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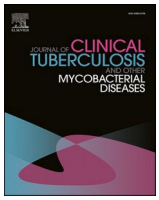

Buruli ulcer: Current landscape, challenges, and future directions

Buruli ulcer (BU) is a neglected tropical disease (NTD) caused by *Mycobacterium (M.) ulcerans*, characterized by debilitating skin ulcers that can lead to severe disfigurement and disability. While primarily prevalent in West and Central Africa, BU cases have also been reported in other regions, such as the Americas, Asia and the Western Pacific, including non-tropical countries like Australia and Japan. Around 2000 to 3000 new cases are reported annually to the World Health Organization (WHO) [1], although the true burden may be higher due to underdiagnosis and unrecognized endemic areas. BU's unique pathogenesis, driven by the lipid toxin mycolactone produced by *M. ulcerans* rather than solely bacterial growth, distinguishes it from other non-tuberculous mycobacterial diseases. Deep cutaneous ulceration often with undermining, a characteristic feature of the disease, is caused by its cytotoxic effects. Mycolactone also has other interesting functions such as immunomodulatory and anesthetic effects. Despite scientific interest, significant gaps remain in understanding BU's transmission route, diagnosis, optimal case management, including antimicrobial use and wound care. Given the limited number of patients, integrating BU control with other skin-related neglected tropical diseases (skin NTDs) is crucial. This special issue aims to highlight neglected and emerging research areas and guide future studies on BU. The six articles featured explore various aspects, such as transmission, diagnosis, treatment, wound healing, and integration with other skin NTDs.

1. Transmission dynamics of Buruli ulcer

The transmission route of BU remains poorly understood, but cases are concentrated near slow-moving or stagnant bodies of water, suggesting an environmental origin. This hypothesis is further supported by the distribution of lesions, often appearing on exposed body areas like the limbs and faces. Ongoing investigations are identifying possible vectors, which may vary across regions. Tchatchouang *et al.*'s review analyzed data from 155 articles published across 16 countries identifying *M. ulcerans* in over 38 animal species and various environmental samples, emphasizing the importance of understanding its transmission dynamics [2]. The study also investigated BU-related case fatality, revealing a total of 24 deaths in five countries, including African nations and Australia [2]. Although rare, this highlights that BU can be fatal, furthering the need for more transmission studies to enable preventive strategies.

2. Diagnosing Buruli ulcer – the need for novel tools

PCR for the *M. ulcerans* IS*2404* is currently the gold standard for diagnosing BU exhibiting sensitivity ranging between 100 % and 98 % [3]. Other diagnostic methods also have shortfalls- Ziehl Nielsen stain for acid fast bacilli, is not sensitive, and *M. ulcerans* culture and histopathology are impractical for guiding immediate treatment decisions. There is a pressing need for point-of-care diagnostics that can be deployed in health facilities, particularly in endemic, resource-limited areas.

To address this, several novel approaches are being explored, including fluorescent thin-layer chromatography, loop-mediated amplification (LAMP) PCR, and recombinase polymerase assays. Sakakibara *et al.* tested a rapid diagnostic test (RDT) prototype that employs mycolactone-specific monoclonal antibodies in a case of Buruli ulcer [4]. The prototype was successfully used to analyze for the presence of mycolactone at different sites during treatment. Studies are urgently needed to validate this new innovative tool, and similar innovations, to establish its efficacy and reliability in diverse clinical forms. In low-income settings, RDTs, such as those used in malaria, are deployed to the lowest level of the health system.

3. Treatment and monitoring in Buruli ulcer

The treatment for BU has changed over the last two decades. Initially, only surgery was used, but now daily rifampicin (10 mg/kg) and clarithromycin (15 mg/kg) for 8 weeks are the mainstay of treatment [5]. Despite improved treatment outcomes, healing times vary amongst lesions of equal size. The time it takes for the BU wound to completely close is important for clinicians. Tools to guide critical care decisions, such as time to healing or healing rate, are in high demand. Using BU measurements obtained with acetate sheet tracings or digital photography, Agbavor *et al.* examined the absolute area, percentage area reduction, and linear methods for determining rate of healing and their use in predicting time to healing [6]. All measurement techniques can identify both slow and fast healers in BU. The linear method effectively predicted the healing time for fast healers. Further improvements could be explored in developing patient-centred disease management plans.

