Nematode Infections: Filariases

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KEYWORDS

• Filariasis • *Dracunculus medinensis* • *Loa loa* • *Mansonella perstans* • *Onchocerca volvulus* • *Wuchereria bancrofti* • Epidemiology • Control

KEY POINTS

- More than 150 million people are affected by filarial infections that cause debilitating and irreversible disease outcomes; yet they belong to the "neglected tropical diseases."
- Filariae are not transmitted in Europe and North America, but travel clinics must be aware as infections might occur in immigrants, refugees, and long-term travelers.
- Available drugs reduce filariae transmission in endemic areas but do not mitigate disease symptoms.
- Current drugs can cause severe adverse reactions due to dying microfilariae, and must be applied with great care.
- Diagnostic tools to differentiate between pre-patent, patent, and post-patent infections are important for patient management and filariasis control with the ultimate goal of elimination.

Human diseases caused by filarial nematode infections are among the most debilitating and disfiguring ones described in the literature. Tens of millions of people are affected, yet they belong to the "neglected tropical diseases" and the "neglected infections of poverty."[1,2] One reason for this general neglect is that filarial nematodes

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are restricted to the tropics and subtropics, and are not transmitted in Europe and North America.[1] However, imported infections do occur in immigrants and refugees from endemic countries, and may occasionally be seen in long-term travelers and expatriates. Hence, clinics specialized in tropical and travel medicine must be aware of these diseases.[3]

Filariae larvae are transmitted by insect vectors. Adult worms live in defined areas of the body, specific for each filariae species. Several months or years after infection, either adult worms or their offspring (ie, microfilariae), cause disease-specific symptoms.[1] Among them are well-known disease outcomes, characterized by the emergence of a spaghetti-like worm (dracunculiasis), awfully enlarged extremities (elephantiasis), blindness and leopard skin (onchocerciasis), or small worms migrating through the eye (loiasis). Considerable progress has been made in the control and eventual elimination of filariae infections since the new millennium.[1,4,5] Mass drug administration (MDA) and large-scale vector control serve as the backbone of interventions.[6–9] While *Dracunculus medinensis* is close to being eradicated,[10] there are still an estimated 120 million people infected with lymphatic filariae (Wuchereria bancrofti, Brugia malayi, Brugia timori),[1] and 37 million people infected with *Onchocerca volvulus*.[1] Far fewer people are currently infected with *Loa loa* and *Mansonella perstans*, yet diseases caused by these filarial nematodes are of considerable public health importance.[11,12] At present, global burden of disease estimates are only available for lymphatic filariasis and onchocerciasis; they are as high as 5.9 million and 0.4 million disability-adjusted life years (DALYs), respectively.[2,13] Drugs, currently applied against filarial infections for mass treatment of at-risk populations, such as albendazole and ivermectin, are effective against larvae, but do not kill adult worms.[1,14] Hence, transmission can be reduced, but the diseases cannot be cured by drug intake and require other measures of mitigation.

This article describes the epidemiology of the most important filarial infections, including current distribution, life cycles, clinical features and associated burden, diagnostic approaches and treatment, and tools for prevention and control. Moreover, preventive measures for travelers are suggested (**Box 1**), and vulnerable groups and case numbers in North America identified (**Box 2**).

DRACUNCULIASIS OR GUINEA WORM DISEASE (*DRACUNCULUS MEDINENSIS*)

Life Cycle and Epidemiology

D medinensis, also known as the fiery serpent or guinea worm, is a memorable parasite. Humans become infected with guinea worm when drinking surface water that contains the intermediate host, a copepod of the genus *Cyclops*, which harbors infective third-stage larvae (L_3) (**Table 1**). Within the stomach, gastric juices kill the *Cyclops* and the guinea worm larvae are released. Those then migrate to the small intestine, penetrate the intestinal wall, and enter the abdominal cavity and retroperitoneal space. Male and female worms mate 60 to 90 days after infection. Within a year, fertilized female guinea worms grow and migrate to the skin surface, particularly of the lower limbs. The male worms die shortly after mating and are sometimes found calcified in different parts of the body (**Fig. 1**). Once the female worm reaches its final destination, it induces the formation of an aching blister and starts to emerge through the skin. Patients, who cool their aching legs in water, stimulate the female worm to release thousands of larvae. The larvae then live up to 3 days in the water or until they are ingested by *Cyclops*, in which, over a period of 2 weeks and 2 molts, they develop into infective larvae. The life cycle is completed when humans swallow infected *Cyclops*.[19,20] Dracunculiasis shows a strong seasonal pattern, and is associated

