Indian J Med Res 161, February 2025, pp 120-124
DOI: 10.25259/IJMR_195_2025

Perspective

Leprosy research updates: Shaping the future of global health

Leprosy, or Hansen's disease, remains a majorly neglected tropical disease. In 2023, 1,82,815 new cases were reported globally, primarily from India, Brazil, and Indonesia. The disease, caused by *Mycobacterium leprae* (*M. leprae*) and *M. lepromatosis*, is known for its skin lesions but often leads to severe complications, including neural damage resulting in permanent disabilities.

Despite significant advances, leprosy's transmission mechanisms remain unclear, with zoonotic transmission *via* armadillos emerging as a concern, especially in Latin America. Diagnostic challenges persist, with skin smears offering limited sensitivity, underscoring the need for advanced, point-of-care diagnostics, such as anti-PGL-I antibody tests and multiplex PCR assays. Recent advancements in PCR technology and *M. leprae* genotyping have enhanced the accuracy of diagnostics, aiding in the detection of the disease and understanding its transmission patterns. Additionally, new therapies, including bedaquiline, and Telacebec, show promise in treating leprosy, although management of reactions and neuritis remains a challenge.

Leprosy prevention efforts are focused on post-exposure prophylaxis (PEP) and vaccines, with the BCG vaccine showing limited efficacy in leprosy prevention. Innovative approaches, including single-dose rifapentine and bedaquiline for PEP, are being explored. Mental health support and addressing stigma through human rights-based interventions are critical for improving the quality of life for those affected.

Artificial intelligence (AI) tools, like the WHO Skin NTD app, are emerging as valuable resources for early diagnosis and management, particularly in resource-limited settings. Continued research and global collaboration are essential for overcoming the remaining barriers to eliminating leprosy, focusing on diagnostics, treatment, and reducing stigma.

Leprosy, or Hansen's disease, is a neglected tropical disease reported by 184 (out of 221) countries and territories in 2023. India, Brazil, and Indonesia account for 79.3 per cent of 1,82,815 new cases detected globally[1]. These figures represent a five per cent increase compared to the situation in 2022[1].

Although leprosy is an infectious condition, mostly known as a skin disease characterised by anaesthetic patches and nodules, it is often accompanied by inflammatory events that can lead to neural damage and result in permanent disabilities, mainly of the hands, feet, and eyes[2]. In 2023, globally, advanced and visible disabilities, known as grade 2 disability (G2D), were reported in 5.3 per cent of all new cases, highlighting the challenge of delayed diagnosis. Leprosy in children is of particular concern, accounting for 5.7 per cent of all new cases reported globally, of which 266 were diagnosed with G2D[1].

The World Health Organization's (WHO) leprosy elimination strategy aims to interrupt transmission and eliminate the disease through four pillars: implementing country-owned Zero Leprosy Roadmaps, scaling up prevention with active case detection, managing complications to prevent disabilities, and combating stigma while protecting human rights.

Transmission mechanisms and One Health approach

Despite leprosy being one of the first infectious diseases to have an identified cause and a long-standing global effort to control it, there are many scientific advances still to be made. Disease transmission mechanisms have not yet been fully understood. Leprosy is caused by *M. leprae* and *M. lepromatosis*, with transmission primarily occurring from person to person, but this mechanism is poorly understood. Zoonotic transmission, widely reported in the southeastern United States through nine-banded armadillos, has emerged as a significant concern in endemic regions of Latin America. In Brazil, approximately 10 per cent of the animals appear to be contaminated[3], and hunting poses a higher risk of transmission[4]. The presence of *M. leprae* in the

environmental reservoir further complicates efforts to achieve leprosy elimination[5].

Diagnostic challenges

The diagnosis of leprosy is based on any of the three cardinal signs: (*i*) the presence of skin lesions with definite loss of sensation, (*ii*) a thickened or enlarged peripheral nerve, and (*iii*) the presence of *M. leprae* in a slit-skin smear (SSS). The latter only occurs in about 20-40 per cent of cases. With decreasing expertise in clinical diagnosis and skin smear testing, the need for newer diagnostics is important.

Anti-phenolic glycolipid (PGL-I) antibodies strongly correlate to patients' bacterial load and *M. leprae* DNA present in the SSS of patients and contacts[6], rendering this host biomarker practical in detecting *M. leprae* infections, diagnosing multibacillary (MB) patients, and monitoring treatment[7].

