

EDITORIAL

Leprosy and Buruli ulcer: similarities suggest combining control and prevention of disability strategies in countries endemic for both diseases

DOUGLAS S. WALSH*, BOUKE C. DE JONG**,
WAYNE M. MEYERS*** & FRANÇOISE PORTAELS**

**Dermatology and Research & Development Services,
Veterans Affairs Medical Center, Syracuse, New York, USA*

***Institute of Tropical Medicine, Antwerp, Belgium*

****Formerly, Division of Microbiology, Armed Forces Institute of
Pathology, Washington DC, USA*

Leprosy and Buruli ulcer (BU), after tuberculosis (TB), are the 2nd and 3rd most common mycobacterial diseases in humans, and are included in the World Health Organization's (WHO) list of 17 neglected tropical diseases (NTD).^{1,2} Despite the declaration of leprosy elimination by WHO in 2000 in most countries, leprosy incidence remains fairly stable, highlighting the unintended consequences (e.g. prematurely shutting down control programmes), of randomly setting targets to eliminate complex infectious diseases like leprosy.^{3,4} Continued case notifications arising among children moreover suggest ongoing transmission. Elimination targets also put undue pressure on national programmes to reach elimination, decreasing the incentive to find and report new cases, resulting in underreporting. By comparison, BU is far less common and found in far fewer countries. BU is considered a re-emerging disease attributed to environmental factors such as deforestation, artificial topographic alterations (dams and irrigation systems), increasing populations engaged in basic manual agriculture in wetlands.⁵

Financial support for leprosy research has dramatically diminished over the past three decades, and this decline is reasonably attributed to the elimination targets of WHO. In contrast for BU, there has been a spectacular increase in the number of peer reviewed papers since the creation of the WHO Global BU Initiative (GBUI) in 1998, thanks to notable financial support by nongovernmental (NGO) and international organisations.

Leprosy and BU are complex diseases with specific clinical similarities and differences (Table 1).

For leprosy, invasion of nerves by *Mycobacterium leprae* in untreated patients, and uncontrolled inflammatory immune reactions, which may develop in patients on treatment, may lead to permanent peripheral neuropathy, blindness, or both.⁶ The WHO strategy for leprosy from 2011 to 2015 includes efforts to focus on and reduce Grade 2 disability, but the benefits to patients may be much delayed.⁷ For BU, severe scarring with limb contractures

Table 1. Comparison of features of leprosy and Buruli ulcer (BU)

	Leprosy	Buruli ulcer
Characteristic Geography	In > 90 countries (especially Brazil, India, Indonesia, Nepal)	In > 30 countries (especially Benin, Côte d'Ivoire, Ghana)
Epidemiology	2 nd most common human mycobacterial disease Reported 2013 > 200,000 cases on treatment > 200,000 new cases diagnosed	3 rd most common human mycobacterial disease Reported cases: 5–6K/year Estimated: > 10,000 cases/year (most 5–15 years old especially in Africa)
Underreporting Organism	Yes <i>M. leprae</i>	Yes (reported cases not always confirmed) <i>M. ulcerans</i>
Evolution Microbiology	<i>M. lepromatosis</i> (controversial) East African origin; clonal, massive gene decay Obligate intracellular 3-3 M base pairs, 50% protein coding genes; Generation time: 12–14 days	<i>M. ulcerans</i> ssp <i>shinshuense</i> From <i>M. marinum</i> , clonal, gene decay Intra- and extracellular 5-8 M base pairs (0-17 bp in plasmid), 70% protein coding genes; Generation time: ~ 20 hours Mycolactone (encoded by plasmid)
Toxin in vitro cultivation	No	Yes
Clinical presentation	No Skin patches, papules, plaques, nodules; anesthesia, nerve thickening; other organs: eyes, testes	Skin papules, plaques, nodules, ulcers, edemas; especially extremities; bone lesions in ~ 10% (Africa)
Favors cooler body parts	Yes	Yes
Disease spectrum	- Tuberculoid (localized; paucibacillary [PB]); few lesions - Lepromatous (disseminated; multibacillary [MB]): many lesions	Papule, nodule or plaque, then self-heals or enlarges, often ulcerating
HIV a risk factor	No	Yes; more severe disease observed
Tuberculosis co-infection	Rare (pulmonary form only)	Both organisms, same skin lesion: 3 /> 5000 Pulmonary TB after BU Rx: 1 /> 5000 Investigations on-going
Molecular epidemiology	Gene polymorphism associations, especially innate immunity	Non-contagious
Transmission	Contagious Nasal droplet, skin shedding of <i>M. leprae</i> , zoonosis in southern USA	Traumatic implantation; aquatic insect bites? zoonosis in Australia (via mosquitoes?)
Reservoir	Humans, armadillos, non-human primates	Environment, some mammals (Australia)
Incubation	Estimated 5 to 7 years	3 months

