Recent advances in leprosy and Buruli ulcer (*Mycobacterium ulcerans* infection)

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Purpose of review

After tuberculosis, leprosy (*Mycobacterium leprae*) and Buruli ulcer (*M. ulcerans* infection) are the second and third most common mycobacterial infections in humankind, respectively. Recent advances in both diseases are summarized.

Recent findings

Leprosy remains a public health problem in some countries, and new case detections indicate active transmission. Newly identified *M. lepromatosis*, closely related to *M. leprae*, may cause disseminated leprosy in some regions. In genome-wide screening in China, leprosy susceptibility associates with polymorphisms in seven genes, many involved with innate immunity. World Health Organization multiple drug therapy administered for 1 or 2 years effectively arrests disseminated leprosy but disability remains a public health concern. Relapse is infrequent, often associated with higher pretreatment *M. leprae* burdens. *M. ulcerans*, a re-emerging environmental organism, arose from *M. marinum* and acquired a virulence plasmid coding for mycolactone, a necrotizing, immunosuppressive toxin. Geographically, there are multiple strains of *M. ulcerans*, with variable pathogenicity and immunogenicity. Molecular epidemiology is describing *M. ulcerans* evolution and genotypic variants. First-line therapy for Buruli ulcer is rifampin + streptomycin, sometimes with surgery, but improved regimens are needed.

Summary

Leprosy and Buruli ulcer are important infections with significant public health implications. Modern research is providing new insights into molecular epidemiology and pathogenesis, boding well for improved control strategies.

Keywords

Buruli ulcer, leprosy, *Mycobacterium leprae*, *Mycobacterium ulcerans*

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Leprosy

Leprosy, or Hansen's disease, is a chronic infection caused by *Mycobacterium leprae* that primarily affects the cooler body areas to include skin, upper respiratory passages, anterior segments of eyes, superficial segments of peripheral nerves, and testes. A newly identified mycobacterium causing disseminated leprosy, *M. lepromatosis* sp *nov*, may explain some clinical variability [1]. Comparative analysis of *M. leprae* and *M. lepromatosis* indicate common ancestry [2•].

Leprosy, a complex disease spectrum, is often classified by clinical and histopathological criteria, from tuberculoid (localized) to lepromatous (disseminated) poles. A World Health Organization (WHO) simplified field classification is limited to paucibacillary (localized) and multibacillary (disseminated) disease, based primarily on lesion numbers [3]. Paucibacillary and multibacillary leprosy are characterized by robust Th-1 (cell-mediated) and Th-2 (humoral) immune responses, respectively. Leprosy is punctuated by acute immunologically mediated reactions called type 1 (reversal reaction) and type 2 (erythema nodosum leprosum; ENL). Neuritis is common and responsible for much of the sensory loss and deformity in leprosy.

Microbiology

The *M. leprae* genome contains 3.3 million base pairs with 3240 genes, of which only 1604 (about 50%) encode proteins, reflecting gene decay and formation of abundant pseudogene and noncoding regions [4]. Massively reduced metabolic capabilities may explain long multiplication and incubation times in mice and humans, respectively, and noncultivability *in vitro* [5].

M. leprae originated as a single clone and evolved with no genetic exchange, conferring extreme genetic stability [6]. Whole genome sequencing, and the definition of 16 single nucleotide polymorphism (SNP) subtypes in geographically diverse extant and extinct *M. leprae* isolates, indicate *M. leprae* likely originated in East Africa,

spread to Europe and Asia by two separate routes, then from Europe to West Africa [7,8••]. The pattern of spread parallels early human migration. The earliest DNA evidence of *M. leprae* is from the first century Tomb of the Shroud in Jerusalem, and ancient skeletal evidence in India suggests leprosy was present by 2000 B.C. [9•,10•].

Population-based variable number tandem repeat (VNTR) and SNP genotyping analyses conducted on clinical *M. leprae* samples, including archaeological sources, are mapping loci and differentiating genotypes, tracking community transmission, and identifying strain variations in many regions [11–13]. However, VNTR profiles vary among *M. leprae* from different lesions on the same patient, limiting usefulness [14,15].

