Trends in Parasitology

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Review

Innovative Surveillance Strategies to Support the Elimination of Filariasis in Africa

Louise A. Kelly-Hope,[1,*] Harriet J. Blundell,[1] Cara L. Macfarlane,[1] and David H. Molyneux[1]

Lymphatic filariasis (LF) and onchocerciasis are two neglected tropical diseases (NTDs) of public health significance targeted for global elimination. The World Health Organization (WHO) African Region is a priority region, with the highest collective burden of LF and onchocerciasis globally. Coendemic loiasis further complicates elimination due to the risk of adverse events associated with ivermectin treatment. A public health framework focusing on health-related data, systematic collection of data, and analysis and interpretation of data is used to highlight the range of innovative surveillance strategies required for filariasis elimination. The most recent and significant developments include: rapid point-of-care test (POCT) diagnostics; clinical assessment tools; new WHO guidelines; open-access online data portals; mHealth platforms; large-scale prevalence maps; and the optimisation of mathematical models.

Highlights

New guidelines for LF with the introduction of triple drug therapy using a combination of ivermectin, diethylcarbamazine, and albendazole (IDA).

New guidelines for the new onchocerciasis 'elimination' goal.

Development of POCT diagnostics for all three filarial infections.

New 'test and not treat' (TaNT) strategy for *Loa loa*.

New community-based morbidity mapping methods for LF.

New tools for measuring lymphoedema and impact of interventions.

Online NTD portals – repositories increasing data availability and connectivity.

mHealth tools to enable electronic capture and connectivity of field data.

Continental prevalence maps to determine populations at risk.

Mathematical models to help determine critical transmission reduction thresholds and time-bound elimination endpoints.

A Public Health Surveillance Framework for Filariasis in Africa

The African Context

LF and onchocerciasis are two vector-borne **neglected tropical diseases (NTDs)** (see Glossary) of public health significance currently targeted for global elimination [1]. The filarial nematode *Wuchereria bancrofti*, transmitted by mosquitoes predominantly of *Anopheles* and *Culex* spp., is responsible for 90% of the global infection and the clinical manifestations of LF, which include limb lymphoedema, genital disease such as hydrocoele and chylocele, and acute dermatolymphangioadenitis (ADLA) [2]. *Onchocerca volvulus,* a filarial worm transmitted by black flies of the genus *Simulium*, is the causative agent of onchocerciasis and clinical manifestations of the disease, which include blindness, visual impairment, and intensely pruritic skin lesions [2]. Heavy infection with *O. volvulus* has been associated with an increased risk of death over and above that associated with blindness [3], particularly in children and young adults [4].

The main elimination strategy for both diseases aims to interrupt transmission through large-scale community-based preventive chemotherapy programmes, which are implemented through national NTD programmes in coordination with the WHO, and international pharma, bilateral and philanthropic donors, research organizations and nongovernmental development organisation (NGDO) partners [5,6]. Preventive chemotherapy for filariasis includes the donated drugs ivermectin, diethylcarbamazine (DEC), and albendazole, administered in different combinations through community **mass drug administration (MDA)** campaigns. In recent decades, there has been significant scaling up of MDA, with widespread reductions in transmission across many endemic countries. As national programmes progress towards the endpoint, it is becoming increasingly important to monitor and document the changing epidemiology, elimination successes and failures in order to refine strategies and learn how elimination is best achieved.

[1]Department of Parasitology, Liverpool School of Tropical Medicine, Liverpool, UK

*Correspondence: Louise.Kelly-Hope@lstmed.ac.uk (L.A. Kelly-Hope).

The WHO African Region (AFRO) is a priority region with a planned accelerated MDA programme, and increased funding and technical support provided through the new Expanded Special Project for Elimination of NTDs (ESPEN) entity based in the WHO/AFRO Regional Office, and a wide range of international partners. The African region has the highest collective burden of filariasis, with over 500 million people requiring preventive chemotherapy for LF (371 m), and onchocerciasis (197 m) in 2016, accounting for 43.3% and 99.5% of the global total, respectively [5]. Further, many programmes are behind essential targets, and ten countries have the additional complication of loiasis (tropical eye worm), caused by infection with the filarial nematode *Loa loa* and transmitted by Tabanidae flies of the *Chrysops* species in Central and West Africa [7]. The main clinical manifestations of loiasis include subconjunctival migration of the adult worms (eye worm) and localised skin angioedema (Calabar swelling) [8–10].

The wide distribution of loiasis remains a major barrier for LF and onchocerciasis programmes in Central and West Africa, as ivermectin and DEC cannot readily be used in areas with high *L. loa* prevalence due to the risk of **severe adverse events (SAEs)** in people with high **microfilarial (mf)** densities [8,11,12]. Therefore, alternative intervention strategies are required for LF and onchocerciasis programmes in loiasis coendemic areas, and understanding the extent of overlapping endemicities between the three filarial infections – and the associated risks and benefits – is crucial to implementing safe interventions and meeting the elimination goals set out by the WHO.

A Surveillance Framework

The African Region is ecologically complex and will require a unique suite of surveillance strategies to help document the impact of interventions, track progress toward the elimination goals, and to monitor and describe the changing epidemiology in order to set priorities and inform public health policy and practice [13]. The WHO defines public health surveillance as 'the continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice' (http://www.who.int/topics/public_health_surveillance/en/). This definition is used as a framework to highlight that surveillance is a dynamic cycle with key interlinked components (Figure 1), and to provide a holistic overview of new strategies that are relevant to filariasis elimination in Africa, which are, or have the potential to be, integrated into standard practice in the future.