Table 1. *continued*

	Leprosy	Buruli ulcer
Immunology	<ul style="list-style-type: none"> - Tuberculoid (localized): strong innate, cell mediated immunity (CMI); few mycobacteria - Lepromatous (disseminated): weak innate, CMI; many mycobacteria 	<ul style="list-style-type: none"> Innate: investigations on-going CMI: increases with treatment
Immune reactions	<ul style="list-style-type: none"> Reversal reaction Erythema nodosum leprosum Target: Schwann cells → nerve destruction 	<ul style="list-style-type: none"> Paradoxical; lesions may inflame and worsen during, or after, treatment Target: skin, bone
Pathogenesis	<ul style="list-style-type: none"> Tuberculoid: robust CMI, reactions Lepromatous: <i>M. leprae</i> infiltration, reactions 	<ul style="list-style-type: none"> Mycolactone-mediated tissue and bone destruction
Diagnosis	<ul style="list-style-type: none"> Clinical and Laboratory Slit skin smear for AFB (multibacillary), histopathology, PGL-1 antibody, PCR: sensitivity: 95% MB, 55% PB 	<ul style="list-style-type: none"> Clinical and Laboratory Direct lesion smear for AFB (swabs or fine needle aspiration), culture, histopathology, PCR (<i>IS2404</i>): sensitivity > 95% (> 200 copies in genome); radiography (bone lesions)
Histopathology	<ul style="list-style-type: none"> - Tuberculoid: epithelioid cell granulomas, few or no organisms - Lepromatous: mononuclear infiltrate, foamy macrophages, numerous organisms 	<ul style="list-style-type: none"> - Early: organisms intracellular, little inflammation, necrosis, apoptosis, vasculitis - Later: organisms extracellular, mononuclear infiltrate, (OMIT), necrosis, scarring
Treatment Medication	<ul style="list-style-type: none"> - Multiple drug therapy (MDT) Tuberculoid: 6 months; Lepromatous: ≥ 1 year 	<ul style="list-style-type: none"> - Streptomycin + rifampin; or oral therapy (clarithromycin or a fluoroquinolone) for 8 weeks, with surgery for larger/bone lesions
Prevention of Disability	<i>Both diseases, including physical therapy and case management (self-care), and helping to identify new cases in the community</i>	
Drug resistance	Yes	No
Reactivation	Yes (persister organisms)	Yes
Prevention	No formal guidelines, no vaccine (BCG: some protection; single dose rifampin)	No formal guidelines, no vaccine (BCG: short term protection)
Government control programs	Dwindling in most countries	Yes

may develop at sites of healed skin lesions, from surgical resections of lesions, or both, making physically demanding activities or employment impossible.

Most of the characteristics listed in the Table are not directly relevant for control programmes, except for similar approaches to early diagnosis (early skin signs can be overlooked by patients and health care workers alike), and to case management (in particular, the need for self-care, rather than just physical therapy). The diagnosis of multibacillary leprosy and BU can be confirmed by similar microbiological tests, namely direct skin or lesion smears stained by the Ziehl-Neelsen method to demonstrate mycobacteria.⁸ Both diseases can be treated and arrested, but new approaches are needed for control and management, particularly for the prevention of disabilities.⁹ Disabilities from both diseases are largely preventable if the disease is diagnosed and treated early with anti-mycobacterial drugs. In BU, antibiotic therapy (oral or injectable) is largely replacing surgical removal of active disease; however, surgery followed by physical therapy may be required for contractures. In leprosy, surgery and physical therapy have a long history of successful correction of both the cosmetic and functional disabilities. Ideally, patients should be involved in their own care, including action to prevent disability and in helping to find new cases in the community.

