TARGET PRODUCT PROFILE

for a rapid test for diagnosis of Buruli ulcer at the primary health-care level

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1. Epidemiology

Buruli ulcer is a chronic debilitating skin disease caused by infection with *Mycobacterium ulcerans*. It has been reported in 33 countries in Africa, the Americas, Asia and the Western Pacific. Most cases occur in tropical and subtropical regions except in Australia, China and Japan. Of these 33 countries, 14 regularly report data to the (WHO. The highest burden of the disease is in sub-Saharan Africa, where most of those affected are children aged below 15 years. The annual number of suspected cases reported globally was around 5000 cases until 2010, then progressively decreased until 2016 to reach its minimum of 1961 cases. Since then, the number of cases increased until 2018 (2713 cases), only to decrease again in 2020 (1458 cases). The reasons for these fluctuations are unclear. *M. ulcerans* is an environmental bacterium that produces a unique toxin (mycolactone), which is responsible for the pathogenesis of disease. Buruli ulcer often starts as a painless swelling (nodule), a large painless area of induration (plaque) or a diffuse painless swelling of the legs, arms or face (oedema). The disease may progress with no pain or fever. Without treatment, or sometimes during antibiotic treatment, the nodule, plaque or oedema will ulcerate within 4 weeks. Bone is occasionally affected, causing deformities. Although mortality from the disease is low, the main problem is long-term disability in an estimated 25% of those affected. The mode of transmission to humans remains unknown. Therefore, the objective of Buruli ulcer control is to minimize the suffering, disabilities and socioeconomic burden. Early detection and antibiotic treatment are the cornerstones of the control strategy *(1,2)*.

2. Public health response

In 2004, the Fifty-seventh World Health Assembly adopted resolution WHA57.1 on surveillance and control of Buruli ulcer, urging Member States in which the disease is or threatens to become endemic to support enhanced surveillance of the disease and accelerate the development of tools for its diagnosis, treatment and prevention. The *Cotonou Declaration on Buruli ulcer (3)*, adopted by the Heads of States of affected countries in Benin in 2009, called on countries to ensure that cases are detected at an early stage in order to reduce the frequency of disabilities. Confirmation of cases is essential to ensure that patients treated with antibiotics for 8 weeks are true cases of Buruli ulcer, and WHO thus requires all endemic countries to ensure that at least 70% of cases reported are laboratory-confirmed *(3)*.

3. Available diagnostic tools

Some progress has been made on diagnostic tools for Buruli ulcer. The current diagnostic tests are microscopy, bacterial culture, histology and polymerase chain reaction (PCR) for insertion sequence (IS) 2404. Microscopy is the most widely available method in endemic countries but has challenges with sensitivity. Of the four traditional methods used for diagnosis, PCR is considered the gold standard *(4–6)*. Although this method is accurate, reference laboratories tend to be far from affected areas, making it a challenge to obtain immediate results for management of patients.

Another indirect gap in diagnostics is a lack of sustained capacity-building for all peripheral health facility laboratories and health workers in endemic areas. These facilities are often remote from the locations in which the disease is endemic, and continuous training must therefore be provided for laboratory staff who provide routine diagnostic services for clinics at which patients with Buruli ulcer present. Bringing diagnostic services closer to patients in remote areas will help to reduce turnaround time compared to transporting samples to reference laboratories, which are usually located in cities *(7)*. In addition, training of health workers to enhance their awareness of case identification and management is a key need identified in the road map for neglected tropical diseases 2021–2030 *(5)*. For instance, this could be part of a training module provided by the health ministry. Country ownership through domestic funding

of these interventions should be encouraged to ensure that it becomes routine practice in peripheral health facilities *(5)*. Operational and implementation research is required to address programmatic bottlenecks in local health systems. New diagnostic tools can be fully tested in peripheral health facilities to foster tailor-made innovative approaches to synergizing regular operations of district health facilities with provision of NTD diagnostics *(8)*.

4. The WHO Diagnostic Technical Advisory Group for Neglected Tropical Diseases

The WHO Department of Control of Neglected Tropical Diseases set up the Diagnostic Technical Advisory Group as the principal advisory group to WHO on diagnostics for NTDs. This group works to ensure use of a unified method to solve diagnostic needs and to direct WHO strategies to develop efficient diagnostic tools. At its first meeting in 2019 (4) the following diagnostic needs for Buruli ulcer were identified:

- rapid point-of-care tests targeting mycolactone, for individual diagnosis at primary health care/ community level;
- loop-mediated isothermal amplification and/or recombinase polymerase amplification design-locked tests to replace home-brewed PCR methods, for individual diagnosis.

