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Primer

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Leprosy

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Abstract

Leprosy, a neglected tropical disease, causes significant morbidity in marginalized communities. Before the COVID-19 pandemic, annual new case detection plateaued for over a decade at ~200,000 new cases. The clinical phenotypes of leprosy strongly parallel host immunity to its causative agents *Mycobacterium leprae* and *Mycobacterium lepromatosis*. The resulting spectrum spans from paucibacillary leprosy, characterized by vigorous pro-inflammatory immunity with few bacteria, to multibacillary leprosy, harbouring large numbers of bacteria with high levels of seemingly non-protective, anti-*M. leprae* antibodies. Leprosy diagnosis remains clinical, leaving asymptomatic individuals with infection undetected. Antimicrobial treatment is effective with recommended multidrug therapy for 6 months for paucibacillary leprosy and 12 months for multibacillary leprosy. The incubation period ranges from 2 to 6 years, although longer periods have been described. Given this lengthy incubation period and dwindling clinical expertise, there is an urgent need to create innovative, low-complexity diagnostic tools for detection of *M. leprae* infection. Such advancements are vital for enabling swift therapeutic and preventive interventions, ultimately transforming patient outcomes. National health-care programmes should prioritize early case detection and consider post-exposure prophylaxis for individuals in close contact with affected persons. These measures will help interrupt transmission, prevent disease progression, and mitigate the risk of nerve damage and disabilities to achieve the WHO goal 'Towards Zero Leprosy' and reduce the burden of leprosy.

Sections

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Introduction

Leprosy, also called Hansen disease, is a chronic infectious disease caused by the bacterium *Mycobacterium leprae* and, to a lesser extent, by *Mycobacterium lepromatosis*, and is the second most common human mycobacterial disease after tuberculosis[1]. *M. leprae* is an obligate aerobic, intracellular microorganism that has a predilection for dermal macrophages and Schwann cells of the neuronal sheath in the peripheral nervous system[2]. This tissue tropism leads to damage of peripheral nerves, skin and mucous membranes, which may in turn cause sensory and motor impairment and chronic wounds that result in severe, lifelong, structural and functional disabilities.

Leprosy is characterized by a wide range of clinical manifestations reflecting the diverse immune responses of individuals to the mycobacterium[3]. The spectrum ranges from tuberculoid leprosy, with one or two well-defined skin lesions or nerve involvement and strong cell-mediated immunity (CMI), to lepromatous leprosy, with widespread disease, deficient CMI and detectable bacilli. The borderline forms of leprosy account for the majority of cases and are subdivided into borderline tuberculoid, mid-borderline and borderline lepromatous.

Leprosy is often associated with stigma, discrimination, and mental health problems and it remains a health and human rights challenge concern, particularly in low-income and middle-income countries (LMICs)[4].

Box 1 | The Global Leprosy Strategy 2021–2030

Long-term vision

- Zero leprosy
- Zero infection
- Zero disability
- Zero stigma and discrimination

Current goal

- Elimination of leprosy (defined as interruption of transmission, absence of disease)

Targets

- 120 countries with zero autochthonous cases
- 70% reduction in annual number of new cases detected
- 90% reduction in rate per million population of new cases with grade 2 disabilities
- 90% reduction in rate per million children of new child cases with leprosy

Key pillars

- Implement integrated, country-owned zero leprosy road maps in all endemic countries
- Scale up leprosy prevention alongside integrated active case detection
- Manage leprosy and its complications and prevent new disability
- Combat stigma and ensure human rights are respected

This Box draws on concepts and data developed in ref. 5.

Leprosy is a poverty-associated disease, affecting individuals in their economically most productive stage of life, thereby imposing a significant social and financial burden on communities. Despite its profound impact, leprosy remains a neglected tropical disease. The WHO developed the 2021–2030 strategic roadmap 'Towards Zero Leprosy' to address global targets and reduce morbidity, disability and psycho-social impacts in countries where leprosy is endemic[5] (Box 1). While the aims are commendable, achieving 'zero' by 2030 presents significant challenges due to the numerous unresolved questions related to disease mechanisms, transmission, diagnosis, treatment, and prevention of leprosy and its inevitably concomitant reactions. Setting such an ambitious target may lead to unintended consequences, including underreporting and suspension of contact tracing, as observed in former campaigns[4].

In this Primer, we provide an updated overview of leprosy describing its epidemiology, pathophysiology, clinical manifestations and management. Using an interdisciplinary view, we highlight current knowledge gaps and research priorities to contribute to an informed and effective approach towards combating leprosy. Since most human infections are caused by *M. leprae* and only a minority by *M. lepromatosis*, we will focus on *M. leprae* unless otherwise indicated.

Epidemiology

History and prevalence

Leprosy is one of the oldest known human diseases with skeletal evidence and written records dating back to 1500–3500 BCE and 600 BCE, respectively[6–8]. Although, for several year,s *M. leprae* was thought to originate from East Africa, the exact origin and dispersal of leprosy is still disputed, as later ancient *M. leprae* DNA analysis reported a possible origin in Eurasia, from which it may have spread following human migrations, colonization, wars and trade routes to Asia such as the Silk Route linking Europe to China[9–12]. During the Middle Ages, leprosy was endemic in Europe and subsequently introduced into West Africa and the Americas through explorers.

In the mid-1980s the number of annual registered cases was 5 million; today, ~200,000 new leprosy cases are detected annually. This reduction was largely attributed to the successful implementation of multidrug therapy (MDT), which reached over 18 million individuals over the past four decades, replacing lifelong dapsone treatment as was given in the past.

This reduction may have been augmented by the widespread implementation of neonatal vaccination against tuberculosis with *Mycobacterium bovis* Bacillus Calmette–Guérin (BCG), which induces cross-reactive anti-mycobacterial immunity[13–15]. However, the criteria for classification as a registered case also played an essential role in this 95% reduction in registered cases[16] as only those who were treated entered the statistics, whereas the total number of cases was divided by the entire world population, including areas where leprosy did not occur.

Leprosy still occurs in >120 countries, mostly in LMICs. In 2023, Brazil, India and Indonesia reported >10,000 new cases each, together accounting for ~79.3% of all reported cases[17,18] (Fig. 1). Factors contributing to the persistence of leprosy in endemic areas include poverty, limited access to health-care services, inadequate public health infrastructure, lack of awareness, and the stigma and discrimination associated with leprosy. Additionally, the uniquely long incubation period of leprosy, typically 2–10 years[19], and the complex and variable interaction between the bacterium and the host immune response, contribute to the sustained prevalence of leprosy.

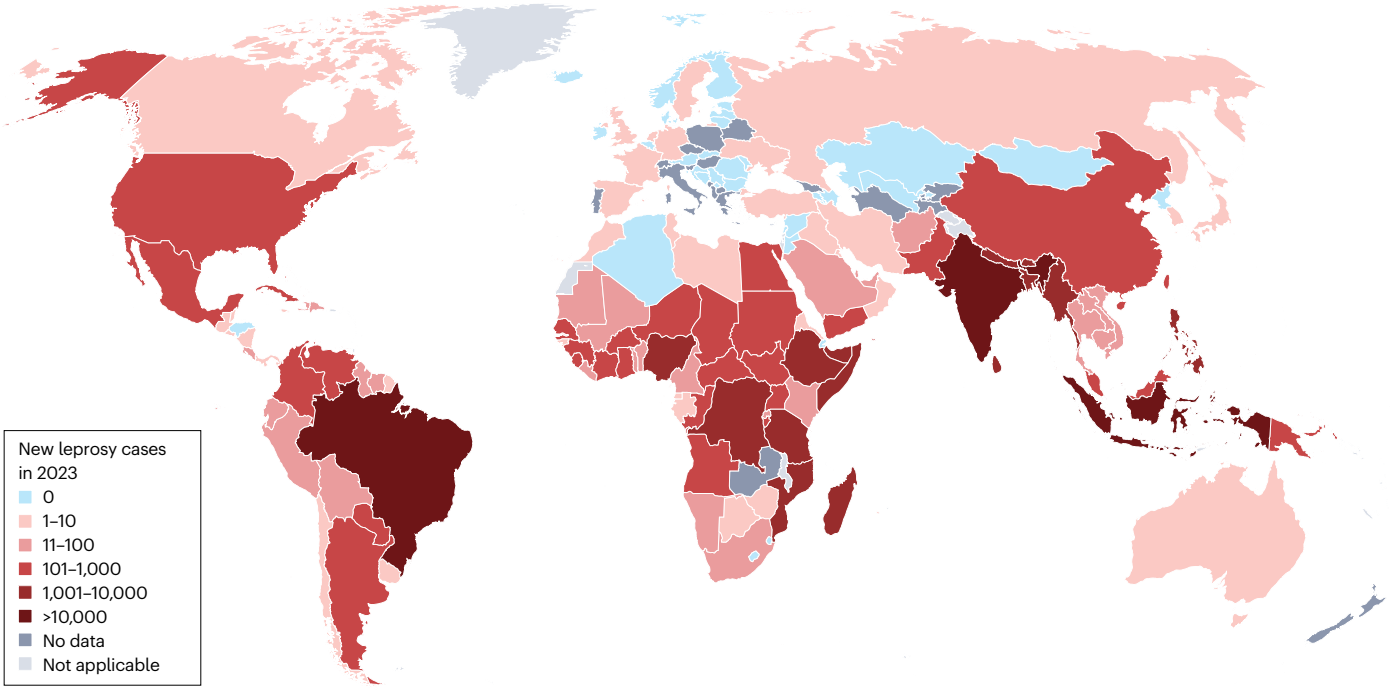

Fig. 1 | Global burden of leprosy. In 2023, 182,815 new cases were documented by the WHO from 184 of 221 (83%) countries and territories, which represents an increase of ~5% compared with 2022. Most cases were found in low-income and middle-income countries, with India, Brazil, and Indonesia accounting for ~79.3% of the global cases. Data from refs. 18,306.

