Target Product Profiles (TPP) for visceral leishmaniasis diagnostics for detection of visceral leishmaniasis disease and post-treatment test of cure

Epidemiology

Leishmaniasis is caused by protozoan parasites which are transmitted by the bite of infected female phlebotomine sandflies. The disease is poverty-related and is associated with malnutrition, poor housing, conflict situations, population displacement, illiteracy, gender discrimination, weakness of the immune system, and lack of resources.

There are three main forms, namely visceral leishmaniasis (VL) also known as kala-azar, which is the serious form because it is fatal if not treated timely, cutaneous leishmaniasis which is the most common form causing skin ulcers and mucocutaneous which affects the mouth, nose, and throat [1].

Visceral leishmaniasis is characterized by irregular bouts of fever, weight loss, enlargement of the spleen and liver, and anaemia. Most cases occur in Brazil, East Africa, and India. An estimated 50 000 to 90 000 new cases of visceral leishmaniasis occur worldwide annually [2].

Early detection and appropriate treatment are key strategies in visceral leishmaniasis control. Signs and symptoms of visceral leishmaniasis are non-specific, therefore diagnosis is confirmed by combining clinical signs with *Leishmania*-specific laboratory tests. Diagnostic policy for health services in endemic areas depends on the level of the health system. Two serological tests, the direct agglutination test, and the rK39 antigen-based immunochromatographic tests are developed for field use in most endemic areas [3]. An RDT for visceral leishmaniasis detects antibodies and is a simple test that can be used at both peripheral and central levels. A scientific review of published studies estimates that the sensitivity of RDTs varies with the eco-epidemiological regions specially its low sensitivity in East Africa [4,5]. Due to the persistence of antibodies for long periods after cure, the limitations of all serological tests are they cannot reliably diagnose relapse and a significant proportion of healthy people living in endemic areas with no history of visceral leishmaniasis are positive for antileishmanial antibodies due to asymptomatic infections. Therefore antibody-based tests must therefore always be used in combination with a standardized clinical case definition for visceral leishmaniasis diagnosis.

Thus, there is a need for an *in vitro* point-of-care test to confirm or exclude active cases for early diagnosis, in order to benefit both patients and communities as untreated cases are reservoirs of infection and therefore put the community at risk of ongoing

Leishmania transmission. Similarly, an *in vitro* laboratory test is needed for confirming or rejecting whether visceral leishmaniasis has been successfully cured post-treatment.

Public Health Response

In 2007, World Health Assembly 60.13, in its Resolution on the Control of Leishmaniasis, urged Member States, among other actions:

i) “to strengthen prevention, active detection and treatment of cases of both visceral and cutaneous leishmaniasis in order to decrease the disease burden; “

ii) “to strengthen the capacity of peripheral health centres to deliver primary and secondary care so that they provide appropriate affordable diagnosis and treatment and act as sentinel surveillance sites;”

and requested that WHO’s Director-General “promote research pertaining to leishmaniasis control, including in the areas of safe, effective and affordable vaccines, diagnostic tools and medicines with less toxicity, and dissemination of the findings of that research” [6].

Available Diagnostic Tools

Signs and symptoms of visceral leishmaniasis, alone or in combination, are not specific enough to differentiate from clinical conditions like chronic malaria, or other systemic infections. In patients with HIV coinfection, the clinical features may be atypical. Therefore, *Leishmania*-specific laboratory tests are required for diagnostic confirmation.

The minimal platform for techniques for the diagnosis of visceral leishmaniasis in endemic areas depends on the health system level. The most commonly used is the rK39 antigen-based immunochromatographic test at the primary health care centre. At the district level, rK39 RDTs, direct agglutination test as well as microscopy on bone marrow, spleen or lymph node aspiration is used. At the tertiary level, additional serological (IFAT, ELISA) and molecular tests (PCR) can be used.

The sensitivity of RDTs varies with the eco-epidemiological endemic regions specially its low sensitivity in East Africa. Due to the persistence of antibodies for long periods after cure, the limitations of all serological tests are they cannot distinguish between active cases and relapse in previously treated cases, also in patients with advanced HIV infection a negative result cannot rule out the diagnosis of VL as well as a significant proportion of healthy people living in endemic areas with no history of visceral leishmaniasis may be positive for antileishmanial antibodies due to asymptomatic infections. Therefore antibody-based tests must therefore always be used in combination with a standardized clinical case definition for visceral leishmaniasis diagnosis.

Thus, there is a need for an *in vitro* point-of-care test to confirm or exclude active cases for early diagnosis, in order to benefit both patients and communities as untreated cases are reservoirs of infection and therefore put the community at risk of ongoing *Leishmania* transmission. Similarly, an *in vitro* laboratory test is needed for confirming or rejecting whether visceral leishmaniasis has been successfully cured post-treatment.

The WHO Diagnostic Technical Advisory Group for Neglected Tropical Diseases

The WHO Department of Control of Neglected Tropical Diseases (NTD) set up the Diagnostic Technical Advisory Group (DTAG) to be the principal advisory group to WHO on NTD diagnostics. This group works to ensure a unified method will be used to solve NTD diagnostic needs and to direct WHO strategies to develop efficient diagnostic tools. The first meeting of the Diagnostic Technical Advisory Group (DTAG), an advisory group to the Department of Control of Neglected Tropical Diseases, was held in Geneva, Switzerland, on 30 and 31 October 2019 [7]. 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 meetings, as it had been made clear that all NTDs had diagnostic needs which would have to be addressed in due course. In its second meeting, the Diagnostic Technical Advisory Group recommended constituting a subgroup on visceral leishmaniasis to cater to diagnostic requirements specially in the context of elimination [8].

NTD Roadmap 2021-2030

Visceral leishmaniasis is one of the diseases targeted for elimination as a public health problem in the 2021–2030 NTD roadmap. At least 64 countries are expected to be validated for the elimination of visceral leishmaniasis as a public health problem by 2030. Since 2019, visceral leishmaniasis endemic countries in Eastern Africa are contributing around 67% of the global burden of the disease. In order to meet the global targets, more sensitive rapid diagnostic tests in Eastern Africa and elsewhere are needed, particularly in the context of elimination. Also, a laboratory-based test is needed to confirm a cure following successful treatment.

Scope for the TPP

The visceral leishmaniasis subgroup under DTAG held its inaugural meeting on 11 October 2021. The TPP was defined through several rounds of discussions on two use cases-

- An *in vitro* point-of-care test for the detection of analyte-specific to *L. donovani* or *L. infantum* to enable the detection of VL disease.

- An *in vitro* **laboratory-based test** for the detection of analyte-specific to *L. donovani* or *L. infantum* for confirming or rejecting whether VL has been successfully cured post-treatment.

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