Diagnostic test to confirm the diagnosis of leprosy in individuals with clinical signs and symptoms, target product profile

Epidemiology

Leprosy, also known as Hansen’s disease, is a chronic infectious disease caused by *Mycobacterium leprae* or *M. lepromatosis*. These bacteria are likely transmitted via tiny droplets (aerosols), from the nose and mouth, during close and frequent contact with untreated cases. In some circumstances, skin-to-skin contact has also been implicated. Close and frequent contact increases the risk of contacts developing leprosy. Stigmatization and discrimination impede the life of an individual suffering from leprosy; overcoming them is an essential part of leprosy control. As with other NTDs, the occurrence of leprosy is often related to socioeconomic determinants of health.

*M. leprae* multiplies slowly and the incubation period of the disease, on average, is 5 years. Symptoms may occur within 1 year but can also take as long as 20 years or even more to occur. The disease mainly affects the skin, the peripheral nerves, mucosal surfaces of the upper respiratory tract and the eyes. Leprosy is known to occur at all ages ranging from early infancy to very old age. Leprosy is curable with multi drug therapy (MDT) and treatment in the early stages can prevent disability. Untreated, leprosy can cause progressive and permanent damage to the skin, nerves, limbs, and eyes.

Despite the available treatment, over 200 000 new leprosy patients were diagnosed globally in 2019. In 2019, leprosy was reported from more than 120 countries (including imported cases); 80% of the burden is in India, Brazil and Indonesia. Early detection of cases is important to help contain the spread of infection and prevent disabilities.

Public Health Response

The first treatment for leprosy became available in the 1940s with the development of the medicine dapsone. In the 1960s, it was recognized that *M. leprae* started to develop resistance to dapsone. In the early 1960s, rifampicin and clofazimine were discovered to be efficacious and they were added to the treatment regimen, which was labelled multidrug therapy (MDT). In 1981, WHO recommended that all patients be treated with MDT. The currently recommended MDT regimen consists of dapsone, rifampicin and clofazimine for multi-bacillary (MB) cases, whereas pauci-bacillary (PB) treatment contains only dapsone and rifampicin. The treatment lasts for 12 months for MB and six months for PB disease. MDT kills the pathogen, thereby curing the patient.

In the NTD road map 2021–2030, leprosy is targeted for elimination (interruption of *M. leprae* transmission). The critical actions identified to reach the 2030 targets for leprosy are:

- Update country guidelines to include use of single-dose rifampicin for post-exposure prophylaxis for contacts, advance research on new preventative approaches
- Continue investment into diagnostics for disease and infection. Develop surveillance strategies, systems and guidelines for case-finding and treatment. Ensure resources for validation.
- Ensure medicines supply, including access to multi-drug therapy, single-dose rifampicin, second-line treatments and medicines to treat reactions. Monitor adverse events (pharmacovigilance) and resistance to antibiotics.

Available Diagnostic Tools

Leprosy can be classified as PB or MB, based on the number of skin lesions, presence of nerve involvement and identification of bacilli in slit-skin smears. The WHO guidelines for diagnosis, treatment and prevention of leprosy recommend no additional tests in addition to standard methods for diagnosis of leprosy: the diagnosis of leprosy is based on the presence of at least one of three cardinal signs:
(i) definite loss of sensation in a pale (hypopigmented) or reddish skin patch;
(ii) thickened or enlarged peripheral nerve with loss of sensation and/or weakness of the muscles supplied by that nerve;
(iii) presence of acid-fast bacilli in a slit-skin smear.

With the dwindling clinical expertise in leprosy, clinical diagnosis of indeterminate, pure neuritic and certain cases of PB and MB leprosy with confusing clinical signs, can be challenging. Therefore, a number of point-of-care and laboratory assays have been developed and tested in various patient and control groups to supplement clinical diagnostic methods. These assays encompass both direct (pathogen) and indirect (host response) detection of the disease, utilizing various technologies such as enzyme-linked immunosorbent assays (ELISA), lateral flow assays (LFA) and polymerase chain reaction (PCR) based assays. However, most of the currently developed tools are only of research grade and are not available commercially for broad use in clinical settings. Additionally, some of these tools face various challenges such as: low diagnostic accuracy for PB leprosy, lack of standardization and high level of complexity or excessive instrumentation for most primary health-care settings.