'Elimination' of leprosy as a public health problem was achieved in 2000, when WHO declared the registered global prevalence was <1 case per 10,000 population[20]. Yet, mathematical modelling suggests thousands of cases are unrecognized annually[21]. The word 'elimination' led to the perception that leprosy was eradicated, a distant past, resulting in knowledge, expertise, resources and funding being significantly diminished[22].

Despite the efficacy of MDT, the global number of newly detected cases has remained stable, relying largely on passive case detection, that is, screening of individuals who report at health-care facilities. Approximately 10% of new cases are children, suggesting continued transmission despite effective treatment[23,24]. Moreover, consistent discovery of cases with grade 2 disabilities, which only occur in advanced stages of leprosy, indicates a lack of timely diagnosis. A systematic review from 2022 described that delays in leprosy diagnosis occur because of misdiagnosis[25], likely caused by the lack of expertise required to confirm diagnosis[26]. In Brazil, it was estimated that >33,000 cases were missed by the health-care system between 2007 and 2015 (ref. 27). It is key for governments and stakeholders to adequately train health professionals, improve community awareness, invest in the development of new tools for early diagnosis and build sustainable, accessible services for leprosy and other skin disorders[28]. In this respect, current technology, particularly applications for mobile phones to which access is increasingly available in low-resource and remote areas, holds promise for the future of leprosy management. If such applications are evaluated globally and used alongside expert online advice, they could substantially enhance patient care and support health-care providers. This combination of technology and expertise can lead to better diagnosis, treatment adherence and overall management of leprosy cases[29,30].

Transmission

M. leprae transmission pathways are not fully elucidated[31]. Bacterial transmission via aerosols from the respiratory tract, similar to *Mycobacterium tuberculosis* transmission, is considered most likely[32], although skin-to-skin contact and shedding of bacteria into the environment cannot be ruled out as alternative routes[33,34]. *M. leprae* is not very virulent: most individuals exposed to the bacterium never develop leprosy[35]. Several factors influence transmission of *M. leprae*: the bacterial load of the index case (for example, individuals with lepromatous leprosy shedding high numbers of bacteria); the immunogenetic susceptibility of an individual; and the duration of contact with an infectious source[31,36]. Food insecurity and malnutrition may increase susceptibility to leprosy[37–40]. This applies to both individuals with underweight and reduced immunity and individuals with overweight and metabolomic disorders favouring intracellular mycobacterial survival[41]. Household contacts of untreated individuals with leprosy have a 5–10 times higher risk of developing leprosy than the general population[42–45]. However, geospatial studies indicate that patients with leprosy cluster beyond the household[46]. The incubation period of leprosy varies and typically ranges from 2 years for tuberculoid leprosy to 10 years for lepromatous leprosy, although 20 or even 50 years have been described[47–49].

In non-endemic areas, most cases of leprosy occur owing to migration from regions where leprosy is more prevalent[48,50]. These cases typically do not lead to secondary infections in the local population. However, leprosy has been reported among travellers and second-generation immigrants[49]. This evolving pattern reveals the complexities of transmission and the interconnectedness of global health.

To interrupt transmission, it is vital to identify and treat sources of infection at an early stage[24,51] (see section Treatment and prevention) but transmission could be further interrupted if rates and their decline, along with progression to a status of elimination in certain countries, could be monitored. Using new cases to monitor this process does not provide sufficiently accurate and up-to-date information on actual transmission since only a small percentage of individuals with *M. leprae* infection progresses to disease and it takes several years before symptoms of leprosy manifest[47].

However, since *M. leprae* infection in young children is recent by definition, *M. leprae*-specific seroprevalence in healthy young children is suggested by the WHO Task Force on Criteria for Elimination of Leprosy as an objective indicator for monitoring (the interruption of) transmission in areas aiming at elimination of leprosy[52–54].

Non-human sources of transmission. Worldwide, it remains a given that the main source of *M. leprae* infection are humans. However, the nine-banded armadillos (*Dasypus novemcinctus*) serve as a zoonotic reservoir for human infection in regions such as Mexico[55], Brazil[56], Colombia[57] and southeastern USA[58–60]. The landscape of leprosy in the latter area has shifted notably, with reported cases more than doubling between 2015 and 2020 (refs. 61–63), of which 34% are locally acquired, a trend that aligns with the presence of armadillos[60]. Research indicates that direct and indirect exposure to armadillos is a significant risk factor for leprosy in both endemic[56,64] and non-endemic countries[58,65]. To fully understand the extent to which leprosy can be attributed to armadillos in the Americas, further defining which mycobacterial strain is causing leprosy in both armadillos and patients co-inhabiting these areas will be essential.

In addition to armadillos, *M. leprae* and *M. lepromatosis* have also been detected in red squirrels (*Sciurus vulgaris*) in the British Isles[66–68]. However, there is currently no evidence of the mycobacterium being present in squirrels from the European mainland[69] or in other rodent species[70]. Furthermore, *M. leprae* has also been detected in two wild chimpanzees living in nature reserves in Côte d'Ivoire and Guinea-Bissau[71]. Despite the genetic closeness of chimpanzees and humans, it is unlikely, based on this study, that *M. leprae* was transmitted from humans to these chimpanzees as the mycobacteria were genetically distinct from those previously isolated in humans.

These emerging data underscore the potential existence of non-human or environmental reservoirs of *M. leprae*, including various vectors such as ticks[72,73], arthropods[74], amoebae[75,76] and soil[33]. While the possibility of these infectious sources is intriguing, it is important to note that no confirmed relationship between *M. leprae* infection in humans and the presence of *M. leprae* in these vectors or in soil has been established[77]. Exploring the potential role of vector candidates or an environmental source of transmission could necessitate a comprehensive strategic overhaul of the 'zero transmission' goals[78].

Mechanisms/pathophysiology

Bacteriology

M. leprae is an intracellular, acid-fast, rod-shaped, non-motile, slow-growing, gram-positive bacillus with a division rate of 11–14 days[19,78] and cannot be cultured in vitro. Thus, for research purposes, the bacterium is grown in vivo in nine-banded armadillos or the mouse footpad, from which it can be isolated. Knowledge of the composition and structure of the cell wall of *M. leprae* has derived largely from other, culturable, mycobacteria (Fig. 2). *M. leprae* has a thick cell wall composed of an inner and an outer layer. The inner layer consists of peptidoglycan, arabinogalactan and mycolic acids[79]. The outer layer consists of an extensive network of glycolipids, composed mostly of phthiocerol dimycocerosates and phenolic glycolipid-I (PGL-I)[80], and lipid-linked polysaccharides such as lipomannan and lipoarabinomannan[81,82]. PGL-I modulates host immunity by limiting nitric oxide synthase production in a complement receptor 3-dependent manner[83], enabling immune evasion of mycobacteria. Although various mycobacteria contain phenolic glycolipids, the virulent factor PGL-I is unique for *M. leprae* and *M. lepromatosis*[83–85]. The trisaccharide of PGL-I mediates binding to the laminin-α2 chain in the basal lamina of Schwann cell–axon units, suggesting a critical role of PGL-I in the invasion of *M. leprae* of Schwann cells[86,87]. Novel evidence shows that both *M. leprae* and PGL-I induce a toxic Schwann cell phenotype by modifying the host lipid metabolism, resulting in profound implications for neuronal loss[88]. Besides glycolipids, lipoarabinomannans confer immunomodulatory properties, including suppression of T cell activation[89,90] and inhibition of oxygen radicals[91].

Strain genomics

M. leprae. *M. leprae* shows remarkably low genetic diversity among strains from different locations. This limited occurrence of single nucleotide polymorphisms (SNPs) created the basis for the establishment of a genotyping system characterized by four SNP genotypes (SNP types 1–4)[9] and 16 SNP subtypes (SNP subtypes A–P), which was used to retrace local and large-scale transmission of the pathogen[11]. Moreover, whole-genome sequencing has enabled a more refined classification of SNP subtypes[92,93]: for example, SNP subtype 1D into 1D-1, 1D-2 and 1D-Madagascar; SNP subtype 3K into 3K-0 and 3K-1; and SNP subtype 3I into 3I-1 and 3I-2. The 1B-Bangladesh genotype clusters separately between the 1A and 1B[93] (Supplementary Figure 1). Thus, whole-genome-based phylogenies have potential to further differentiate genotypes, thereby increasing the resolution of the existing SNP genotyping scheme.