Box 1
Preventive measures against filarial infections for travelers

Dracunculus medinensis

- Avoid the ingestion of *Cyclops*
  - Do not drink unfiltered water from ponds or slow flowing rivers

Onchocerca volvulus

- Avoid bites of the day-active *Simulium* vector
  - Wear long clothes
  - Use insect repellents
  - Stay indoors
  - Ivermectin 150 μg/kg twice a year as preventive measure

Lymphatic filariae

- Avoid bites of the mosquito vectors
  - Wear long clothes
  - Use insect repellents
  - Sleep under a bednet (preferably long-lasting insecticide treated)

Loa loa

- Avoid bites of the day-active *Chrysops* vector
  - Wear long clothes
  - Use insect repellents
  - Diethylcarbamazine 300 mg/wk in long-term travelers to areas of high endemicity[3,15]

Mansonella perstans

- Avoid bites of the *Culicoides* vector
  - Wear long clothes
  - Use insect repellents

with either the rainy or dry seasons, whenever drinking from ponds or stagnant water sources becomes more likely and water bodies are of a size that favors transmission of the worm.

In 1986 guinea worm was still endemic in 20 countries of Africa and Asia, with an estimated 3.5 million people infected. The yearly incidence rate was 400,000 cases. In 1991, during the 44th World Health Assembly (WHA), member states endorsed the eradication of guinea worm disease.[21] In the meantime, great progress has been made in this regard thanks to concerted efforts spearheaded by the Carter Center (http://www.cartercenter.org/index.html). Indeed, in 2010 fewer than 2000 cases of guinea worm were reported in just a few very remote villages in only 6 African countries, namely Chad, Ethiopia, Ghana, Mali, Niger, and Sudan.[21–23] Provisional data for 2011 suggest that case numbers dropped to 1060, and that dracunculiasis only occurred in Chad, Ethiopia, Mali, and South Sudan. Nowadays, the greatest challenges to ultimately reach the goal of eradication are human migration, social and economic crisis, and armed conflict, particularly in areas of South Sudan where 97% of all registered cases occurred in 2011.[21]

Box 2
Filariasis in North America

Although filariases are not transmitted in North America, travel to endemic countries leads to exposure to filarial parasites and renders infections possible. In addition, imported cases are seen among recent immigrants from endemic countries. Currently, all presented filarial infections are listed as "rare disease" by the Office of Rare Diseases Research of the National Institutes of Health, and hence likely affect fewer than 200,000 people in the United States.

Dracunculus medinensis

- No case of dracunculiasis transmitted in the United States has ever been reported[16]
- Two cases (one in 1995 and one in 1997) were seen in the United States among refugees from Sudan[16]

Onchocerca volvulus

- Most infections seen in the United States occur in expatriate groups, such as missionaries, field scientists, and Peace Corps volunteers[17]
- Short-term travelers to endemic areas are at low risk of infection[17]
- Travelers who visit endemic areas for extended periods of time (generally >3 months; see first point) and live or work near blackfly habitats are at risk of infection[17]
- Between 1997 and 2004, a total of 81 cases detected among immigrants and people visiting friends or relatives were reported to the GeoSentinel Surveillance Network; an additional 20 cases were reported among travelers of nonendemic origin[18]

