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Editorial: Advances in the molecular epidemiology and diagnostics of leprosy and other mycobacterial diseases

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Editorial on the Research Topic
Advances in the molecular epidemiology and diagnostics of leprosy and other mycobacterial diseases

Mycobacterial diseases, including tuberculosis, leprosy, and a growing number of nontuberculous mycobacterial (NTM) infections, pose persistent challenges for molecular epidemiology and diagnostics. These pathogens are notoriously difficult to detect and monitor due to their slow growth, genetic diversity, and ability to cause chronic or subclinical diseases. For many species, diagnosis relies on limited tools that lack sensitivity or field applicability, and drug resistance detection remains technically demanding and inconsistent across regions. Paradoxically, despite their slow replication rates, drug resistance in mycobacteria can emerge and spread rapidly, often outpacing surveillance efforts and complicating treatment strategies. Among these, leprosy stands out as particularly challenging because of the uncultivable *Mycobacterium leprae* and *M. lepromatosis* and is characterized by a long incubation period, subtle early manifestations, and limited diagnostic accessibility, especially in low-resource settings (1). These biological and logistical hurdles continue to hinder the timely diagnosis, surveillance, and mapping of transmission dynamics. With 182,815 new cases in 2023, a 5% increase over 2022 (2), leprosy remains a significant but neglected public health concern in countries on every continent. This Research Topic brings together recent advances that

confront these barriers, with a primary focus on molecular tools and epidemiological strategies designed to improve leprosy control.

Faber et al. investigated the introduction and distribution of leprosy in Suriname by using historical records and modern genomic analysis. (Faber et al.) Authors cite that historically, leprosy was likely introduced to Suriname through various migration waves, including the transatlantic slave trade, indentured workers from Asia, European colonizers, and recent Brazilian gold miners. Their study analyzed 26 clinical specimens from leprosy patients using PCR genotyping and whole-genome sequencing. The most common *M. leprae* strain identified was genotype 4P, with West African and Brazilian strains likely originating from the slave trade and gold miners. This study confirms that multiple introduction events shaped the genetic diversity of leprosy in Suriname, emphasizing the importance of historical migration in disease transmission. Furthermore, a mutation associated with dapsone resistance was detected in two strains, thereby highlighting the possible transmission of resistant strains and the need to monitor drug resistance trends over time (Faber et al.).

Another study examined drug resistance and genetic diversity of *M. leprae* in Venezuela. (Sisco et al.). This study did not find any mutations in *rpoB, folP1*, and *gyrA* genes, which are associated with resistance to rifampicin, dapsone, and fluoroquinolones, respectively. Seventy-six percent of the samples were identified as SNP type 3 (predominant strain in the Americas), and 14% were SNP type 4 (West African origin). This could also be indicative of a relatively recent outbreak with low existing diversity. The authors emphasized that a larger surveillance effort is needed to track transmission patterns and potential future drug resistance (Sisco et al.).

Another nationwide retrospective study examined leprosy transmission in China, revealing that, despite official elimination, it persists in a few areas, especially in rural and mountainous regions (Zhou et al.). They reviewed 710 studies from China's databases and revealed that seropositivity against leprosy in healthy children ranged from 7.93% in Yunnan to 32.35% in Jiangsu between 1987 and 2003. According to the authors, a decrease in the prevalence of leprosy in Jiangsu was correlated with lower antibody seroprevalence in children over time. The authors noted that hidden transmission (or unknown exposure) may still occur, as seropositive children were detected in areas with zero reported cases. Future studies focusing on uniform testing methods and targeted interventions in high-risk areas are needed (Zhou et al.).

Lenz et al. have performed a prospective multicentric study evaluating the effectiveness of a Molecular Viability Assay (MVA) developed to assess the viability of *Mycobacterium leprae* in clinical biopsy specimens (Lenz et al.). The MVA measures the *hsp18* and *esxA* gene transcript levels to determine bacterial viability, offering faster and more field-feasible alternatives. The study included 439 leprosy patients from three regions: Cebu, Philippines (199 cases); Addis Ababa, Ethiopia (40 cases); and Kathmandu, Nepal (200 cases). Diagnosis was done through clinical examination, slit-skin smears (SSS), and histopathology. The MVA results were compared with slit skin smear (SSS) Bacteriological Index (BI) and Mouse Footpad (MFP) assays. A strong correlation was found between RLEP qPCR enumeration of nucleic acids from biopsies stored in 70% ethanol and average SSS BI across all cohorts. An average SSS BI ≥ 2 reliably predicted sufficient *M. leprae* recovery for MVA analysis. Viable *M. leprae* was detected in 75.4% (Philippines), 77.8% (Ethiopia), and 75.0% (Nepal) of new cases. The target *hsp18* gene was more consistently expressed than *esxA* (35.0–59.9%). Viability decreased with treatment duration in Nepalese relapse cases. The MVA is much more rapid, sensitive, and specific to *M. leprae* than the MFP assay. However, some discrepancies suggest possible short-term transcript persistence post-treatment. The authors concluded the clinical applications of MVA, including monitoring treatment efficacy, confirming relapse, and aiding drug trials. The limitations include the need for an SSS BI ≥ 2 for reliable results and potential variability in transcript expression (Lenz et al.).

