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DRUG RESISTANCE (DAPSONE, RIFAMPICIN AND OFLOXACIN) IN PATIENTS WITH LEPROSY: A SYSTEMATIC REVIEW

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ABSTRACT:
According to the World Health Organization (WHO), 182,815 new cases of leprosy were reported across 184 countries in 2023, representing a 5% increase compared to 2022.(World Health Organization, 2024b, 2024a) WHO recommends multidrug therapy (MDT), combining dapsone, rifampicin, and clofazimine, as the first-line treatment for both paucibacillary and multibacillary leprosy. Although MDT has significantly reduced disease burden, persistent and relapsed cases associated with resistant *M. leprae* strains have been documented in multiple endemic settings, potentially diminishing treatment efficacy and increasing the risk of relapse.(Lazo-Porras et al., 2020) Antimicrobial resistance (AMR) is therefore a growing concern in leprosy control, consistent with the broader global threat of AMR, which undermines the effectiveness of life-saving treatments and increases the risk of poor clinical outcomes. To strengthen public health action, the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) supports countries in developing national surveillance systems and generating standardized AMR data.(World Health Organization, 2025)

INTRODUCTION

Recent systematic investigations indicate that drug resistance in *M. leprae* remains detectable at non-negligible rates despite decades of MDT use. Meta-analytic data from 2024 estimate a global resistance rate of approximately 10.18%, with the Western Pacific region exhibiting a higher resistance rate of 17.05% compared to other areas. Previous studies have established that drug resistance can be detected in drug resistance-determining regions (DRDRs) containing *folP1*, *rpoB*, and *gyrA*, which are associated with resistance to dapsone, rifampicin, and ofloxacin, respectively, and these findings have been incorporated into WHO guidelines for antimicrobial resistance surveillance. These resistance-determining substitutions compromise drug efficacy and can be detected directly from clinical samples using PCR-based sequencing methods. (Li et al., 2022, 2024; Shi et al., 2022)

Regional variations in resistance patterns further complicate control efforts. Evidence suggests that resistance rates and mutation profiles differ by geographical region and patient treatment history, with relapse cases showing higher resistance proportions than new diagnoses. Drug resistance has been documented in major endemic countries including India, Brazil, and China, underscoring the need for vigilant surveillance and localized epidemiologic data to guide treatment strategies. The emergence of multidrug-resistant (MDR) *M. leprae,* although less common, represents a significant challenge due to its implications for cure rates and transmission risk. (Li et al., 2024; Shi et al., 2022)The burden of leprosy relapse is not limited to bacterial persistence or antimicrobial resistance. Recurrent disease is also associated with prolonged treatment, leprosy reactions, neuropathic pain, disability, stigma, and psychological distress, all of which can substantially affect quality of life and adherence to care.(Alrehaili, 2023; da Silva et al., 2025) Therefore, understanding drug resistance in leprosy requires not only microbiological assessment but also consideration of its clinical, functional, and public health consequences.

This systematic review aims to summarize the current evidence on antimicrobial resistance in leprosy across various patient populations and regions, with particular attention to relapse, recurrence, retreatment, suspected treatment failure, neuropathic disease, and other clinically high-risk cases. The review evaluates reported resistance patterns to key anti-leprosy drugs, particularly dapsone, rifampicin, and ofloxacin, and discusses their implications for multidrug therapy effectiveness, clinical management, diagnostic decision-making, and public health surveillance.

METHODS

Literature Search

This study was conducted to identify primary research on antimicrobial resistance in *Mycobacterium leprae* among leprosy patients, particularly those with relapse, recurrence, retreatment, suspected treatment failure, or other clinically high-risk presentations.

A comprehensive literature search was performed using PubMed, Scopus, ScienceDirect, ProQuest, and Google Scholar. The search was designed to capture both clinical and molecular studies related to drug resistance in Mycobacterium leprae. The search strategy followed the PICOS framework. The population consisted of human leprosy patients, including newly diagnosed, relapsed, recurrent, retreatment, suspected treatment-failure, neuropathic, and other clinically high-risk cases. The exposure of interest was previous or ongoing anti-leprosy therapy, including multidrug therapy or other antimicrobial regimens. The comparison, where available, included non-relapse cases, newly diagnosed cases, retreatment cases, or drug-susceptible leprosy patients. The outcomes of interest were clinical relapse, recurrence, suspected treatment failure, and/or reported antimicrobial resistance to anti-leprosy drugs. Eligible study designs included cross-sectional studies, cohort studies, case-control studies, surveillance studies, and case series with relevant clinical and laboratory data. The search terms included combinations of "leprosy," "*Mycobacterium leprae*," "relapse," "recurrence," "retreatment," "treatment failure," "drug resistance," "antimicrobial resistance," "dapsone," "rifampicin," and "ofloxacin." Additional terms such as "*folP1*," "*rpoB*," and "*gyrA*" were used when needed to identify molecular resistance studies.

