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Background

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What is Lymphatic Filariasis?

Lymphatic filariasis (LF) is caused by a group of parasitic worms that are transmitted through the bites of infected mosquitoes. Although the majority of people infected with these parasites are asymptomatic, slow damage to the lymphatic system and other organs from chronic infection leads to a variety of pathologies ranging from sub-clinical damage through severe disfigurement. The most well recognized manifestation of LF is elephantiasis, the swelling of the limbs or genitals with lymph fluid that results from total blockage of the lymphatic system by adult worms.

Global Burden



Countries endemic for lymphatic filariasis (WHO, 2006)

LF is estimated to affect more than 120 million people worldwide, 98% of whom live in the tropical and subtropical regions of Africa and Asia.¹ There are 81 countries with endemic LF and a total population of more than 1.3 billion at risk for infection.² Approximately one third of infected individuals have physical manifestations of elephantiasis.

Physical disabilities due to elephantiasis and other chronic organ damage result in the loss of nearly 6 million DALYs per year as summarized in the table below. The greatest impact is in Asia followed by Africa.

WHO Region	DALY (in thousands) ³
Africa	2,263
Americas	10
Eastern Mediterranean	75
Southeast Asia	3,525
Western Pacific	65
Total:	5,938

In 1997, the World Health Assembly called for a resolution to eliminate LF as a global health problem within 20 years. As a result, the World Health Organization (WHO) launched the Global Program to Eliminate Lymphatic Filariasis (GPELF) in 2000 with the goal of eliminating LF by the year 2020.

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Causative Agent and Transmission



Microfilaria of the LF pathogen *Wuchereria* bancrofti in a blood smear. (photo: CDC/Mae Melvin)

LF is caused by three species of filarial worms (a subset of roundworms and other helminths): *Wuchereria bancrofti, Brugia malayi*, and *Brugia timori*. Nearly 90% of all infections are caused by *W. bancrofti*. Brugia spp. are far less common and are more restricted to Asia, especially India, Malaysia, Indonesia, and the Philippines. Larvae of all three species are transmitted to humans through the bite of an infected mosquito.

Upon taking a blood meal, an infected mosquito introduces larvae of the parasite into the skin. The larvae migrate through the skin to the lymphatic system where they mature into adult male and female worms over the course of 6-12 months. The term macrofilariae describes the adult worms. The term "filariae" means "thread-like,"□ an appropriate description for a parasite where female adult worms can grow up to 10 cm in length. The adult male and female worms continue to reside in the lymphatics where they mate and produce large numbers of eggs, called microfilariae. The microfilariae circulate in the blood stream where they can be picked up by a biting mosquito. Adult worms can live for many years, continuously producing microfilariae and contributing to ongoing transmission of the disease.



W. bancrofti life cycle. Click to view

Unlike many other vector-borne parasitic diseases, where parasites are only transmitted by a very narrow range of vector species, LF parasites are transmitted by many species of mosquitoes across the genera of *Culex*, *Aedes*, *Anopheles*, and *Mansonia*. Mosquitoes become infected when taking a blood meal from a person with circulating microfilariae. Within the mosquito, the microfilariae egg hatches and the parasite begins larval development. Larvae are then injected into the skin of another human when the infected mosquito takes a blood meal. There is no animal reservoir for the parasites that cause human LF, so mosquitoes transmit parasites directly from humans to humans.

Pathogenesis

Adult worms, or macrofilariae, cause long-term damage to the vessels of the lymphatic system. The strong inflammatory response to the presence of adult worms causes dilation, thickening, and eventually incompetence of lymph vessels. This damage results in lymphedema or swellings of the limbs due to accumulation of lymphatic fluids, thus producing the classic presentation of elephantiasis. Of those infected with LF parasites, approximately 20% (predominantly men) have genital manifestations of disease and an additional 13% (predominantly women) have elephantiasis or lymphedema of the leg.⁴

Beyond classic elephantiasis, imbalances in the lymphatic system due to LF can cause damage to multiple organs. Nearly 40% of those affected by LF have measurable kidney damage.⁴

