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

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 (King, 2020)

Epidemiology

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 swelling of legs (lymphoedema), scrotum (hydrocele) and other parts of the body which is associated with increased risk of acute attacks of bacterial lymphadenitis and lymphangitis. LF is a major cause of disability and is responsible for more than 1.3 million Disability Adjusted Life Years (DALYs) worldwide each year (IHME, 2017) , leading to productivity loss at the individual and national level, and are a major cause of mental illness amongst those affected (Ton, 2015) .

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, a significant reduction since WHO launched the Global Programme to Eliminate Lymphatic Filariasis (GPELF). GPELF aims to interrupt transmission and stop new infections through the WHO recommended strategy of mass drug administration (MDA) using combination regimens of the three drugs 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 and inducing a temporary sterilization of adult worms. However, because macrofilariae continue to live in the body, they eventually produce new microfilariae, often before the next MDA, thus requiring repeated MDAs for several years to decades.

In 2017, WHO recommended the combination of ivermectin, DEC, and albendazole, known as IDA or triple-therapy for MDA in certain settings (WHO, 2017). IDA is more effective in clearing microfilaria for longer periods of time than the two-drug regimens (Christopher L. King, 2018). 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 (Weil GJ, 2019).

As of 2019, 11 countries have adopted the WHO recommendation implementing IDA MDA in at least 1 LF endemic district and more than 13 million people have received treatment. 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 CFA for *W. bancroft*i 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 lymphatic filariasis is no longer a public health problem in the region assessed. For GPELF, a transmission assessment survey (TAS) has been defined to support the decision to stop MDA. The TAS is based on testing children for the presence of CFA or BmR1. In principle, children born

following the implementation of MDA should have been protected from infection and therefore be antigen-negative.

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. 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 the 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. 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.

One of the recommendations was that TPPs for diagnostics were needed for the Global Programme to Eliminate Lymphatic filariasis and specifically, a TPP for a diagnostic to support stopping IDA.

Purpose of the TPP

Use of IDA reduces the number of MDA rounds, limiting the potential to use testing of children for the TAS. Follow-up evidence from initial studies show continued clearance of microfilaria 5 years after a single IDA treatment but continued persistence of circulating filarial antigen (CFA). (King, 2020). Testing older age groups for microfilariae is possible but is not ideal because of limitations in technical capacity, low sensitivity after MDA and the nocturnal periodicity of the parasite in many endemic settings presents logistic challenges and security risks for survey teams. New tools are needed to ideally to detect the presence of viable worms or microfilaria following introduction of IDA.

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 (WHO, 2017).

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 proposed by WHO NTD is to lead to development of new diagnostic tools to measure 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).

Bibliography

Christopher L. King M.D., Ph.D., James Suamani, B.S., Nelly Sanuku, B.S., Yao-Chieh Cheng, B.S., A Trial of a Triple-Drug Treatment for Lymphatic Filariasis [Journal] // New England Journal of Medicine . - 2018 . - pp. 1801-10.

Cobo Fernando. Determinants of parasite drug resistance in human [Journal] // Revista Española de Quimioterapia. - 2016. - pp. 29(6):288-295.

Hotez PJ Fenwick A, Savioli L, Molyneux DH. Rescuing the bottom billion through control of neglected tropical diseases. [Journal] // Lancet. - 2009. - pp. 373(9674);1570-1575.

IHME Findings from the Global Burden of Disease Study 2017 [Report]. - Seattle : IHME , 2017.

King C. L., Weil, G. J., & Kazura, J. W. Single dose triple drug therapy completely suppresses Wuchereria bancrofti microfilaremia for 5 years [Journal] // The New England journal of medicine. - 2020. - pp. 1956–1957.

King Christopher L. Lymphatic Filariasis [Book Section] // Hunter's Tropical Medicine and Emerging Infectious Diseases. - [s.l.] : Elsevier, 2020.

Mark J. Taylor Thomas W. von Geldern, Louise Ford et al Preclinical development of an oral anti-Wolbachia macrolide drug for the treatment of lymphatic filariasis and onchocerciasis [Journal] // SCIENCE TRANSLATIONAL MEDICINE . - 2019.

Ton T.G., Mackenzie, C. & Molyneux, D.H. The burden of mental health in lymphatic filariasis. [Journal] // Infectious Diseases Poverty. - 2015. - pp. 4,34.

Weil GJ Bogus J, Christian M, Dubray C, The safety of double- and triple-drug community mass drug administration for lymphatic filariasis: A multicenter, open-label, cluster-randomized study [Journal] // Plos Medicine . - 2019.

WHO
https://www.who.int/neglected_diseases/news/WHO_recommends_triple_medicine_therapy_for_LF_elimination/en/ [Online]. - 2017. - May 2020.