The close relationship between human migration and the spread of infectious diseases is particularly evident for *M. leprae*[9]. The introduction of the pathogen in the Americas is ascribed to the first Europeans who settled in the New World: the genome of genotype 3I-2 strains recovered from medieval European skeletons bears striking identity to *M. leprae* strains found among patients with leprosy as well as naturally infected armadillos in the southern USA and South America[60,94,95].

M. lepromatosis. In 2008, *M. lepromatosis* was identified in patients who presented with diffuse lepromatous leprosy[96]. *M. lepromatosis* is less common and primarily found in Central America and the Caribbean, with some scattered cases reported around the globe, specifically in Singapore, Canada, Brazil, Myanmar and India[97–99], although such reports need to be verified using *M. lepromatosis*-specific genomic regions or multicopy sequences such as RLPM (family of repeats in the *M. lepromatosis* genome)[100]. *M. lepromatosis* is associated with diffuse cutaneous infiltration, vascular invasion and systemic disease, clinical hallmarks that in part formed the basis for the name of this pathogen[96]. Comparative genomic analysis of the two species showed 93% and 83% identity in the nucleotide sequences corresponding to the protein-coding genes and pseudogenes, respectively[101,102]. *M. leprae* and *M. lepromatosis* are phylogenetically closely related to *Mycobacterium uberis*, a newly identified species found in livestock with nodular thelitis[103] and *Mycobacterium haemophilum*, which may cause ulcerating skin infections, arthritis or disseminated infections in immunocompromised individuals or older adults[101,104,105].

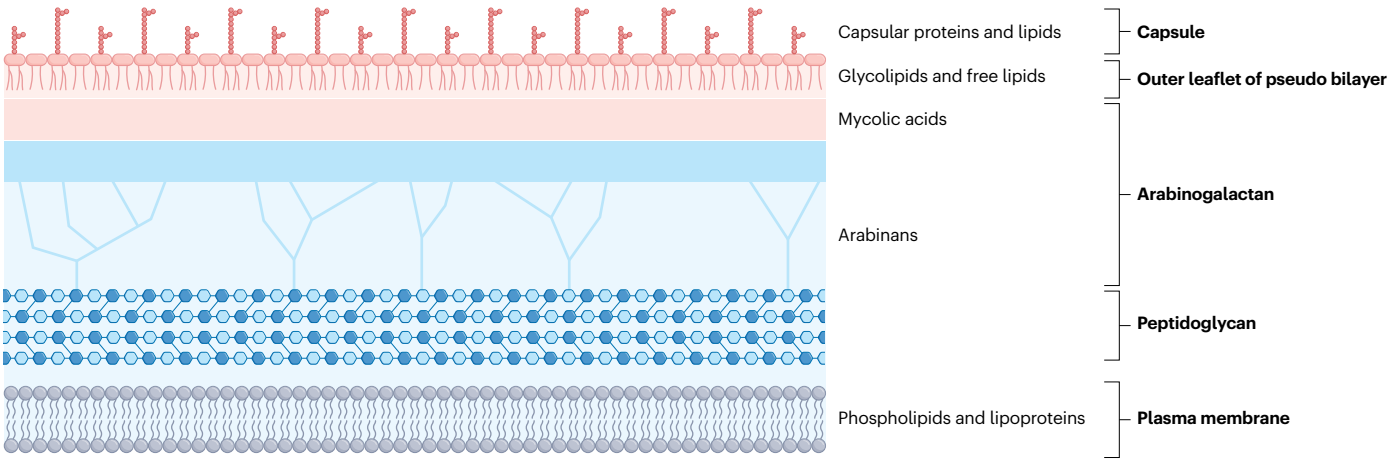

Fig. 2 | Cell envelope of *M. leprae*. Cell envelope of *Mycobacterium leprae*, consisting of a plasma membrane covered by a core cell wall of peptidoglycan, arabinogalactan and mycolic acids. Surrounding the mycobacterium is a capsule composed of phenolic glycolipids, phthiocerol dimycocerosates, phospho-inositol mannosides and phospholipids.

Phylogenetic analysis reveals that, compared with *M. tuberculosis*, *M. leprae*, *M. lepromatosis* and *M. uberis*[103] show significant downsizing and pseudogenization[9,101,104,106–109] since they diverged from the most recent common ancestor[110–112]. The *PE* and *PPE* genes, which are critical to the virulence and immune modulation of *M. tuberculosis*, are almost absent in the genomes of leprosy bacilli[104]. Marked differences between *M. leprae* and *M. lepromatosis* include HemW (which is only present in *M. lepromatosis*), 3 copies of the genes encoding diguanylate cyclase and phosphodiesterase in *M. lepromatosis* juxtaposed to a single copy in *M. leprae*, and 11 copies of the TetR family transcriptional regulators in *M. leprae* in contrast to only 6 copies in *M. lepromatosis*[101,104]. The functions of these genes and their significance, although currently not completely understood, could explain the variability in pathology between infections with the two species. Although significant insights can be gained through comparative genomics[96], research into pathogenesis and host immunity to *M. lepromatosis* remains in an early stage.

Disease mechanisms

Innate immune response to *M. leprae*. Since clinical manifestations after exposure to *M. leprae* strongly parallel host immunity against this mycobacterium, various outcomes, ranging from clearance, colonization, infection or disease, represent possible scenarios[113,114]. The interindividual differences in coping with the presence of the mycobacterium become particularly apparent when disease occurs, with multiple phenotypes reflecting the unique immunopathological spectrum of leprosy, providing useful insights beyond the immunology of leprosy[115–119] (Fig. 3).

The initiation of the innate immune response to *M. leprae* is thought to be dependent on the critical interaction between *M. leprae* and epithelial cells of the nasal mucosa and/or keratinocytes of the compromised skin and associated tissue-resident macrophages[120]. A synchronous host response to the recognition of surface bacterial ligands is internalization. The recognition of mammalian cell entry protein 1A (Mce1A) by unknown host factors is critical to internalization of *M. leprae*[121], potentially explaining its tropism for nasal epithelial cells and keratinocytes. In addition, the two major mycobacterial adhesin proteins, histone-like protein (Hlp) and the heparin-binding haemagglutinin (HBHA) on the surface of *M. leprae* mediate bacterial adhesion to epithelial cells[122].

Phagocytosis of *M. leprae* by macrophages is mediated by the recognition of PGL-I by complement C3 and the activation of complement receptors CR1, CR2 and CR4 (ref. 123). Once internalized or phagocytosed, *M. leprae* peptidoglycan-derived muramyl dipeptides are recognized by host cytoplasmic NOD2 (ref. 124), which triggers a signalling cascade leading to activation of NF-κB, inflammasome-mediated IL-1β secretion, and antigen processing and presentation[125,126]. Other possible molecules associated with *M. leprae* recognition and entry in host cells are CD163 (refs. 127,128) and DC-SIGN/CD209 (ref. 129).

As most studies focus on the interaction of *M. leprae* with macrophages and Schwann cells, the response of nasal epithelial cells, keratinocytes and tissue-resident macrophages to *M. leprae* needs to be further investigated as it establishes the immune microenvironment that determines the outcome after invasion: mucosal immunity exerted by epithelial cells may contribute to modulating the adaptive response, whereas adipocytes are found to contribute to persistence of *M. leprae* by downregulating innate immunity[41].

The encounter between host cells and *M. leprae* is governed by a series of receptor–ligand interactions. *M. leprae* triacylated lipopeptides have been shown to be recognized by TLR1 and TLR2 heterodimers. This interaction is central to the initiation and secretion of pro-inflammatory cytokines, such as TNF and IL-15, as well as the differentiation of monocytes into macrophages[130]. In particular, IL-15 is relevant to the vitamin D-dependent production of antimicrobial peptides in macrophages[131]. It is important to note that Schwann cells also express TLR2, and TLR2 has been proposed to contribute to pathogenic demyelination in *M. leprae* infection, although the exact mechanism is unknown[121,132]. It has been reported that the bacilli may enhance myelin breakdown into lipid droplets by augmenting the autophagic myelin destruction pathway, which may benefit *M. leprae* viability inside the Schwann cell[133].