Control and Elimination Programmes

The WHO Global Programme to Eliminate Lymphatic Filariasis (GPELF) was established in 2000 after LF was identified as one of several diseases that could be eliminated as a public health problem through safe and affordable drug regimens. Global elimination of LF is targeted for 2020 [14]. The GPELF is one of the longest running NTD elimination programmes, and has two well-defined goals and step-wise phases: (i) interruption of transmission using MDA, with supplementary vector control/integrated vector management (VC/IVM), and (ii) alleviate suffering through morbidity management and disability prevention (MMDP), shown in Figure 2A. The GPELF strategy provides a clear framework for national LF elimination programmes to assist in reaching targets, which includes regular monitoring and evaluation (M&E) and a post-MDA surveillance in endemic districts or implementation units (IUs).

In contrast to the GPELF, the goal of global onchocerciasis elimination is relatively new, and evolved from decades of control efforts [15,16]. The first programme, the Onchocerciasis Control Programme (OCP), aimed to control the disease in West African countries, using vector control (aerial larviciding), and later through a combination of vector control and ivermectin treatment following the donation by Merck & Co. in 1987 [17,18]. The African Programme for Onchocerciasis Control (APOC) was subsequently established to control onchocerciasis in meso- to hyper-endemic areas in countries not covered by the OCP, through the then-new

Glossary

Community-directed treatment with ivermectin (CDTI): a strategy for mass drug administration of ivermectin to communities for onchocerciasis. Drug distribution is directed by the community and delivered by community drug distributors (CDDs).

Enzyme-linked immunosorbent assay (ELISA): a common microplate-based technique used in the laboratory to determine the presence and abundance of antibodies or antigens. The intensity of colour that develops as an end-product is measured and this correlates to the amount of the target present in the sample.

Loop-mediated isothermal amplification (LAMP): a method for rapid amplification of DNA or RNA under isothermal conditions. This method does not require a thermal cycler, and is lower cost and more suitable for point-of-care testing than PCR.

Mass drug administration (MDA): anthelmintic drugs are given to the entire population at risk at regular intervals, irrespective of the individual infection status.

Microfilariae (mf): larvae released from the adult female worms that are taken up by the vector species, enabling the infection to be transmitted to a new host. Mf in the peripheral blood (lymphatic filariasis and loiasis) is referred to as microfilaraemia, and mf in the skin (onchocerciasis) is referred to as microfilaridermia.

Mobile health (mHealth): use of mobile devices, such as mobile phones and other wireless devices, to support medical and public health practice. mHealth involves utilising short messaging service (SMS) as well as more advanced features and functionalities, such as global positioning system (GPS).

Neglected tropical diseases (NTDs): a collective term encompassing a diverse group of (mostly) communicable diseases of poverty (excluding malaria, HIV, and TB), which was coined against the backdrop of these 'big three' to raise the profile of, and unite efforts against, tropical/subtropical infections/conditions.

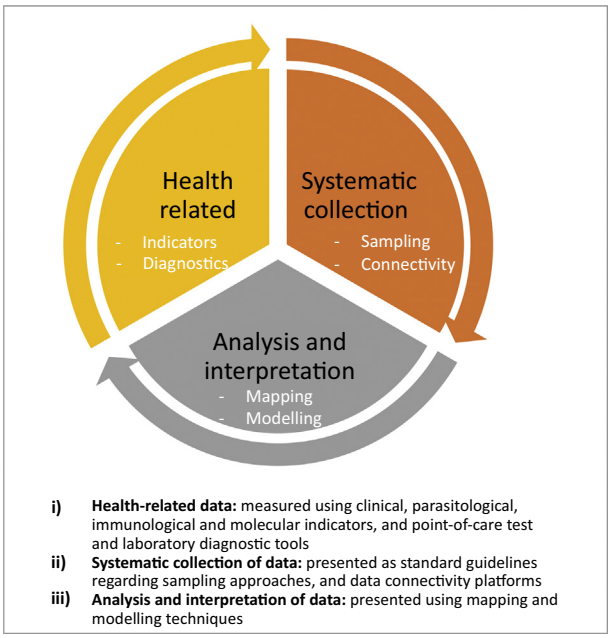


Figure 1. Key Components of Public Health Surveillance.

community-directed treatment with ivermectin (CDTI) strategy [19]. The achievements of the OCP and APOC led to a shift in strategy from the control to the elimination of onchocerciasis, which now includes untreated hypo-endemic areas [20,21]. The ESPEN recently replaced APOC, and promotes an integrated approach to eliminating onchocerciasis together with other NTDs, including LF. The new strategy has three key phases to help achieve elimination (Figure 2B) [21].

In contrast to LF and onchocerciasis, loiasis is not classified as an NTD by the WHO, and consequently there are no formalised control or elimination strategies for the disease itself. However, there is increasing recognition that more research is urgently needed to assess the public health burden of *L. loa* in endemic communities [10,22–24]. In recent years infection has also been associated with arthritis, cardiomyopathy, encephalopathy, lymphangitis, peripheral neuropathy, retinopathy, and an increased risk of death [25], with animal models investigating the pathogenesis of *Loa*-associated encephalopathy following ivermectin treatment [26].

