TARGET PRODUCT PROFILE

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

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Contents

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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