Leprosy diagnosis is primarily based on the identification of clinical signs and detection of pathogens in skin biopsy, as the causative agents, *Mycobacterium leprae* and *Mycobacterium lepromatosis*, cannot be cultivated under laboratory conditions. Sharma and Singh have reviewed diagnostic techniques and discussed the progress in leprosy diagnosis, emphasizing the importance of early detection to prevent disability (Sharma and Singh) Authors note that despite global efforts to eradicate leprosy, it remains a significant health problem, particularly in India, Brazil, and Indonesia. This review highlights the challenges of traditional diagnostic methods such as bacillary counts of skin smears and histology, which have limited sensitivity. Molecular and biotechnological advances have led to the development of rapid diagnostic assays, such as antigen-antibody detection, nucleic acid amplification tests (NAAT), host biomarkers, emerging diagnostic techniques, and commercially available products like the NDO-LID® Test, NAT-HANS Test, HLAssure™ SE SBT Kit, GenoType LepraeDR, Genesig Kits for Leprosy, and the RLEP qPCR Biomeme. Digital applications like SkinApp and the Leprosy Alert and Response Network System (LEARNS) are also discussed. Authors emphasized the need for specific and inexpensive point-of-care technologies to improve leprosy diagnosis, particularly in endemic areas. It emphasizes the development of rapid, sensitive, and field-deployable diagnostic tools to support early detection and treatment, ultimately aiming to further reduce the transmission of pathogens (Sharma and Singh).

The study by Gobbo et al. explores the use of serological tests (ELISA) and quantitative PCR (qPCR) for early leprosy diagnosis in the hyperendemic region of Mosqueiro Island, Pará, Brazil (Gobbo et al.) The research involved 894 individuals from Mosqueiro Island, including school children and household contacts, and compared these findings with those diagnosed at a reference center. The study found that 105 new cases (11.7%) were diagnosed, with most being early cases without the development of any disability. The serological results showed low antibody titers in field cases, but higher titers were observed in URE (URE_{NC} State of Pará located in Marituba) cases. Region Under Curve (ROC) analysis showed high AUC for URE cases but poor discrimination for field cases, indicating serological tests are less effective for early, oligosymptomatic cases. qPCR was found to be a robust

confirmatory tool across both settings, with 68/79 field cases testing positive for RLEP. Serological tests were more effective for well-defined MB cases at URE but unreliable for early field cases due to low sensitivity or specificity. The authors conclude that current serological biomarkers (NDO-BSA, LID-1, and NDO-LID) are inadequate for early leprosy diagnosis in the field, particularly for oligosymptomatic cases. However, RLEP qPCR is a valuable confirmatory tool, supporting clinical diagnosis and potentially enhancing leprosy control strategies in hyperendemic areas like Pará, Brazil. Active case finding by experts outperforms serology for early detection, while qPCR can validate diagnosis, aiding leprosy control in endemic regions (Gobbo et al.).

Together, these diverse studies—spanning different regions with varying leprosy burdens and control strategies—highlight the urgent need for systematic molecular surveillance to define the true burden of the disease. A central message emerging from this Research Topic is that leprosy's persistence is driven by a complex interplay of historical migrations, hidden or undetected transmission, and persistent diagnostic limitations. To effectively address this challenge, three key priorities must be emphasized: (1) Transmission: Expand surveillance efforts in endemic hotspots and rural areas by integrating molecular data with historical and social context to better map pathogen' spread; (2) Diagnosis: Overcome the limitations of conventional and serological approaches by scaling up molecular tools such as RLEP qPCR for pathogen detection and the Molecular Viability Assay (MVA) to measure treatment efficacy, in combination with active case-finding; (3) Management: Monitor emerging drug resistance through genomics and develop accessible, field-friendly diagnostics that support early treatment initiation; (4) Intensified research: Develop new therapeutic schemes using existing antimycobacterial drugs like pretomanid, delamanid or bedaquiline, to be used in those resistant cases.

From a pertinent research focus, in addition to current approaches, emerging evidence suggests that environmental factors may significantly influence the transmission dynamics of leprosy. Recent studies have proposed that exposure to contaminated soil and water, the involvement of insect vectors, and the role of free-living amoebae, such as *Acanthamoeba* spp., could contribute to the environmental persistence and viability of *Mycobacterium leprae* in certain ecosystems. (3) In addition, zoonotic reservoirs have gained increasing attention, with natural infections documented in armadillos in the Americas (4), red squirrels in the United Kingdom (5), and more recently in wild chimpanzees in Africa. (6) These findings challenge traditional paradigms of leprosy transmission and highlight the complex interplay between environmental conditions, animal reservoirs, and human exposure. Despite these important insights, the extent to which ecological factors shape leprosy transmission in hyperendemic areas remains poorly understood. Addressing this knowledge gap is critical for developing more effective control strategies, particularly in regions where environmental exposure and wildlife contact may contribute to sustained transmission.

Collectively, the articles in this Research Topic highlight how innovative molecular tools, when combined with targeted public health strategies, can help move us closer to the goal of interrupting transmission and achieving zero leprosy. Achieving this will require a coordinated, multidisciplinary approach that prioritizes both scientific advancement and equitable access to diagnostics and care.

Author contributions

YG: Writing – review & editing, Writing – original draft, Conceptualization. CA: Writing – review & editing, Conceptualization. LV: Conceptualization, Writing – review & editing. AP: Writing – review & editing, Conceptualization. VS: Writing – review & editing. PS: Conceptualization, Writing – review & editing, Supervision, Resources, Writing – original draft.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The author(s) declare that no Generative AI was used in the creation of this manuscript.

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