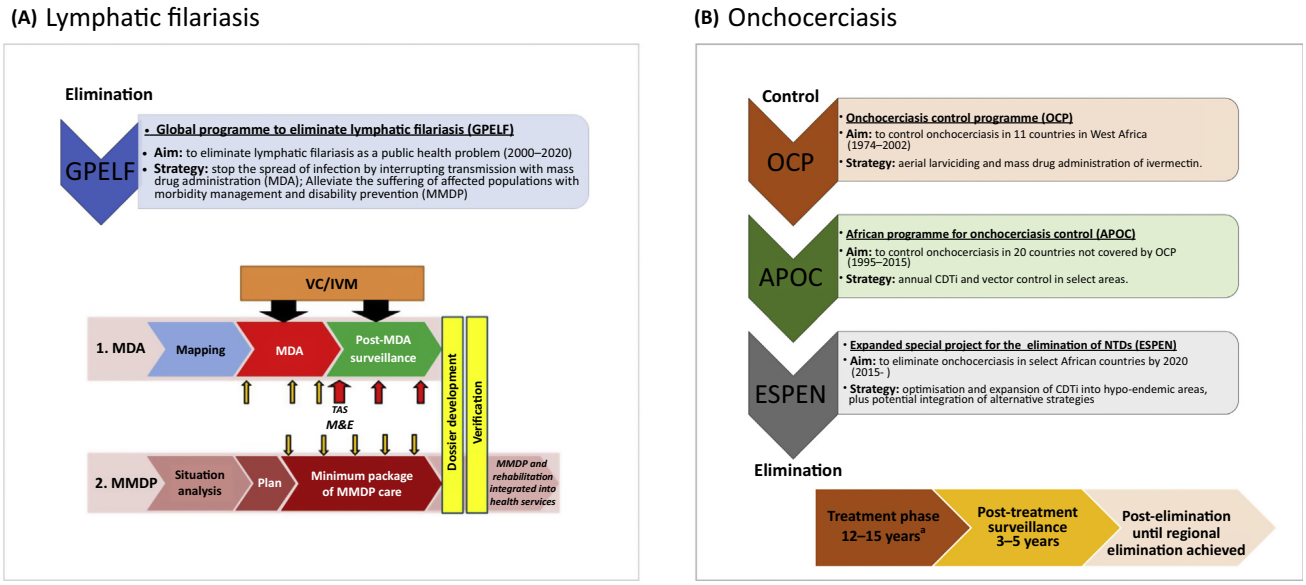
Health-Related Data: Prevalence Indicators and Diagnostics

To meet the GPELF and onchocerciasis elimination targets, sensitive, specific, cost-effective and field-applicable diagnostics are required for all three filarial infections and may include a range of clinical, parasitological, immunological, and molecular indicators and diagnostic tools (Figure 3). Several reviews related to LF and onchocerciasis diagnostics have recently been published [27–32], and those commercially developed and relevant to programmatic surveillance are summarised below.

LF

The primary indicators and diagnostic tools for the different stages of the GPELF strategy include parasitological identification of mf in blood collected at night using thick smear microscopy [33]

Point-of-care tests (POCTs): diagnostic tests that are designed to be used outside of the laboratory at or near the site of patient care.
Rapid diagnostic tests (RDTs): are generally simple to perform and interpret, provide results rapidly, require limited training, and allow for the diagnosis at the community level. They may detect antigens of the parasite or antibodies to the parasite.
Severe adverse event (SAE): an untoward medical occurrence as a result of treatment that results in death; is life-threatening; requires hospitalization; results in disability/incapacity; or requires intervention to prevent permanent impairment or damage.
Skin snip: a small skin sample or biopsy (~1–2 mg) collected from multiple sites (iliac crests, shoulder blades) using a razor blade or skin punch. Skin snips are immersed in saline, and the emergence of *Onchocerca volvulus* microfilariae is diagnostic for onchocerciasis infection.
Transmission assessment survey (TAS): a study intended to determine whether or not infection levels within an evaluation unit have diminished to an extent such that recrudescence of infection is unlikely to occur, even in the absence of continued intervention efforts.
Xenomonitoring: testing the insect vectors for the presence of parasites to monitor the prevalence and transmission potential within a community.



Note. LF framework figure source: Ichimori *et al.* 2014 [14]

VC = vector control IVM = integrated vector control
TAS = transmission assessment survey M&E = monitoring and evaluation

Note. [a]timescale may be longer or shorter due to therapeutic coverage /compliance, the frequency of treatment (biannual/annual), and transmission intensity

CDTI = community-directed treatment with ivermectin

Figure 2. LF and Onchocerciasis Control and Elimination Frameworks. Also see [14].

and filarial-antigen tests which detect adult *W. bancrofti* antigens in blood. The BinaxNOW® Filariasis immunochromatographic card test (ICT) was introduced in the late 1990s as the first rapid antigen test detecting *W. bancrofti* circulating filarial antigen (CFA), using an antifilarial monoclonal antibody (AD12.1) [34], and has since been used extensively for national endemicity mapping. This-easy-to-use **point-of-care test (POCT)** is more sensitive than mf microscopy and can be used at any time of the day. In recent years, there has been an increased use of POCTs for MDA impact and endpoint assessments, which is largely due to the increase in donor funding to support procurement. The main limitation of the ICT is that it can result in false positives, as the ICT has been shown to be cross-reactive in people with high *L. loa* mf densities [35–38]; alternative tools are therefore required to measure LF in loiasis coendemic areas. Other secondary LF diagnostic tools available include the TropBio Og4C3 Ag **enzyme-linked immunosorbent assay (ELISA)** to detect *W. bancrofti* CFA using the monoclonal antibody Og4C3 (a new version of the kit, 'Tropbio Filariasis Antigen II' was released in 2014), antibody testing in blood and urine [39], and polymerase chain reaction (PCR)/quantitative PCR (qPCR) for detection of *W. bancrofti*-specific DNA both in blood and in mosquitoes for **xenomonitoring** [40]. However, they are not routinely used and/or included in WHO guidelines for LF [27,28].