M. leprae infection may induce modifications in glucose[134], lipid[2], amino acid[135] and iron[136] metabolism in host cells. Several in vitro studies suggest that non-viable bacilli and mycobacterial antigens induce

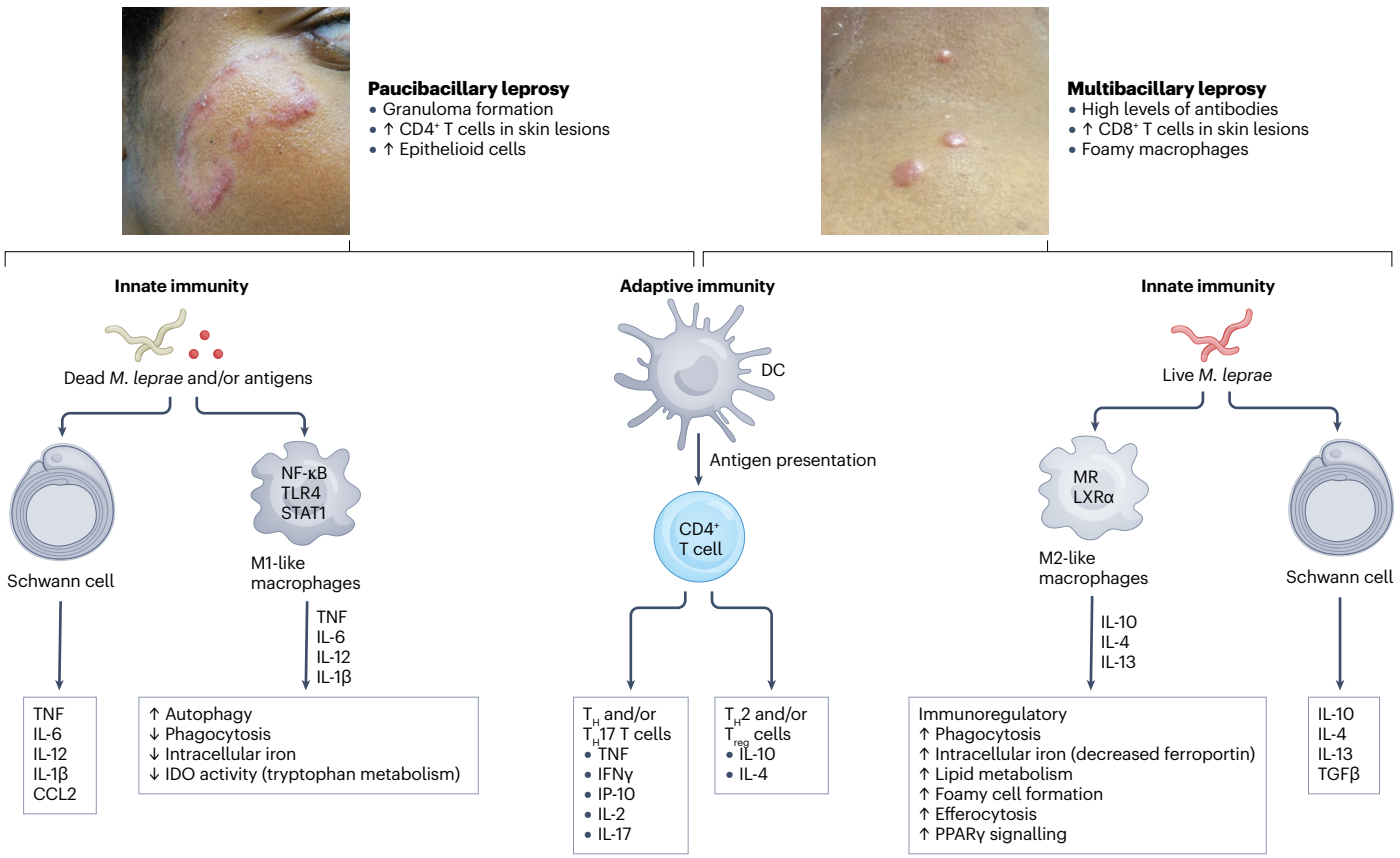

Fig. 3 | Innate and adaptive immunity against *M. leprae* across the clinical spectrum. Cells, cytokines and pathways involved in innate and adaptive immunity against *Mycobacterium leprae* across the clinical spectrum. Far left, innate immunity in paucibacillary disease; left, adaptive immunity in paucibacillary disease; right, adaptive immunity in multibacillary disease; far right, innate immunity in multibacillary disease. DC, dendritic cell; IDO, indoleamine 2,3-dioxygenase; T_H, T helper; T_{reg}, T regulatory.

increased levels of pro-inflammatory cytokines[2,137]. In contrast, live *M. leprae* induces the production of anti-inflammatory cytokines that are associated with the impairment of autophagy flux in macrophages, contributing to its intracellular survival in lesions of patients with multibacillary leprosy[2,137]. The impairment of autophagic flux is associated with inflammasome activation and the outcome of reversal reaction[138,139]. It will be pivotal to investigate contacts of index cases or individuals who have been exposed to *M. leprae* but did not develop leprosy. Contrary to what has been observed in patients with multibacillary leprosy, arginase and haem oxygenase 1 (HO1) are associated with protection in contacts[140], suggesting that immunoregulatory mechanisms are important in early stages, in which pro-inflammatory input could trigger bacterial spread and consequently a higher bacillary load. However, further studies are needed to dissect the mechanisms of innate immunity associated with infection control.

Adaptive immune response to *M. leprae*. The adaptive immune response, which is essential in controlling *M. leprae* infection, is initiated once the innate immune response fails to successfully eradicate *M. leprae* invasion. The differential response of $CD4^+$ T helper (T_H) cells is a hallmark of anti-*M. leprae* adaptive immunity[114]. The classical paradigm of clinical leprosy is that disseminated (multibacillary) and self-limited (paucibacillary) disease are associated with T_H2 and T_H1 immunity, respectively[115]. However, several studies using T cell clones isolated from patients with leprosy have indicated that immunity against *M. leprae* extends beyond the T_H1 or T_H2 paradigm involving other T cell subsets such as T_H9, T_H17, T_H22 and regulatory T (T_{reg}) cells[114,141]. Thus, assessment of T cell responses by only measuring IFNγ may not fully reflect the protective potential[142]: for example, the pathogenesis of relapse in multibacillary leprosy is associated with inhibition of CD86-expression causing reduction in effector T cell responses. In contrast, FoxP3 T_{reg} cells can suppress effector CD4 T cell function via secretion of TGFβ and IL-10, whereas T_H17 cells function in a reciprocal fashion by promoting a pro-inflammatory state[116,143].

Interestingly, CD8 T cells have contrasting functions in leprosy, showing IL-4 secretion and suppressor phenotypes in lepromatous leprosy[144] and a cytotoxic phenotype critical to the killing of *M. leprae* in tuberculoid leprosy[145,146]. Age-related alterations of T cell subsets were found to be associated with the onset of leprosy in older patients such as accumulation of memory $CD8^+$ T cells as well as reduced $CD8^+CD28^+$ cell expression in skin lesions compared with younger patients[19]. Additionally, programmed death 1 (PD1) overexpression on various immune cells has been linked to leprosy severity. In this respect, higher expression of PD1 on T_{reg} cells results in lower IL-10 levels,

whereas blocking of PD1 restores the T_{reg} cell-mediated suppression of effector T cells and increases secretion of the immunosuppressive cytokine IL-10 (ref. 147).

The humoral immune response, augmented by T_H2 cytokines, is thought to be largely ineffective against *M. leprae* and was thus historically under-characterized. However, regulatory B cells, secreting IL-10, can confer immunosuppressive functions, thereby influencing the immunopathogenesis of leprosy[148,149]. Studies using cutting-edge technology and new research angles focus on how these seemingly polarized T and B cell responses are developed, and how they can be modulated to mitigate adverse immune sequelae in patients with leprosy.

Host genetic susceptibility and resistance

Although leprosy is not a genetic disease, certain SNPs and gene mutations have been shown to increase susceptibility or resistance to *M. leprae* in various populations[150,151]. Polymorphism N248S of TLR1 was found to be associated with leprosy in Bangladesh[152], while certain SNPs in NOD2 are associated with leprosy in Han Chinese[148] and Nepali populations[153]. Production of antimicrobial peptides in response to *M. leprae* is partly dependent on (signalling via) vitamin D. The TaqI polymorphism in the 3′ region of the vitamin D receptor *VDR* gene has been shown to be associated with leprosy in Indian populations[154] but not in Nepali populations[155].

Human leukocyte antigen (HLA) genes have been investigated broadly regarding susceptibility to or protection against leprosy. In a Mexican population, the class I HLA-A*28 gene increases susceptibility while the class II HLA-DQB1*07 seems to confer resistance[156]. Similarly, in Vietnamese and Brazilian populations, the HLA-DRB1*04 gene is associated with resistance while HLA-DRB1*10 increases susceptibility[157]. Additionally, elevated frequency of HLA-DR2 and HLA-DR3 genes have been observed in patients with tuberculoid leprosy, whereas the frequency of HLA-DR2 and HLA-DQ1 is elevated in patients with lepromatous leprosy[158–161].

Several genes involved in the adaptive immune response have also been associated with leprosy. In a Brazilian population, the polymorphism +874T>a of the T_H1 cytokine *IFNG* gene was found to confer resistance to leprosy[162] while, in two different Chinese populations, variants of *LRRK2*, a gene implicated in the IFNγ response, and the 590T/C polymorphism of the T_H2 cytokine *IL4* gene were found to increase susceptibility[163,164]. Likewise, the GG and G genotypes of the T_H17 *IL17A* (rs2275913A/G) polymorphism were found in higher frequencies in patients with lepromatous leprosy in an Egyptian population[165]. Strikingly, mutations in *LRRK2* and *NOD2* associated with Crohn's disease and Parkinson disease were shown to play a role in apoptosis activity following mycobacterial challenge as well as on BCG-induced respiratory burst consistent with a role of the identified mutations in early-onset leprosy[166]. Research on genetic risk markers can inform dissection of yet unsolved mechanisms of leprosy, particularly in early phases of the disease.