Lymphatic filariae

- Short-term travelers to endemic areas are at low risk of infection[17]
- Travelers who visit endemic areas for extended periods of time (generally >3 months) and who are intensively exposed to infected mosquitoes are at risk of infection[17]
- Between 1997 and 2004, a total of 49 *Wuchereria bancrofti* cases among immigrants and people visiting friends or relatives were reported to the GeoSentinel Surveillance Network; 18 cases were reported among travelers of nonendemic origin[18]

Loa loa

- Imported cases are observed occasionally in North America[18]
- Between 1997 and 2004, a total of 25 cases among immigrants and people visiting friends or relatives were reported to the GeoSentinel Surveillance Network; 43 cases were reported among travelers of nonendemic origin[18]

Mansonella perstans

- Imported cases are observed occasionally in North America[18]

Clinical Features and Associated Burden

Infections with guinea worm usually remain undiscovered until the painful blister develops as a result of an immunologic reaction to a few released larvae, and the female worm starts to emerge (**Box 3**). The closed blisters are sterile. Once open, the worm tracks caused by the emerging worm often become infected with bacteria. These secondary infections, if not disinfected and properly handled, can develop to painful inflammation of the surrounding tissue and finally the formation of abscesses. Development of tetanus, septic arthritis, or systemic sepsis may result. Despite dracunculiasis being rarely fatal and seldom causing permanent disability, the temporary morbidity negatively affects health and well-being, with considerable socioeconomic impact on patients and communities. Among other issues, there are negative

Table 1
Characteristics of filarial infections

	Infection by	Adult Worm Final Destination	Adult Worm Length (mm)	Egg/Larvae Final Destination	Number of Eggs/Larvae Shed by Female Worm per Day	Life Span of Adult Worms (Years)	Intermediate Host/Vector	Time in Vector/ Until Larvae are Infective
Dracunculus medinensis	Drinking water contaminated with water-flea (*Cyclops*)	Skin surface of lower limbs	Female: 600–1000 × 1.5–2.0 Male: 15–40 × 0.4	Larvae released into fresh water bodies	>1000 larvae	~1	Water-flea (*Cyclops*)	~2 wk
Onchocerca volvulus	Bite from blackfly (*Simulium*)	Subcutaneous worm bundles	Female: 350–700 × 0.4 Male: 20–50 × 0.2	Larvae found in upper dermis, nodules, and eyes	Up to 1500 larvae	~10	Blackfly (*Simulium*)	1–2 wk
Lymphatic filariae	Bite from mosquito (*Aedes, Anopheles, Culex*)	Lymphatic vessels	Female: 80–100 × 0.25 Male: 40 × 0.1	Larvae migrate in peripheral blood vessels	Up to 50,000 larvae	~10	Mosquito (*Aedes, Anopheles, Culex*)	At least 10–12 d
Loa loa	Bite from bloodsucking fly (*Chrysops*)	Worms migrate under skin in subcutaneous tissues	Female: 50–70 × 0.5 Male: 30–35 × 0.4	Larvae found in lung, peripheral blood, and in rare cases in urine, saliva, cerebrospinal and other body fluids	Several thousand larvae	Up to 17	Bloodsucking fly (*Chrysops*)	9–10 d
Mansonella perstans	Bite from midge (*Culicoides*)	Serous cavities, mesentery, and retroperitoneal tissues	Female: 70–80 × 0.1 Male: 35–45 × 0.06	Larvae found in blood stream	No number available	Unknown	Biting midge (*Culicoides*)	7–9 d

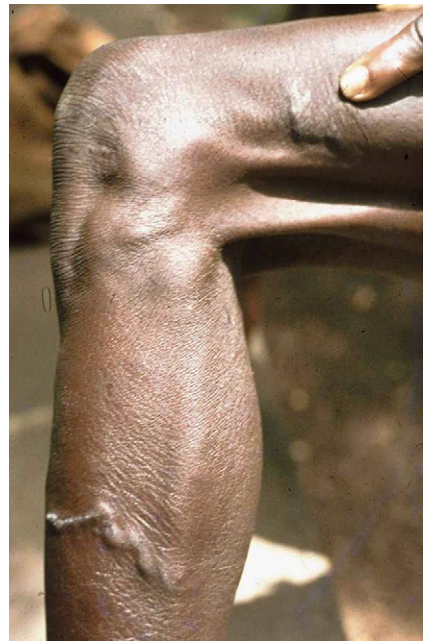

Fig. 1. Calcified guinea worm. (*Courtesy of* Peter J.T. Mayer, MD, Ringelai, Germany.)