What's New in Diagnostic Tests

The most recent and significant developments for the transmission of *W. bancrofti* include the further development of the *W. bancrofti* BinaxNOW® Filariasis ICT, known as the Alere Filariasis Test Strips (FTS). The new FTS is increasingly being used in all steps of the GPELF strategy as it is lower in cost, has increased stability, and is considered to be more sensitive and stringent for surveillance [41–43]. However, it has the same limitations as the ICT in LF-loiasis coendemic areas. Other diagnostic developments for LF include an antibody-based ELISA, the Inbios

Health-related data	Lymphatic filariasis[a]	Onchocerciasis	Loiasis
Clinical	• Limb examination • Groin examination • Scrotal ultrasonography • Dreyer's clinical staging • **Simple clinical staging** • **Portable scanning device** • **Tissue tonometers**	• Eye examination • Skin examination • Nodule ultrasonography • Rapid epidemiological mapping of onchocerciasis (REMO)	• Eye examination • Skin examination • Rapid epidemiological assessment of *Loa loa* (RAP-LOA)
Parasitological	**Direct:** • **Blood smear for microfilariae** (night)	**Direct:** • **Skin snips for microfilaridermia** **Indirect:** • DEC patch test • **LTS-2 DEC patch**	**Direct:** • **Blood smear for microfilariae** (day) • **Loascope**
Immunological	**Antigen:** • **BinaxNOW ICT (RDT)** • **Filariasis test strip (FTS) (RDT)** • Og4C3 filariasis antigen ELISA **Antibody:** • Bm14 ELISA • **Wb123 ELISA** • **Wb123 RDT** • **Biplex Wb123/Ov16 (RDT)** • Wb-SXP-1 ELISA	**Antigen:** • No antigen detection test[b] **Antibody:** • Ov16 lateral flow card test[c] • Ov16 ELISA • **Ov16 RDT** • **Biplex Wb123/Ov16 (RDT)**	**Antigen:** • No antigen detection test[b] **Antibody:** • **Loa antibody rapid test (LI-SXP-1) (RDT)[d]**
Molecular	• Blood PCR • **Multiplex PCR**	• Skin snip PCR • **Biomarkers[e]**	• Blood PCR • **Biomarkers[f]**

➢**Current gold standard**
➢**What's new**

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Figure 3. Tabulated Summary of Lymphatic Filariasis, Onchocerciasis, and Loiasis Diagnostics.
[a]Diagnostic tests for bancroftian lymphatic filariasis (caused by infection with *W. bancrofti*) only are discussed here.
[b]There are currently no commercial tests available for programmatic use. Antigen-detection tests so far have not had the necessary sensitivity or specificity, or been practical for use in the field.
[c]This test was developed and evaluated, but it was not commercialised and is not in use.
[d]The Loa Antibody Rapid Test is for Research Use Only (RUO), and is indicated mainly for epidemiological and not diagnostic purposes.
[e]Point-of-care tests (POCTs) that can detect biomarkers of active onchocerciasis infection are not yet available, but several promising biomarkers are being evaluated.
[f]There are no POCTs for detecting biomarkers of current infection with loiasis; however, there are potential biomarkers under review.
Abbreviations: ICT, immunochromatographic card test; RDT, rapid diagnostic test; ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction.

International, Inc. Filaria Detect™ anti-Wb123 human IgG4 ELISA, and a **rapid diagnostic test (RDT)**, the Standard Diagnostics (SD) BIOLINE lymphatic filariasis IgG4 test (Wb123), for detection of antibodies specific to *W. bancrofti*. In addition, a biplex antibody-based RDT, SD BIOLINE Oncho/LF IgG4 biplex rapid test, has been developed to detect IgG4 antibodies

against both *W. bancrofti* and *O. volvulus* specific antigens Wb123 and Ov-16, respectively [44]. More recently, a multiplex bead platform for antibody detection to species of malaria and LF has been trialled [45].

What's New in LF Clinical Disease Classification

New developments related to LF clinical manifestations include identifying lymphoedema and hydocoele, and the simplification of the lymphoedema classification from seven to three stages [46,47] for large-scale community-based cases estimates and morbidity mapping [48,49]. In addition, a new clinical algorithm has been used to help differentiate LF from podoconiosis lymphoedema in coendemic communities [50]. In terms of measuring and monitoring the impact of interventions, two new tools have been developed and trialled. The first is a novel portable 3D imaging system to measure limbs in people affected by filarial lymphoedema [51], and the second a hand-held tissue tonometer used to assess the compressibility, compare differences between stages, and monitor the progression of lymphoedema [52,53].

Onchocerciasis

The primary indicators have included **skin snip** microscopy, involving the examination of a skin biopsy for direct diagnosis of microfilaridermia using a light microscope, and the DEC Patch test [54], which involves the topical application of DEC to provoke a localized Mazzotti reaction and indirect diagnosis of *Onchocerca* microfilaridermia. However, skin snips have low sensitivity in areas with low infection intensity [55], and for several months following ivermectin treatment when microfilaridermia has been reduced or cleared. Furthermore, skin snipping is painful and has been rejected by entire communities [55,56]. DEC patch tests are less invasive and may be more acceptable to communities, but the sensitivity has been variable, and will likely also decrease following MDA. Secondary clinical indicators and tools include examination of the skin to identify pruritic and atrophic skin lesions, and of the eyes to identify mf in the anterior chamber of the eye by slit lamp. The examination of onchocercal nodules has been used to estimate infection prevalence in villages for mapping purposes, and involves palpating a proportion of adult men to determine the level of onchocerciasis endemicity, that is, Rapid Epidemiological Mapping of Onchocerciasis (REMO) [57]. Nodule palpation is not suitable for diagnosis due to the presence of deeper and impalpable nodules that may be missed, and the potential for misclassification of lumps and bumps that resemble nodules [58]. Ultrasound of nodules can also be used to visualize adult *O. volvulus* worms, and has been used to confirm infection or monitor treatment efficacy in clinical studies [59,60]. However, this technique has several limitations and is not used in onchocerciasis elimination programmes. Immunological indicators include the anti-Ov-16 ELISA for detecting IgG4 antibodies to the recombinant antigen Ov-16, which can detect exposure to *O. volvulus* and infection during the prepatent period, but cannot distinguish between current infection and historic exposure to the parasite. Molecular indicators include PCR for the detection of the *O. volvulus* O-150 tandem repeat DNA sequence to identify the presence of *O. volvulus* DNA in skin [61–63], and for xenomonitoring of the black fly vector population [64]. Entomological evaluation by O-150 PCR aims to determine the prevalence of the infective-L3 stage larvae by pool-screening hundreds of black fly heads using an *O. volvulus*-specific O-150 DNA probe [65].