Diagnosis, screening and prevention

Clinical spectrum and classification

Leprosy mainly affects the skin and peripheral nerves but may also involve the mucosa, upper respiratory tract, testes and eyes. The clinical phenotype reflects the host immunological response to the bacterium. The Ridley–Jopling classification is based on the morphology of skin lesions and the bacterial load[167] (Fig. 4). Tuberculoid leprosy presents with one or two well-defined hypopigmented or erythematous anaesthetic skin lesions, typically with central healing and/or a thickened nerve and no detectable bacilli. Lepromatous leprosy is characterized by numerous nodular lesions and/or plaques without reduced sensation. Patients with lepromatous leprosy may have symmetrical 'glove-and-stocking' anaesthesia (that is, loss of sensation of hands and feet), enlarged peripheral nerves, madarosis (eyebrow loss) and diminished sweating[3,168]. Borderline leprosy is immunologically unstable and may either downgrade towards lepromatous or upgrade towards tuberculoid forms. This instability increases the risk of developing reactions. The Ridley–Jopling classification does not include indeterminate leprosy or pure neural leprosy; in the latter, merely the peripheral nerves are affected. Pure neural leprosy is based on palpable nerve enlargement and/or nerve tenderness and is typically confirmed with a nerve biopsy. Indeterminate leprosy is the earliest clinical manifestation of leprosy as a solitary, ill-defined erythematous or hypopigmented patch. It may resolve spontaneously or evolve into one of the Ridley–Jopling forms depending on the CMI of the host. Infections with *M. lepromatosis* tend to occur in younger individuals and are often linked to diffuse lepromatous leprosy, which is characterized by diffuse cutaneous infiltration. Individuals with diffuse lepromatous leprosy can develop the Lucio phenomenon, a severe reactional state (discussed below in Leprosy reactions) that, in some cases, may be fatal[169].

WHO introduced a simplified classification system based on clinical manifestations and slit-skin smear results for community health workers: paucibacillary leprosy, five skin lesions or fewer without demonstrated presence of bacilli in a skin smear; multibacillary leprosy, six skin lesions or more, nerve involvement or presence of bacilli in a skin smear irrespective of the number of skin lesions[170].

Diagnosis and screening

The diagnosis of leprosy is based on at least one of the three clinical signs: (1) the presence of skin lesions with definite loss of sensation; (2) a thickened or enlarged peripheral nerve; or (3) presence of *M. leprae* in a slit-skin smear[170], which is prepared by intradermal scraping of tissues (for example, earlobes) and staining it with the Ziehl–Neelsen method. In diagnostically ambiguous cases, histopathological sections and quantitative PCR, if available, for skin, nerve or even skin scrapings can be considered. Several types of PCR have been validated for this purpose, including 16S rRNA and RLEP[92,171] PCR as well as multiplexed quantitative PCR for *M. lepromatosis*[69,100].

The bacteriological index reflects the extent of the bacterial load and is reported as a logarithmic scale from zero to six. In the early phase of the disease, involvement of small sensory and autonomic nerve fibres and adnexal structures in the skin may cause localized anhidrosis, loss of sensation (especially temperature discrimination followed by fine touch and pain) and hair loss in a skin lesion. Sensory loss can be assessed using cotton wool or Semmes–Weinstein monofilaments. In rural areas, where no laboratory facilities are available, health-care workers need to rely on detecting the sometimes subtle signs and symptoms of leprosy. Lepromatous leprosy and borderline leprosy may not show loss of sensation in the skin lesions (or infiltrated skin) and enlarged nerves or detectable nerve damage may be absent, making diagnosis challenging. In case of any doubt, clinical reassessment is recommended after 3 months.

The differential diagnosis of leprosy is extensive and includes but is not limited to pityriasis alba, vitiligo, pityriasis versicolor, seborrhoeic dermatitis, fungal infections, granuloma annulare or cutaneous discoid lupus erythematosus[172].

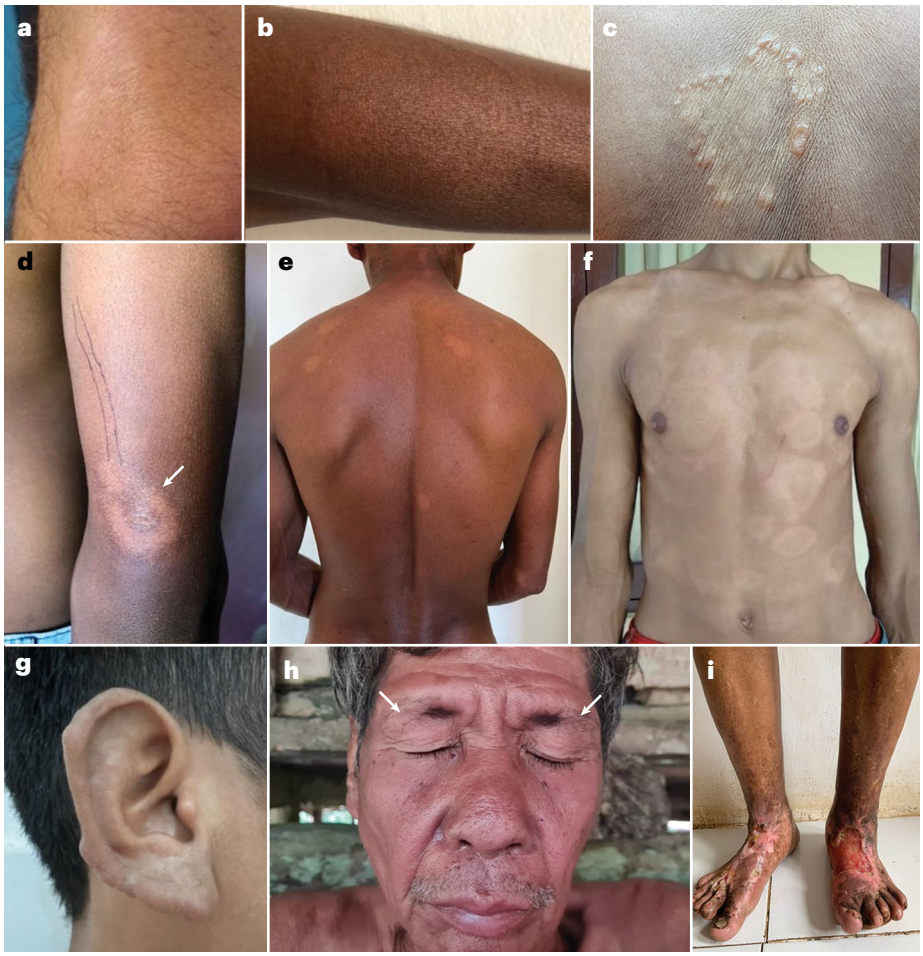

Fig. 4 | Clinical images of leprosy. Tuberculoid leprosy (part **a**). A well-demarcated hypopigmented macule with reduced sensation and hair loss. Borderline tuberculoid leprosy (parts **b**,**c**). A well-defined annular hypopigmented anaesthetic lesion on the forearm (part **b**) and upper back (part **c**) with an infiltrated border. Borderline leprosy (part **d**). Annular lesion with irregular edge and hyperpigmented punched-out centre. The enlarged superficial nerve in the vicinity of the lesion is marked (arrow). Borderline lepromatous leprosy (parts **e**,**f**). Multiple annular hypopigmented anaesthetic lesions in the neck and upper back (part **e**) and chest and abdomen with central re-pigmentation (part **f**). Lepromatous leprosy (parts **g**,**h**,**i**). Infiltrated ears showing multiple nodules (part **g**), diffuse thickening of the skin with madarosis (that is, hair loss of the eyebrows) (part **h**) and chronic ulcers (part **i**).

Immunodiagnostic tests. Recognizing signs and symptoms of leprosy is challenging, especially at an early stage. Improved (adjunct) diagnostic tests meeting recent WHO Target Product Profiles for infection or disease[173] can become game changers by identifying individuals in need of post-exposure prophylaxis (PEP), reducing diagnostic delays, preventing misdiagnosis, and monitoring treatment efficacy and (interruption of) *M. leprae* transmission[52]. Since leprosy is a poverty-associated disease with high endemicity in remote locations, such tests should enable application at point-of-contact in low-resource areas by health-care staff after limited training. In this respect, the use of variable test cut-off levels, or qualitative measurements only, should be avoided in future health strategies as these impede the comparison of prevalence and transmission rates at a global scale and complicate the monitoring of transmission reduction in time[52,174]. Thus, acceptance and implementation of quantitative rapid tests for various use cases (detection of infection, disease, reactions, classification) should be evaluated in a coordinated, collaborative global effort.

Blood levels of certain host proteins or RNA genes change upon encounter with pathogens. Immunodiagnostic tests utilize this host immunity to detect infection and (early) disease even when the causative agent is not detectable (anymore) or when its detection requires invasive sampling[175].

