Diagnostic test for surveillance of lymphatic filariasis

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). All but 3 of the 72 endemic countries have established national LF elimination programmes and implemented MDA (*3*). Currently, 23 of 72 endemic countries have reduced infection levels below target thresholds and no longer require MDA nationally. WHO has acknowledged 17 of these 23 countries for meeting the criteria for achieving elimination of LF as a public health problem.

As more national programmes see success and begin to stop MDA, the importance of monitoring for resurgence through surveillance activities increases. As defined in the new NTD Road Map, all LF endemic countries should be implementing post-MDA or post-validation surveillance by 2030 (*3*).

Available Diagnostic Tools

WHO recommends repeating the transmission assessment survey (TAS) twice in 2 to 3-year intervals after MDA has stopped (*4*). Successful results in both surveys i.e. passing TAS, indicates incident infection remains below target thresholds over all endemic geographical areas and meets the epidemiological criteria for elimination as a public health problem. While the TAS is useful for stop-MDA decisions, it is not powered to measure reductions in prevalence or incidence over time or to be a sensitive measure of recrudescence in transmission potential.

This limitation of the TAS for surveillance is compounded by limitations of the available diagnostics. 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 circulating filarial antigen (CFA) is used in all steps of the GPELF strategy. However, CFA takes 12 months or more to appear after infection and persists several years after adult worms can no longer reproduce or have died. New diagnostics targeting analytes which represent recent exposure are needed to inform LF post-MDA and post-elimination surveillance and response activities.

Other diagnostic tools available for LF have been reviewed and include antibody-based ELISA formats and antibody-based point of care rapid diagnostic tests specific to *W. bancrofti* and *Brugia* spp. WHO has not recommended these diagnostic tests because the tests have not met required performance characteristics.

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 (5). 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 (*5*).

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 for surveillance, a need previously highlighted by WPRO during its meeting on NTD post-elimination surveillance in the Western Pacific (*6*). The need for feasible diagnostic formats and new biomarkers was reiterated by WHO expert panel members during a WHO expert consultation to establish the post-2020 targets for GPELF.

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

The purpose of this TPP is to communicate the minimum and ideal characteristics desired to meet the need for discriminating low levels of risk for transmission, i.e. targeted prevalence thresholds in the surveyed areas. An in vitro diagnostic test is needed for the detection of analyte(s) specific to *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori* to aid in the surveillance of defined geographic areas as to whether infection and/or transmission potential has increased (recrudescence) or decreased (elimination of transmission).

Characteristics of a needed diagnostic test for surveillance of lymphatic filariasis

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 the surveillance of defined geographic areas as to whether recrudescence has/has not occurred.	An *in vitro* test for the detection of analyte(s) specific to *Wuchereria bancrofti*, *Brugia malayi*, or *Brugia timori* to aid in the surveillance of defined geographic areas as to whether recrudescence has/has not occurred.
1.2 Targeted population	All ages of individuals resident in the population living in the defined geographic area.	All ages of individuals resident in the population living in the defined geographic 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	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 venepuncture sampling.[1]
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]	Antibody(s) or other biomarker(s) specific for early exposure or pre-patent infection of *Wuchereria bancrofti (W.b), Brugia malayi (B.m),* or *Brugia timori (B.t)*	Antibody(s) or other biomarker(s) specific for early exposure or pre-patent infection of *Wuchereria bancrofti (W.b), Brugia malayi (B.m),* or *Brugia timori (B.t)*.