What's New in Diagnostic Tests

The most recent developments related to onchocerciasis transmission include a pre-prepared version of the DEC patch, the LTS-2 Patch [66] and the new RDT and biplex RDT for antibody detection [67,68]. The LTS-2 Patch has been trialed in a small Phase 2 trial that assessed the safety, tolerability, and ability to induce Mazzotti reactions, but requires further validation in larger studies with evaluation of the test's sensitivity and specificity. The SD Bioline

Onchocerciasis IgG4 rapid test is an extension of the Ov-16 ELISA, and uses the recombinant antigen Ov-16 to detect IgG4 antibodies to the parasite. The SD BIOLINE Oncho/LF IgG4 biplex rapid test detects IgG4 antibodies against both *O. volvulus* and *W. bancrofti* antigens [44]. However the role of the new Ov-16-based IgG4 RDT is yet to be validated for field use as preliminary field studies have indicated that it performed well in hyper- and meso-endemic areas but not in hypo-endemic areas. There are currently no immunoassays commercially available that can detect *O. volvulus* antigens (signifying current infection); however, new biomarkers which can detect subnanogram levels of circulating antigen in *O. volvulus*-infected individuals and may provide a platform to detect low-level infections during surveillance in the future [68].

Loiasis

The primary indicators and diagnostics for loiasis include parasitological identification of mf in day blood smears to identify microfilaraemia using light microscopy [69]. Secondary clinical indicators include the examination of the skin, for Calabar swellings, and the eyes to identify the adult worm, which has also been used to estimate village prevalence for mapping purposes, that is, Rapid Assessment Procedure for Loiasis (RAPLOA) using a noninvasive method involving the questioning of an individual's eye worm history [70].

What's New in Diagnostic Tests

The most recent developments related to loiasis transmission include the LoaScope, which involves the examination of a blood smear for microfilaraemia using an adapted iPhone with image analysis software to quantify the number of mf/ml of blood inserted into a magnifying device. This new method is part of a new 'Test and (not) Treat' (TaNT) Strategy for onchocerciasis elimination, which excludes high-risk individuals from treatment [71,72]. A new immunological indicator for *L. loa* infection includes the Loa Antibody Rapid Test by Drugs & Diagnostics for Tropical Diseases, which adapts the recombinant antigen LI-SXP-1 to a lateral-flow assay (LFA) platform [73]. This Loa Antibody Rapid Test is currently for research purposes and has an optional smartphone reader to quantify the line intensity and record GPS coordinates useful for mapping. Other diagnostic tools developed include molecular assays for **loop-mediated isothermal amplification (LAMP)** and qPCR, and the identification of *L. loa*-specific biomarkers; however, they are not yet POCT [74–76].

Systematic Collection of Data: Standardised Guidelines and Data Connectivity

Standardised Guidelines

To meet the GPELF and new onchocerciasis elimination targets it is essential that there are standardised guidelines, which enable endemic countries to systematically collect measures that are comparable within and between populations over time. The WHO guidelines, reports, and manuals for LF and onchocerciasis provide a framework for field sampling, target populations, thresholds and tools. The most recent guidelines for LF (2017) [77] and onchocerciasis (2016) [21] were approved by the WHO Guideline Review Committee (GRC), an internal regulatory body responsible for ensuring that WHO guidelines meet the highest international standards and disseminate recommendations that are trustworthy [78]. See Box 1 for the most recent publications.

For LF

The new WHO guidelines recommend different approaches for the mapping, monitoring, and post-MDA surveillance phases, which are summarised in Table 1 [79], and considered key components of the new Dossier template that will help countries achieve validation of LF

Box 1. WHO Guidelines, Reports, Manuals Related to Lymphatic Filariasis (LF) and Onchocerciasis Surveillance and Elimination

Lymphatic filariasis

2011. Lymphatic filariasis: monitoring and epidemiological assessment of mass drug administration: a manual for national elimination programmes. WHO/HTM/NTD/PCT/2011.4

2012. Integrated vector management to control malaria and lymphatic filariasis – WHO position statement. WHO/HTM/NTD/2011.2

2013. Lymphatic filariasis: managing morbidity and preventing disability: an aide-mémoire for national programmes managers. WHO/HTM/NTD/PCT/2013.7

2013. Lymphatic filariasis: a handbook of practical entomology for national lymphatic filariasis elimination programmes. WHO/HTM/NTD/PCT/2013.10

2016. Strengthening the assessment of lymphatic filariasis transmission and documenting the achievement of elimination: WHO/HTM/NTD/PCT/2016.9

2016. Responding to failed transmission assessment surveys WHO/HTM/NTD/PCT/2016.10

2017. Validation of elimination of lymphatic filariasis as a public health problem. WHO/HTM/NTD/PCT/2017.1

2017. Guideline: alternative mass drug administration regimens to eliminate lymphatic filariasis WHO/HTM/NTD/PCT/2017.07

Onchocerciasis

2015. Strategic options and alternative treatment strategies for accelerating onchocerciasis elimination in Africa. WHO/MG/15.20

2015. Guide for decision making and implementation of vector control as alternative treatment strategies for elimination of onchocerciasis. WHO/MG/15.22

2016: Guidelines for stopping mass drug administration and verifying elimination of human onchocerciasis: criteria and procedures. WHO/HTM/NTD/PCT/2016.1

Filariasis coendemicity

2012. Provisional strategy for interrupting lymphatic filariasis transmission in loiasis-endemic countries. WHO/HTM/NTD/PCT/2012.6

2016. Integrating national programmes to eliminate lymphatic filariasis and onchocerciasis. WHO/HTM/NTD/PCT/2016.4

elimination [80]. Currently, the new FTS is the main diagnostic tool being used to assess the different phases of transmission. For mapping in LF–loiasis coendemic areas, the antigen test cross-reactivity problem suggests that the specificity of the Wb123 or Ov-16/Wb123 tests may be considered conditional or alternatives that can better discriminate between *W. bancrofti* and *L. loa* infections [36,81].

