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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Diagnostic test for lymphatic filariasis to support decisions for stopping triple-therapy mass drug administration: target product profile

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Contents

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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).

Characteristics of a needed diagnostic test for lymphatic filariasis to support decisions for stopping triple-therapy MDA

1. Product use summary	**Ideal**	**Minimum**
1.1 Intended use	An in vitro point-of-care test for the detection of analyte(s) specific to *Wuchereria bancrofti*, *Brugia malayi* or *Brugia timori* to aid in decision-making in defined geographical areas for stopping mass drug administration of IDA.	An in vitro test for the detection of analyte(s) specific to *Wuchereria bancrofti*, *Brugia malayi* or *Brugia timori* to aid in decision-making in defined geographical areas for stopping mass drug administration of IDA.
1.2 Targeted population	All ages of individuals resident in the population living in the defined geographical area.	All ages of individuals resident in the population living in the defined geographical area.
1.3 Lowest infrastructure level	The test will be performed in health facilities or under "zero-infrastructure" conditions including but not limited to community health centres, households and outdoor conditions.	If the required levels of performance necessitate a laboratory-based test, tests can be performed in a regional or national diagnostic testing laboratory.
1.4 Lowest level user	This test will be performed by health personnel and community health workers.	If testing must be performed in a regional or national diagnostic testing laboratory, the test will be performed by trained laboratory technicians.
1.5 Training requirements	One day for community volunteers and lay persons; testing job aid/instructions for use should be made available via the Internet for download (i.e. are publicly available).	If testing must be performed in a regional or national diagnostic testing laboratory, less than 10 days for trained laboratory technicians; testing job aid/instructions for use should be made available via the Internet for download (i.e. are publicly available).

2. Design	**Ideal**	**Minimum**
2.1 Portability	Highly portable with no specialized transport needs.	If needed to obtain the required levels of performance, a laboratory-based test is acceptable.
2.2 Instrument/power requirement	Self-contained kit operates independent of any mains power.	If a laboratory-based test is required, access to mains power is acceptable.
2.3 Water requirement	Self-contained kit operates independent of any water supply.	If a laboratory-based test is required, access to laboratory-grade water is acceptable.
2.4 Maintenance and calibration	No maintenance required (i.e. disposable) and no calibration required.	If a laboratory-based test is required, periodic maintenance and calibration of any instrumentation must be available in the countries, and should not be needed more frequently than once a year.
2.5 Sample type/collection[1]	Peripheral whole blood from finger stick.	If a laboratory-based test is required, peripheral whole blood from finger stick, EDTA/heparinized sample or DBS. No venipuncture sampling.

Annotation on Design

1. If EDTA/heparinized sample, would need to ensure there is the ability to either transport immediately or store suitably

2. Design continued	Ideal	Minimum
2.6 Sample preparation/transfer device	Sample preparation should not exceed transfer of sampled whole blood to the testing device, either directly or by use of a predefined and provided device (e.g., inverted cup, transfer loop, etc; may provide their own validated transfer device.)	If a laboratory-based test is required, preparation of serum/plasma from EDTA/heparin anticoagulated blood *or* elution from DBS is acceptable.
2.7 Sample volume	1–10 µL	1–100 µL
2.8 Target analyte[2]	Antigen(s) or other biomarker(s) specific for *Wuchereria bancrofti*, *Brugia malayi* or *Brugia timori* and indicative of the capability to reproduce at the time of testing or thereafter. The absence of biomarker must indicate the worms are either not present, dead or permanently sterilized.	Antigen(s) or other biomarker(s) specific for *Wuchereria bancrofti*, *Brugia malayi* or *Brugia timori* and indicative of the capability to reproduce at the time of testing or thereafter. The absence of biomarker must indicate the worms are either not present, dead or permanently sterilized.
2.9 Type of analysis	Qualitative	Qualitative
2.10 Detection	High contrast, clear result for naked eye; indoor and outdoor reading of a signal that provides a "yes/no" result.	If a laboratory-based test is required, may include instrument-based detection of a signal that provides a "yes/no" result.
2.11 Quality control	Internal process control (i.e. control line) External performance control (i.e. positive control to verify test line is working) [3]	Internal process control (i.e. control line)
2.12 Supplies needed	All reagents and supplies included in kit, with minimal import restrictions (e.g. animal-free).	All reagents and supplies included in kit, with minimal import restrictions (e.g. animal-free).
2.13 Safety	Auto-retracting sterile lancet for drawing blood for finger-stick sampling; normal use does not create any additional hazards to the operator when observing Universal Blood Safety precautions.	If a laboratory-based test is required, auto-retracting sterile lancet for drawing blood for finger-stick or DBS sampling; normal use does not create any additional hazards to the operator when observing Universal Blood Safety precautions.

