INTERNATIONAL JOURNAL OF SOCIAL HEALTH
https://ijsh.ph/index.php/rp
Volume 4 Number 11 November 2025
E-ISSN: 2984-7079

Emerging Therapeutic Strategies for Leprosy: A Narrative Review

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KEYWORDS
Leprosy, Hansen's Disease, Bedaquiline, Drug Resistance, Therapeutic Strategies, Nanoparticles

ABSTRACT
This review aims to summarize the latest advancements in therapeutic strategies for leprosy, focusing on new drug candidates, novel treatment regimens, innovative drug delivery systems, and the ongoing challenge of antimicrobial resistance. Our objective is to provide a comprehensive overview for clinicians and researchers, highlighting promising avenues for improving treatment efficacy, shortening duration, and overcoming resistance. A narrative review of the literature was conducted using PubMed, Google Scholar, and Scopus databases for articles published between 2022 and 2025. Keywords included "leprosy," "Hansen's disease," "bedaquiline," RIMOXCLAMIN, "drug delivery," "nanoparticles," "post-exposure prophylaxis," and "drug resistance." The therapeutic landscape of leprosy is evolving significantly. Bedaquiline has shown potent bactericidal activity against M. leprae in recent trials, with studies on monotherapy and its inclusion in shortened regimens demonstrating high efficacy. The novel RIMOXCLAMIN regimen has shown superiority over standard multidrug therapy (MDT) in neurological recovery. Concurrently, advancements in drug delivery systems, such as nanocarriers and long-acting injectables, promise to improve patient adherence and treatment outcomes. However, the emergence of resistance to dapsone and rifampicin remains a critical threat, necessitating enhanced surveillance and the development of alternative therapies. Recent research offers considerable hope for transforming leprosy treatment. The integration of new drugs like bedaquiline, optimized regimens, and innovative delivery technologies has the potential to lead to a more effective, patient-friendly, and shorter treatment course. Continued investment in research and global collaboration is essential to translate these findings into clinical practice and accelerate progress towards a world free of leprosy.

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INTRODUCTION

Leprosy, or Hansen's disease, caused by the bacterium Mycobacterium leprae, remains a significant public health challenge despite being curable (Collin et al., 2023; Hambridge et al., 2021). The World Health Organization (WHO) reports approximately 200,000 new cases annually, with the majority concentrated in India, Brazil, and Indonesia (World Health Organization, 2023). The cornerstone of leprosy control since the 1980s has been multidrug therapy (MDT), a combination of dapsone, rifampicin, and clofazimine, which has been instrumental in reducing the global disease burden (Verma et al., 2024). Over the past decade, global leprosy burden has shown mixed trends: while the prevalence rate decreased from 0.23 per 10,000 population in 2013 to 0.22 in 2023, the new case detection rate has plateaued at approximately 2.3 per 100,000 population, indicating persistent transmission in endemic regions. Grade 2 disability rates among newly diagnosed cases remain at 4.4%, signaling delayed diagnosis continues to be a critical issue (Pope et al., 2020). The global relapse rate is estimated at 2-3% within five years of treatment completion, though this varies significantly by region and adherence patterns (Ghione et al., 2022). India, Brazil, and Indonesia collectively

account for over 80% of global cases. Specifically, Indonesia ranks third globally with 13,487 new cases reported in 2023, showing a 7.2% increase from 2022. Within Indonesia, the prevalence rate stands at 0.51 per 10,000 population, with significant geographic variation: provinces such as Maluku (2.1 per 10,000), Papua (1.8 per 10,000), and East Java (0.9 per 10,000) show substantially higher burdens than the national average. The disability grade 2 rate in Indonesia is 8.3%, nearly double the global average, indicating critical gaps in early detection and treatment initiation (Tjahjadi, 2025). Moreover, multibacillary (MB) leprosy accounts for 68% of Indonesian cases, requiring more intensive 12-month treatment regimens and carrying higher transmission risk (Krismawati et al., 2024).

However, the standard 12-month regimen for multibacillary (MB) leprosy presents challenges, including patient adherence, adverse drug reactions, and the looming threat of antimicrobial resistance (AMR) (Lukito et al., 2024; Sardana et al., 2025). The persistence of leprosy transmission and the occurrence of irreversible nerve damage underscore the urgent need for more effective, safer, and shorter treatment regimens (Calderone et al., 2024; Mehta et al., 2025). This review synthesizes the most recent advancements in leprosy therapeutics, exploring promising new drugs, innovative regimens, and novel drug delivery systems that are poised to reshape the future of leprosy management (Aamir et al., 2018; Chaves et al., 2020; da Rocha et al., 2022). The urgent need for more effective, safer, and shorter treatment regimens stems from multiple converging factors: first, the prolonged treatment duration leads to adherence rates as low as 65% in some settings, contributing to treatment failure and disease relapse; second, the three-drug MDT regimen (rifampicin, dapsone, clofazimine) causes adverse reactions in 15-30% of patients, ranging from mild skin discoloration to severe hypersensitivity reactions requiring treatment discontinuation; third, emerging resistance to rifampicin (detected in 2-5% of isolates globally) threatens to undermine the cornerstone of current therapy; and fourth, the lack of bactericidal activity assessment during treatment prevents early identification of treatment failure, as M. leprae cannot be cultured in vitro.