For post-MDA surveillance, a geographical area or an evaluation unit (EU) is used for the new **transmission assessment survey (TAS)**. The TAS is a survey tool with LQAS-like critical cut-off for decision making, which is used to assess if the prevalence is <2% in children aged 6–7 years, and is conducted three times over a period of 5–6 years as TAS1, TAS2, and TAS3 [79].

Table 1. WHO Recommended Surveillance Strategies for Lymphatic Filariasis (LF) Elimination in Africa

Elimination phases	Duration/timing	Purpose	Host	WHO test	Target population	Sample size and thresholds	New test	Conditional/potential alternative test
Mapping Phase	Before the start of MDA	Establish the endemicity in an area considered to be possibly endemic and may require MDA	Human	mf or ICT	>15 years living in community for >10 years	50–100 people per site in two high-risk villages at least 25 km apart ≥1% endemicity cut-off	FTS	Wb123 RDT (SD Bioline) Biplex Wb123/Ov-16 in *Loa* endemic areas
MDA Phase	Over 5–6 years at baseline, before 4th MDA round (optional) and before 6th MDA round	Monitor trends in infection; determine eligibility for stopping MDA	Human	mf or ICT	People aged >5 years at one sentinel and spot-check site per 1 million population	300 people in villages with more than 500 people	FTS	Wb123 RDT (SD Bioline) Biplex Wb123/Ov-16 in *Loa* endemic areas
Post-MDA surveillance phase	Over 4–6 years with TAS to be conducted at 2-yearly intervals – TAS 1, TAS 2, and TAS 3	Confirm interruption of transmission at the end of MDA	Human	ICT	Children 6–7 years selected from census, systematic if cluster surveys in schools or communities	~1500 to 3000 children depending upon sampling approach <2%	FTS	
Ongoing surveillance	Regular	Detect recurrence of transmission	Human		Mixed population groups	–		

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Additional WHO reports have addressed reasons for TAS failure and to help identify corrective actions useful for national programmes [82]. However, overall, the TAS methodology is considered to be a useful survey platform and is increasingly being used to assess other diseases and strategies concurrently, or low transmission areas in Africa and elsewhere [83–85].

For LF morbidity, the WHO has developed a manual [86] and list of key indicators within the new Dossier template, which are required for the validation of elimination of LF as a public health problem, and will help to strengthen health systems to deliver the minimum package of care: (i) disease burden – estimates of the number of lymphoedema and hydrocoele patients per IU; (ii) availability of MMDP services – the number of facilities providing services for IUs with known patients; and (iii) readiness and quality of MMDP – preferred assessment of at least 10% of designated facilities [87].

For Onchocerciasis

The recent WHO elimination guidelines outline three phases requiring two different approaches in human populations and female black fly vectors, summarised in Table 2 [21]. Vector surveillance by O-150 PCR is recommended for use at the end of treatment (Phase 1) to demonstrate the interruption of transmission and discontinue MDA, at the end of post-treatment surveillance (Phase 2) to confirm the interruption of transmission, and regularly for post-elimination surveillance (Phase 3). Surveillance requires a sample of 6000 flies collected from a transmission zone, where less than 1 in 1000 parous flies (<0.1%) and less than 1 in 2000 flies in total (<0.05%) should carry infective L3 larvae, at the upper bound of the 95% confidence interval [21].

Human surveillance to detect exposure to *O. volvulus* and ongoing transmission using the Ov-16 ELISA is recommended at the end of Phase 1, and conditionally in Phase 2, when the result of black fly O-150 PCR equals or is near the threshold, or in the case of insufficient flies or their absence [88]. A sample of 2000 children <10 years of age from sentinel populations is required, and <0.1% of children should have positive serology at the upper bound of the 95% confidence interval. The Ov-16 RDT has the potential to replace the ELISA, but requires further validation in different settings before it can be used in elimination programmes [89]. Skin snip PCR is also indicated during Phase 1 and 2 for use in some limited situations where there are a few seropositive children (<10 children). Skin snip microscopy and the DEC-patch test may only be used during Phase 1, and not to demonstrate interruption of transmission. Skin snips may be used during transition to using Ov-16 serology at this time, where the tests should be used in parallel.

For Loiasis Coendemicity

For LF–loiasis coendemic areas, the WHO published a provisional strategy recommending biannual albendazole plus vector control, including insecticide treated/long-lasting impregnated bednets (ITNs/LLINs), for the elimination of LF in loiasis-endemic areas [90,91]. A practical approach for scaling up this alternative strategy has been developed to help national programmes prepare action plans and start implementation [92].

For onchocerciasis hypo-endemic areas, where the risk of SAEs in people with loiasis is considered to outweigh the benefits of implementing CDTI, alternative TaNT strategies are recommended. The initial recommendation included using microscopy to identify people with *L. loa* microfilaraemia at risk of SAEs in order to exclude them from treatment [93]. This has been extended to include the use of the new rapid LoaScope, with two possible TaNT approaches: Loa-first and Oncho-first [71,72]. Loa-first tests people for *L. loa* first to identify those with high mf levels

Table 2. WHO Recommended Surveillance Strategies for Onchocerciasis Elimination in Africa

