



The urgent need for clinical, diagnostic, and operational research for management of Buruli ulcer in Africa

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Despite great advances in the diagnosis and treatment of Buruli ulcer, it is one of the least studied major neglected tropical diseases. In Africa, major constraints in the management of Buruli ulcer relate to diagnosis and treatment, and accessibility, feasibility, and delivery of services. In this Personal View, we outline key areas for clinical, diagnostic, and operational research on this disease in Africa and propose a research agenda that aims to advance the management of Buruli ulcer in Africa. A model of care is needed to increase early case detection, to diagnose the disease accurately, to simplify and improve treatment, to reduce side-effects of treatment, to deal with populations with HIV and tuberculosis appropriately, to decentralise care, and to scale up coverage in populations at risk. This approach will require commitment and support to strategically implement research by national Buruli ulcer programmes and international technical and donor organisations, combined with adaptations in programme design and advocacy. A critical next step is to build consensus for a research agenda with WHO and relevant groups experienced in Buruli ulcer care or related diseases, and we call on them to help to turn this agenda into reality.

Introduction

Buruli ulcer, the necrotising lesion of skin and soft tissue caused by *Mycobacterium ulcerans*, is the third most common mycobacterial infection worldwide.¹ Most of the burden of disease is in tropical climates, mainly in Africa, but cases have been reported in 33 countries.² In Africa, more than 50% of cases affect children younger than 15 years living in remote and rural areas with restricted access to health care.¹ The method of acquisition is unclear, but once disease develops lesions usually progress, leading to pronounced tissue destruction and morbidity. However, early diagnosis leads to simplified treatment and reduced morbidity and costs.³

Major advances in the diagnosis and treatment of Buruli ulcer have been made. Traditionally, wide surgical excision of lesions was recommended because antibiotics were considered ineffective.^{4,5} More recently, antibiotics have been shown to be very effective in sterilising lesions and preventing disease recurrences whether used alone^{6–8} or with surgery.⁹ WHO now recommends combined antibiotic treatment with rifampicin and streptomycin for 8 weeks as first-line therapy for all *M ulcerans* lesions, with surgery reserved mainly for removal of necrotic tissue, treatment of large skin defects, and correction of deformities.¹ Additionally, the development of IS2404 PCR testing has allowed more accurate diagnosis of *M ulcerans*.¹⁰

However, despite these advances, Buruli ulcer is one of the least studied of the major neglected tropical diseases.¹¹ In Africa, major constraints in the management of Buruli ulcer remain: delayed presentation and diagnosis; difficulties in the establishment of diagnosis in resource-poor settings that do not have sufficient laboratories and diagnostic instruments (thus diagnosis and treatment remaining mainly centralised and far from where patients live); treatment of long duration that often necessitates prolonged admission to hospital and can be toxic, poorly tolerated or accepted, difficult to give and

adhere to, or not available at peripheral health centres; difficulties in diagnosis and management of paradoxical reactions occurring secondary to antibiotic treatment; lack of access to surgical services; intensive, suboptimum, and expensive dressing regimens; difficulties in screening for co-infections such as HIV and tuberculosis that potentially affect Buruli ulcer management; and a lack of information to guide management of co-infected patients.

In this Personal View, we outline key areas for clinical, diagnostic, and operational research on this disease in Africa. Our aim is to propose a research agenda that advances the effectiveness, accessibility, acceptability, and feasibility of treatment for Buruli ulcer in Africa.

Early diagnosis and treatment

Large numbers of people continue to present with advanced Buruli ulcer disease with reports¹ from Africa showing 35% presenting with WHO category 2 lesions (5–15 cm in diameter) and 33% with WHO category 3 lesions (>15 cm in diameter, multiple lesions or lesions involving bone or a crucial site). Compared with early diagnosis when lesions are in WHO category 1 stage (<5 cm diameter), categories 2 and 3 result in increased morbidity including high rates of permanent disability and time in care or hospital, and high cost of care.³ Early diagnosis and treatment is crucial to reduce these adverse outcomes and usually results in cure of the disease with minimum patient morbidity or permanent disability and with reduced costs.³

One of the important constraints to early diagnosis is the restricted availability of instruments to rapidly and accurately diagnose Buruli ulcer in resource-poor settings close to where patients live. PCR testing that targets insertion sequence 2404 (IS2404) is the most sensitive and specific diagnostic test,¹⁰ but requires a sophisticated laboratory with good quality control and is expensive, meaning it is often not available and results can be