Qualitative and quantitative lateral flow tests detecting anti-PGL-I antibodies have been developed[8] but not widely implemented as a point-of-care (POC) test. Multiple host biomarkers (αPGL-I IgM, IP-10, CRP, ApoA1, S100A12, CCL4) are required to capture the different clinical presentations across the leprosy disease spectrum[9].

Ideally, affordable POC immunodiagnostic tests, like lateral flow assays detecting multiple biomarkers simultaneously, that recognise early stages of leprosy would play an important part in identifying individuals in need of PEP, reducing diagnostic delays and preventing misdiagnosis.

New advancements in PCR tests and *M. leprae* genotyping

Molecular diagnostics have significantly improved the detection and characterisation of *M. leprae*. PCR-based assays offer higher sensitivity and specificity, allowing early detection of *M. leprae* DNA in clinical and environmental samples. Recent advancements in PCR technology have led to the development of multiplex PCR assays that simultaneously amplify multiple target genes, improving diagnostic accuracy[10]. Given the complex nature of leprosy, a combination of molecular and biological markers enhances accuracy. Multiplex PCR assays have also been valuable for differentiating *M. leprae* from *M. lepromatosis*, which is increasingly recognised as a causative pathogen in leprosy cases. Additionally, multiplex PCR, along with other methods such as multiplex loop-mediated isothermal amplification (mLAMP) assays, have proven effective in diagnosing multiple diseases co-endemic with leprosy, simultaneously offering more cost- and time-efficient solutions[11]. This aligns with the broader integration of leprosy diagnosis within skin-neglected tropical diseases (skin NTD), as the WHO advocates.

Expanding sample types beyond traditional SSS smears or skin biopsies which are invasive can be another key innovation. A recent study comparing blood, stool, and urine samples for paediatric leprosy diagnosis found that blood yielded the best results[12]. While prior research suggested limited diagnostic utility of blood or even stool and urine, emerging technologies – such as nanoparticle-based detection – may allow us to revisit these approaches with improved sensitivity.

Beyond diagnosis, *M. Leprae* genotyping provides valuable epidemiological insights by tracking transmission patterns and identifying strain variations. Whole-genome sequencing (WGS) and single nucleotide polymorphism (SNP) analysis have refined our understanding of *M. Leprae* evolution and geographic distribution[13]. Advances in targeted sequencing approaches enable the differentiation of strains at a finer resolution, which is critical in tracing zoonotic and human-to-human transmission. These molecular tools contribute to precision in public health strategies by enabling early diagnosis, monitoring transmission routes, and guiding targeted interventions. They ultimately advance leprosy control and reduce disease burden.

Treatment challenges

Antimicrobial therapy against leprosy was introduced in the 1940s, and resistance to dapsone became a significant issue. Since 1982, the preferred leprosy multidrug therapy (MDT) has been a combination of dapsone, rifampicin, and clofazimine taken daily for up to a year. Rifampicin is the main bactericidal drug, taken once a month.

The WHO monitors the emergence of global resistance to anti-leprosy drugs. In 19 leprosy endemic countries participating in a surveillance study, molecular detection of resistance genes identified an antimicrobial resistance rate of eight per cent towards dapsone, rifampicin, and ofloxacin, with a higher percentage in relapse *versus* new cases[14]. Of additional concern are the findings that show high numbers of

resistance to drugs used for second-line therapy, such as ofloxacin[15]. Alternatives to MDT also can include monthly ROM (rifampicin, ofloxacin, and minocycline) and moxifloxacin[16]; however, more trials are needed.

Bedaquiline targeting and binding with bacterial adenosine triphosphate leads to the death of mycobacteria. The long 5.5-month half-life and the higher activity compared to rifampicin make bedaquiline an attractive choice for treating leprosy. A phase 2 trial in Brazil showed that bedaquiline monotherapy for MB patients cleared *M. Leprae* within four wk of treatment and resulted in improvements in the appearance of skin lesions by week seven[17]. A phase 3, active-controlled study to assess the efficacy and safety of bedaquiline in combination with rifampicin and clofazimine for the treatment of multibacillary leprosy (CT N. 2021-006613-10) is underway.