Epidemiology

Leprosy is most common in Asia (Fig. 1). Leprosy is more common in men but women may under report [16]. In most endemic areas, only 5–10% of infected persons develop clinical disease. The incubation period of leprosy in most patients, ranging from 3 to 7 years, is an important factor in developing control strategies [17].

The accepted mode of leprosy transmission is by nasal droplet from infected untreated persons but *M. leprae* shedding from skin may also be relevant [18]. Leprosy can occur as a zoonosis in the southeastern United States (US) and South America, after contact with wild, naturally infected armadillos [19–22]. In the US, leprosy in armadillos may be expanding geographically [23]. Viable *M. leprae* can be found in soil [24].

HIV seropositivity may be associated with variation in leprosy presentation, and HIV seropositive leprosy patients on HIV treatment may develop reversal reaction as part of immune reconstitution inflammatory syndrome [25,26]. In leprosy endemic areas, anti-HIV treatment may increase incident leprosy cases [27].

Leprosy prevalence has fallen remarkably since the WHO implemented multiple drug therapy (MDT) in 1982. In 2001, the WHO pronounced the 'elimination' of leprosy as a global public health problem, defined as less than 1 registered patient under treatment per 10 000 persons [17]. Leprosy support is integrating into general medical services [28], perhaps prematurely, threatening the sustainability of elimination. At the country level, Brazil, Nepal, and Timor-Leste have not met the elimination goal, and new case detections remain high in India and Indonesia [29].

WHO reports the 2009 global prevalence of leprosy as 213 036 patients, and 249 007 new case detections in 2008 [30]. However, some authorities argue the burden of leprosy is higher, and progressively lower new case detections, especially over the last 5–7 years, partly reflect reduced case finding efforts [31]. Leprosy is not eradicable with currently available diagnostics or interventions, echoed in the WHO 2011–2105 global strategy stressing early diagnosis and treatment, and reducing severe disability [29]. Leprosy is one of the WHO's 13 'neglected

Figure 1 Leprosy is present in nearly every country

The 17 darkened countries contributed 94% of the world's 249 007 new case detections in 2008.

tropical diseases', yet research funding is falling despite many unanswered questions.

Molecular epidemiology

Susceptibility loci occur on chromosome 6, within the major histocompatibility complex, and 10p13, proximal to the mannose receptor gene, mediating macrophage phagocytosis [32]. Recent reports of genetic variants (polymorphisms) include those related to: susceptibility [*HLA-DR* [33,34], interleukin (*IL*)-*10* promoter [35•], Toll-like receptor (*TLR*) 1 [36], nucleotide-binding oligomerization domain containing 2 (*NOD2*) [37•]]; protection (*HLA-DR* [33,34], *TLR4* [38•]); and risk of reactions (*TLR1* [39], *TLR2* [40], *NOD2* [37•]).

In the first genomewide association study in leprosy, conducted in China, polymorphisms were found in seven genes (*CCDC122, C13orf31, NOD2, TNFSF15, HLA-DR, RIPK2, LRRK2*) associated with leprosy susceptibility, the latter five being involved in NOD2-mediated regulatory node of innate immunity [41••]. This underscores the importance of host immunogenetics. In a forward genetic screen, polymorphic heterozygosity at the *lta4h* locus, regulating pro- and anti-inflammatory leukotriene B_4 and lipoxin synthesis, respectively, programs balanced eicosanoid production, protecting against multibacillary leprosy [42•]. Balanced immune responses may limit immunopathology, possibly explaining value of a *TLR1* SNP that reduces signaling, yet protects against reversal reaction [39].

Pathogenesis and immunity

The Schwann cell of peripheral nerves is the primary target for *M. leprae* [43]. Nerve damage, the pathogenic hallmark of leprosy, is largely mediated by cellular immune responses and inflammatory reactions. Other factors include matrix metalloproteinases induced by *M. leprae*, causing demyelination, and Schwann cell TLR2 recognition of *M. leprae* 19 kDa lipoprotein, triggering apoptosis [44,45].