Leprosy and BU are endemic in some of the same West and Central African countries. Leprosy and BU coinfection although uncommon is seen (Figure 1).¹⁰

Prevention of disability (POD) is a shared goal for both diseases, but solely targeting disability without elimination efforts may increase the incidence of both diseases. Given the similarities of both diseases in diagnosis, treatment and POD, ideally, health care for both, perhaps along with TB (though not a NTD), might be delivered in an integrated, horizontal



Figure 1. Patient in DR Congo with leprosy and BU coinfection; leprosy lesion on left shoulder (large arrow) and BU lesion on upper abdomen (small arrow). Coinfection of leprosy and other mycobacterial diseases is known, but uncommon.

approach.¹¹ In practice, however, TB programmes are not integrated with leprosy or BU control programmes, and TB tends to be financed through the Global Fund, whereas NGOs cover leprosy and BU control in rather vertical structures. Indeed, some of the countries where leprosy and BU control programmes are integrated in national public health programmes include Benin, Cameroon, Congo Brazzaville, Gabon, Papua New Guinea and Togo; Nigeria combines leprosy, BU and TB. However, some countries still have separate control programmes, such as Côte d'Ivoire, Democratic Republic of Congo, and Ghana (K. Asiedu, personal communication).

In countries where leprosy and BU are both found, we support that control should be performed under the same national programme, with combined public health activities put in place. This is important because of the loss of provider skills when leprosy programmes have shut down. Indeed, leprosy is no longer emphasised in the medical school curriculum in some endemic countries; and for BU, it still does not figure in the medical school curriculum in many endemic countries. Combining control of both diseases would be expected to retain some workers with needed skills, improve early detection and treatment outcome, prevent disabilities, and ease burdens for governmental and NGOs.

References

- ¹ Walsh DS, Portaels F, Meyers WM. Recent advances in leprosy and Buruli ulcer (*Mycobacterium ulcerans* infection). *Curr Opin Infect Dis*, 2010; **23**: 445–455.
- ² Neglected tropical diseases: no longer someone else's problem. *Lancet Infect Dis*, 2014; **14**: 899.
- ³ Smith C, Richardus JH. Leprosy strategy is about control, not eradication. *Lancet*, 2008; **371**: 969–970.
- ⁴ Lockwood DN, Shetty V, Penna GO. Hazards of setting targets to eliminate disease: lessons from the leprosy elimination campaign. *Bmj*, 2014; **348**: g1136.
- ⁵ Meyers WM, Tignokpa N, Priuli GB, Portaels F. *Mycobacterium ulcerans* infection (Buruli ulcer): first reported patients in Togo. *Br J Dermatol*, 1996; **134**: 1116–1121.
- ⁶ Polycarpou A, Walker SL, Lockwood DN. New findings in the pathogenesis of leprosy and implications for the management of leprosy. *Curr Opin Infect Dis*, 2013; **26**: 413–419.
- ⁷ Alberts CJ, Smith WC, Meima A. Potential effect of the World Health Organization's 2011–2015 global leprosy strategy on the prevalence of grade 2 disability: a trend analysis. *Bull World Health Organ*, 2011; **89**: 487–495.
- ⁸ Portaels F ed. Laboratory diagnosis of Buruli ulcer: a manual for health-care providers. Geneva, World Health Organization, 2014 (WHO/HTM/NTD/IDM/2014.1): 104 pages.
- ⁹ Saunderson PR. Current challenges in leprosy research. *Trans R Soc Trop Med Hyg*, 2013; **107**: 533–534.
- ¹⁰ Meyers WM, Connor DH. *Mycobacterium ulcerans* infections in leprosy patients. *Lepr Rev*, 1975; **46**: 21–27.
- ¹¹ Molyneux DH. Neglected tropical diseases: now more than just 'other diseases' – the post-2015 agenda. *Int Health*, 2014; **6**: 172–180.