Telacebec, a drug with established safety, tolerability, and efficacy against *M. tuberculosis*, has shown activity against intracellular and extracellular *M. leprae* at nanomolar concentrations *in vitro*, with activity superior to rifampicin[18]. Phase 2 studies are being planned, but are yet to be registered.

The management of leprosy reactions and neuritis remains a challenge. The WHO guidance document on the management of leprosy recommends a 20-wk regimen of prednisolone for the management of type 1 lepra reactions. Azathioprine, cyclosporine, and methotrexate have been used in controlled clinical trials but have failed to show higher efficacy compared to prednisolone[19].

Thalidomide is the first choice for treatment for erythema nodosum leprosum (ENL); however, its limited availability, teratogenic effects, and the need for strict pregnancy prevention programmes have restricted its use in many countries. Biological drugs, including TNF-α inhibitors like etanercept and infliximab, have shown effective responses in managing ENL[20].

Prevention of leprosy challenges

Despite great strides in controlling leprosy and reducing the number of cases, the number of newly detected cases has plateaued over the last 10 yr. Vaccines and post-exposure chemoprophylaxis are among the strategies being trialled to interrupt transmission.

Bacillus of Calmette and Guerin (BCG) vaccine, mainly used to prevent TB meningitis, offers cross-reactivity and protection against leprosy, with decreasing efficacy over time. Revaccinating children as part of a leprosy prevention strategy in a Brazilian study showed no results, making BCG a poor candidate vaccine for leprosy control[21].

LepVax is the first specific vaccine for leprosy[22]. Phase 1 trials in humans demonstrated safety and the ability to generate an immune response in healthy volunteers[22]. Results from ongoing trials are awaited.

Post-exposure prophylaxis is given as a single dose of rifampicin (SDR-PEP) or combined with other antibiotics like clarithromycin (SDR-PEP+)[23]. Since 2018, the WHO has recommended SDR as leprosy preventive treatment for contacts of persons affected by leprosy, and a number of countries have introduced SDR-PEP for contacts of new cases as part of the leprosy control programmes despite it being less effective among household contacts, and more effective among non-blood relatives, neighbours of neighbours and other social contacts.

Single dose rifapentine (which has greater bactericidal activity than rifampicin) was shown to be protective in household contacts of index cases in a study in China[24]. 'Single Double Dose Rifampicin' trialled in a cluster randomised control study (PEOPLE-trial) showed a reduction of 40 per cent in leprosy incidence in the Comoros and Madagascar[25]. Alternative PEP-interventions, *e.g*., using bedaquiline as PEP (BE-PEOPLE trial), are ongoing[26]. Major concerns of PEP are the risks associated with patient confidentiality, cost-effectiveness, the limited duration of protection, and the risks of inducing rifampicin resistance, especially when administered intermittently.

Challenges in disability management, including mental health

Leprosy is a highly stigmatising disease. This stigma is a significant barrier to its elimination. A rough estimation suggests that 3-4 million people live with visible impairments caused by leprosy, while social exclusion likely affects many more due to the disease's label and associated disabilities. Efforts to combat stigma include human rights-based interventions such as repealing discriminatory laws and terminologies, promoting social inclusion, and providing counselling services to address the mental health impacts of diagnosis, disability, and exclusion[27].

Artificial intelligence in diagnosis and management

AI offers transformative potential for the diagnosis and management of leprosy. Integrated with AI, tools like the WHO Skin NTD app enable healthcare workers to identify leprosy cases early. Preliminary findings in Kenya revealed that both algorithms reached an average sensitivity of 80 per cent compared to diagnoses by certified dermatologists, highlighting AI's capacity to enhance diagnostic accuracy and support healthcare systems in resource-limited settings[28].

Overall, leprosy research is shaping the future of global health by addressing diagnostic challenges, treatment limitations, and the stigma associated with the disease. Integrating AI into diagnostic tools, expanding molecular techniques, and advancing treatments for leprosy reactions and drug resistance exemplify the progress. Sustained global efforts are essential to achieve elimination, focusing on improving public health education, investing in innovative research, and ensuring access to advanced diagnostics and therapies. Together, these strategies will bridge gaps in care and empower healthcare systems to reduce the burden of leprosy worldwide.

***Financial support & sponsorship*:** None.

***Conflicts of Interest*:** None.

***Use of Artificial Intelligence (AI)-Assisted Technology for manuscript preparation*:** The authors confirm that there was no use of AI-assisted technology for assisting in the writing of the manuscript and no images were manipulated using AI.