During early *M. leprae* infection, innate immunity mediates antimicrobial responses and, largely through dendritic cells (professional antigen presenting cells), begins and shapes the adaptive T-cell response [46]. Pattern recognition receptors, such as TLR2/1 heterodimers on dendritic cells and macrophages, recognize pathogen-associated molecular patterns of *M. leprae*, including 19 and 33 kDa lipoproteins, and *M. leprae* major membrane protein-II. Tumor necrosis factor-α (TNF-α) and IL-12 are produced, the latter mediating an adaptive Th-1, disease-localizing response.

Robust innate immunity that limits *M. leprae* involves dendritic cell and macrophage differentiation, upregulation of antimicrobial pathways, such as vitamin D-dependent cathelicidin production and, subsequently, T cell activation [47]. In a notable divergence, IL-15 induces antimicrobial peptide production, associated with paucibacillary (localized) leprosy, whereas IL-10 (anti-inflammatory) induces phagocytosis, associated with multibacillary (disseminated) leprosy and accumulation of host-oxidized phospholipids [48•].

In less vigorous innate responses associated with multibacillary disease, lesional TLR2/1 expression is reduced, perhaps reflecting inefficient upregulation or signaling, or downregulation by Th-2 cytokines IL-4 and IL-10 (anti-inflammatory). Multibacillary disease is characterized by fewer and less differentiated dendritic cells, perhaps contributing to weak T-cell responses [49•].

Cell-mediated (T-cell) immunity against *M. leprae* ultimately determines disease type. In multibacillary disease, striking T-cell anergy to *M. leprae* may reflect ineffectual innate immunity, possibly involving *M. leprae* interference with early T-cell receptor/CD28-induced signaling events, inhibiting IL-2 production and T-cell proliferation [50•]. Leprosy lesions contain T regulatory cells ($CD4^+$ $CD25^+$ $FoxP3^+$), suggesting a role in disease progression [51•].

Diagnosis and disease status

Beside conventional diagnostic procedures, serologic tests for *M. leprae*-specific phenolic glycolipid 1 (PGL-1) IgM and IgG antibodies aid in diagnosis of leprosy, especially multibacillary disease, and may indicate treatment response [52]. In India, however, sera from visceral leishmaniasis patients may react with PGL-1 [53•].

Increasingly sensitive diagnostic PCR assays detect highly conserved *M. leprae*-specific 16s ribosomal RNA (rRNA) in tissue sections, skin, and nasal smears [54]. Assays to monitor disease status or treatment response include PCR depiction of *M. leprae* DNA and *hsp*18 mRNA copy numbers [55•], and *M. leprae* viability assays, combining PCR targeting 16s rRNA with *M. leprae* repetitive element DNA to enumerate bacteria [56•].

Efforts to identify peripheral blood biomarkers associated with type 1 and type 2 reactions aim to predict higher risk patients, or monitor response to therapy [57–59]. Endocrine dysfunction in multibacillary leprosy is underestimated [60•].

Treatment

In most leprosy endemic regions, multibacillary disease is treated with WHO MDT, consisting of dapsone, rifampin, and clofazimine given for 1 year, reduced from 2 years in 1998. Alternate regimens, such as combined rifampin–ofloxacin–minocycline (ROM), are useful for dapsone intolerance, avoiding stigmatic clofazimine-induced skin

pigmentation or increasing convenience [61]. A small proportion of *M. leprae* isolates, especially from relapsed patients, is resistant to dapsone or rifampin, underscoring the importance of MDT [62,63•].

As adherence to WHO MDT for multibacillary leprosy is difficult, shorter regimens, such as 6-month 'uniform MDT', and others are being assessed, but relapse rates are problematic [64•,65]. Fluoroquinolones, such as ofloxacin and moxifloxacin, and the macrolide clarithromycin are potent anti-*M. leprae* drugs that may shape new regimens. Moxifloxacin improves lesion appearance quickly [66•].

Relapse rates in multibacillary leprosy following 2-year WHO MDT are less than or equal to 10% in most studies [67,68••], acceptably low by most authorities. Relapse rates are higher in patients with high pretreatment *M. leprae* burdens. Relapses occurring in a peak-like pattern after MDT completion suggest a role for 'persisters' [68••], dormant *M. leprae* not killed by MDT that activate after treatment completion [69,70]. The ability of molecular assays to distinguish relapse from new infection is uncertain [14,15].