4. Wound healing in Buruli ulcer: implications of bacterial diversity and nutritional status

Wound care plays a crucial role in the healing of BU. In this special edition, multiple factors are shown to influence healing outcomes in BU including bacterial load, persistence of mycolactone, persistent *M. ulcerans* organisms, and paradoxical reactions [4,6]. Ackam *et al.* further demonstrate that a higher bacterial diversity of organisms

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colonizing BU lesions may impact clinical outcomes [7]. ESBL-producing bacteria and MRSA were found in slow healing BU lesions. Organisms highly resistant to antimicrobials in BU lesions can contribute to delayed healing and increase treatment costs as they may require hospitalization and additional antibiotics. Treatment guidelines for simultaneous management of *M. ulcerans* and other potential pathogens within lesions are needed.

Nutritional status plays a key role in wound healing, yet malnutrition is prevalent in NTD endemic areas, with many showing significant micronutrient deficiencies [8]. BU patients were found to eat relatively little animal protein and had significantly lower levels of essential micronutrients such as serum zinc and vitamin C [9]. Koffi *et al.* launched a study to compare BU wound healing outcomes following food supplementation (protein and micronutrients) [10]. Some BU wounds regressed more rapidly when antibiotic treatment was combined with Skin Renewal Medicine 1 (SRM1) composed of 60 % cereals, 25 % vegetables, and 15 % herbal concentrate. This emphasizes the potential benefit of improved nutrition on wound healing in BU. While further studies with larger sample sizes are needed, it is consistent with existing knowledge that nutritional supplements can aid wound healing. However, the specific types of nutritional supplements that would be most beneficial for BU patients remain to be determined.

5. Integrated management of Buruli ulcer with other skin NTDs

BU, if not detected and treated early, can severely impact patients' quality of life and cause lasting deformities and disabilities, and disease control efforts must continue. However, with only a few thousand reported cases annually, challenges arise to gather interests and resources. Following the WHO road map 2021–2030, an integrated strategy with other diseases and disease groups are expected [11]. BU, classified as a skin NTD, shares symptoms, distribution areas, and social impacts with other skin NTDs such as leprosy, yaws, and lymphatic filariasis. Integration among these diseases or with other diseases with similar manifestations is a way forward. The WHO framework for integration of skin NTDs identifies at least 20 cross-cutting areas for integration [12,13]. Laboratories are crucial for implementing integrated control programs for skin NTDs in endemic countries. In this special edition, Agbanyo *et al.* discusses how BU and other skin NTDs can be jointly diagnosed [14]. Expanding such integrated efforts is essential for improving BU disease control and patient outcomes in the future.

6. Conclusion

This special issue on BU shed lights on the current landscape, challenges, and future directions in understanding and managing this debilitating disease. Continued efforts in these areas will be essential for advancing BU control, improving patient outcomes, and addressing the persistent challenges faced by those affected and by healthcare providers in endemic areas. The findings presented in this issue aim to support future research and inspire ongoing efforts to combat BU.

Ethical statement

This editorial is based on a review of studies that were featured in the special issue of the *Journal of Clinical Tuberculosis and Other Mycobacterial* Diseases and does not involve any new research involving human participants, animals, or sensitive data. Therefore, no ethical approval was required for the writing of this editorial.

CRediT authorship contribution statement

Rie R. Yotsu: Conceptualization, Supervision, Validation, Writing – original draft, Writing – review & editing. **Richard O. Phillips:** Conceptualization, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Rie R. Yotsu[a,b,c,*], Richard O. Phillips[d,e]
[a] *Department of Tropical Medicine and Infectious Disease, Tulane School of Public Health and Tropical Medicine, New Orleans, Louisiana, USA*
[b] *Department of Dermatology, National Center for Global Health and Medicine, Tokyo, Japan*
[c] *School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan*
[d] *Kwame Nkrumah University of Science and Technology, Kumasi, Ashanti, Ghana*
[e] *Kumasi Centre for Collaborative Research in Tropical Medicine, Kumasi, Ashanti, Ghana*

[*] Corresponding author at: Department of Tropical Medicine and Infectious Disease, Tulane School of Public Health and Tropical Medicine, New Orleans, Louisiana, USA.
E-mail address: ryotsu@tulane.edu (R.R. Yotsu).