To date, only a few leprosy diagnostic assays detecting *M. leprae*, or immune responses to it, possess in-vitro diagnostic use authorization and are commercially available. Hain Lifesciences has a test system for the identification of *M. leprae* and its resistance to rifampicin, ofloxacin and dapsone. GenoType Leprae DR is a PCR based DNA strip technology requiring 3 separate instruments, and as such not suitable for low resource setting.

Orange Life Sciences in Brazil, in collaboration with Infectious Disease Research Institute in Seattle, USA, has developed a qualitative LFA to detect *M. leprae* specific IgM antibodies against PGL-1 and IgG antibodies to LID-1. CTK Biotech (San Diego, USA) has developed qualitative GOLD-LFA, utilizing the same antigens as Orange Life Sciences. However, both of these assays are for research use only (RUO) and may no longer be available at this time.

Once appropriate diagnostic tools are developed it would be imperative to ensure the products stay on market, as efforts towards leprosy elimination would be hampered if tests are not maintained. Mechanisms to have commitment from vendors should be explored.

**Diagnostic Technical Advisory Group**

The WHO Department of Control of Neglected Tropical Diseases (NTD) manages a diverse portfolio of twenty diseases, each with its own unique epidemiological and diagnostic challenges. The Strategic and Technical Advisory Group (STAG), the principal advisory group to WHO for the control, elimination and eradication of NTDs, decided that a single WHO working group would help ensure that a unified approach could be used to identify and prioritize diagnostic needs, and to inform WHO strategies and guidance on the subject.

Thus, the Diagnostic Technical Advisory Group (DTAG) was formed as an advisory group to the Department of Control of Neglected Tropical Diseases. The first meeting of the DTAG was held in Geneva, Switzerland, on 30 and 31 October 2019.

DTAG members discussed priorities for the year ahead as well as how to manage the complexity of supporting the diagnostics agenda across the entirety of the WHO NTD portfolio. Recommendations were made, based on the understanding that they would be reviewed at the next meeting, as it had been made clear that all NTDs had diagnostic needs which would have to be addressed in due course.

The diagnostic priorities for leprosy, determined by the DTAG at that meeting, were:

- Detection of *M. leprae* infection – to provide prophylaxis to those most at risk
- Screening for potential leprosy cases – to better identify individuals with suggestive signs of leprosy
• Diagnosis of leprosy – to confirm diagnosis of all forms of leprosy (especially indeterminate and PB leprosy)
• Prediction of future disease - to identify those at risk of disability
• Diagnosis of nerve function loss – to recognize early nerve function changes that can lead to sensorimotor neuropathy associated with leprosy

Purpose of the TPP

As the number of leprosy cases is decreasing, so is the clinical expertise even in endemic countries. This often leads to delayed or mis-diagnosis and delayed initiation of MDT. Early detection and treatment of leprosy is important to prevent disability but may also aid in breaking the transmission chain.

As identified in both the NTD road map 2021–2030 and first DTAG meeting report, a test providing confirmation (or exclusion) of leprosy of all types, including indeterminate and PB leprosy, is of high priority. The purpose of this TPP is to guide development of a tool that can be used at all health care levels where MDT is prescribed, to aid health care provider in decision making for initiation of treatment. The clinical validation of such test should take into account performance requirements for the whole spectrum of leprosy, including manifestations with low levels of bacilli. Even though ideally such a test would be available as a point-of-care test, it is recognized that to reach the required sensitivity and specificity, lab-based testing might be required.

The TPP target performance characteristics were modelled to reduce health care provider delays in diagnosis as a function of diagnostic performance. In the modeling, prevalence of leprosy in tested populations assumed endemicity levels similar to household contacts, as this would be the most likely group to seek medical consultation. It was observed through modeling that, to have a meaningful impact on reduction on time to diagnosis, very high stringency around specificity is required. It is of note that in cases where performance requirements are high and cannot be met with a single test, a combined, 2-step test approach may be used to achieve the required testing specificity.