Reversal reactions are treated with oral corticosteroids [71]. For ENL, oral corticosteroids and clofazimine are often used [72], but thalidomide is most effective, with fewer relapses or longer periods of remission [73•]. Thalidomide's efficacy likely depends on inhibiting TNF-α and neutrophil recruitment [74•]. Thalidomide teratogenicity results from drug binding to a protein called cereblon, inhibiting ubiquitin ligase [75••].

Prevention of disability

Prevention of disability programs incorporate physical medicine to reduce disability and nerve function impairment (NFI) [76]. Nerve damage in leprosy is more widespread than earlier estimated [77•]. In Brazil, risk factors for significant disability (WHO grade 2) include multibacillary leprosy, two or more thickened nerves and age under 15 years old [78•]. Patients at higher risk for NFI may be identified earlier by several risk variables, including leprosy classification and anti-PGL-1 antibody levels [77•,79]. In the field, nerve palpation with monofilament and voluntary muscle testing is acceptable for assessing NFI [80].

Prevention and control

There are no formal recommendations for preventing leprosy. Periodic assessments of close (household) contacts of leprosy patients, considered at highest risk, are useful for detecting early disease [81]. Geographic information systems may identify clustering [82•]. Screening tests for detecting early leprosy, including preclinical disease, are in development and would be highly useful [83•,84,85•].

Chemoprophylaxis with a single dose of rifampin given to close contacts of a newly diagnosed leprosy patient, to interrupt transmission, significantly reduces the risk of developing clinical leprosy for at least 2 years [86]. This may become a public health intervention. Combining rifampin with ofloxacin and minocycline would address rifampin resistance concerns [87]. Bacille Calmette-Guérin (BCG) vaccination given during infancy, followed by rifampin chemoprophylaxis upon household leprosy exposure, may be more protective than either intervention alone [88•].

Vaccination strategies for leprosy are being explored. BCG vaccination provides some protection, ranging from 20 to 90%, depending on many factors [89]. Meta-analyses of BCG leprosy protection studies conclude that BCG could substantially impact leprosy control if vigorously implemented, especially as a two-dose prime boost [90•,91]. Efforts to improve the immunogenicity of BCG by recombinant technologies are ongoing [92]. Several immunogenic *M. leprae* proteins may be suitable vaccine candidates [93] but a clinical vaccine efficacy trial faces many challenges.

Buruli ulcer

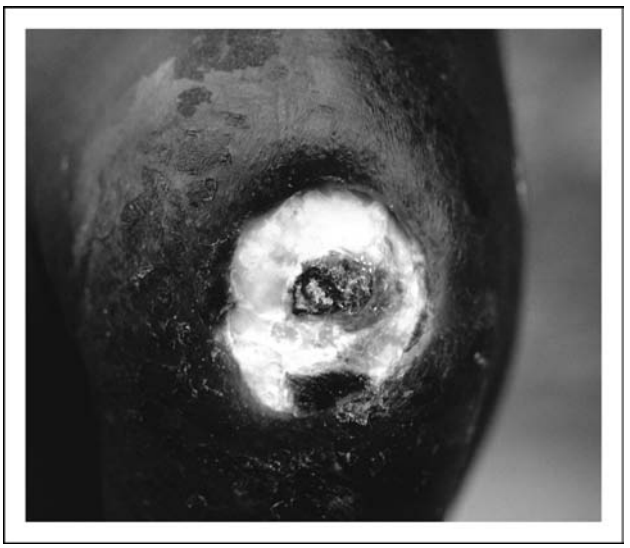
Buruli ulcer, an emerging infection caused by *M. ulcerans*, is characterized by indolent, typically painless, necrotizing skin lesions [94]. A lesion often begins as papule or nodule, progressing to an undermined ulcer, plaque or edema (Fig. 2). Mean incubation time is 3 months. Approximately 10% of patients develop bone involvement subjacent to skin lesions, or metastatic osteomyelitis from lymphohematogenous spread of *M. ulcerans*. Pathogenesis is mediated by mycolactone, a necrotizing, immunosuppressive macrolide toxin produced by *M. ulcerans* [95•].

Buruli ulcer is one of the WHO's 13 'neglected tropical diseases', yet research support remains modest [96]. Most funding is provided through the WHO, and increasingly philanthropic, academic and governmental agencies [93].