It has been amply shown that anti-PGL-I antibodies strongly correlate with the bacterial index of patients and with *M. leprae* DNA present in slit-skin smears of patients and contacts[93,176,177]. Compared with the invasive nature of slit-skin smears, which lead to significant discomfort, assessment of this humoral host biomarker is a practical tool to detect *M. leprae* infection to diagnose patients with multibacillary leprosy and monitor their treatment[174,178,179].

Qualitative and quantitative lateral flow tests detecting anti-PGL-I antibodies have been developed[174,180] but are still not widely implemented in the field. Moreover, to capture the different clinical outcomes across the leprosy disease spectrum, multiple host biomarkers are required.

Since the host immune response against *M. leprae* determines the outcome of infection, diagnostic tools that can detect cellular as well as humoral immune markers can jointly provide diagnostic value. Biomarker research for leprosy demonstrated that a host biomarker signature of αPGL-I IgM, IP-10, CRP, ApoA1 and S100A12 can identify patients at various points of the immunopathological leprosy spectrum[179,181]. Furthermore, CCL4 levels measured in overnight stimulated whole blood[181] correlate with *M. leprae* infection, enabling detection of patients with paucibacillary leprosy as well as infected household contacts[177]. Field-friendly lateral flow assays detecting multiple biomarkers simultaneously have demonstrated feasibility in

identifying individuals with *M. leprae* infection in areas with high (Bangladesh) and low (South Korea) endemicity[182]. Broad-scale evaluation in various geographic areas, preferably combined with tests that directly detect the pathogen, is now required. Moreover, the concurrent utilization of direct (pathogen-based) and indirect (host immunity-based) tests in trials involving PEP or new vaccines is essential and should be complemented by consultation with health-care professionals.

Prevention

Since the number of newly detected cases has plateaued over the past decade, additional interventions, besides active case finding and early treatment, are needed to interrupt transmission and prevent disease such as post-exposure immunoprophylaxis and chemoprophylaxis among contacts of newly diagnosed individuals[183,184]. PEP has been explored over the past years through different strategies using dapsone, acedapsone or rifampicin; the latter is administered as a single dose (SDR-PEP) or combined with other antibiotics[178,184–186]. According to mathematical modelling, global roll-out of SDR-PEP would contribute significantly to the reduction of leprosy incidence and accelerate the interruption of transmission[187]. Since 2018, the WHO recommends SDR as leprosy preventive treatment for contacts of persons affected by leprosy[188] based on findings from the COLEP trial in Bangladesh, which showed a reduction of 56% in leprosy incidence within the first 2 years after SDR-PEP[189–191]. SDR-PEP was particularly effective among non-blood relatives, neighbours of neighbours and other social contacts but less so among household members who may already have subclinical infection[190,192]. Findings in the COLEP trial were confirmed in studies situated in Indonesian islands reporting a threefold reduction in leprosy incidence when SDR-PEP was dispensed as a blanket approach. However, no effect on close contacts was found[185]. Furthermore, the feasibility of SDR-PEP on eligible contacts was demonstrated in the LPEP programme[193] in seven countries and its long-term effect on leprosy incidence was predicted by mathematical modelling[187].

Mouse models indicate that potent regimens are likely needed to increase the effect of PEP[194]. A cluster randomized clinical trial (RCT) in China reported that the cumulative incidence of leprosy among household contacts of index cases over 4 years was significantly lower ($P = 0.02$) with single-dose rifapentine[195], which has greater bactericidal activity than rifampicin[196], whereas this did not differ significantly between the rifampicin and the no intervention group[195]. Results from the PEOPLE trial[197], a cluster RCT in which three different single double-dose rifampicin PEP strategies were compared with no intervention, showed a reduction of 40% in leprosy incidence in the Comoros and Madagascar. Previous and alternative PEP interventions, such as using bedaquiline as PEP, as well as studies investigating the direct effect of PEP on host immunity in contacts are ongoing[198–200] (Table 1).

The interventions described have primarily targeted the reduction of incident cases, although their direct effect on *M. leprae* infection in treated individuals, the duration of this effect, and their effect on transmission have not yet been investigated. Major concerns of PEP are the risks associated with reduced case detection, patient confidentiality, the limited duration of protection, and the risks of inducing rifampicin resistance[201], which could affect both leprosy and tuberculosis control programmes[202,203]. Although it is argued that the risk of drug resistance is minimal with SDR due to its short-acting nature[204], the question remains whether this holds true when PEP is administered intermittently[201]. Further investigations are needed to assess the implications of (intermittent) PEP on resistance development and overall treatment outcomes for both leprosy and tuberculosis. Continuous resistance monitoring and cost-effectiveness studies performed in different epidemiological settings will be key to evaluating the risks and guiding evidence-based decision-making in leprosy prevention and control efforts.

Vaccines. The BCG vaccine is administered to newborns in tuberculosis-endemic regions to prevent tuberculosis and meningitis and reduce childhood mortality. In addition, it offers cross-reactivity and protection against leprosy. Like its effects on tuberculosis, BCG-mediated immunity against leprosy is strongest in younger individuals, with efficacy decreasing over time[205,206]. However, a study on the effect of BCG revaccination in schoolchildren that were vaccinated at birth in Brazil, as part of a leprosy prevention strategy, found no evidence of protective benefits[207]. An alternative immunomodulatory vaccine is the killed *Mycobacterium indicus pranii* (MIP) vaccine; clinical studies have shown that, when administered as an adjunct to standard MDT, this vaccine promotes increased, rapid bacterial clearance and recovery compared with the MDT control group[208].

LepVax, the first specific vaccine for leprosy, has undergone phase Ia trials in humans, demonstrating safety and the ability to

Table 1 | Post-exposure prophylaxis trials

Trial acronym	Trial number	Approach	Country
COLEP	ISRCTN61223447	Determine effect of SDR	Bangladesh
LPEP	Not applicable	Feasibility study for SDR	Brazil, India, Indonesia, Myanmar, Nepal, Sri Lanka, Tanzania
Maltalep	NTR3087	SDR after BCG	Bangladesh
PEP4LEP	NL7294/NTR7503	Integrated skin screening combined with SDR	Ethiopia, Mozambique, Tanzania
INDIGO#2	NCT06222372	Direct assessment of effect of SDR/SDDR on host immunity	Bangladesh
PEP++	NL7022	Enhanced preventive regimen (three doses of rifampicin and clarithromycin)	Bangladesh, Brazil, India, Nepal
PEOPLE	NCT03662022	SDDR-PEP in households and/or close community contacts	Comoros, Madagascar
BE-PEOPLE	NCT05597280	SDR-PEP + bedaquiline versus SDR-PEP	Comoros
Not applicable	ChiCTR-IPR-15007075	SDR versus single-dose rifapentine	China

BCG, *Mycobacterium bovis* Bacillus Calmette–Guérin vaccination; SDR, single-dose rifampicin; SDDR, single double-dose rifampicin; PEP, post-exposure prophylaxis.

generate an immune response in healthy volunteers[209]. This recombinant protein vaccine incorporates the *M. leprae* antigens ML2531, ML2380, ML2055 and ML2028, collectively known as LEP-F1, along with a synthetic TLR4 agonist glucopyranosyl lipid adjuvant in a stable emulsion. In 2024, a phase Ib–IIa clinical trial started to further assess the safety and immunogenicity of LepVax in endemic regions (NCT03947437)[210]. This research marks an important step forward in the effort to combat leprosy.

Management

Dapsone was introduced in 1941 but it soon became clear that relapses occurred, even after prolonged treatment[211], and in the 1970s, dapsone resistance became a problem. In 1982, MDT was introduced, consisting of dapsone, rifampicin and clofazimine, with rifampicin, the most potent drug, as the backbone of MDT[212]. In the early 1990s, this combination therapy enabled the length of the treatment to be reduced to 24 months and later, by the end of the 1990s, to 12 months[213]. MDT is provided free of charge by WHO, through the support of Nippon Foundation (1994–2000) and Novartis (2000 onwards)[212]. The recommended MDT for paucibacillary leprosy comprises 6 months of daily dapsone and monthly rifampicin; for multibacillary leprosy, it is 12 months of daily dapsone and clofazimine with monthly rifampicin[214]. However, the latest WHO guidelines recommend a triple-drug regimen for paucibacillary leprosy, analogous to multibacillary leprosy, during 6 months[170]. Nevertheless, this recommendation was criticized by experts since the quality of evidence to support the modification was low and the exposure of patients to additional side effects was high, particularly skin pigmentation caused by clofazimine, which contributes to stigma and jeopardizes drug adherence[215]. MDT is provided in 4-week blister packs with separate dosages for adults and children[170]. No differentiation is made in the treatment of *M. leprae* and *M. lepromatosis*. Comprehensive counselling is essential to manage expectations, ensure treatment adherence, and explain the risks and symptoms of leprosy reactions. Even after successful treatment, patients may suffer long-term complications, such as reactions, paresis, neuropathic pain and ulcers, vision disorders, infertility, or hand and foot deformities, that require lifelong follow-up and care through a multidisciplinary team including dermatologists, plastic surgeons, rehabilitation doctors, physiotherapists, ophthalmologists and other specialists.