Control Strategy

The current control strategy for LF is guided by the GPELF and includes:

- 1. Extensive mapping to understand the full extent of the burden of LF
- 2. Vector control
- 3. Mass drug administration (MDA)
- 4. Integration of LF control programs with other neglected tropical disease control programs

Mapping is being used to help guide control programs and determine optimal interventions for different countries or regions. The global status of LF has been mapped for 68 of the 81 endemic countries and mapping is ongoing to 10 additional countries. Mapping remains challenging in several countries. Areas with extreme government instability, limited infrastructure, and the potential for violence against surveyors are difficult to access to conduct surveys and analysis.

Vector control for LF, focusing on indoor residual spraying and the use of long lasting insecticide treated nets (LLITNs), overlaps with vector control strategies for other diseases such as malaria. In countries with both malaria and LF, particularly in Africa, integrated strategies for vector management are poised to benefit control programs for both diseases.

MDA is the cornerstone of the LF elimination program. The goal is to target all individuals, including children, in endemic areas to take a once yearly dose of a combination of two medications for 4-6 years or to use drug-fortified table salt for 1-2 years (see next section on Existing Products: Drugs for details of these medications). The rationale is that by decreasing the number of microfilariae circulating in the human population, transmission of parasites to mosquitoes will be interrupted followed by interruption of transmission to humans. MDA programs began in 2000 with the help from drug donations from GlaxoSmithKline (GSK) and Merck. Cumulatively since 2000, over 2.8 billion MDA doses have been given in 53 endemic countries.⁵

Both vector control and MDA overlap with strategies being employed for other neglected tropical disease control programs. Better integration of activities across programs with different disease focuses will help ensure that resource use is optimized to provide the greatest health benefit.

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Existing Products

Drugs

There are three drugs currently in use for the treatment of LF: albendazole (GSK), ivermectin (Merck), and diethylcarbamzine/DEC. Albendazole is administered in combination with either ivermectin or DEC through MDA programs. DEC is also used in fortified salt for use in cooking as an alternative MDA strategy. Both albendazole and ivermectin are donated by GSK and Merck for MDA programs, while DEC must be purchased. The estimated cost for one MDA dose per person is US\$0.05-0.10.²

Although these drugs are highly effective in removing microfilariae from the blood, there are several limitations:

- 1. None of these three drugs kills the adult worms requiring retreatment each year until the adult worm dies
- 2. DEC cannot be used in regions with co-endemic onchocerciasis (a related filarial worm) due to the risk of serious side effects
- 3. Ivermectin cannot be used in regions with co-endemic Loa Loa disease (a related filarial worm) due to the risk of serious side effects

Vaccines

There is currently no vaccine for the prevention of LF.

Diagnostics

Diagnosis of LF is primarily done through immunochromatographic cards test kits. These kits rapidly detect antigen in blood samples collected during MDA treatment programs. When parasite antigen is no longer detectable in the blood of a sampling of patients in a village, decisions regarding stopping MDA in that village can be made. There are two disadvantages to this test: 1) the test only detects *W. bancrofti*, and 2) the test costs US\$2-4 per person which is too expensive to support programs actively treating more than 380 million people per year.⁵

Traditional diagnosis of LF is conducted by microscopy to detect circulating microfilariae. As the microfilariae primarily circulate at night, it is not easy to obtain appropriate blood samples to evaluate by microscopy. Furthermore, microscopy requires equipment and a

trained technician which are not practical for accompanying MDA programs to rural areas.

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References

- 1. WHO Lymphatic Filariasis.
- 2. WHO (2010) First WHO report on neglected tropical diseases 2010: working to overcome the global impact of neglected tropical diseases.
- 3. WHO (2004) Global Burden of Disease.
- 4. WHO Lymphatic Filariasis.
- 5. WHO (2010) Progress report 2000-2009 and strategic plan 2010-2020 of the global programme to eliminate lymphatic filariasis: halfway towards eliminating lymphatic filariasis.