Epidemiology

In 1998, the WHO recognized Buruli ulcer as a re-emerging infectious disease in West and Central Africa, with an important public health impact [97]. Most Buruli ulcer occurs in West Africa, with highest incidences in Benin, Ghana, and Côte d'Ivoire, but the disease has been reported in about 30 countries (Fig. 3) [98,99•]. Buruli ulcer prevails in rural tropical wetlands, especially areas with stagnant water, including ponds and swamps. The rapid re-emergence of Buruli ulcer, beginning in the early

Figure 2 Buruli ulcer in the deltoid area of a 12-year-old Angolan boy



This 'pristine' lesion developed 3 months after an anticholera immunization at this site. Characteristic features include undermining of symmetrical borders, necrotic base, and induration with scaling of adjacent skin.

1980s, is believed attributable to environmental factors, such as deforestation, artificial topographic alterations, enlarging rural populations engaged in manual agriculture in wetlands, and possibly global climate changes.

Estimates are that 10 000 persons develop Buruli ulcer annually, undoubtedly low because of geopolitical factors where Buruli ulcer typically develops. Incidence of Buruli ulcer is highest in children 5–15 years old, with lesions most commonly on the lower extremities. Buruli ulcer is a growing public health problem, with psychosocial and socioeconomic implications in endemic regions. Disabling and stigmatizing sequelae include scarring, contractures and bone destruction, in up to 60% of patients [100]. Buruli ulcer is occasionally diagnosed in North American and European clinics in travelers [101].

Buruli ulcer is directly related to environmental factors, and thus is considered noncommunicable [94]. The most plausible mode of transmission is through local trauma. Insect bites are under investigation, in part because *M. ulcerans* DNA is present in some aquatic insects. Australian investigators propose that Buruli ulcer is a zoonosis transmitted by mosquitoes, from possums to humans. Indeed, *M. ulcerans* DNA was found in mosquitoes during an outbreak of human Buruli ulcer in Australia, and human Buruli ulcer incidence correlates with that of vector-borne notifiable diseases in Victoria [102•]. In Africa, terrestrial mammals are being investigated as reservoirs of *M. ulcerans* [103].

Risk factors for Buruli ulcer within endemic areas include inadequate wound care, failure to wear protective clothing, and exposure to unprotected water sources [104]. HIV seropositivity may increase risk for Buruli ulcer, or render Buruli ulcer highly aggressive [105]. BCG

Figure 3 Buruli ulcer worldwide distribution

Distribution is denoted by the darkened areas, to include those countries considered endemic or reporting sporadic cases (suspected or confirmed).

vaccination provides evanescent (<1 year) protection against Buruli ulcer and prevents osteomyelitis [106]. Vaccines with prophylactic and therapeutic effects based on DNA engineering and virulence factors of *M. ulcerans*, such as mycolactone, are under study [93,107•].

Microbiology and etiologic agent

Standard and real-time PCR techniques for identifying *M. ulcerans*, primarily by detecting two *M. ulcerans* insertion sequences (IS*2404*, IS*2606*), recognize *M. ulcerans* in the environment in Australia and West Africa [108•]. Improving *M. ulcerans* DNA extraction procedures should enhance environmental isolations, advancing understanding of reservoirs [109]. The first direct isolation of *M. ulcerans* from nature was reported in 2008 from a water strider, an aquatic insect that does not bite humans [110].

Unlike *M. leprae* and *M. tuberculosis*, *M. ulcerans* produces a necrotizing and immunosuppressive polyketide toxin, called mycolactone [95•]. Genes in a virulence plasmid of *M. ulcerans*, controlled by SigA-like promoters [111], encode the synthases that generate mycolactone. Identifying SigA-like promoters led to *M. ulcerans*-green fluorescent protein, linking fluorescence with toxin gene expression, a promising tool for studying Buruli ulcer pathogenesis and transmission [111].

Comparative genomics indicate *M. ulcerans* likely diverged from *M. marinum*, acquiring a 174-kb virulence plasmid (pMUM001) with genes coding for mycolactone production and 10 proteins, all potential immunogenic targets for vaccine development or serodiagnosis [112••]. Accordingly, phenolic mycosides of *M. ulcerans* and *M. marinum* are identical, and sequences for the 16s rRNA gene are highly similar [94]. As *M. ulcerans* evolved toward becoming an intracellular organism, it lost nonessential genes through reductive evolution, likely enhancing pathogenicity [112••].