Overall, MDT is well tolerated. Rifampicin is a rapid and potent bactericidal drug that effectively interferes with mycobacterial RNA synthesis, thereby killing >99% of susceptible mycobacteria within a few days after a single dose[216]. Hepatotoxicity with mild transient elevation of hepatic transaminases may occur but is rare with monthly dosages. Patients should be informed that the drug may cause an orange-reddish discolouration of urine, faeces and lacrimal (tear gland) secretions. Dapsone is associated with acute haemolysis[217], particularly in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and with the life-threatening dapsone hypersensitivity syndrome, which is correlated with the HLA-B*13:01 polymorphism and typically occurs 4–6 weeks after treatment initiation[218]; it is an important cause of death in patients with leprosy[219,220]. The major side effects of clofazimine are gastrointestinal symptoms and pigmentation of the skin, which contributes to stigmatization, and may last for 1 or 2 years after treatment has been discontinued.

Management of relapse and reinfection

The rate of bacterial clearance is related to the host immune response. The clearance is 0.5–1.0 log per year in lepromatous leprosy once effective chemotherapy is supplied and increases progressively as the disease is more tuberculoid[221]. A relapse is defined as the reappearance of clinical signs and symptoms, that is, development of new skin lesions and/or nerve damage, combined with an increase in the number of bacilli on slit-skin smear test results, following a complete course of MDT[222]. The occurrence of relapse after 12 months of multibacillary MDT is generally low[223–226], although several studies have shown its prevalence increases with a high bacterial load (bacteriological index ≥4+) prior to MDT initiation or a high number of skin and nerve lesions[227–230]. Clinically, it can be challenging to distinguish a relapse from a type 1 reaction or a reinfection. Changes in bacteriological index and response to treatment with corticosteroids may help to differentiate a reaction from relapse: a clinical improvement in a reaction is expected within 2–4 weeks whereas, in case of a relapse, no response is observed[231]. Patients presenting with a relapse should be re-treated with MDT or, if available, second-line drugs should be considered such as rifampicin, ofloxacin and minocycline (ROM; single monthly dose). A reinfection can be differentiated through whole-genome sequencing[232], enabling detection of detailed strain differences.

Despite the efficacy of MDT[214], its implementation poses multiple challenges, as it relies on accurate disease classification. In the case of multibacillary leprosy, the prolonged treatment duration increases the risk of poor compliance, potentially leading to drug resistance and relapses[233]. Consequently, at the 2002 WHO Technical Advisory Committee Meeting, it was proposed to simplify MDT into one uniform regimen, referred to as uniform-MDT, containing dapsone, rifampicin and clofazimine for 6 months for all patients diagnosed with leprosy independent of the type of leprosy[234]. Several studies, including an open-label RCT comparing standard MDT (12 months) versus uniform-MDT (6 months) in multibacillary leprosy, have shown comparable outcomes concerning the number of reactions, relapse rates and level of disabilities between both groups[224,235–237]. Nevertheless, concerns remain of an increased risk of developing relapses and reactions once patients have been released from treatment, particularly for those with a high bacteriological index[238]. Long-term follow-up of at least 10–15 years will be crucial to answering this question[239].

Alternative antimicrobial therapies

Effective alternative drug regimens that offer shorter durations and less toxicity are warranted. One example is ROM, which has a favourable safety profile and was shown to be effective[214,240–244]. Ofloxacin and minocycline are considerably more potent against *M. leprae* than dapsone and clofazimine[245–248]. Equivalent treatment outcomes between ROM and standard MDT have been suggested, although these conclusions should be interpreted with caution as the majority of the studies were of poor methodological quality and had relatively limited follow-up periods[249,250]. ROM does not seem to increase the risk of leprosy reactions during or after treatment[251]. A retrospective study from the Philippines, where rifampicin resistance is relatively high, showed that MDT plus adjunctive lymecycline in multibacillary leprosy significantly reduced bacteriological index, recurrence of skin lesions and nerve function impairment[252]. RCTs and long-term follow-up data are needed to study effectiveness, side effects, relapse rates and potential induction of drug resistance of these regimens.

Investments need to be made to develop or repurpose new antimicrobials and immunomodulating drugs. Bedaquiline (R207910 or TMC207), a diarylquinoline developed for multidrug-resistant tuberculosis that targets the electron transport chain inhibiting ATP synthesis, has a long half-life and represents a promising candidate

to simplify leprosy treatment, with significant bactericidal activity against *M. leprae* in mice studies[253]. While, to date, no human trial results have been published, an open-label safety and efficacy study with bedaquiline monotherapy is currently being assessed in persons with multibacillary leprosy in Brazil (NCT03384641)[254] and a pilot study of bedaquiline combined with MDT in multibacillary leprosy is ongoing in Mali[255].

A new class of bactericidal drugs with remarkable potency and shorter duration includes telacebec (Q203) and related QcrB inhibitors, which have been shown effective in phase I and II tuberculosis trials[256,257]. Telacebec is a small-molecule drug that blocks *M. tuberculosis* growth by inhibiting the cytochrome bc1 complex[258]. Further studies are planned to determine the optimal dosage against *M. leprae*, establish the safety, tolerability and efficacy of telacebec, and evaluate combination therapies with existing first-line and second-line drugs[259].

The emergence of global resistance to anti-leprosy drugs is a rising concern. A WHO surveillance study, performed in 19 leprosy endemic countries using molecular detection of resistance genes, found an antimicrobial resistance rate of 8%: this concerned mostly antimicrobial resistance towards either dapsone, rifampicin or ofloxacin but resistance to two drugs (rifampicin/dapsone or ofloxacin/dapsone) was also observed (1.2%). Rifampicin resistance was more often observed in relapse cases (5.1%) than in new cases (2.0%) in 12 countries[260]. However, the clinical implications on MDT outcomes of patients with proven resistance are not known. Studies across India found high numbers of ofloxacin resistance patterns of *M. leprae*, both in treatment-naive and recurrence cases, which is likely related to the extensive use of quinolones in managing other infections, and questions whether they are suitable as second-line therapy[261,262]. WHO advocates for implementation of robust surveillance programmes to monitor drug resistance and antimicrobial stewardship initiatives in endemic countries[263].

Leprosy reactions

Leprosy is complicated by acute immune-mediated inflammatory episodes known as leprosy reactions, which affect 30–50% of individuals[3,264]. Reactions mostly occur before or during treatment but can also occur years after successful MDT completion. They are often chronic and recurrent and require prolonged immunosuppressive therapy. Reactions represent the major cause of irreversible nerve damage and consequent disabilities and deformities, imposing a social and financial burden on patients and their households[265–267]. They are often overlooked due to a lack of awareness and experience among health-care professionals and the lack of low-complexity diagnostic tests.

Two types of reactions occur: type 1 (reversal) reaction (T1R) and type 2 reaction (T2R). T1R is a delayed hypersensitivity reaction to *M. leprae* antigens, mostly occurring in borderline disease, reflecting an abrupt shift towards T_H1-associated cytokines[268]. T1R is characterized by CD4 T cell infiltration in skin and nerve lesions resulting in acute inflammation of pre-existing skin lesions, oedema of extremities and face, and/or neuritis[269,270]. Risk factors for T1R are borderline forms of leprosy, age (≥15 years), postpartum, WHO grade 1 or grade 2 disabilities, and high anti-PGL-I antibody levels at diagnosis[264,269,271].

T2R, or erythema nodosum leprosum, is a multisystem inflammatory disease with sudden onset of new painful, widely distributed, erythematous subcutaneous nodules accompanied by fever, neuritis, arthritis, osteitis, orchitis, dactylitis and/or nephritis that occur in 10% of patients with borderline leprosy and up to 50% with lepromatous leprosy[272–274]. The pathogenesis is unclear and argued to result from immune-complex deposition in tissues and in part characterized by T_H17-immunity. TNF is also an important inflammatory mediator. Risk factors for T2R include lepromatous leprosy, high bacteriological index, intercurrent infections (for example, malaria, helminths, dental cavities), vaccination and hormonal alterations[272,274].

The diagnosis of reactions is clinical and is supported by histopathology. In view of their clinically complex nature and heterogeneity, the urge for objective tests is clear but requires long-term follow-up studies in large patient numbers and concomitant funding[272]. Longitudinal studies, involving follow-up of patients with leprosy with and without reactions during MDT treatment in Brazil, Bangladesh, Ethiopia, Nepal and the Netherlands have identified transcriptomic biomarkers for reactions predominantly associated with upregulated inflammatory proteins and downregulated IL-10 (refs. 139,268,275–279). Moreover, an IFNγ inducible antimicrobial RNA signature in whole blood enabled prediction of T1R 2 months prior to symptom onset[280]. Novel diagnostic and therapeutic approaches, possibly including leprosy-specific vaccines[209], are nevertheless needed through translational research to further elucidate the immunopathogenesis and identify biomarkers of reactions, which may identify those at risk of developing reactions, aid early diagnosis, and target therapeutic interventions as well as monitoring their effect.