2. Design continued	Ideal	Minimum
2.9 Type of analysis	Quantitative [3]	Qualitative
2.10 Detection	High contrast, clear result for naked eye; indoor and outdoor reading of a signal that provides unambiguous determination of a qualitative measure.	If a laboratory-based test is required, may include instrument-based detection of a signal that provides unambiguous determination of a quantitative measure.
2.11 Quality control	· Internal process control (i.e. control line) · External performance control (i.e. positive control to verify test line is working) [4]	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 blood draw in the case of 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 blood draw in the case of 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

1. If EDTA/heparinized sample, would need to ensure there is the ability to either transport immediately or store suitably
2. Antibody-based markers are expected to provide the earliest sign of exposure, so discovery and validation of such a marker would need to identify an antibody with rapid clearance post-treatment. Alternatively, note that a (non-antibody) marker to detect live/viable worm would also be useful in post-validation surveillance. However, current antigen-based biomarkers such as circulating filarial antigen (CFA) or other IgG-based biomarkers possess half-life kinetics that enable determination of *exposure to W.b, B.m*, or *B.t* which: a) may have occurred years prior and, b) may or may not still be an active infection/viable parasite. For these reasons and since it may take significant time/effort for biomarker discovery and validation, this is a **high-risk** requirement.
3. Quantitative assay may provide additional information regarding overall "decay" of biomarker levels/concentration within a sampled population.
4. **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.b, B.m,* or *B.t*	*W.b, B.m,* or *B.t*
3.2 Diagnostic/clinical sensitivity[2]	**>99% sensitivity**	>85% sensitivity
3.3 Diagnostic/clinical specificity[3]	**>99.8% specificity**	>98.8% specificity
3.4 Time to results[4]	<0.5 hour to developed test result	If a laboratory test is required, <48 hours to developed test result
3.5 Result stability[5]	Developed test result remains stable for 24 hours	Developed test result remains stable for 0.5 hour
3.6 Throughput	≥ 10 tests per hour	If a laboratory test is required, 120 tests per day/per technician If field-based test, ≥ seven tests per hour

3. Performance continued	Ideal	Minimum
3.7 Target shelf life/stability	≥24 months, 4 C - 40 C, 50% RH (no cold chain required); temperature excursion/prolonged deviation of 50 C for two weeks acceptable.	≥18 months, 4 C - 37 C; temperature excursion/prolonged deviation of 40 C for two weeks acceptable.
3.8 Ease of use[6]	One timed step; ten or less 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, five or fewer timed steps; fifteen or less 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 C - 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. In the context of post-validation surveillance, it will be important to identify remaining foci of potential transmission. Information on early exposure or pre-patent infection from population-based surveys (e.g. TAS, DHS, MICS, PHIA, etc.), as well as the epidemiologic situation, will be useful in guiding more targeted village-based surveillance efforts to identify remaining transmission foci. While there is no WHO target for surveillance, researchers have proposed a provisional threshold of 5% antibody prevalence in children ((Rao, 2014)), where an antibody analyte was used as the basis for assigning this as a **high-risk** "Ideal" requirement.

   Assumptions made in sensitivity calculations:
   1) The diagnostic will be used to identify evidence of transmission hotspots; if this is done using an LQAS approach where the goal is that the upper 1-sided confidence interval around the prevalence should be <5%
   2) The calculations take into account a finite population correction for village level prevalence; villages of sizes 300 - 5,000 were included in the calculation considerations
   3) α ≤5% (i.e. Type 1 error rate); this means that using this diagnostic, the survey would incorrectly conclude prevalence in a defined population is below the 5% threshold <5% of the time.
   4) The power was set at 80%; to correctly conclude prevalence in a defined population with a true prevalence ≤2% (ideal); and ≤1% (minimum) is below the 5% threshold.
   NOTE: need to have means for validating sensitivity (i.e. microfilariae (Mf)-positive sample panels).
3. Specificity to be defined as follows:
   1) 99.8% specificity, no more than 1 false positive in 400 negative samples (specificity = 99.8%; 95% CI 98.6 – 100%)
   2) 98.8% specificity, no more than 2 false positive in 200 negative samples (specificity = 99.0%, 95% CI 96.4 – 99.9%)
   3) Manufacturer will be assisted by WHO and partners to demonstrate the desired 99.8% specificity at the lower-bound 95% CI in field trials powered with 1500 people or more
   NOTE: need to have means for validating specificity (i.e. Mf-positive 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]	<$2	(TBD)
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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