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substantially delayed. Mycobacterial cultures are rarely available, take 6–12 weeks to provide a result, and are positive in only about half of confirmed cases.¹⁰ Furthermore, PCR and culture testing make diagnosis at a primary care clinic level difficult, impeding efforts to decentralise diagnosis and treatment. Although use of acid-fast bacilli stains for specimens in some settings might be feasible, this test lacks sensitivity¹⁰ and is non-specific, potentially leading to Buruli ulcer being mistakenly diagnosed instead of other mycobacteria, such as *Mycobacterium tuberculosis*.¹² Histopathology requires a sophisticated laboratory and trained staff, and is an invasive procedure, expensive, and not usually available.

Thus, clinicians are often forced to rely on clinical diagnosis. Many other disorders can mimic Buruli ulcer¹ and false-positive diagnoses are common.¹³ A simple, rapid, reliable, and inexpensive point-of-care diagnostic test for *M ulcerans*, which can be used in the primary care context, is urgently needed. Promising advances have been made with the loop mediated isothermal amplification method, which offers the potential for rapid field-based PCR diagnostic testing,¹⁴ and mycolactone based point-of-care diagnostic testing techniques are being investigated.¹⁵ However, field assessment studies for these approaches are yet to be done. Exploration of the feasibility of linking Buruli ulcer PCR-based diagnostic technologies to those being rolled out in resource-poor settings for tuberculosis and HIV, such as the Xpert MTB/RIF test (Cepheid, Sunnyvale, CA, USA)¹⁶ and point-of-care HIV viral load testing, would be useful.¹⁷ Additionally, low technology methods, such as the addition of fluorescence to microscopy, could be studied to determine whether the sensitivity of detection of acid-fast bacilli in samples could be increased, as has been achieved for tuberculosis.¹⁸ Following the lead from tuberculosis, options for urine diagnostic testing could be explored and developed.¹⁹ Finally, studies designed to improve the clinical accuracy of Buruli ulcer diagnosis by focusing on the symptoms and signs that help to distinguish this disease from other potential diagnoses in an African environment and provide validated clinical diagnostic differential algorithms would be beneficial for clinicians working with Buruli ulcer in resource-poor settings.^{12,13}

Several other factors that lead to late diagnosis include late presentation resulting from community stigma, mistaken beliefs about the cause of disease and its management, preferential seeking of treatment from traditional practitioners, lack of awareness of available treatments and their effectiveness, inability to adhere to present onerous treatment regimens for economic or social reasons, fear of toxic effects of treatment, and poor access to health facilities or absence of trained health staff.^{20–23} On the basis of the success of similar models of care for Buruli ulcer in Ghana²⁰ and HIV programmes generally across Africa,²⁴ several similar operational changes could increase the likelihood of early diagnosis and treatment across the continent. First, implementation and investigation of

community-based interventions that increase community awareness and understanding of the disease and its treatment. Second, education about the benefits of early referral for diagnosis and care. Third, introduction of community-based screening and decentralised models of diagnosis and treatment, with strong community involvement including the use of community health workers and trained non-health-care personnel such as peer counsellors.^{20,24} Publication of lessons learned from the programme changes described could help to inform developments in the diagnosis and treatment of Buruli ulcer. Further, anthropological research that builds on previous understanding of community perceptions, barriers, and myths related to Buruli ulcer programmes, might also help to develop more appropriate and acceptable models of care for affected communities.

Towards all-oral antibiotic treatment for Buruli ulcer

The move towards antibiotic treatment of Buruli ulcer was supported by high rates of cure and few recurrences when antibiotics were given alone^{6–8} or in combination with surgery,^{25,26} and in-vitro data^{27–29} suggesting effectiveness of antibiotics against *M ulcerans*. However, in the present recommended regimen, streptomycin requires daily intramuscular injections that are painful and because of a lack of resources or training can require administration at a central hospital, potentially negatively affecting early presentation for care or adherence to treatment. Streptomycin injections are also associated with pronounced adverse events, such as vestibular toxicity (0.1–2.0% of patients)^{6,8} and nephrotoxicity (5–10%).³⁰ Additionally, because of scarce production and contamination during manufacture worldwide, streptomycin is in short supply.³¹ Therefore, alternatives to a rifampicin plus streptomycin treatment combination are attractive, especially for patients for whom streptomycin is contraindicated, not tolerated, or not accessible.