The first-line treatment of leprosy reactions is oral corticosteroids. For T1R, individuals should be treated with daily prednisolone (or its equivalent), gradually tapering the dosage to zero over the course of 20 weeks[281]. However, 15–50% of patients require additional prednisolone[282,283]. T2R is usually treated with a higher dose of daily prednisolone. The prolonged exposure to steroids, particularly in chronic and recurrent T2R, may cause serious adverse effects, including diabetes mellitus, osteoporosis and opportunistic infections, and is associated with mortality[265]. The TRIPOD 1 study evaluated the addition of low-dose prophylactic prednisolone during the first 4 months of MDT in multibacillary leprosy and revealed it prevented leprosy reactions and nerve function impairment in the short-term, but that the protective effects were not maintained after 1 year[284]. In combination with prednisolone, other immunosuppressive agents, like azathioprine, ciclosporin, methotrexate and biologics (infliximab, etanercept), have shown benefits for both reactions. Thalidomide is an effective steroid-sparing agent in T2R. Its mechanism of action is ascribed to an anti-TNF effect. A retrospective study from the UK found that 77% of patients with T2R could discontinue corticosteroids within 2 months of using thalidomide[285]. However, due to its teratogenic effects in early pregnancy, thalidomide is often not available in endemic countries. Particularly for women of child-bearing age, appropriate counselling, close supervision and adequate contraception are strongly recommended, posing significant challenges to the implementation of thalidomide in remote underserved areas, where most individuals affected by leprosy reside.

There is a great need to enhance the treatment of leprosy reactions and develop effective, safe and affordable interventions. A phase II proof-of-concept RCT is ongoing to evaluate the effectivity, tolerability and safety of adjunctive metformin combined with MDT to mitigate leprosy reactions and its associated nerve damage in patients with multibacillary leprosy[286]. A multicentre RCT is under way to examine the efficacy of methotrexate in the management of T2R[287]. Additionally, Dovramilast (C-11050), a type 4 phosphodiesterase inhibitor with anti-inflammatory properties that was given as adjunctive treatment in adults with pulmonary tuberculosis in a phase II study[288], will also be tested in a phase II clinical trial for T2R in Nepal. Before initiating immunosuppressive therapy, patients should be screened

or receive empirical treatment for *Strongyloides stercoralis* to prevent strongyloides hyperinfection[289].

In addition, it is suggested to prescribe a gastric acid suppression agent and assess the need for corticosteroid-induced osteoporosis prevention therapy, which is often not available in under-resourced settings.

The Lucio phenomenon is observed in diffuse lepromatous leprosy with a high bacillary index. It is characterized as an occlusive vasculopathy rather than an immune-mediated response. In this condition, mycobacteria block the lumina of medium-sized blood vessels[290], resulting in painful, irregular purpuric and necrotic lesions on the distal lower limbs, forearms or buttocks. This can lead to extensive ulceration, which is susceptible to secondary bacterial infections, potentially resulting in sepsis and, in severe cases, death[291].

Quality of life

Despite leprosy being curable, complications such as nerve damage, physical discomfort, disability and disfigurement may be lifelong. Prevention of (worsening) disability is crucial in leprosy. Self-care consists of targeted and, when possible, personalized actions to care for affected eyes, insensitive hands and feet, painless wounds, or weakened muscles. Access to surgical and rehabilitation services is an important aspect of improving quality of life (QoL). An estimated 3–4 million people affected by leprosy globally are at risk of poor mental health and QoL, stigma, and social and economic disadvantages[5]. Depression and anxiety disorders were found to be very common among persons affected by leprosy[292]. WHO has also highlighted mental health issues and their effect on persons affected by leprosy, including suicidal tendency[293]. A study from India illustrated that the prevalence of depression and anxiety was 33% and 19%, respectively, whereas this prevalence in the general population was estimated at 5% and 3%[294].

Studies have shown that leprosy-affected individuals had significantly lower QoL than individuals with other dermatoses or the general population, affected by factors such as delayed diagnosis, leprosy reactions, physical disabilities, neuropathic pain and stigma[295].

The stigma associated with leprosy has deep historical origins, with references found in religious scriptures of Christianity, Hinduism and Islam, which perpetuated the belief that leprosy was a form of punishment or a curse; this, with the added fear of contagion, resulted in the exclusion of affected individuals from their communities to live in forced segregation on islands or isolated leprosaria[296]. These misconceptions have fuelled the deep-rooted fear of leprosy that exists to date. Stigma, which is even present among health workers towards persons affected by leprosy, creates a barrier to health-seeking behaviour, encouraging individuals to conceal their condition, thus prolonging the risk of transmission, undermining treatment, and increasing the risk of developing nerve injuries and disabilities, which further exacerbates stigmatization[297]. Stigma also contributes to psycho-social problems, like exclusion from the community, family, education and work[298]. Stigma not only affects the lives of people affected but also their families[292]. Furthermore, inadequate knowledge among health-care workers can exacerbate stigmatizing attitudes, causing additional barriers to accessing care[299].

One of the strategic pillars of the WHO 2021–2030 strategic roadmap 'Towards Zero Leprosy' is zero discrimination by combating stigma and ensuring human rights are respected[5]. This is addressed by adopting the United Nations Principles and Guidelines for elimination of discrimination against persons affected by leprosy as well as their family members, the inclusion of organizations and networks of persons affected by leprosy, the amendment of discriminatory laws, and encouraging access to social support and rehabilitation[300]. Non-governmental organizations as well as established organizations of persons affected by leprosy, such as MORHAN (Brazil) and ENAPAL (Ethiopia), play an important role in raising public awareness, education communities, offering guidance in self-care and prevention of further disabilities, and encouraging independence through economic activities.

Outlook

In the past decades, substantial progress has been made in the field of leprosy, reflecting commitment to advance its research and improve the clinical care of this neglected disease. This is reflected by ongoing and planned clinical trials for the prevention and treatment of leprosy and leprosy reactions and the development of low-complexity diagnostic tests for several use cases such as early diagnosis, monitoring treatment efficacy, and prediction of leprosy and leprosy reactions. Quantitative rapid tests for detection of *M. leprae*-specific antibodies in serosurveys or other host biomarkers specific for phenotypes across the disease spectrum are currently available but require large-scale worldwide evaluation in field settings.

Nevertheless, many knowledge gaps persist, ranging from basic science to the implementation of community-based interventions. A deeper understanding of the molecular mechanisms of infection and nerve damage is required. The same applies to the mode and route of transmission, the role of the environment, and the socioeconomic and behavioural factors that promote *M. leprae* transmission as well as strategies to interrupt this. Moreover, there is a need to identify safer, shorter treatment regimens and to acquire innovative strategies for preventing nerve inflammation and improving the treatment of reactions. A promising approach addressing the most pressing challenges in leprosy could involve exploring cross-linkages and synergies with other mycobacterial infections, such as tuberculosis, given their shared challenges (for example, chronic granulomatous mycobacterial disease, long incubation period and the need for long-term combination therapy).

However, conducting large, well-designed RCTs poses a challenge as valid outcome measures necessitate prolonged observation to identify relapses and are constrained by limited funding. It is fundamental to gain a better understanding of possible transmission pathways of this in vitro uncultivable mycobacterium to comprehend the effect of poverty and malnutrition and investigate the role of animal and environmental reservoirs in the global incidence of leprosy.

To meet the ambitious goals set out in the WHO 2021–2030 strategic roadmap, we must embrace a One Health, transdisciplinary research approach[301]. This means shifting our focus from close contacts only to entire communities in high-endemicity areas. We need bold, innovative research and evidence-based interventions that can make a real impact. Such an approach calls for new surveillance tools and community engagement to evaluate the impact of these interventions on local communities.

Public awareness and literacy play a crucial role in improving early diagnosis and treatment of leprosy in endemic areas and is of great importance for the success of studies, particularly if these involve individuals without leprosy. By educating communities and health-care professionals about the signs and symptoms of leprosy, we can facilitate prompt intervention and prevent irreversible nerve damage, disabilities and deformities. This proactive approach not only leads to better health outcomes for affected individuals but also enhances

the overall QoL within their surroundings. By addressing these key factors, we can effectively remove perceived barriers in the care cascade, promote positive health-seeking behaviour, and ultimately reduce the disability, stigma, and discrimination associated with leprosy.

Leprosy is a neglected, poverty-associated infectious disease, afflicting individuals mostly in their most productive stage of life[302–304]. Despite worldwide efforts to interrupt transmission and decades-long endeavour for elimination, leprosy still poses a public health problem in LMICs, causing lifelong physical and social disabilities[17]. Stable numbers of new cases are being identified in endemic countries, which translates into >22 newly diagnosed patients per hour. Diagnostic delay leading to neurological disabilities is an area of great concern as clinical expertise is disappearing. Integrated approaches involving active case finding, innovative diagnostic tools, access to (alternative) treatment, public engagement and preventive strategies, will accelerate progress towards interruption of *M. leprae* transmission and limit the development of irreversible nerve damage and subsequent disabilities[305]. As a global health community, it is our responsibility to keep the interest in leprosy alive, to foster scientific awareness, and to educate (bio) medical students, frontline health-care workers and medical doctors to prevent loss of expertise. To make these targets obtainable, major multidisciplinary commitments and funding resources need to be made accessible in the coming years.

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