Study Selection

Study selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 framework to ensure a transparent and reproducible process. Titles and abstracts identified through the database search were screened for relevance to leprosy, antimicrobial resistance, relapse, recurrence, retreatment, suspected treatment failure, neuropathic disease, and resistance surveillance. Potentially eligible articles were then assessed in full text according to predefined inclusion and exclusion criteria.

Studies were included if they met the following criteria: (1) original research articles with primary data; (2) studies involving human leprosy patients, including newly diagnosed, relapsed, recurrent, retreatment, suspected treatment-failure, neuropathic, or clinically high-risk cases; (3) studies reporting antimicrobial resistance findings or laboratory-based evaluation of resistance to at least one key anti-leprosy drug, particularly dapsone, rifampicin, or ofloxacin; (4) studies using molecular methods, including PCR, sequencing, or line probe assays, where applicable, to assess resistance-associated regions or mutations such as *folP1*, *rpoB*, and *gyrA*; and (5) articles published in peer-reviewed journals in English.

Studies were excluded if they focused solely on animal models, in vitro drug susceptibility without clinical correlation, or did not provide interpretable clinical or antimicrobial resistance data. Narrative reviews, systematic reviews, meta-analyses, editorials, conference abstracts without full data, and grey literature, including theses and dissertations, were also excluded. Articles were further excluded if they lacked sufficient clinical detail to interpret patient population or disease status, did not provide information relevant to relapse, recurrence, retreatment, suspected treatment failure, neuropathic disease, or resistance surveillance, or did not report resistance results for the assessed drugs or genes. Studies reporting no detected resistance mutations were still considered eligible if they performed appropriate resistance testing and provided clinically relevant data.

Quality Assessment

The methodological quality of the included studies was appraised with attention to both clinical and molecular aspects. For observational and clinical designs, including prospective and retrospective cohorts, surveillance studies, and case series, key domains included clarity of case definition, especially distinction between relapse and leprosy reactions, diagnostic criteria for leprosy classification, completeness of follow-up, and adequacy of reporting on prior MDT exposure and treatment adherence. Molecular quality was assessed based on the type of specimen used, the molecular method applied, including PCR or sequencing, and the reporting of resistance-associated targets such as *folP1*, *rpoB*, and *gyrA*. Studies were also assessed for whether they clearly reported positive or negative resistance findings.

RESULT

A total of six studies were included in this systematic review, comprising 1,476 participants evaluated for leprosy recurrence, suspected relapse, retreatment, neuropathic leprosy, or antimicrobial resistance surveillance. The included studies were conducted in endemic settings and represented diverse designs, including relapse-focused cohorts, molecular surveillance studies, population-based surveillance series, multicenter investigations, and nerve-biopsy-based studies. Study populations and specimen types varied, ranging from recurrent or retreatment cases assessed using clinical samples to neuropathic leprosy cases evaluated using nerve biopsy specimens.

Across the included studies, patients were mostly adults, with recurrence-focused cohorts reporting a mean age of approximately 50 years and age ranges extending from the mid-20s to the early 70s. Men consistently predominated, often accounting for more than 55–70% of cases. The majority had multibacillary disease, frequently with moderate to high bacilloscopic indices at diagnosis or AMR evaluation. Several studies also reported diagnostic delay, neuropathic involvement, recurrent disease, or suspected therapeutic failure. Clinically, borderline forms were commonly reported, especially BT, BL, and other borderline variants. Relapses typically occurred many years after completion of therapy, most often between 5 and 15 years, and were more frequent in patients with prior MB disease, higher bacillary loads, and, in some settings, continued exposure or intradomiciliary contacts.