educational consequences, as children might miss several weeks of schooling because they have difficulties to walk or have to take care of relatives with dracunculiasis. Similarly, adults with dracunculiasis often cannot work, and hence their subsistence agricultural activities are compromised. Because of the seasonal peak of dracunculiasis, many people in endemic villages are affected at the same time, further exacerbating the societal impact of the disease.[20]

Diagnosis and Treatment

The macroscopic diagnosis of a *D medinensis* infection is straightforward when the blister develops and the female worm starts to emerge. The detection of prepatent infections with immunodiagnostic methods has been a research topic[26,27] but has never reached broad application in the field.

The treatment of dracunculiasis is limited to the extraction of the worm by winding it around a stick, which, of note, is one explanation for the origin of the international sign of medicine and healing, the Asclepius rod. Pulling out the worm is painful and can take several days, because worms usually can be extracted only centimeter by centimeter. Massaging the skin and muscles, if not inflamed, and cooling with ice can accelerate the extraction and mitigate the pain (S. Knopp, personal observation in Togo; **Fig. 2**). To avoid secondary infections, an antibiotic ointment should be applied around the wound.[28] Anthelmintic drugs that are widely and effectively used against other nematode infections did not prove to have any direct effect on *D medinensis*,[20] and there is currently no vaccine available against dracunculiasis.[21]

Control and Prevention

There are several intervention points to control dracunculiasis: (1) the prevention of infection by filtering drinking water through a cloth filter; (2) vector control by killing

Box 3
Clinical manifestations of filarial worms

Cutaneous

- *Dracunculus medinensis*
- *Onchocerca volvulus*
- *Loa loa*
- *Mansonella perstans*
- *Dirofilaria repens*[a], *Dirofilaria immitis*[a]

Lymphatic

- *Wuchereria bancrofti*
- *Brugia malayi*, *Brugia timori*

Ocular

- *Onchocerca volvulus*
- *Loa loa*
- *Dirofilaria repens*[a], *Dirofilaria immitis*[a]

Pulmonary

- *Dirofilaria repens*[a], *Dirofilaria immitis*[a]

[a] *D repens* and *D immitis* are the heart worms of cats and dogs, respectively[24,25]: accidental infections of humans can occur in the Mediterranean but are not covered in this review devoted to tropical diseases.

Fig. 2. Guinea worm extraction. (*Courtesy of* Stefanie Knopp, PhD, Swiss Tropical and Public Health Institute, Basel, Switzerland.)

Cyclops through treatment of open stagnant water bodies with a larvicide such as temephos (Abate); (3) educating patients with emerging worms to avoid contact with open water bodies; (4) treatment and care to safely extract the worm and disinfect and bandage the wounds; (5) infrastructure interventions to provide safe drinking water from boreholes or wells; (6) close surveillance of endemic villages and case containment; and (7) promotion of control efforts through local media, political leaders, and other champions.[29] Additional features that triggered the 1991 WHA declaration to eradicate guinea worm are the restricted potential of the intermediate host to spread to new habitats (*Cyclops* cannot fly or crawl out of water bodies), coupled with the seasonality of the disease.

Current efforts to control guinea worm disease are driven by the National Guinea Worm Elimination Programs of endemic nations, which work in close collaboration with the Global Guinea Worm Eradication Program championed by the Carter Center, Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and the United Nations Children's Fund (UNICEF). Since 1996, the WHO certifies countries to be free of dracunculiasis if they maintain adequate nationwide surveillance for at least 3 consecutive years and record no indigenous cases during this period.[30] In early 2012, 192 countries and territories had been certified to be free of or have eliminated dracunculiasis. However, the last steps toward eradication usually are the most difficult ones. As the original goal to eradicate guinea worm in 2009 was not achieved, in May 2011, during the 64th WHA, the call for dracunculiasis eradication has been reiterated (WHA resolution 64.16). Eventually achieving the goal of guinea worm eradication would constitute the first human parasitic infection to be eradicated even in the absence of a vaccine.

