Diagnostic test for lymphatic filariasis to support decisions for stopping triple-therapy Mass Drug Administration

TARGET PRODUCT PROFILE

World Health Organization

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Background

Lymphatic filariasis (LF) is a mosquito-borne parasitic infection that is endemic in 72 countries. Adult worms live in the host lymphatic system for years causing lymphatic dysfunction.

LF is caused by parasitic worms; *Wuchereria bancrofti*, *Brugia malayi*, or *Brugia timori*. *W. bancrofti* is found in nearly all LF endemic countries and Brugia spp are found only in limited areas of a few countries across South-east Asia. The adult worms cause lymphangiectasia, leading to swelling of legs (lymphoedema), scrotum (hydrocele) and other parts of the body. LF is a major cause of disability and is responsible for at least 1.6 million Disability Adjusted Life Years (DALYs) each year (*1*), resulting in productivity loss at the individual and national level.

Public Health Response

WHA 50.29 called for the elimination of LF as a public health problem. An estimated 51.4 million people were infected with LF as of 2018 (*2*), a significant reduction since WHO launched the Global Programme to Eliminate Lymphatic Filariasis (GPELF). GPELF aims to interrupt transmission and prevent new disease through the WHO recommended strategy of mass drug administration (MDA) using combination regimens of the three medicines currently available for treatment: diethylcarbamazine (DEC), albendazole, and ivermectin. MDA drugs used currently can prevent the vector-borne transmission for several months by killing mainly the microfilariae. However, the adult worms often remain viable after treatment and can reproduce new microfilariae prior to the next annual MDA. Therefore, several years of MDA have been required with previous regimens to reduce infection to below elimination thresholds.

In 2017, WHO recommended the combination of ivermectin, DEC, and albendazole, known as IDA or triple-therapy for MDA in certain settings (*3*). IDA is more effective in clearing microfilariae for longer periods of time than the two-drug regimens (*4*). Persons can remain clear of microfilariae for years after a single IDA treatment indicating a potential sterilization effect on the adult worms (*5*). IDA is seen as an intervention to accelerate the interruption of transmission outside of Africa and in areas of Africa that are not co-endemic with loiasis or onchocerciasis (*6*).

As of 2019, 11 countries have adopted the WHO recommendation implementing IDA MDA in at least 1 LF endemic district and more than 45 million people have received treatment (*7*). By 2021, IDA is projected to be adopted by all countries where warranted.

Available Diagnostic Tools

The progress of programs to eliminate lymphatic filariasis is monitored by testing residents of communities under treatment for the presence of microfilariae or circulating filarial antigen (CFA) for *W. bancrofti* and microfilaria and antifilarial antibodies (BmR1) for *Brugia* spp. Demonstration that the population prevalence of positive tests for these analytes is below a defined threshold is an indication that transmission has been reduced and assumed no longer sustainable. Therefore, at this point, MDA is no longer warranted in the geographical area assessed. For GPELF, a transmission assessment survey (TAS) has been defined to support this decision to stop MDA. The TAS is based on testing children for the presence of CFA or BmR1. Follow-up evidence from initial studies show continued clearance of microfilariae 5 years after a single IDA treatment but continued persistence of CFA (*5*). Testing older age groups for microfilariae is possible but is not ideal because of limitations in technical capacity in slide preparation and microscopy, low sensitivity of night blood films on small samples of blood after MDA and the nocturnal periodicity of the parasite in many endemic settings presents logistic challenges and security risks for survey teams.

WHO recommends the Alere Filariasis Test Strip (FTS) for all areas endemic for *W. bancrofti* and Brugia Rapid Test for all areas endemic for *Brugia* spp. The FTS which measures CFA is used in all steps of the GPELF strategy. However, CFA can take 12 months or more to appear after infection and persists several years after adult worms can no longer reproduce or have died. New tools are needed to detect, ideally, the presence of viable worms or microfilariae following introduction of IDA.

Development of the TPP

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. It was decided by the Strategic and Technical Advisory Group (STAG), the principal advisory group to WHO for the control of NTDs, 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.

The first meeting of the Diagnostic Technical Advisory Group (DTAG), an advisory group to Department of Control of Neglected Tropical Diseases, 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 (*7*). One of the recommendations was that there should be a diagnostic disease specific group to support the GPELF noting the diagnostic gaps in settings co-endemic with loiasis, areas implementing triple-therapy MDA and areas under post-treatment or post-elimination surveillance (*7*).

A DTAG sub-group of LF technical experts, end users and other stakeholders was formed and met 29th April 2020 virtually. The sub-group identified the need for improved diagnostics to support decisions for stopping IDA MDA. The DTAG sub-group drafted the TPP for this specific use case and WHO posted the draft TPP for public comment. Comments received were discussed with the DTAG sub-group and revisions were made where warranted.

Purpose of the TPP

A provisional strategy for monitoring and evaluating the impact of IDA was proposed after 2 annual IDA rounds, but the Guideline Development Group identified that current strategies for determining when to stop IDA may not be sufficient and further research was needed (*3*). As countries approach the 2nd IDA MDA round, programmes urgently need a new diagnostic with specific characteristics and a new survey methodology. The purpose of this TPP is to communicate the minimum and ideal characteristics desired to meet the need for measuring when there is evidence to support stopping IDA MDA. The tools must be able to discriminate targeted prevalence threshold in the tested areas (<1% microfilaremia or <2% antigenemia).