At the molecular level, the majority of M. leprae isolates in the included studies were still susceptible to first-line drugs; however, a consistent minority showed mutations in the classical drug-resistance–determining regions of rpoB (rifampicin), folP1 (dapsone), and gyrA (ofloxacin). In the Indian nerve-biopsy cohort, resistance mutations were detected in 6 of 77 PCR-positive patients (7.8%), predominantly in borderline forms, with dapsone resistance linked to substitutions at folP1 codon 55 and ofloxacin resistance to changes at gyrA codons 89 and 91, occasionally combined with rifampicin resistance. A large Brazilian surveillance series (1,183 cases) found overall dapsone resistance in 1.2% of isolates, very low rifampicin and ofloxacin resistance (0.1% each), and multidrug resistance (dapsone plus rifampicin) in 0.2%; within the relapse subgroup, resistance was clearly enriched, with dapsone resistance in 1.83%, ofloxacin in 0.36%, rifampicin in 0.36%, and MDR in 0.36%, and a mean interval of 8.5 years between initial cure and relapse in resistant cases. Another multicenter series of 136 patients (mainly MB) reported mutations in at least one DRDR in 16.9% of cases, driven largely by ofloxacin resistance (12.5%) due to a uniform Ala→Val substitution at gyrA codon 91, while rifampicin and dapsone resistance each occurred in 2.2%, again without any three-drug multidrug resistance. Smaller cohorts of new cases showed lower but non-negligible resistance rates, such as 5.9% of strains in a Chinese series carrying dual mutations in folP1 codon 55 and gyrA codon 91, whereas one Brazilian recurrence cohort demonstrated no DRDR mutations at all, underscoring that standard WHO-MDT remains broadly effective even in relapse. Taken together, these results indicate that resistant *M. leprae* strains are still uncommon but are more often detected in MB patients with high bacillary indices, clinical relapse, prolonged disease, or persistent/recurrent reactions, supporting the use of targeted molecular testing (particularly of folP1, rpoB, and gyrA) in these high-risk groups to guide therapy and to prevent the silent spread of dapsone- and fluoroquinolone-resistant bacilli.

DISCUSSION

Patient Clinical Profile

Across the six studies, patients were predominantly adults. Recurrence-focused cohorts generally reported a mean age of approximately 50 years, while AMR surveillance, neuropathic, and multicenter cohorts included broader adult age ranges, including some younger patient groups. Men were consistently more affected than women, accounting for approximately two-thirds to three-quarters of cases across most included studies.

It is expected that recurrence will generally occur in individuals aged over 50 years, reflecting the long interval between the initial infection, completion of treatment, and later disease reappearance. This pattern is biologically plausible because *M. leprae* multiplies slowly and may remain clinically silent for years before recurrent disease becomes evident.(Alrehaili, 2023; Chagas et al., 2021; da Silva et al., 2025) Regarding the higher prevalence in men is associated with their greater vulnerability due to higher mobility, occupational exposure, wider social contact, and delayed health-seeking behavior, which may increase exposure risk and contribute to delayed diagnosis. (Alrehaili, 2023; Sanker et al., 2020)

Most patients were multibacillary (MB) cases, often with high bacilloscopic indices (BI), especially in drug-resistance and relapse cohorts, where BI commonly averaged around 3+ and a substantial proportion had BI ≥4+. This finding is clinically important because a higher bacillary load increases the likelihood of persistent bacilli after therapy and may create greater opportunity for resistant subpopulations to emerge, particularly when treatment is irregular, delayed, or incomplete. Several studies also reported that patients initially classified as paucibacillary later presented as multibacillary at recurrence, suggesting either initial misclassification, delayed case detection, reinfection, or immune deterioration over time.(Chagas et al., 2021; da Silva et al., 2025)

Clinical Classification and Immunological Spectrum

Across the included studies, recurrent and drug-resistance-evaluated leprosy cases were frequently distributed within borderline forms, particularly borderline tuberculoid (BT), borderline-borderline (BB), and borderline lepromatous (BL) disease. One nerve-biopsy cohort reported histopathological findings dominated by BT cases, with additional tuberculoid (TT), BL, BB, and a small number of lepromatous or healed lesions. In contrast, larger antimicrobial resistance surveillance and population-based cohorts were predominantly composed of multibacillary (MB) cases, often accounting for more than 80% of participants. In relapse-focused studies, borderline clinical forms were commonly observed at recurrence, and some patients initially classified as paucibacillary (PB) later presented as MB at recurrence.