Recent research has significantly advanced our understanding of leprosy therapeutics, yet critical gaps remain. Barreto et al. (2024) demonstrated in a phase 2 trial that bedaquiline monotherapy achieved rapid bacterial clearance in MB leprosy patients, with solid proportion reaching undetectable M. leprae DNA within 8 weeks—a finding that challenges the necessity of prolonged combination therapy. Similarly, Fomba et al. (2025) reported unprecedented bactericidal activity of bedaquiline in the BDQ4LEP trial, showing a 3.5-log reduction in bacterial load, significantly superior to standard MDT. Frade et al. (2025) introduced the RIMOXCLAMIN regimen (rifampicin, moxifloxacin, clarithromycin, minocycline), which not only shortened treatment duration but also promoted faster nerve function recovery compared to WHO-MDT, addressing a critical gap in neurological outcome optimization. However, these studies primarily focus on efficacy endpoints, with limited long-term safety data and minimal investigation of regimen applicability in resource-limited settings. Furthermore, while Chauffour et al. (2025) identified telacebec (Q203) as having exceptional anti-M. leprae activity in animal models, clinical translation remains in early phases. The challenge of antimicrobial resistance has been highlighted by Rosa et al. (2020) and Cambau et al. (2018), who documented rifampicin resistance rates of 2-5% globally through molecular surveillance, yet systematic resistance monitoring frameworks remain absent in most endemic countries. Critically, no studies have comprehensively integrated these emerging therapeutic strategies with innovative drug delivery systems, which could address adherence barriers that plague current regimens.

This narrative review aims to systematically synthesize current evidence on emerging therapeutic strategies for leprosy, with three specific objectives: first, to evaluate the efficacy, safety, and potential clinical applications of new and repurposed anti-leprosy drugs,

particularly bedaquiline and telacebec; second, to critically assess novel treatment regimens designed to shorten duration and improve patient outcomes; and third, to examine innovative drug delivery systems that could enhance adherence and therapeutic efficacy. The benefits of this review are multifold: for clinicians, it provides evidence-based guidance on incorporating emerging therapies into practice; for researchers, it identifies critical knowledge gaps requiring further investigation, particularly regarding long-term safety, resistance patterns, and cost-effectiveness in endemic settings; for policymakers, it offers insights into therapeutic innovations that could inform treatment guidelines and resource allocation strategies; and for patients, it highlights promising developments that may lead to shorter, safer, and more effective treatment options. By integrating evidence across pharmacological innovation, clinical outcomes, and delivery mechanisms, this review contributes to the global effort toward leprosy elimination and addresses the urgent need for therapeutic advancement in a disease that continues to affect vulnerable populations worldwide.

METHOD

This study employed a narrative review methodology to synthesize current evidence on emerging therapeutic strategies for leprosy. A comprehensive narrative literature review was conducted to examine recent advances in leprosy treatment, including new drugs, novel regimens, and innovative delivery systems. Electronic databases including PubMed, Scopus, Web of Science, and Google Scholar were systematically searched for relevant publications. Additional sources included WHO technical reports, clinical trial registries (ClinicalTrials.gov), and grey literature from international leprosy conferences. The literature search covered publications from January 2020 to January 2025, using combinations of keywords: 'leprosy' OR 'Hansen's disease' AND 'treatment' OR 'therapy' OR 'therapeutics' AND 'bedaquiline' OR 'new drugs' OR 'novel regimens' OR 'drug delivery systems' OR 'antimicrobial resistance'. Studies were included if they reported primary data or systematic analyses on therapeutic interventions for leprosy, including clinical trials, observational studies, pharmacological investigations, and systematic reviews. Articles were excluded if they were case reports with fewer than five patients, non-English publications without accessible translations, or studies focusing solely on diagnosis, epidemiology, or immunology without therapeutic implications.

Relevant data were extracted from selected studies including study design, sample size, intervention details, primary and secondary outcomes, safety profiles, and key findings. Evidence was narratively synthesized and organized thematically into four main categories: (1) new and repurposed drug candidates, (2) novel treatment regimens, (3) antimicrobial resistance challenges, and (4) innovative drug delivery systems. Quality appraisal focused on study design rigor, sample adequacy, outcome measurement validity, and potential biases. The review encompasses studies conducted globally, with particular attention to high-burden countries including India, Brazil, Indonesia, and African nations where leprosy remains endemic. The target population includes adult and pediatric patients with both paucibacillary (PB) and multibacillary (MB) leprosy across various stages of disease and treatment.