ONCHOCERCIASIS (*ONCHOCERCA VOLVULUS*)

Life Cycle and Epidemiology

People get infected with *O volvulus* when bitten by a blackfly of the genus *Simulium* containing the infective L_3 of the parasite. From the bite wound the larvae migrate to the subcutaneous tissues. After 2 molts, the larvae develop into adult worms that mate and encapsulate in fibrous tissues, which might clinically present as worm nodules mostly located over bony prominences (ie, chest, hips, shoulders, and head). Adult female worms have a life expectancy of 9-14 years, of which they reproduce during 9 to 11 years (see **Table 1**). Female worms are vivipar, and each fertilized female releases up to 1500 unsheathed microfilariae per day. The life span of microfilariae is about 2 years and they live mainly in the upper dermis and nodules, but are also often found in the eye where, on death, they induce an immune reaction eventually leading to blindness. From the dermis microfilariae can be sucked up by a blackfly while feeding from blood pools. In the blackfly, the first-stage larvae migrate from the gut to the thoracic muscles, molt twice, and develop into infective L_3 within 1 to 2 weeks. Larvae then migrate to the head and proboscis. People living in hyperendemic areas often carry multiple adult worms and have up to 2000 microfilariae per mg of skin, thus virtually guaranteeing the uptake and transmission of the parasite via the *Simulium* vector.

O volvulus is currently endemic in 27 countries of sub-Saharan Africa, Yemen, and 6 countries of Latin America. It is estimated that globally, some 37 million people are infected with the parasite, and that more than 102 million people are at risk of infection.[14,31–33] The transmission of *O volvulus* depends on the presence of the day-active blackfly *Simulium*, which breeds in fast-flowing rivers or streams.[34] Hence, people living in communities located in close proximity to rivers are at highest risk of infection and disease, reflected in the reference to the disease as "river blindness."

The prevalence and intensity of infection in humans increases with age, reaching a peak at an age of approximately 30 years. Overt morbidity such as depigmentation of the skin (leopard skin) and blindness are most common in people aged 40 years and older.[35]

Clinical Features and Associated Burden

Onchocerciasis includes an array of symptoms, mostly associated with immune reactions induced by dead microfilariae. Skin-related problems and blindness are primary symptoms and major causes of morbidity (see **Box 3**). Inflammation of the skin can result in intense itching, papular dermatitis, and lichenified onchodermatitis. Chronic *O volvulus* infections can lead to depigmentation of the skin (leopard skin) or its loss of elasticity and structure (lizard skin or hanging groin).[35] Hyperpigmentation (sowda) is rare and only appears in immunologic hyperactive individuals with severe chronic papular dermatitis. Whereas the microfilarial load is low in sowda patients, the immune response, and particularly the Th2 type response, is increased.[1,36] Blindness results from punctate keratitis, which develops around dead microfilariae and presents as a small white dot, followed by sclerosing keratitis, iridocyclitis and, finally, permanent visual impairment and blindness.[1] It has been hypothesized that the proinflammatory events leading to increased corneal opacity are stimulated not only by the parasite itself but also by endosymbiotic *Wolbachia* bacteria released by dying microfilariae.[33,37]

Blindness, visual impairment, and severe itching exert strong negative socioeconomic impacts on afflicted populations. It is estimated that in Africa alone, onchocerciasis caused a burden of 389,000 DALYs in 2004[13] (**Table 2**). Historically, the parasite has also blocked human settlement and land use in large swathes of fertile riverine land.

