Additionally, we appreciate the efforts of peer reviewers and journal editors whose feedback has helped strengthen the rigor and clarity of this work.

f) Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The work was conducted independently as part of a broader academic effort to synthesize and disseminate knowledge on antimicrobial resistance in tuberculosis. However, the authors acknowledge the importance of sustained investment in TB research, particularly in advancing diagnostics, treatment innovations, and global surveillance programs to combat the growing threat of MDR-TB and XDR-TB.

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Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol. 6 No. 3 (2025): March 2025 Issue
https://doi.org/10.51168/sjhrafrica.v6i3.1591
Original Article

PUBLISHER DETAILS:

Student's Journal of Health Research (SJHR)
(ISSN 2709-9997) Online
(ISSN 3006-1059) Print
Category: Non-Governmental & Non-profit Organization
Email: studentsjournal2020@gmail.com
WhatsApp: +256 775 434 261
Location: Scholar's Summit Nakigalala, P. O. Box 701432, Entebbe Uganda, East Africa