Get Involved

To learn how you can get involved in neglected disease drug, vaccine or diagnostic research and development, or to provide updates, changes, or corrections to the Global Health Primer website, please view our FAQs or contact us at globalhealthprimer@bvgh.org.

Pipeline & Analysis

Drugs | Vaccines | Diagnostics | Get Involved

Drugs

PIPELINE

Product/Research Program	Developers	Discovery	Pre-clinical	Phase I	Phase II	Phase III
Anti-wolbachia consortium	Bill & Melinda Gates Foundation Liverpool School of Tropical Medicine					
Oxaboroles for the treatment of human lymphatic filariasis	Anacor Pharmaceuticals, Inc.					

ANALYSIS

There are no new drugs in clinical development for LF. Instead, efforts are focused on increasing access and distribution of existing drugs through MDA programs.

There are two discovery stage drug development programs for LF focusing on identification of new drugs that can kill the adult form of the worm, i.e., macrofilaricides. Killing the adult worm would prevent production of new microfilariae rather than just killing currently circulating microfiliariae. This process would speed the progress toward elimination by reducing the number of rounds of MDA required to stop transmission of the parasite. This strategy may be particularly beneficial in countries with government instability, conflict, or other factors limiting the implementation of multi-year MDA programs with existing drugs.

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Vaccines

PIPELINE

Product/Research Program	Developers	Discovery	Pre-clinical	Phase I	Phase II	Phase III
rWbGST	University of Illinois - Chicago					
Immunodominant B epitopes (TRX(P1) and TRX(P2)) from thioredoxin	Anna University, Chennai					

ANALYSIS

There are no vaccines in clinical development for LF. Although there are discovery programs underway to assess antigens for potential vaccine development, the extremely low cost of current medications in combination with the huge at risk population that would need to be vaccinated would suggest development and rollout of a vaccine would be far less cost effective than continuing to scale up MDA.

As with new drug development, a vaccine that could block the production of new microfilariae would have value beyond existing tools to fight LF. It might also be easier to produce than a fully preventive vaccine. Again, the high cost of new vaccine development relative to the cost of scaling up of existing MDA programs is likely to be prohibitive.

Diagnostics

Future generations of LF diagnostics should be less expensive, detect both *W. bancrofti* and *Brugia* spp. parasites, and would preferably work with urine or saliva samples in place of blood to simplify use.

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Tools

Drugs | Vaccines | Diagnostics | Get Involved

The following series of tables describe the availability of tools for research, discovery, and development of novel drugs, vaccines, and diagnostics for lymphatic filariasis. The tools listed in the following tables are not intended to be an all-inclusive list but rather capture the most common tools used for drug, vaccine, and diagnostic development. The tools for lymphatic filariasis are extremely limited.

Drug Development Tools

Basic Research: Target Identification	Target Validation	Screening: Hit/Lead Identification Optimization	Pre-clinical Validation	Clinical Validation
Genome: Draft genome, <i>Brugia</i> malayi only Genome sequences for symbiotic wolbachia bacteria (potential alternative drug target) Key databases: GenBank: AAQA0000000 (<i>B. malayi</i>) and AE017321 (wolbachia) In vitro culture: Yes, <i>B. malayi</i>	Gene knock-outs: NoConditional gene knock-outs: NoTransposon mutagenesis: NoTransposon mutagenesis: NoRNAi: NOOther antisense technology: NoOther antisense technology: NoViability assays: Yes, B. malayiTranscription microarrays: Yes, B. malayiProteomics: Yes, B. malayiCrystal structures: Yes, limited	Whole-cell screening assays: No Enzymatic screening assays: Minimal	Animal models: Limited, <i>B. malayi</i> in Mongolian jird, ferret, or immune deficient mouse	Monitoring treatment efficacy: Yes Availability of endpoints: Yes, clearance of microfilariae Availability of surrogate endpoints: No Access to clinical trial patients/sites: Yes

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Vaccine Development Tools

Basic Research: Antigen Identification	Immune Response Characterization	Clinical Validation
See drug development tools	Predictive animal models: No	Surrogate markers of