Diagnosis and Treatment

A still widely applied method for the point-of-care diagnosis of *O volvulus* infections is the skin snip, a biopsy of the upper dermis from the iliac crests or the scapulae. Tiny snips of the dermis are transferred into normal saline solution and examined under a microscope, enumerating the number of microfilariae. However, the sensitivity of the skin-snip test is low, particularly in low-endemicity areas. Moreover, the test is unpopular because of its painful invasiveness. Hence, the commercially available diethylcarbamazine (DEC)-based patch test has been developed.[40] For this test, body lotion containing DEC is applied to the skin, which locally kills dermal microfilariae. A papular rash 24 hours after application of the cream indicates an infection with *O volvulus*. Additional diagnostic methods, such as antigen or antibody detection tests, have been developed and show promising results, but are not yet routinely applied.[1,41] Rapid appraisal tools applied in onchocerciasis control programs involve estimating the proximity of communities to blackfly breeding sites and determining the nodule frequency in a sample of 50 men aged 20 years or older who had resided in endemic communities for a maximum of 10 years.[1,40]

The standard treatment against onchocerciasis is ivermectin (150–200 μg/kg oral dose), which is distributed to entire at-risk communities (pregnant women and children weighing <15 kg are ineligible) every 6 or 12 months.[1,3] The treatment does not kill adult worms but microfilariae, and hence does not clear infections but controls the disease and its transmission. Patients with high microfilarial load who are treated with ivermectin often experience severe skin disease caused by immune reactions to parasite antigen or endotoxins released by *Wolbachia* bacteria (**Fig. 3**). Suboptimal responses or resistance to ivermectin have not yet been unequivocally demonstrated for *O volvulus*.[41,42] DEC, which is used for MDA against lymphatic filariasis, should not be

Table 2
Epidemiology and burden of filarial infections

	Geographic Distribution	Population at Risk	Population Infected	Global Burden (DALY) (year)
Dracunculus medinensis	Six countries in Africa (2010)[23]	No number available	1797 (2010)[38]	No number available
Onchocerca volvulus	30 countries in Africa Yemen Six countries in Central and South America	>102 million in Africa[31]	37 million[32]	388,576 (2004)[13]
Lymphatic filariae	72 countries in Africa, Asia, the Western Pacific, parts of the Caribbean, and South America	1.39 billion[39]	120 million (2010)[39]	5,940,641 (2004)[13]
Loa loa	West- and Central Africa	No number available	No number available	No number available
Mansonella perstans	Central and South America At least 33 countries in Sub-Saharan Africa	No number available	At least 114 million in Africa (2010)[12]	No number available

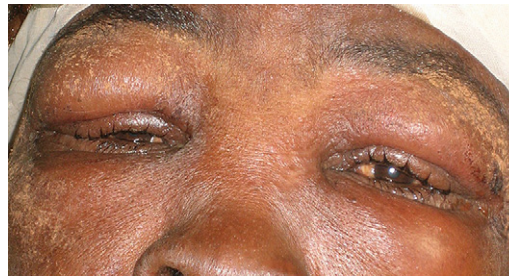

Fig. 3. Adverse reactions (swollen face and streaming eyes) after ivermectin treatment of an onchocerciasis patient. (*Courtesy of* Cornelia Mai, MSc, Tübingen, Germany.)

applied against *O volvulus*, or in areas where onchocerciasis is coendemic unless eye involvement of *O volvulus* is ruled out, because the death of microfilariae can induce strong local inflammation in the eyes. Moxidectin, a macrofilaricide, has been suggested as backup for ivermectin.[41] Suramin, previously applied to kill adult worms, has been abandoned because of its toxicity.[1,41] Doxycycline, an antibiotic active against the endosymbiotic *Wolbachia* bacteria that are essential for the development, embryogenesis, and survival of *O volvulus*, results in long-term sterilization of female worms and thus absence of microfilariae, if given over 6 weeks at 100 mg per day.[43] Considering the length of treatment, the anti-*Wolbachia* therapy is valuable for individual patient management but unsuitable for MDA in the context of onchocerciasis control programs.[1]