Patricia Duarte Deps[1*], Indira Kahawita[2], Rie Yotsu[3] & Saba M. Lambert[4]

[1]Department of Social Medicine, Federal University of Espirito Santo, Vitoria, Brazil, [2]Department of Dermatology, National Hospital of Sri Lanka E.W. Perera Mawatha, Colombo, Sri Lanka, [3]Department of Tropical Medicine, Tulane University School of Public Health and Tropical Medicine, New Orleans, USA & [4]Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School Hygiene and Tropical Medicine, London, United Kingdom

[*]*For correspondence*: patricia.deps@ufes.br

Received January 21, 2025; Accepted January 24, 2025; Ahead of print March 21, 2025; Published March 26, 2025

References

1. World Health Organization. Institutional Repository for Information Sharing. *Weekly Epidemiological Record 2024, Vol. 99, 37 [full issue]*. Available from: *https://iris.who.int/handle/10665/378893*, accessed on March 13, 2025.
2. Florian MC, Enechukwu NA, Deps PD. Clinical aspects and classification of Hansen's disease. In: Deps PD, editor. *Hansen's disease*. Cham: Springer International Publishing; 2023. p. 81-108.
3. Deps P, Antunes J, Santos A, Collin S. Prevalence of mycobacterium leprae in armadillos in Brazil: A systematic review and meta-analysis. *PLoS Negl Trop Dis* 2020; *14* : e0008127.
4. Deps P, Antunes JMA de P, Collin SM. Zoonotic risk of Hansen's disease from community contact with wild armadillos: A systematic review and meta-analysis. *Zoonoses Public Health* 2020; *68* : 153-64.
5. Turankar R, Lavania M, Darlong J, Siva Sai K, Sengupta U, Jadhav R. Survival of mycobacterium leprae and association with acanthamoeba from environmental samples in the inhabitant areas of active leprosy cases: A cross sectional study from endemic pockets of Purulia, West Bengal. *Infect Genet Evol* 2019; *72* : 199-204.
6. Lyon S, Lyon A, Da Silva R, Grossi M, Lyon S, Bührer-Sékula S, *et al*. A comparison of ML flow serology and slit skin smears to assess the bacterial load in newly diagnosed leprosy patients in Brazil. *Lepr Rev* 2008; *79* : 162-70.
7. van Hooij A, Tjon Kon Fat E, de Jong D, Khatun M, Soren S, Chowdhury A, *et al*. Prototype multi-biomarker test for point-of-care leprosy diagnostics. *iScience* 2020; *24* : 102006.
8. Duthie M, Balagon M, Maghanoy A, Orcullo F, Cang M, Dias R, *et al*. Rapid quantitative serological test for detection of infection with mycobacterium leprae, the causative agent of leprosy. *J Clin Microbiol* 2014; *52* : 613-9.
9. Nausch N, Jacobsen M. Identification and validation of host biomarkers for leprosy: A step forward to establish point-of-care tests. *E Bio Medicine* 2019; *48* : 9-10.
10. Manta F, Jacomasso T, Rampazzo R, Moreira S, Zahra N, Cole S, *et al*. Development and validation of a multiplex real-time qPCR assay using GMP-grade reagents for leprosy diagnosis. *PLoS Negl Trop Dis* 2022; *16* : e0009850.
11. Joshi S, Dixit K, Sharma V, Ramesh V, Singh R, Salotra P. Rapid multiplex loop-mediated isothermal amplification (m-LAMP) assay for differential diagnosis of leprosy and post-kala-azar dermal leishmaniasis. *Am J Trop Med Hyg* 2021; *104* : 2085-90.
12. Sharma S, Dayal R, Kamal R, Singh D, Patil S, Kumar N, *et al*. Comparative evaluation of multiplex PCR, RLEP PCR and LAMP PCR in urine, stool and blood samples for the diagnosis of pediatric leprosy - A cross-sectional study. *Indian Pediatr* 2024; *61* : 661-5.
13. Avanzi C, Lécorché E, Rakotomalala F, Benjak A, Rapelanoro Rabenja F, Ramarozatovo L, *et al*. Population genomics of mycobacterium leprae reveals a new genotype in Madagascar and the Comoros. *Front Microbiol* 2020; *11* : 711.