Detection of endogenous antigen specific response in clinical samples: Yes

Natural immunity well characterized: Minimal understanding

protection: No

Challenge studies possible: No

Diagnostic Development Tools

Basic Research: Biomarker Identification	Biomarker Validation	Clinical Validation
See drug development tools above	 Biomarkers known: Yes Access to clinical samples: Yes, from MDA program monitoring Possible sample types: Blood, urine, or saliva would be preferred but not well explored 	Access to clinical trial patients/sites: Yes Treatment available if diagnosed: Yes

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Product Details

Anti-wolbachia consortium

Synonyms: Anti-wolbachia co	Disease: Disease: Lymphatic fila	Target/Technology:ariasis (LF)Unknown
	Specific Indi Product Type Drug	cation: Mechanism of Action: Microbicide of symbiotic wolbachia bacteria e: Molecule Class:
	PRV Elegible Yes	? Administration Route:
Notes:	Clinical Trials:	Publications:

Immunodominant B epitopes (TRX(P1) and TRX(P2)) from thioredoxin

Synonyms: Immunodominant B epitopes (TRX(P1) and TRX(P2)) from thioredoxin	B epitopes (TRX(P1)	Disease: Lymphatic filariasis (LF)	Target/Technology: Peptide
	m thioredoxin	Specific Indication: Brugia malayi	Mechanism of Action: Molecule Class:
		Product Type: Vaccine	Administration Route:
		PRV Elegible? Yes	
Notes:	Clinical Trials:		Publications:
			20685198
Oxaboroles for	r the treatment of h	uman lymphatic filaria	sis

Synonyms: Oxaboroles for the treatment of human lymphatic filariasis	Disease: Lymphatic filariasis (LF)	Target/Technology: Boron Chemistry
	Specific Indication:	Mechanism of Action:
	Product Type: Drug	Molecule Class: Oxaborole
	PRV Elegible? Yes	Administration Route:

Notes:

Publications:

rWbGST

Synonyms: rWbGST	Disease: Lymphatic filariasis (LF)	Target/Technology: Recombinant/purified protein vaccines
	Specific Indication: Wuchereria bancrofti	Mechanism of Action:
		Molecule Class:
	Product Type: Vaccine	Administration Route:
	PRV Elegible?	
	Yes	
Notes:	Clinical Trials:	Publications:
		19513102

Developer Details

University of Illinois - Chicago (United States)

Туре	Disease	Product/Research Program	Current Phase
Vaccine	Lymphatic filariasis (LF)	rWbGST	Discovery

Anna University, Chennai (India)

Туре	Disease	Product/Research Program	Current Phase
Vaccine	Lymphatic filariasis (LF)	Immunodominant B epitopes (TRX(P1) and TRX(P2)) from thioredoxin	Discovery

Bill & Melinda Gates Foundation (United States)

Туре	Disease	Product/Research Program	Current Phase
Drug	Lymphatic filariasis (LF)	Anti-wolbachia consortium	Discovery

Liverpool School of Tropical Medicine (United Kingdom)

Туре	Disease	Product/Research Program	Current Phase
Drug	Lymphatic filariasis (LF)	Anti-wolbachia consortium	Discovery

Anacor Pharmaceuticals, Inc. (United States)

	Туре	Disease	Product/Research Program	Current Phase
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Drug L	Lymphatic filariasis (LF)	Oxaboroles for the treatment of human lymphatic filariasis	Discovery
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GlaxoSmithKline (United Kingdom)

Туре	Disease	Product/Research Program	Current Phase
Drug	Lymphatic filariasis (LF)	Albendazole	Approved

<u>Eisai Inc.</u> (Japan)

Туре	Disease	Product/Research Program	Current Phase
Drug	Lymphatic filariasis (LF)	DEC	Approved

SAFC Global

Туре	Disease	Product/Research Program	Current Phase
Drug	Lymphatic filariasis (LF)	DEC	Approved

Merck & Co., Inc. (United States)

Туре	Disease	Product/Research Program	Current Phase
Drug	Lymphatic filariasis (LF)	Ivermectin (for LF)	Approved