Non-controlled trials have reported the effectiveness of all-oral antibiotic regimens. A pilot study⁷ from Benin of 30 patients with lesions who were given the oral combination of rifampicin (10 mg/kg once daily) and clarithromycin (12 mg/kg once daily) over 8 weeks reported that all patients successfully healed by 12 months without recurrences or adverse events during treatment. Observational data from an Australian cohort showed the successful treatment of 78 patients with the oral combination of rifampicin (10 mg/kg once daily) with either a fluoroquinolone (ciprofloxacin 500 mg twice daily or moxifloxacin 400 mg once daily) or clarithromycin (500 mg twice daily) combined with surgical treatment,⁹ and 42 patients treated with these oral antibiotic combinations without surgical excision.³²

Because oral regimens allow care to be provided on an outpatient basis, they offer the potential for decentralisation of treatment to the community or village, including home-based treatment. Furthermore, oral regimens are better

tolerated than streptomycin and avoid daily intramuscular injections. Such factors can increase the likelihood of patients presenting early for diagnosis and improve adherence, which could greatly improve outcomes and reduce common and devastating long-term physical deformities.³³ All-oral antibiotic regimens are now used for most cases treated in south east Australia.^{9,32,34} WHO does not recommend all-oral antibiotic regimens as standard treatment unless streptomycin is contraindicated (eg, during pregnancy).¹ The results of a prospective multicentre randomised trial of all-oral treatment (rifampicin and clarithromycin) versus streptomycin and rifampicin treatment is awaited before a decision on whether to advocate changing to all-oral regimens is made. However, the trial will not be completed before 2015 (NCT01659437).

Although we eagerly await publication of the trial results, other clinical drug trials of Buruli ulcer treatment are needed. In case of drug intolerance, drug interactions (HIV antiretrovirals),³⁵ or contraindications, more than one oral antibiotic regimen is urgently needed.³⁶ Operational research can help to pave the way for all-oral

antibiotic regimens in Africa by studying the feasibility and acceptability of oral antibiotic regimens compared with present regimens in a field context outside the environment of a controlled trial. Results from in-vitro studies and previous experience suggest that well organised and supported Buruli ulcer treatment programmes in Africa could introduce and study oral antibiotic regimens in an operational research context with close monitoring, assessment, and dissemination of results. Such an approach has been supported by WHO¹ and could provide important supportive evidence to supplement data from the controlled trial,³⁷ and is likely to benefit patients directly, to simplify treatment, and to reduce costs.

Paradoxical reactions to antibiotic treatment

Paradoxical reactions are newly recognised events that occur during or after antibiotic treatment of Buruli ulcer and complicate treatment in about one in five patients treated for the disease in Africa.³⁸⁻⁴⁰ Paradoxical reactions probably result from antibiotic-mediated killing of

Key research aims	
Late presentation of patients	Implement and investigate community-based interventions aimed to increase education, awareness, and early diagnosis and treatment
Absence of decentralised services	Implement decentralised models of care that ensure close monitoring, investigation, and dissemination of outcomes
Low clinical accuracy of diagnosis	Determine the sensitivity and specificity of clinical features associated with ulcerative lesions, develop validated clinical algorithms for diagnosis
Reduced sensitivity of acid-fast bacilli stains on routine microscopy	Compare sensitivity of fluorescent microscopy with routine microscopy
No POC diagnostic test	In-field conditions, develop and study POC diagnostic tests
Lack of evidence for the effectiveness of all-oral regimens compared with existing treatment	Initiate clinical drug trials studying alternative oral drug combinations; implement all-oral antibiotic regimens in an operational research context with close monitoring, investigation, and dissemination of outcomes
Little information about paradoxical reactions	Close surveillance of Buruli ulcer antibiotic treatment outcomes with documentation of incidence and clinical presentation of paradoxical reactions
No POC diagnostic test for paradoxical reactions	In field conditions, investigate a paradoxical reactions diagnostic test that is easy to use, accurate, and inexpensive
No information about the use of prednisolone for severe paradoxical reactions in Africa	Implement a controlled trial assessing the use of prednisolone for treatment of severe paradoxical reactions
Little information about the prevalence of Buruli ulcer and HIV infection co-infection	Study HIV prevalence in populations with and without Buruli ulcer in endemic regions
Little information about the effect of HIV on presentation and severity of Buruli ulcer	Comparison of the clinical presentation and severity of Buruli ulcer between populations with HIV and without HIV, stratified by level of immune suppression associated with HIV
Little information on the effect of HIV on Buruli ulcer treatment outcomes	Comparison of Buruli ulcer treatment outcomes between populations with HIV and without HIV
No information about when to start ART	Comparison of Buruli ulcer treatment outcomes stratified by the timing of ART
Interactions between Buruli ulcer drugs and ART	Determine the effectiveness and safety of rifampicin plus moxifloxacin combination in the treatment of Buruli ulcer in patients on ART
Lack of capacity to diagnose and treat HIV in Buruli ulcer treatment centres	Integration of HIV diagnosis and treatment in Buruli ulcer treatment centres with dissemination of treatment outcomes and lessons learned
Suboptimum current dressing regimens	Develop, implement, and investigate simple, effective, cheap, and easy to administer dressing regimens and materials
Long wound healing times	Investigate field-based interventions, including the use of adapted negative-pressure wound therapy devices