Gene sequences of the 3′ end of 16s rRNA in *M. ulcerans* vary by geographic origin, and divide *M. ulcerans* broadly into African, American, Asian, and Australian strains, with many substrains on each continent [113,114]. Each major strain generally differs in clinical presentation, mycolactone type and virulence, and host immune responses [115•]. Mycolactone type coding by geographical origin includes A/B (Africa), the most pathogenic, C (Asia, Australia) and D (Asia) [95•].

Understanding the evolution of *M. ulcerans* has been limited by a high degree of clonality among *M. ulcerans* isolates and a lack of known genetic polymorphisms. *M. ulcerans* isolates from a small endemic area in Ghana lacking insertional–deletional genomic polymorphisms underscored SNP analysis for differentiating substrains of *M. ulcerans* within localized areas [116]. Current efforts identifying SNPs and establishing SNP typing assays are increasing the understanding of the micro-epidemiology, genetic diversity and evolution of *M. ulcerans* [117•]. For example, SNPs identified in a highly clonal population of *M. ulcerans* from Ghana differentiated a group of *M. ulcerans* isolates into 54 strains, with 13 distinct SNP haplotypes [118].

Pathogenesis and immunity

Initial infection is primarily related to two properties of *M. ulcerans*: optimal growth at 30–33°C, and elaboration of mycolactone. The temperature requirement of *M. ulcerans* favors development of lesions in the skin and subcutaneous tissue, and mycolactone destroys tissue by apoptosis and necrosis and suppresses host immune responses [95•].

Mycolactone profoundly suppresses elements of both innate and adaptive cell-mediated immunity, likely enhancing progression of Buruli ulcer. Mycolactone inhibits macrophages, monocytes, B cells, and T cells at least in part by inhibiting production of IL-1, IL-2, IL-6, IL-10, TNF-α, interferon-γ (IFN-γ), and the chemokine IL-8 [119•,120,121]. The immunosuppressive effects of mycolactone extend beyond skin lesions, to circulating leukocytes and lymphoid organs [122]. Indeed, peripheral whole blood samples from Buruli ulcer patients, stimulated with mitogens, produce comparatively smaller amounts of Th-1, Th-2, and Th-17 cytokines, resolving upon treatment completion [123•].

The clinical and histopathological characteristics of Buruli ulcer suggest an immunological spectrum, relevant for vaccine development. Early or progressive ulcers are characterized by abundant IL-10 with little inflammation (Th-2 response) and numerous, often extracellular *M. ulcerans*, within areas of coagulation necrosis. The latter features are presumably from mycolactone killing of tissue and inflammatory cells. Maturing Buruli ulcer lesions, especially under antibiotic treatment, are characterized by IFN-γ with granulomatous inflammation, organizing lymphoid aggregates, and fewer, typically intracellular *M. ulcerans*, consistent with Th-1 and delayed-type hypersensitivity (DTH) responses [95•,124,125•,126]. Indeed, persons uninfected or those with early Buruli ulcer lack DTH skin test reactivity to 'burulin', a sonicate of *M. ulcerans*, but the latter develop DTH reactivity as healing begins [127]. In a third category, some minor Buruli ulcer lesions self-heal early, suggesting fundamental elements of high host resistance.

Laboratory diagnosis and treatment monitoring

For laboratory diagnosis, four tests are currently in use: direct smear (with acid fast stains auramine O or Ziehl-Neelsen); culture; PCR; and histopathology. Estimated sensitivities range from ≤60 to >90%, with PCR and

histopathology considered most reliable for all lesion subtypes, followed by direct smears and culture. Current efforts aim to better define the value of the tests, especially PCR, across lesion subtypes and several sampling techniques [128]. PCR is the best overall method and is highly sensitive when applied to punch biopsy samples of nonulcerative lesions and swab material from ulcers [129•]. Alternatively, PCR of nonulcerative lesion samples obtained by less invasive fine needle aspiration is acceptably sensitive, less so when samples are cultured [130•,131,132].