Elimination phases	Duration/timing	Purpose	Host	WHO test	Target population	Sample size and thresholds	New test	Conditional test/potential alternative test
Phase 1 Treatment phase	At least 12–15 years	Demonstrate interruption of transmission for purpose of stopping MDA	Human	Ov-16 ELISA	Children in sentinel sites aged <10 years	Sample 2000 children. An upper bound of the 95% confidence interval (CI) <0.1%	Ov-16 RDT	(i) Skin snip microscopy: May only be used in parallel to Ov-16 serology, during transition to serological testing (ii) DEC-patch test: Monitor progress during treatment (iii) Skin snip PCR: Indicated for use where few Ov-16 serologically positive children (<10) are detected >0.1% threshold (iv) LoaScope (TaNT strategy)
			Vector	O-150 PCR	Black flies (pool screen)	Minimum 6000 flies An upper bound 95% CI of <0.1% (<1/1000) in parous files and <0.05% (<1/2000) in all flies		
Phase 2 Post-treatment phase	3–5 years	Confirm interruption of transmission at the end of the post-treatment period	Human	Ov-16 ELISA	Children in sentinel sites aged <10 years	–	Ov-16 RDT	Skin snip PCR: Indicated for use where few Ov-16 serologically positive children (<10) are detected >0.1% threshold
Phase 3 Post-elimination surveillance	Regularly until the no risk of recrudescence	Confirm elimination of transmission has been sustained	Vector	O-150 PCR	Black flies (pool screen)	–		

at risk of SAEs, and excludes them from treatment with ivermectin. People infected with high levels of *L. loa* can then be tested for infection with *O. volvulus*, and if positive, can be given an alternative treatment such as the macrofilaricidal drug doxycycline. Oncho-first tests people for onchocerciasis first, and positive individuals can then be tested for *L. loa* before making decisions on what treatment can be safely administered, whereas the *O. volvulus*-negative individuals do not receive treatment [60,94,95]. However, none of the currently available POCTs for onchocerciasis, such as skin snips, the DEC patch test, or the Ov-16 RDT, are sensitive enough to completely rule out infection, particularly in hypo-endemic areas where measures of infection may be very low or absent [55,89]. Therefore, a caveat to strategies that rely on detecting people with *O. volvulus* before providing treatment is that this may result in withholding treatment from people who are actually positive but test false-negative.

Data Connectivity

In terms of data connectivity, the most recent and significant development is the availability of programmatic and research data via online open-access data portals, which aim to harmonise data flow into a single repository. Rapid advances in mobile technology have enabled the expansion of smartphone-based data collection platforms.

Data Portals

There are now many NTD data portals available online – see Box 2. The WHO has increased its scope and availability of data with the aim of strengthening effective data storage, data management and sharing, as well as to improve the timeliness and completeness of reporting through more standardised forms to WHO and NTD partners. Currently the portal with the largest and most detailed data related to LF, onchocerciasis, and loiasis in Africa is via the ESPEN. The integrated database provides continental-, national-, and subnational-level

Box 2. Data Portals Related to Lymphatic Filariasis (LF) and Onchocerciasis Surveillance

World Health Organization

Integrated NTD database: http://www.who.int/neglected_diseases/data/ntddatabase/en/

PC Data Portal: http://apps.who.int/gho/cabinet/pc.jsp

PCT databank: http://www.who.int/neglected_diseases/preventive_chemotherapy/databank/en/

Global Health Observatory data repository: http://apps.who.int/gho/data/node.main.A1629?lang=en

Global Health Observatory data: http://www.who.int/gho/neglected_diseases/en/

ESPEN AFRO-NTD Portal: http://espen.afro.who.int/

Other

NTD Map: http://www.ntdmap.org/

Global NTD database: https://www.gntd.org/

Global Atlas of Helminth Infection data: http://www.thiswormyworld.org/data-download

NTD database: https://www.ntddatabase.org/?q=content/welcome

ChEMBL-NTD: https://www.ebi.ac.uk/chemblntd

information on endemicity, coendemicity, mapping surveys, sentinel sites, TAS, MDA rounds, and MDA coverage. There are several other data portals with a variety of programmatic and research-based data available; however, the detail on LF, onchocerciasis, and loiasis in Africa varies considerably and the extent to which they link with WHO portals and national programmes is unclear.

mHealth Tools

Rapid developments in mobile technology have enabled the development of smartphone-based data collection platforms, such as the LINKS system, an Android-, web-based system [96]. The LINKS system allows the collection of a wide range of data through the open source project Open Data Kit (ODK), helping to reduce costs, increase speed and flexibility, and improve data quality. By incorporating the inbuilt GPS component of modern smartphones, LINKS has also been used to map the prevalence of NTDs in 37 countries, demonstrate scalability, and specifically to conduct a large-scale integrated TAS assessment [84].

The **mobile health (mHealth)** tool 'MeasureSMS-Morbidity' has provided a unique platform for readily reporting morbidity cases in endemic IUs, which is required by the Dossier in order for National programmes to show they can appropriately plan and deliver the minimum package of care to those people affected by lymphoedema and hydrocoele [48,49,97,98]. The tool is innovative as it allows community health workers to use their own phone to send clinical information in a simple format using short message service (SMS). The data are sent to a server in-country, which then automatically collates the data via a web browser for analysis. From this, morbidity maps can be developed and the distribution of interventions monitored by the National programmes. The tool has been used in more than seven countries covering more than 30 million people to date.

Analysis and Interpretation: Mapping and Modelling

Mapping

There has been an increase in the use of large-scale multicountry prevalence, environmental and demographic data to create continental-level risk maps using geo-spatial-statistical methods. For LF, maps were developed from mf (1224 surveys) and ICT (3519 surveys) data in the literature, and by using environmental and demographic data and spatiotemporal models within a Bayesian framework [99]. The predicted mf distribution is shown in Figure 4A. However, these maps need to be revised with different diagnostic and sampling strategies as a recent review highlights that there is increasing evidence of low or no LF in high-risk *L. loa* areas [100], and surveys using ICT in these areas are likely to be invalid due to the *L. loa* cross-reactively problem [35–38]. For onchocerciasis, the first precontrol map was developed from microfilarial (737 villages) data collected across 11 OCP countries in West African using Bayesian geostatistical methods and environmental covariates [101]. Further, estimated prevalence maps of palpable nodules were developed from REMO survey data collected across 20 APOC countries (14 473 villages), and by using environmental and demographic data for model-based geostatistical analysis (Figure 4B) [102]. For loiasis, maps were developed from RAPLOA survey data collected across 11 countries (4798 villages) with the geostatistical method of kriging used to produce interpolated prevalence estimates of eye worm history (Figure 4C), and predictive probability maps of prevalence >40% to highlight areas at risk of SAEs [70].