As a literature review of published data, this study did not require institutional review board approval. All included studies were conducted in accordance with ethical principles and had received appropriate ethical clearances as reported in their original publications.

RESULTS AND DISCUSSION

New and Repurposed Drug Candidates

The search for new anti-leprosy agents has identified several promising candidates, with drug repurposing playing a pivotal role. Bedaquiline, a diarylquinoline originally developed

for tuberculosis, has emerged as a frontrunner.

Bedaquiline

Recent clinical trials have demonstrated the potent bactericidal activity of bedaquiline against M. leprae. An open-label trial in Mali (BDQ4LEP) showed that an 8-week course of bedaquiline resulted in a 96% culture negativity rate in skin biopsies from MB patients by day 56. Another proof-of-concept study confirmed that bedaquiline monotherapy cleared M. leprae within four weeks of treatment, accompanied by visible improvement in skin lesions. With a long half-life of 5.5 months and higher in-vitro activity compared to rifampicin, bedaquiline is an attractive component for future shortened leprosy treatment regimens. Its potential is also being explored for post-exposure prophylaxis (PEP).

Other Candidates

Telacebec (Q203), another drug developed for tuberculosis, has also shown unprecedented in-vivo activity against M. leprae, with bactericidal effects comparable to standard MDT. These findings highlight a promising pipeline of drugs that could be integrated into novel combination therapies.

Novel Treatment Regimens

Beyond single-drug discovery, research is focused on creating new combination regimens to shorten treatment duration and improve outcomes, particularly neurological recovery.

The RIMOXCLAMIN Regimen

A recent study evaluated a new regimen named RIMOXCLAMIN, consisting of Rifampicin, Moxifloxacin, Clarithromycin, and Minocycline. The results indicated that RIMOXCLAMIN was superior to the standard WHO-MDT in promoting the recovery of neurological damage, showing a significant reduction in pain scales and a 17.9% improvement in foot sensitivity. This focus on neurological outcomes is a critical advancement, as nerve damage is the primary cause of disability in leprosy.

Shortened Regimens

The success of bedaquiline has spurred investigations into shortened MDT protocols. The goal is to reduce the treatment duration from 12 months to 6 months or even less for MB leprosy, which would significantly improve patient adherence and reduce the burden on healthcare systems. These studies are ongoing, but initial results are highly encouraging.

The Challenge of Antimicrobial Resistance

The emergence of drug-resistant M. leprae poses a serious threat to global leprosy control efforts. Resistance to dapsone has been documented for decades, but resistance to rifampicin, the most effective anti-leprosy drug, is of greater concern. A 2020 study identified multidrug resistance (rifampicin + dapsone) in both relapse and new cases, indicating active transmission of resistant strains.

Global surveillance of AMR in leprosy is challenging because M. leprae cannot be cultured in vitro. However, molecular methods for detecting resistance-conferring mutations in genes like folP1 (dapsone), rpoB (rifampicin), and gyrA (quinolones) are now the standard. A systematic review highlighted the global prevalence of resistance, emphasizing the need for routine surveillance to guide treatment policies. In countries like Indonesia, concerns about the safety of dapsone-containing MDT without pharmacogenetic screening are growing, further complicating the treatment landscape.

Innovative Drug Delivery Systems

To address issues of poor adherence and optimize drug efficacy, researchers are exploring innovative drug delivery systems.

Table 1. Drug Delivery System Innovation for Leprosy Therapy

Delivery System	Description	Potential Benefits	Key References
Nanocarriers	Polymeric nanoparticles, solid lipid nanoparticles, and liposomes encapsulating anti- leprosy drugs.	Sustained drug release, targeted delivery to infected macrophages, reduced dosage and frequency, improved bioavailability.	[15], [16]
Transdermal Patches	Adhesive patches that deliver a controlled dose of medication through the skin over an extended period.	Non-invasive, improved patient compliance, avoidance of first-pass metabolism, stable plasma drug levels.	[17]
Long-Acting Injectables	Formulations that release drugs slowly over weeks or months after a single injection.	Drastically reduced dosing frequency, ensures adherence, suitable for prophylactic use in contacts.	[8], [17]

These systems offer a paradigm shift from daily oral medication. For example, polymeric nanoparticles have been shown to enable sustained co-delivery of dapsone and clofazimine, potentially allowing for dose reduction. Long-acting injectable formulations of bedaquiline are also being tested in animal models, showing promise for both treatment and prophylaxis.

CONCLUSION

The fight against leprosy is advancing through powerful new drugs like bedaquiline, innovative regimens such as RIMOXCLAMIN, and cutting-edge drug delivery systems, offering the promise of shorter, more effective, and patient-friendly treatments. Yet, antimicrobial resistance remains a critical challenge, demanding coordinated global efforts in molecular surveillance and ongoing research. Future studies should focus on developing resistance-resistant therapies and evaluating the long-term impacts of these novel treatments in diverse populations to ensure sustainable progress toward eradicating leprosy worldwide.

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