5. The NTD road map 2021–2030

Buruli ulcer is one of the diseases targeted for control in the new NTD road map; the main target for 2030 is to reduce the proportion of cases diagnosed in Category III from 30% (baseline) to less than 10%. To achieve this goal, decentralized testing, that is, testing in public health centres and/or communities, is key. Therefore, one of the critical actions highlighted in the road map is to "develop rapid diagnostic tools for use in public health and community centres to ensure early diagnosis, reduce morbidity and confirm cases". A rapid test targeting the toxin mycolactone will address a second priority to "improve detection of viable *M. ulcerans* in wound samples to distinguish between treatment failure and paradoxical reaction with methods such as mycolactone detection and 16S rRNA".

6. Background and scope for the target product profile

In 2009, WHO's Second International Conference on Buruli Ulcer Control and Research resolved to strengthen the capacity of national laboratories to confirm cases of the disease, but advised that "efforts are still needed to develop simple diagnostic tools usable in the field as well as disability prevention methods" *(3)*.

In 2013, WHO and the Foundation for Innovative New Diagnostics convened a meeting of Buruli ulcer experts in Geneva, Switzerland *(9)* at which two priority unmet needs in diagnosis were identified:

- a diagnostic test for early detection of Buruli ulcer in symptomatic patients with sufficient positive predictive value to put patients on appropriate treatment; and
- a screening test at the primary health care or community level for symptomatic patients with ulcer.

In March 2018, they convened a global meeting with the aim of establishing an action plan to develop new diagnostic solutions for Buruli ulcer and to create a framework of collaboration to address unmet needs in diagnostics for the disease (8). The participants agreed to develop a target product profile (TPP) to address the need for a rapid diagnostic test for use at the primary health-care level.

7. Audiences engaged and external consultations to develop the TPP

Before the WHO-FIND meeting on diagnostics on Buruli ulcer, held in March 2018 *(8)*, a small group of experts developed use cases for a diagnostic test that could be used at the point of care and in community or public health centres. During the meeting, the 21 participants from research institutions, nongovernmental organizations, industry and product development partnerships, national programmes and WHO reviewed these use cases and prepared the corresponding TPP. A representative from the industry participated to the March 2018 meeting as informant but had no role in the drafting of the TPP per se or its finalization. The draft was presented at this meeting and discussed by participants. Drs Michael Frimpong, Isra Cruz and Kingsley Asiedu finalized what appeared in the report after receiving comments from the meeting participants. When the NTD Department started to work on TPPs, the published TPP was reviewed by Dr Michael Frimpoing, Dr Isra Cruz, Dziedzom de Souza and Kingsley Asiedu in line with the WHO TPP development guide that was provided. The draft was submitted to the D-TAG group chair for comments before finalization and publication for the online consultation. It was published on the WHO website for public consultation from 1 to 31 October 2021. Feedback was received from 3 individuals (from academia, an NGO and industry) and were reviewed by the writer, Dr Michael Frimpong, as well as the chair of the D¬ TAG subgroup on skin NTDs and WHO staff, and incorporated when relevant.

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TPP for a rapid test for diagnosis of Buruli ulcer at the primary health-care level

1. Scope	Minimum	Ideal	Annotations
1.1 Goal of the test. Intended use	Confirmation of Buruli ulcer (BU)	Confirmation of Buruli ulcer (BU)	Used in patients who self-present at health centres, or in active case-finding activities. The test is done after clinical assessment.
1.2 Target population	Suspected cases, ulcerated lesions (advanced stages)	Suspected cases early and advanced stages	
1.3 Target operator of the test	Nurse, laboratory technician	Nurse, laboratory technician, community health worker	
1.4 Lowest setting for implementation	Health centre	Community, as part of active case-finding campaigns	
1.5 Target analyte to be detected	Mycolactone, bacterial protein or DNA	Mycolactone, bacterial protein or DNA	Antibody response is not a good marker of disease in BU-endemic areas. DNA and proteins are usually an integral part of bacteria, which may not be distributed homogeneously in the lesion. However, DNA detection (by PCR) is the recommended test for confirmation. Mycolactone is secreted and could be detected throughout the lesion.
2. Performance characteristics	Minimum	Ideal	Annotations
2.1 Clinical sensitivity (assessed in a latent class analysis)	Non-inferior than Ziehl–Neelsen microscopy, > 65% in samples confirmed by PCR	± 10% of that of PCR, when compared to the assessment of a clinical expert panel	Usual diagnostic tests are acid-fast bacilli microscopy (low sensitivity and specificity) and PCR (at reference centre level). At community level diagnosis is based on clinical signs. In highly endemic settings, judgement by a panel of experienced clinicians usually has higher sensitivity than laboratory tests (included PCR). The specificity of current laboratory tests is > 90% in suspected BU cases *(10)*.
2.2 Clinical specificity (assessed in a latent class analysis)	> 90%	> 90%	Usual diagnostic tests are acid-fast bacilli microscopy (low sensitivity and specificity) and PCR (at reference centre level). At community level diagnosis is based on clinical signs. In highly endemic settings, judgement by a panel of experienced clinicians usually has higher sensitivity than laboratory tests (included PCR). The specificity of current laboratory tests is > 90% in suspected BU cases *(10)*.