Annotation on Design

2. Biomarkers based on antigens or other types (e.g., certain nucleic-acid based markers) will presumably provide more favourable half-life kinetics that enable more accurate determination of current infection from/viability of *W. bancrofti*, *B. malayi* or *B. timori* in all age groups. However, current antigen-based biomarkers such as circulating filarial antigen (CFA) or other IgG-based biomarkers possess half-life kinetics that enable determination of prior infection from/viability of *W. bancrofti*, *B. malayi* or *B .timori* which may or may not still be an active infection/viable parasite, and discovery and validation of alternative markers may require significant time/effort. For this reason, this is a **high-risk** requirement.
3. **NOTE**: there would need to be definition of how external positive controls should/would be used if they are to be included with a test. Controls should have a shelf life consistent with the shelf life of the test.

3. Performance	**Ideal**	**Minimum**
3.1 Species differentiation[1]	*W. bancrofti, B.malayi* or *B. timori*	*W. bancrofti, B.malayi* or *B. timori*
3.2 Diagnostic/clinical sensitivity[2]	"Single test" approach: > 60% "Decision confirmatory test" approach: > 85%	"Single test" approach: > 40% "Decision confirmatory test" approach: > 78%
3.3 Diagnostic/clinical specificity[3]	"Single test" approach: > 99.7% "Decision confirmatory test" approach: > 96%	"Single test" approach: > 99.5% "Decision confirmatory test" approach: > 82%
3.4 Time to results[4]	< 0.5 h to developed test result	If a laboratory test is required, < 48 h to developed test result
3.5 Result stability[5]	Developed test result remains stable for 24 h	Developed test result remains stable for 0.5 h
3.6 Throughput	≥ 10 tests per h	If a laboratory test is required, 120 tests per day/per technician If field-based test, ≥ 7 tests per h
3.7 Target shelf life/stability	≥ 24 months, 4–40 °C, 50% RH (no cold chain required); temperature excursion/prolonged deviation of 50 °C for 2 weeks acceptable.	≥ 18 months, 4–37 °C; temperature excursion/prolonged deviation of 40 °C for 2 weeks acceptable.
3.8 Ease of use[6]	One timed step; ≤ 10 user steps, instructions for use should include diagram of method and results interpretation. For field-based test, must be able to use in an unprotected external environment.	If a laboratory test is required, ≤ 5 timed steps; if ≤ 15 user steps, instructions for use should include diagram of method and results interpretation.
3.9 Ease of results interpretation	Interpreted by unaided eye, does not require discrimination of one colour from another	If a laboratory test is required, results can be interpreted by a suitable instrument.
3.10 Operating temperature	15–40 °C	May have to control temperature for laboratory-based test.