As PCR targets IS*2404* and IS*2606* are present in other pathogenic mycobacteria, such as *M. marinum*, VNTR assays can discriminate *M. ulcerans* from other species [133]. Rapid diagnostic tests to detect mycolactone or *M. ulcerans*-specific proteins are in early development.

For assessing treatment response, more often a concern in antibiotic treatment trials, lesion culture is generally recommended [129•]. However, detection of mycolactone in tissues infected with *M. ulcerans* may prove to be a useful alternative to culture [134•].

Treatment

Historically, wide surgical excision has been the standard treatment for all forms of Buruli ulcer, sometimes followed by split-thickness skin grafts. Rifampin was known by the 1970s to heal most early Buruli ulcer lesions, but antibiotics remained largely peri-operative adjunctive therapy, aiming to reduce dissemination and recurrence [135]. The value of antibiotic therapy for surgically excised lesions remains unclear [136,137].

In 2004, with Buruli ulcer incidence rising and limited surgical resources in Africa, supported by experimental murine data and a preliminary human trial [138], the WHO advocated a provisional antibiotic regimen for Buruli ulcer composed of oral rifampin (10 mg/kg) and intramuscular streptomycin (15 mg/kg), both given daily (7 days/week) for 8 weeks under supervision [139]. Patients with early lesions (<5 cm) receive antibiotics alone, and those with moderate lesions (>5 cm) receive 4 weeks of antibiotics, then surgery if necessary, followed by 4 more weeks of antibiotics.

In 2007, a case series study from Benin showed that small and moderate Buruli ulcers resolved when treated with the WHO antibiotic only regimen, with few recurrences [140]. In 2010, the first randomized trial of rifampin + streptomycin for early, limited Buruli ulcer (<6 months duration; nodules and ulcers, <10 cm in diameter) was reported, further bolstering WHO guidelines [141••,142]. Rifampin + streptomycin, given daily for 8 weeks, or rifampin + streptomycin daily for 4 weeks, followed by rifampin + clarithromycin (both oral) daily for 4 weeks, all without surgery, healed lesions in more than 90% of patients by 1 year. These results also raised the possibility of a fully oral, less toxic antibiotic regimen for limited Buruli ulcer. Taken together with experimental data from mice and a report describing resolution of advanced Buruli ulcer after 8 weeks of rifampin + clarithromycin [143], studies of fully oral antibiotic regimens, such as rifampin + clarithromycin or rifapentine + moxifloxacin [144], seem warranted.

The role of antibiotics for advanced Buruli ulcer, akin to the WHO regimen, is under investigation. In Democratic Republic of Congo, among 61 patients with large Buruli ulcer who received daily rifampin + streptomycin, extended to 12 weeks, and surgery at 4 weeks after antibiotics began, 92% were classified as treatment success, with recurrence rates of about 1% [145]. Other modalities, such as local heat therapy, first explored decades ago, may become viable as application systems are simplified [146].

Buruli ulcer under treatment with antibiotics may develop temporary immune-mediated inflammation and clinically worsen, proposed as a paradoxical sign of treatment success [147•]. Awareness of this phenomenon may prevent unnecessary changes in treatment, reduce surgeries, and improve the accuracy of treatment trials.

Conclusion

Leprosy and Buruli ulcer, the first and second most common cutaneous mycobacterial infections in humankind, respectively, present important public health issues. The worldwide burden of leprosy has fallen markedly over the last 2 decades, due largely to MDT, but the disease remains a significant public health concern in some countries. Reducing disability and NFI are increasingly important. Leprosy eradication, the final goal, requires new tools for detecting early or preclinical disease and interrupting or preventing transmission. Buruli ulcer is less common than leprosy but accumulating data suggest that Buruli ulcer incidence is underestimated and the disease more widespread than earlier believed. Modern research techniques are providing insights into Buruli ulcer evolution, pathogenesis and transmission modes, and improving diagnostic capabilities. Buruli ulcer therapy, primarily rifampin and intramuscular streptomycin, sometimes with surgery, is effective for most lesions but alternate antibiotic regimens with improved convenience and less toxicity are expected. Reducing disability from scarring is an increasingly important aspect of Buruli ulcer management.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 531–532).

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