2.3 Strain specificity	African strains	Global	Extremely low level of genetic diversity in *M. ulcerans* would avoid extra effort in identifying targets that are common across *M. ulcerans* isolates from different regions.
2.4 Type of analysis (quantitation)	Qualitative	Qualitative	
3. Test procedure	Minimum	Ideal	Annotations
3.1 Training needs. Time dedicated to training session for end-users, including sample collection	2 days	1 day	Minimally invasive sampling procedures applied to skin lesion (nodule or ulcer). Fine-needle aspirate, swab. This may require training in the case of community health workers.
3.2 Sample type	Lesion swab, fine-needle aspirate (FNA)	Lesion swab, fine-needle aspirate (FNA)	Early stage lesions are not ulcerated and a swab cannot be taken, an FNA is needed in these cases.
3.3 Sample preparation. Total steps	3–5 steps	Direct testing on sample	Sample might need to be eluted/added to specific buffer.
3.4 Number of steps to be performed by operator	< 10; 1 timed step	< 3; 1 timed step	
3.5 Need for operator to transfer a precise volume of sample	Acceptable with a disposable transfer device provided	No	Sample may need to be eluted in specific buffer (included in the kit).
3.6 Time to result	Same day	< 20 min	
3.7 Internal control	Included	Included	Positive control to confirm validity of the test.
3.8 Reading system. Interpretation of results	Visual (naked eye) or simple reading device	Visual (naked eye)	See 3.9
3.9 Auxiliary equipment	Test reader (for lateral flow assay, dual path platform, or similar). Colorimetric reader and thermal cycling device for nucleic acid amplification	None, instrument free (required materials are included in the kit)	There are rapid diagnostic tests that generate a fluorescent signal that increases sensitivity; a reader is needed to detect this signal. In cases where a reader is needed a connectivity option could be desirable, enabling sending results to a reference laboratory, coordinator, reporting system, etc.

3.10 Power requirements	Battery operated	None required	If a reading and/or thermal cycling device is needed it should be a small, portable or hand-held instrument (< 1 kg) that can operate on rechargeable battery or solar power lasting at least 4 h (8 h preferred).
3.11 Need for maintenance/spare parts	None	None	
4. Operational characteristics	Minimum	Ideal	Annotations
4.1 Operating conditions	20–35 °C, 80% relative humidity	5–50 °C, 90% relative humidity	High environmental temperatures and high humidity are often a problem in countries where BU is endemic.
4.2 Reagent kit transport	No cold chain required. Tolerance of transport stress for a minimum of 72 h at –15 °C to +50 °C	No cold chain required. Tolerance of transport stress for a minimum of 1 week at –15 °C to +50 °C	Refrigerated transport is costly and often cannot be guaranteed during the entire transportation process. Frequent delays in transport are common.
4.3 Reagent kit storage/stability	No cold chain required; > 12 months at 40 °C, 70% relative humidity	No cold chain required; 24 months at 50 °C, 90% relative humidity	Should be able to tolerate transport stress (48 h at 50 °C). To include test quality detector (for surpassed temperature or humidity).
4.4 Reagents reconstitution. Need to prepare the reagents before use	A few simple steps	All reagents ready-to-use	Simple steps such as resuspension of lyophilized reagent can be accepted.
4.5 In-use stability	> 1 h for a single-use test after opening the pouch	> 2 h for a single-use test after opening the pouch	
4.6 Waste disposal	Does not include material that cannot be disposed of in normal laboratory biohazard waste streams.	Does not include material that cannot be disposed of in normal laboratory biohazard waste streams.	
4.7 Labelling and instructions for use	Compliance required per CE mark for in vitro diagnostic devices and/or WHO prequalification. Product insert shall be available in relevant local language(s) and shall include instructions for use for the test; if appropriate, photos/images of example test results (i.e. positive, weak positive, negative) should also be included in the instructions.	Compliance required per CE mark for in vitro diagnostic devices and/or WHO prequalification. Product insert shall be available in relevant local language(s) and shall include instructions for use for the test; if appropriate, photos/images of example test results (i.e. positive, weak positive, negative) should also be included in the instructions.	Still not confirmed that WHO prequalification will process dossiers on diagnostics for neglected tropical diseases.
5. Cost	Minimum	Ideal	Annotations
5.1 Cost per test	< 1 US$	< 5 US$	Below cost of treatment.
5.2 Instrumentation (if needed)	< 1000 US$	< 6000 US$	

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