Control and Prevention

Large-scale control efforts targeting onchocerciasis commenced in the early 1970s. The Onchocerciasis Control Program (OCP) was set up in West Africa in 1974. Within the first 14 years, the OCP emphasized vector control in 11 countries, mainly spraying insecticides from helicopters and airplanes on blackfly breeding sites. Despite the initial success of reducing the risk of transmission among more than 30 million people, reinvasion of the blackfly in areas where transmission had been interrupted resulted in a recrudescence of infection.[36] From 1987 onwards, the focus shifted toward MDA, using ivermectin (Mectizan) given to entire at-risk communities. The drug was, and continues to be, donated by Merck.[44–46] In 1995, the African Program for Onchocerciasis Control (APOC) was initiated, aiming at the elimination of onchocerciasis as a disease of public health importance in Africa. This program is currently in the phasing-out period (2008–2015), and responsibility for sustained control will be taken over by national authorities. The control programs are also facing challenges because MDA using ivermectin in areas coendemic with *L loa* is contraindicated, as severe adverse reactions in *L loa* patients have been observed.[47,48] Further issues are ivermectin treatment in hypoendemic areas hitherto excluded from the APOC, sustainability of ivermectin distribution, postcontrol surveillance for recrudescence detection, surveillance for emergence of resistance, and decisions of when to stop MDA with ivermectin.[49]

LYMPHATIC FILARIASIS (*WUCHERERIA BANCROFTI, BRUGIA MALAYI,* AND *BRUGIA TIMORI*)

Life Cycle and Epidemiology

Lymphatic filariasis belongs to the oldest and most debilitating of the neglected tropical diseases.[50] Humans become infected with lymphatic filariae when mosquitoes carrying the L_3 take their blood meal. The larvae enter the skin and develop into adult

worms, which most commonly reside in nests (lymphangiectasia) within the lymphatic vessels located in the extremities and male genitalia.[1] Over a reproductive life span of 5 to 8 years, a female filaria produces millions of sheathed microfilariae that periodically migrate from the lymphatic system to the peripheral blood vessels, where they are ingested by the feeding mosquito (see **Table 1**). In the mosquito, the microfilariae shed their sheath, penetrate the midgut wall, and migrate to the thoracic muscles, where they molt twice and finally migrate to the mosquito's proboscis, ready to be transmitted. Filarial worms are transmitted by a wide range of mosquitoes including *Culex* (in urban and semiurban areas), *Anopheles* (in rural areas of Africa and elsewhere), and *Aedes* (on the Pacific islands).

The 3 species causing lymphatic filariasis, namely *W bancrofti*, *B-malayi*, and *B timori*, are endemic in different tropical regions of the world and affect specific parts of the body. *W bancrofti* is the most widely distributed species and is responsible for 90% of the global number of cases. The distribution of *B malayi* is restricted to Southeast Asia, and the closely related *B timori* fills the niche in southeastern Indonesia.[1] Children living in endemic areas usually get infected within the first years of their life but then show no disease symptoms. The prevalence of lymphatic filariasis increases with age, and the disease becomes more overt in puberty and adulthood.[1,51]

Clinical Features and Associated Burden

Most infected people living in endemic areas present as asymptomatic carriers of microfilariae, but virtually all of them show subclinical damage of the lymphatic system and kidney, and have an altered immune system. It is widely assumed that filarial nematodes are able to modulate their host's immune system in such a way that it tolerates the long-term presence of the parasites without producing major disease signs.[52] However, about a third of infected people develop clinical signs attributable to damage of the lymphatic system, manifested mainly as lymphedema, hydrocele, and elephantiasis (see **Box 3**).[1,53] The most common acute manifestation is acute adenolymphangitis (ADL), which is characterized by fever attacks, painful swellings of the affected body area, and inflamed lymph nodes in the groin and axilla.[53] Episodes of ADL are caused by secondary infections due to bacteria that enter the body via skin lesions caused by fungal infections, injuries, eczema, insect bites, or other infections. Such infections are common on the affected limbs because normal immune defenses are impaired by the underlying lymphatic damage. Some episodes of local inflammation are also caused by the humans' immune response to adult worms that have been destroyed in the lymphatics, called acute filarial lymphangitis. The chronic manifestation of lymphatic filariasis is characterized by lymphedema (tissue swelling) or elephantiasis (skin/tissue thickening) of limbs and hydrocele (fluid accumulation) (**Figs. 4** and **5**).