Annotation on Performance

1. There should be no interference from other filarial parasites such as *Loa loa*, *Onchocerca volvulus*, *Mansonella* spp., etc. (Potential for interference may not be applicable in parts of the world not endemic for these non-lymphatic filarial parasites.)
2. Current WHO guidance in the transmission assessment survey (TAS) is to measure a < 2% prevalence threshold (<1% in *Aedes* areas) in a population. Considering the new analyte(s) proposed (2.8) is a more direct measure of transmission potential and taking into consideration recent operational research that has found LF recrudescence post-mass drug administration, a more stringent threshold of < 1% prevalence is proposed. The sensitivity calculations are based on testing this 1% threshold and consider two potential scenarios:
   (i) a "single test" approach in which a new assay replaces the current tools (i.e. Filariasis Test Strip (FTS)/Brugia Rapid Test (BRT)) in the TAS; and
   (ii) a "decision confirmatory test" approach in which individuals are screened with FTS/BRT first; the new diagnostic is used as a confirmatory assay on individuals testing positive by FTS/BRT. Results of the confirmatory test are used to make a programme decision at a population level as opposed to an individual clinical treatment decision or confirmation of the first test result.

Assumptions made in sensitivity calculations:

a) FTS/BRT is 90% sensitive for detecting microfilariae (Mf)-positive individuals
b) Single test approach: 80% power to correctly conclude a defined population with a true prevalence ≤0.2% (ideal) or = 0% (minimum) is below the 1% threshold
c) Decision confirmatory test approach: 80% power to correctly conclude a defined population with a true prevalence ≤0.5% (ideal) or ≤ 0.2% (minimum) is below the 1% threshold
d) α ≤ 5% (i.e. Type 1 error rate); meaning that using this diagnostic, the survey would incorrectly conclude prevalence in a defined population is below the 1% threshold < 5% of the time
e) survey design: 30 cluster; equal probability

NOTES: Since the analyte has yet to be defined, there is no basis for assigning a level of risk here (which may be low or high); need to have means for validating sensitivity (i.e. Mf-positve sample panels).

3. The specificity calculations are based on testing the 1% threshold mentioned in 2 above and consider two potential scenarios:

(i) a "single test" approach in which a new assay replaces the current tools (i.e. FTS/BRT) in the TAS; and
(ii) a "decision confirmatory test" approach in which individuals are screened with FTS/BRT first; the new diagnostic is used as a confirmatory assay on individuals testing positive by FTS/BRT. Results of the confirmatory test are used to make a program decision at a population level as opposed to an individual clinical treatment decision or confirmation of the first test result.

Assumptions made in specificity calculations:

a) FTS/BRT is 90% sensitive for detecting Mf-positive individuals
b) decision confirmatory test approach: 80% power to correctly conclude a defined population with a true prevalence ≤0.2% (ideal) or = 0% (minimum) is below the 1% threshold
c) decision confirmatory test approach: 80% power to correctly conclude a defined population with a true prevalence ≤0.5% (ideal) or ≤ 0.2% (minimum) is below the 1% threshold
d) α ≤ 5% (i.e. Type 1 error rate); meaning that using this diagnostic, the survey would incorrectly conclude prevalence in a defined population is below the 1% threshold < 5% of the time
e) survey design: 30 cluster; equal probability sampling

Specificity to be defined as follows:

(i) 99.5% specificity; no more than 1 false positive in 200 negative samples (specificity = 99.5%; 95% confidence interval (CI) 97.2–100%)
(ii) 99.7% specificity; no more than 1 false positive in 350 negative samples (specificity = 99.7%, 95% CI 98.4–100%)
(iii) manufacturer will be assisted by programme partners to demonstrate the desired 99.5% specificity at the lower-bound 95% CI in field trials powered with ≥ 800 people

NOTES: Since the analyte has yet to be defined, there is no basis for assigning a level of risk here (which may be low or high); need to have means for validating specificity (i.e. Mf-positve sample panels). In low prevalence settings, specificity will be the main driver of positive predictive value.