14. Cambau E, Saunderson P, Matsuoka M, Cole ST, Kai M, Suffys P, *et al*. Antimicrobial resistance in leprosy: results of the first prospective open survey conducted by a WHO surveillance network for the period 2009-15. *Clin Microbiol Infect* 2018; *24* : 1305-10.
15. Chhabra S, Narang T, Sahu S, Sharma K, Shilpa S, Sharma A, *et al*. High frequency of ofloxacin resistance patterns of mycobacterium leprae from India: An indication to revisit second line anti-leprosy treatment regimen. *J Glob Antimicrob Resist* 2023; *35* : 262-7.
16. Pardillo F, Burgos J, Fajardo T, Dela Cruz E, Abalos R, Paredes R, *et al*. Powerful bactericidal activity of moxifloxacin in human leprosy. *Antimicrob Agents Chemother* 2008; *52* : 3113-7.
17. Barreto J, Sammarco Rosa P, Adams L, Aguilar Z, Bakare N, Chaplan S, *et al*. Bedaquiline monotherapy for multibacillary leprosy. *N Engl J Med* 2024; *391* : 2212-8.
18. Lahiri R, Adams L, Thomas S, Pethe K. Sensitivity of mycobacterium leprae to telacebec. *Emerg Infect Dis* 2022; *28* : 749-51.
19. Mehta H, Jain S, Narang T, Chhabra S, Dogra S. Leprosy reactions: New knowledge on pathophysiology, diagnosis, treatment and prevention. *Indian J Dermatol Venereol Leprol* 2024 : 1-12.
20. Rao PN, Suneetha S, Rathod SP. Reactions in Hansen's disease. In: Deps PD, editors. *Hansen's Disease. A complete clinical guide*. 1st edition. Springer International Publishing; 2023.
21. Cunha S, Alexander N, Barreto M, Pereira E, Dourado I, Maroja M de F, *et al*. BCG revaccination does not protect against leprosy in the Brazilian Amazon: A cluster randomised trial. *PLoS Negl Trop Dis* 2008; *2* : e167.
22. Duthie MS, Frevol A, Day T, Coler RN, Vergara J, Rolf T, *et al*. A phase 1 antigen dose escalation trial to evaluate safety, tolerability and immunogenicity of the leprosy vaccine candidate LepVax (LEP-F1 + GLA-SE) in healthy adults. *Vaccine* 2020; *38* : 1700-7.
23. Richardus R, Alam K, Kundu K, Chandra Roy J, Zafar T, Chowdhury A, *et al*. Effectiveness of single-dose rifampicin after BCG vaccination to prevent leprosy in close contacts of patients with newly diagnosed leprosy: A cluster randomised controlled trial. *Int J Infect Dis* 2019; *88* : 65-72.
24. Wang L, Wang H, Yan L, Yu M, Yang J, Li J, *et al*. Single-Dose rifapentine in household contacts of patients with leprosy. *N Engl J Med* 2023; *388* : 1843-52.
25. Hasker E, Assoumani Y, Randrianantoandro A, Ramboarina S, Braet S, Cauchoix B, *et al*. Post-exposure prophylaxis in leprosy (PEOPLE): A cluster randomised trial. *Lancet Glob Health* 2024; *12* : e1017-26.
26. Younoussa A, Samidine S, Bergeman A, Piubello A, Attoumani N, Grillone S, *et al*. Protocol, rationale and design of BE-PEOPLE (Bedaquiline enhanced exposure prophylaxis for Leprosy in the Comoros): A cluster randomized trial on effectiveness of rifampicin and bedaquiline as post-exposure prophylaxis of leprosy contacts. *BMC Infect Dis* 2023; *23* : 310.
27. United Nations General Assembly. United Nations Human Rights Council. *Progress and remaining challenges in eliminating discrimination against persons affected by leprosy and their family members: Report of the Special Rapporteur on the elimination of discrimination against persons affected by leprosy and their family members*; 2023. Available from: *https://undocs.org/A/HRC/53/30*, accessed on January 13, 2025.
28. World Health Organization. *The WHO Skin NTDs App shows encouraging results in Kenya study.* Available from: *https://www.who.int/news/item/04-12-2024-the-who-skin-ntds-app-shows-encouraging-results-in-kenya-study*, accessed on January 13, 2025.