POC=point-of-care. ART=antiretroviral therapy.

Table: Current shortfalls and key research aims to improve care of Buruli ulcer in Africa

M. ulcerans bacteria that lead to reversal of the immune-inhibitory effect of mycolactone toxin and enables the development of intense immunological reactions.^{41,42} Clinically, this reaction manifests as a deterioration of the lesion or its surrounding tissues or the appearance of new lesions, either locally or in a distant body site.^{38–40,43} Paradoxical reactions pose notable management challenges in resource-poor settings because of the absence of available diagnostic testing to distinguish them from treatment failure, which is difficult on clinical criteria alone. This distinction is crucially important because the management is different; treatment failure requires a change in antibiotic regimen and surgery might be warranted, whereas mild-to-moderate paradoxical reactions require observation alone, without change to the regimen or surgery.^{1,44}

Clinicians need improved information about the incidence, risk factors, clinical features, and treatment of paradoxical reactions in Africa. Reactions can be severe, require many operations and reconstructive surgery,⁴³ and result in pronounced morbidity and cost.³ In Australia, prednisolone has been successfully used to reduce the severity of paradoxical reactions,⁴⁵ but in Africa, high rates of coexistent infectious diseases such as tuberculosis or strongyloidiasis occur; outcomes of these co-infections can be adversely affected by prednisolone and this leads to additional potential risk.⁴⁶ Although use of prednisolone in Africa warrants further research, much can already be learnt from the use of steroids for severe paradoxical reactions in patients with HIV and tuberculosis in Africa.⁴⁷ Development of new diagnostic tests that are feasible, affordable, and can be made available in resource-poor settings are urgently needed to help make the distinction between paradoxical reactions and treatment failure (table).

Buruli ulcer and HIV co-infection

Areas of Africa with endemic Buruli ulcer also have a high prevalence of HIV, but information about co-infection is scarce. Preliminary evidence from Benin,⁴⁸ Cameroon (Christinet V, unpublished), and Ghana⁴⁹ suggest that HIV infection might increase the risk of Buruli ulcer; however, this association and its prevalence needs to be clarified. HIV seems to affect the clinical presentation and severity of Buruli ulcer disease, with a reported increased incidence of multiple, larger, and ulcerated lesions (Christinet V, unpublished).^{48,50} However, whether the presence and severity of Buruli ulcer indicates the level of underlying immune suppression in a person with HIV and can thus be used as a WHO HIV-associated clinical disorder to help to stage HIV disease is unknown.⁵¹

Improved understanding of the effect of HIV on Buruli ulcer treatment outcomes including cure rates, recurrence rates, and paradoxical reactions is needed. The Médecins Sans Frontières programme in Akonolinga, Cameroon, reported that in patients with Buruli ulcer and HIV, ulcer healing took longer than in patients without HIV with time to heal affected by CD4 counts; and recurrence rates

and numbers of surgical procedures were increased,⁵² but these findings need confirmation in other settings. Knowledge is also scarce about the best way to manage HIV in patients with active Buruli ulcer, such as when to start antiretroviral therapy in co-infected patients and the best antiretroviral therapy regimens. For example, pronounced interactions between drugs used for Buruli ulcer treatment and antiretroviral drugs might reduce the effectiveness of Buruli ulcer treatment and increase toxicity.³⁵ Potentially, Buruli ulcer treatment regimens combining rifampicin and moxifloxacin might avoid these issues, but research to determine their effectiveness and safety in patients with HIV is urgently required.³⁵ Data are also needed to understand whether antiretroviral therapy will affect the incidence and severity of paradoxical reactions, and guide their management in patients on such treatment.