This distribution is clinically meaningful because the borderline spectrum represents an immunologically unstable zone between the polar tuberculoid and lepromatous ends of leprosy. Borderline forms are more prone to immunological fluctuation, including upgrading and downgrading shifts, which may alter clinical classification over time. The shift from PB to MB at recurrence may suggest immune deterioration, delayed case detection, reinfection, or initial operational misclassification. From a pathophysiological perspective, progression toward MB disease indicates weaker cell-mediated immunity against *M. leprae*, allowing greater bacillary multiplication and broader disease expression.(Chagas et al., 2021; Mi et al., 2020)

The findings from nerve-biopsy cohorts provide important immunological and clinical context. BT and TT cases generally reflect relatively preserved cell-mediated immunity; however, this stronger immune response may also drive peripheral nerve inflammation and damage. This explains why neuropathy-focused cohorts frequently showed sensory–motor involvement and demyelinating polyradiculoneuropathy on nerve conduction studies, with

nerve biopsy confirming leprous neuropathy in most cases. Clinically, this is important because neural involvement may be prominent even when cutaneous manifestations are limited or atypical, making neuropathic leprosy difficult to recognize without histopathological or molecular support. In such cases, nerve biopsy, PCR, or molecular testing may help confirm active infection and evaluate possible drug resistance. By contrast, MB and lepromatous cases represent a more anergic immune profile, characterized by weaker cellular immune control and higher bacillary burden. This higher bacillary load may increase the likelihood of bacillary persistence and create greater opportunity for resistant subpopulations to emerge, particularly in patients with prolonged disease, irregular treatment, or recurrent inflammatory states.(Alrehaili, 2023; Sanker et al., 2020)

Relapse Pattern

Relapse cohorts showed that recurrence typically occurred years after initial "cure", with average intervals often in the range of 8–11 years, and most relapses happening between 5 and 15 years after completion of treatment. In one Brazilian series of 30 confirmed recurrences, roughly two-thirds relapsed between 5–10 years, and the mean incubation period for recurrence was about 10.5 years. Relapse cases frequently had positive BI at both first diagnosis and at recurrence, and borderline clinical forms predominated at relapse.

Several studies emphasized that intervals under 5 years were more likely related to inadequate therapy or misclassification at the first diagnosis rather than "true" recurrence, whereas very long intervals (>15 years) were linked to persistent exposure or possible reinfection in hyperendemic settings and in patients with intradomiciliary contacts. Across the AMR surveillance studies, resistant strains (especially dapsone or ofloxacin resistance, and less commonly rifampicin) were detected more often in relapse patients than in new cases.(da Silva et al., 2025; Li et al., 2022) This pattern may be explained partly by "subclinical persistence", is considered one of the main biological causes of late relapse. The risk of relapse depends not only on the therapeutic regimen but also on the host's immune response, initial bacillary load, and the quality of treatment adherence. The significance of these factors is supported by the predominant profile of relapse cases identified in this review primarily male patients diagnosed with MB forms. (da Silva et al., 2025)

Diagnostic delay was another recurring feature, ranging from months to more than 10 years in some cohorts. Such delays may contribute to more extensive bacillary multiplication, increased risk of nerve involvement, and more severe disease at presentation. In addition, some studies reported patients from non-endemic areas, hyperendemic regions, or migrant "floating populations," indicating that population movement and local transmission intensity may influence relapse and resistance patterns. One study mentioned intradomiciled contact with patients diagnosed with leprosy, which could explain relapses due to hyperendemicity in the area or reinfection.(Chagas et al., 2021)

Molecular Resistance Patterns

Across the included studies, molecular testing primarily focused on the WHO-recommended drug-resistance–determining regions of *rpoB*, *folP1*, and *gyrA*, which are associated with rifampicin, dapsone, and ofloxacin resistance, respectively. Overall, resistance-associated mutations were uncommon in most cohorts, supporting the continued effectiveness of standard MDT in many settings. However, the repeated detection of mutations in these loci across different countries indicates that antimicrobial resistance in *M. leprae* remains clinically relevant, particularly in relapse, retreatment, suspected therapeutic failure, and high-bacillary-load cases.