Microstratification overlap mapping (MOM), is a new concept, first used for LF to understand the coendemicity of filarial infections and codistribution of effective interventions to define more

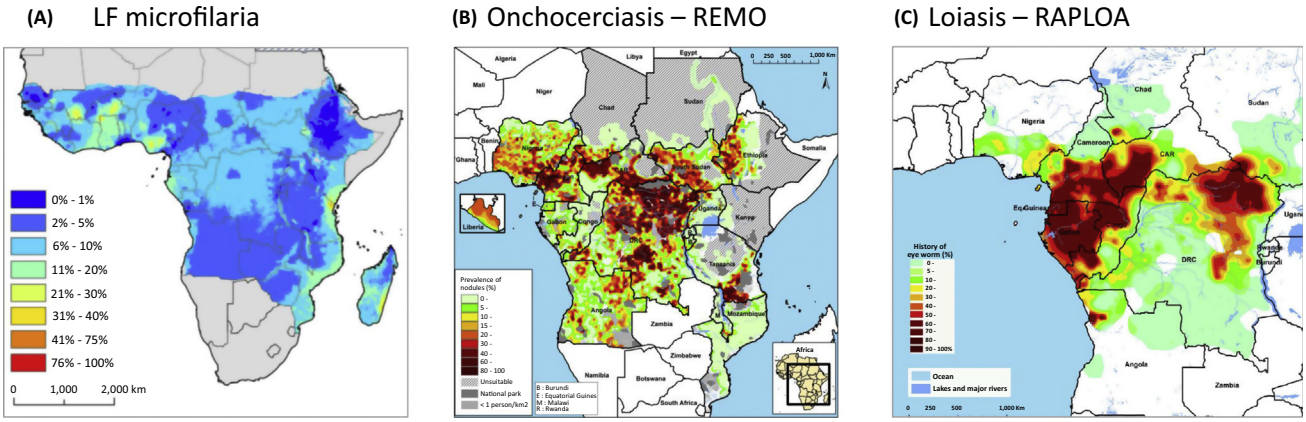

Figure 4. Sub-Saharan African Maps of Lymphatic Filariasis, Onchocerciasis, and Loiasis Distribution. LF, lymphatic filariasis; REMO, Rapid Epidemiological Mapping of Onchocerciasis; RAPLOA, Rapid Assessment Procedure for Loiasis.

precisely where and what strategies may be implemented in *L. loa* coendemic areas [103,104]. The MOM concept has extended to address the risk of SAEs, hypo-endemic hotspots, and help develop mapping, treatment, and surveillance strategies [92,105–107]. Integrated micro-mapping is a further new mapping method, first used with REMO and RAPLOA methods to highlight microepidemiologies [108], and then extended to also include LF clinical indicators [109,110].

Modelling

The new NTD Modelling Consortium brings together infectious disease modellers from 12 academic institutions and aims to reduce the burden of nine NTDs, including LF and onchocerciasis (https://www.ntdmodelling.org/).

With respect to elimination, robust mathematical models are crucial to enable policy makers to consider: whether elimination targets are feasible with current and/or acceleration strategies; whether elimination may be thwarted by systematic nonadherence and/or low coverage, and which criteria could be used to determine when to safely halt MDA for post-treatment surveillance [111].

For both LF and onchocerciasis, there are well established deterministic models (do not account for random variation) and stochastic models (do account for random variation). For LF, these include: EPIFIL (deterministic), LYMFASIM (stochastic), and TRANSFIL (stochastic) [112,113]. For onchocerciasis these include: EPIONCHO (deterministic) and ONCHOSIM (stochastic, with a deterministic component) [114].

It is important to recognise that, as well as using different statistical methods to reach their predictions, each of these models is based on data from different epidemiological settings. Over time, with increasing knowledge of transmission dynamics in different epidemiological settings with different interventions, these models have undergone multiple adaptations to optimise the reliability of their predictions [112].

One innovative adaptation has been to combine three of the key model frameworks together in a ‘multi-model ensemble’ [113]. Despite intrinsic variance between individual models, their

predictions of intervention impact were more plausible when combined than individually. Tools to calibrate simulation models have also been developed, for example a 'Bayesian melding framework' which was developed using surveillance data from 22 geographically distinct sites [115]. Novel models have also been developed, for example a stochastic version of EPIFIL, without immunity [116].

As loiasis is not currently recognised as an NTD by WHO, mathematical models for neither its transmission nor control have been developed but have been suggested as a research and development priority [10]. The main priority for *Loa* modelling has been in predicting the distribution of infection intensity: to determine where the greatest risk of SAEs are during MDA for LF and onchocerciasis [117].

Concluding Remarks

All the new strategies presented in this review will play an essential role in the elimination of LF and onchocerciasis and need to be considered holistically with better linkages and greater cross-disease integration. It will be important to ensure that National NTD Programmes have access to all the available tools, and that there is sufficient national capacity to implement and contextualise these new tools and methodologies. This will require WHO and other stakeholders to prioritise the development of the human resources and specialised capacity within countries to enhance technical knowledge, and importantly, to translate that policy knowledge into practice as the essential framework for satisfying the achievement of the programmatic goal of elimination.

Outstanding Questions

How to better integrate the different components and tools of surveillance into a more holistic format?

How to coordinate the surveillance priorities between the diverse range of partners?

How to maintain updated surveillance strategies as new diagnostics and drug regimens are introduced?

How to combine the different elimination threshold measures between diseases?

How to introduce high-tech complex diagnostic tools to the community level?

How to better use the tools and technologies currently available on a larger scale?

How to ensure NTD programme can access and use the data available to inform decisions?

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