WHO have issued preliminary guidelines on the management of Buruli ulcer and HIV infection,¹ but the process has been restricted by the paucity of information, and the guidelines are largely extrapolated from the experience of tuberculosis and HIV co-infection.⁵³ Organisations working in settings with high rates of Buruli ulcer and HIV co-infection could therefore design and implement research to help answer these important questions (table).

Simplified wound dressings and optimisation of wound healing

At present, dressing regimens are intensive and are usually based on the wet-to-dry concept that is painful to administer and less effective than more advanced techniques.⁵⁴ Such regimens may require admission to hospital, are expensive (with the cost often borne by patients), and lack standardised management protocols. These problems are amplified in severe disease as a result of late presentation or diagnosis.

Next steps would be to ensure advanced wound care is introduced into developed programmes, as well as simplified wound management protocols that are adapted to country or regional contexts as recommended by WHO.⁵⁵ Dressings available in resource-rich settings work well in resource-poor settings, although cost and availability remain obstacles. Standardised dressing protocols and kits would allow uniformity in practices across diverse settings, could ease the procurement and distribution of resources, and reduce the costs of materials through bulk purchase. Furthermore, older or locally available products could replace components of these more complex dressings (eg, replacing hydrogel with a large amount of vaseline, karité butter, or honey and replacing hydrocellular dressings by vaseline gauze and polyethylene wrap). Simplified and cheaper dressings and regimens are in development (eg, Drawtex, Steadmed Medical, Fort Worth, Texas, USA) including those that are outpatient-based and that could reduce the resources needed to manage wounds. Programme leaders could play

Panel: Next steps for research and policy implementation

- Build consensus for a research agenda with relevant groups experienced in Buruli ulcer care or related diseases and WHO
- Engage relevant community groups in the research agenda
- Agree on priorities and apportion specific research specialties to relevant groups
- Strengthen and build research capacity within national Buruli ulcer programmes
- Support national monitoring of Buruli ulcer programmes to acquire data for diagnosis, treatment, and outcomes of Buruli ulcer
- Develop implementation research strategies for national Buruli ulcer programmes

a role in this area of research, including development of clinical trials to investigate standardised dressing protocols and new or adapted products (table). Research focused on the improvement of pain management caused by severe ulcers and dressing changes is also needed.

The time for wounds to heal is often prolonged, often longer than 6 months,⁶ leading to frustration and dissatisfaction on the part of the patients and health-care providers and increased resource utilisation and time. Of advanced wound care techniques, negative pressure wound therapy seems to decrease healing time,⁵⁶ but this technology is not available in most treatment settings for Buruli ulcer in Africa. Simple, portable, and cheap negative pressure wound therapy devices that do not require electricity have been developed,⁵⁷ and future programmes could trial such devices to test their effectiveness, suitability, and cost in resource-poor settings.

The large and deep wounds caused by Buruli ulcer are often a major source of disability, and thus rehabilitation is an important component of care. To optimise results, rehabilitation should begin early and patients should be taught basic exercises appropriate to their condition.^{58,59} Research on how to improve the access and effectiveness of rehabilitation programmes could contribute to reduced disability.

Conclusions and next steps

We have outlined a clinical, diagnostic, and operational research agenda for Buruli ulcer management in Africa that will be feasible to scale up to achieve coverage in populations at risk (panel). Although we focus on the management of Buruli ulcer, research of disease prevention is crucial. Despite many years of study, information about the methods of transmission, environmental reservoirs, and susceptibility to disease are not well defined and need urgent clarification. Conception of an implementation research agenda for Buruli ulcer programmes, such as development of national strategies and standardisation of methods, training, and assessment of programmes should also be a priority.

A critical next step is to build consensus for a research agenda with WHO and relevant groups experienced in Buruli ulcer care or related diseases, and we call on them to help to turn this agenda into reality. To achieve this, commitment and support for strategic implementation of research by national Buruli ulcer programmes, their staff, partners, and international donor organisations is required, as well as adaptations in programme design and focused advocacy on this issue.

Contributions

DPO'B developed the concept and wrote the first draft of the report, PdC developed the concept and commented on subsequent drafts of the report, EC, MS, GE, AA, HV, VC, and MDH commented on subsequent drafts of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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