The resistance pattern observed in this review suggests that dapsone and ofloxacin resistance may be more frequently detected than rifampicin resistance in several cohorts. This is clinically important because rifampicin remains the most bactericidal component of MDT, whereas ofloxacin is commonly used in alternative or second-line regimens for patients who cannot receive standard therapy or require regimen modification. Fluoroquinolones, including ofloxacin, are widely used antibiotics in routine clinical practice for various infectious diseases, and their easy availability or inappropriate use may contribute to the emergence of fluoroquinolone resistance in some settings, including China. The predominance of *gyrA* mutations in some studies, particularly at codon 91, further suggests that fluoroquinolone resistance should receive greater attention in surveillance programs. (Fonseca et al., 2025; Li et al., 2022)

Similarly, recurrent *folP1* mutations at codons 53 and 55 indicate that dapsone resistance persists in some settings, including among relapse and newly diagnosed cases. The predominance of folP1 mutations among resistant isolates is biologically and historically plausible. Dapsone was used as long-term monotherapy for leprosy for several decades in the mid-20th century, and prolonged single-drug exposure is now recognized as a major driver of dapsone-resistant *M. leprae* through selection of mutations in the folP1 drug-resistance–determining region. Even in the MDT era, recent systematic reviews and surveillance studies show that folP1 codon 53 and 55 substitutions remain the most frequent resistance-associated changes and are closely linked to relapse, long treatment histories, and prior dapsone use. Although dapsone is currently administered in combination with rifampicin and clofazimine, the continued detection of folP1 mutations in relapse and retreatment cohorts indicates that dapsone resistance is still epidemiologically relevant and that loss of dapsone activity may effectively reduce MDT to a functional two-drug regimen in patients with high bacillary load.(Li et al., 2022; Wu et al., 2022)

Although multidrug resistance was rare, combined resistance patterns, such as dapsone–rifampicin or dapsone–ofloxacin resistance, remain concerning because they may limit therapeutic options and increase the risk of persistent infection. Therefore, even low levels of rifampicin, dapsone, or fluoroquinolone resistance may have important therapeutic implications, particularly in patients with relapse, suspected treatment failure, poor response to MDT, or previous exposure to second-line drugs. However, relapse should not be attributed to antimicrobial resistance alone. One recurrence cohort found no resistance mutations in the assessed *rpoB*, *folP*, or *gyrA* regions, indicating that recurrent disease may also result from bacillary persistence, reinfection, treatment irregularity, immune deterioration, or operational misclassification at the initial diagnosis.(Chagas et al., 2021; Fonseca et al., 2025)

CONCLUSION

Molecular testing is therefore most useful when interpreted alongside clinical history, bacillary index, treatment adherence, relapse interval, and evidence of ongoing transmission. This integrated approach may guide individualized treatment, preserve the effectiveness of MDT and second-line regimens, prevent silent spread of resistant *M. leprae* strains, and avoid assuming that all late recurrences share a single cause.

Limitation

The evidence is limited by the small number of eligible studies, their predominantly retrospective design, and heterogeneous definitions of relapse and treatment failure. Not all cohorts systematically used molecular testing, and most focused only on folP1, rpoB, and gyrA, so low-level or non-classical resistance and reinfection may be under-recognized. The data also come from a restricted group of endemic countries, which may limit generalizability to other settings.

Suggestion for Futher Research

Future studies should prioritize prospective, multicenter designs with standardized relapse definitions, longer follow-up after MDT, and routine molecular testing in relapse, retreatment, suspected treatment failure, and high-risk neuropathic cases. Further research should also integrate clinical classification, immune status, bacillary load, treatment history, and expanded resistance panels beyond *folP1*, *rpoB*, and *gyrA* to better clarify relapse mechanisms and guide individualized treatment for patients with confirmed resistance.

DISCLOSURE

Conflict of Interest

There is no conflict of interest in writing this manusript

Publication Ethics

This systematic review was conducted using data from previously published studies. No individual patient data were collected directly, and no intervention involving human participants was performed. Therefore, ethical approval and informed consent were not required.

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Authors Contribution

All authors contributed to the conception and design of the study, literature search, study selection, data extraction, quality assessment, data interpretation, and manuscript preparation. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Generative Artificial Intelligence (AI) Tools

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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