4. Laboratory tests assume there will be a workflow into which tests will need to be introduced, i.e., same-day results may not be viable.
5. Ability to interpret final test results in a manner not constrained by timed steps helps greatly in resource-constrained settings
6. Example lab test with more than one timed step and multiple user steps would include a standard colorimetric ELISA.
   For field-based test, must also be able to add a label to the test device.

4. Product Configuration	Ideal	Minimum
4.1 Shipping conditions	Conformance to applicable requirements of ASTM D4169-05 and ISO 11607-1:2006 (or equivalent); no cold-chain shipping required.	If a laboratory-based test is required, cold-chain shipping (e.g., 0-4 C) is acceptable.
4.2 Storage conditions	Ambient storage conditions, 4 C - 40 C; no cold storage required; colorimetric or other indicator of temperature deviation to indicate excessive heat/humidity exposure. It is recommended the indicator be placed inside the carton.	If a laboratory-based test is required, cold storage is acceptable
4.3 Service and support	None required (though can be made available).	If laboratory-based test, support must be available from manufacturer.
4.4 Waste disposal	Does not include material that cannot be disposed of in normal laboratory biohazard waste streams.	Does not include material that cannot be disposed of in normal laboratory biohazard waste streams.
4.5 Labelling and instructions for use (IFUs)[1]	Compliance required per CE Mark or IVDR; Product Insert shall be available in relevant local language(s) and shall include Instructions for Use (IFUs) for the test; if appropriate, photos of example test results (i.e. positive, weak positive, negative) should be included in IFU.	Compliance required per CE Mark or IVDR; Product Insert shall be available in relevant local language(s) and shall include Instructions for Use (IFUs) for the test; if appropriate, photos of example test results (i.e. positive, weak positive, negative) should be included in IFU.

Annotation on Product Configuration

1. If appropriate, photos of example test results (i.e. positive, weak positive, negative) should be included in instructions for use.

5. Product cost, access and equity	Ideal	Minimum
5.1 Target pricing per test[1]	Single test: < US$ 2 Confirmatory test: < US$ 2	Single test: < US$ 3 Confirmatory test: < US$ 5
5.2 Capital cost[2]	No capital costs	If laboratory-based test, capital cost should not exceed $5,000 per instrument
5.3 Product lead times[3]	<4 weeks	<6 weeks
5.4 Target launch countries	WHO prioritized countries	WHO prioritized countries
5.5 Product registration (i.e., substantiation to regulatory body of product claims)	• CE Mark or IVDR • Any registration required for export from country of origin (e.g., KFDA) • WHO PQ (in due course), Expert Panel Review for Diagnostics or evidence from stringent regulatory assessment (GHTF founding members[4]) • Country-level registration (if required/ applicable for target countries)	• CE Mark or IVDR • Any registration required for export from country of origin (e.g., KFDA) • WHO PQ (in due course), Expert Panel Review for Diagnostics or evidence from stringent regulatory assessment (GHTF founding members[4]) • Country-level registration (if required/ applicable for target countries)
5.6 Procurement	Available for procurement by all endemic countries with no restriction.	Available for procurement by all endemic countries with no restriction.
5.7 Cost	Standardized pricing quoted by manufacturer available to all stakeholders Absence of distributor or third-party mark up	Standardized pricing quoted by manufacturer available to all stakeholders Absence of distributor or third-party mark up

Annotation on Product cost, access and equity

1. Should be room for special pricing in special circumstances (e.g., population subset testing for MDA stopping decisions)
2. Capital cost reflects pricing for unused microtiter plate reader (absorbance, colorimetry), but would be equally applicable to other devices.
   NOTE: assumes basic laboratory infrastructure already exists. Costs to establish a lab de novo will require considerable cost not reflected in this document.
3. "Lead time" includes fulfilment and delivery of ordered tests to procurer.
   NOTE: May be adjusted to longer lead times provided shelf life is of sufficient duration, e.g., two years.
4. Founding members of the Global Harmonization Task Force as Australia, Canada, European Union, Japan, USA

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