Lymphatic filariasis is endemic in 72 countries, with an estimated 120 million people infected in 2010.[39] The disease is considered the second-largest cause of permanent and long-term disability (after mental illness) worldwide.[54] The visible effects of the disease result in social stigma, isolation, and psychological stress among affected individuals. In addition, ADL attacks may render affected individuals unable to work and require treatment, and hence lead to a considerable economic loss.[55] The global burden attributable to lymphatic filariasis was estimated at 5.9 million DALYs in 2004 (see **Table 2**).[13,56]

Diagnosis and Treatment

In the past, diagnosis of lymphatic filarial infections relied on clinical examination and on the microscopic detection of microfilariae in thick blood films, with samples

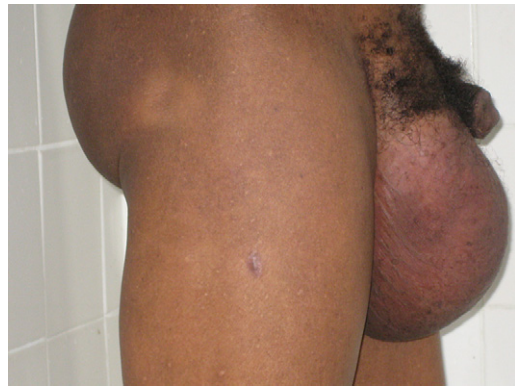

Fig. 4. Hydrocoele. (*Courtesy of* Thomas Fürst, PhD, Swiss Tropical and Public Health Institute, Basel, Switzerland.)

typically taken before midnight because of the predominantly nocturnal periodicity of *W bancrofti*.[1,57] The latter method is specific, inexpensive, and requires little infrastructure, and is still used as point-of-care diagnosis. However, it is not very sensitive and misses people with a low density of microfilariae in blood and those with a microfilaremic infections. In recent years, the diagnosis of filarial infection has been advanced, and several rapid and sensitive tests have been developed. Antigen detection from blood collected during day or night is sensitive for bancroftian filariasis diagnosis and also identifies latent infections. In 1997, a rapid immunochromatographic filariasis card test was introduced.[58] This test proved most useful, and hence is now

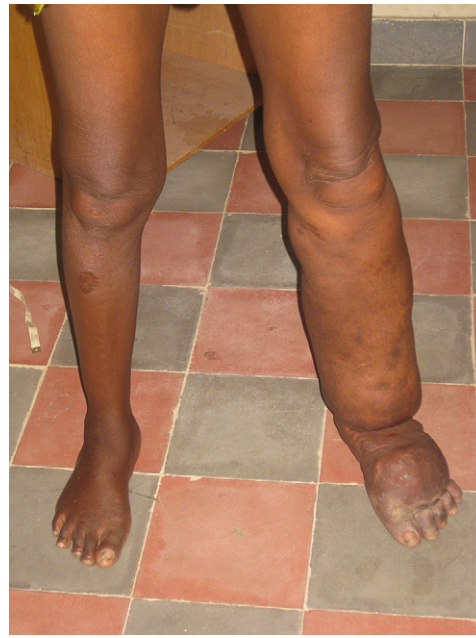

Fig. 5. Elephantiasis leg. (*Courtesy of* Thomas Fürst, PhD, Swiss Tropical and Public Health Institute, Basel, Switzerland.)

recommended by international authorities as the diagnostic method of choice.[57] Advantages are that the test is quick and easy to perform, and is only minimally invasive (100-μl finger-prick blood sample). Disadvantages are that it is not able to distinguish past from present infections, cannot detect *Brugia* infections, is still relatively costly, and might not be available in all endemic settings.[57] Other, less widely used diagnostic approaches include antibody detection to assess the level of contact with antigen in children, polymerase chain reaction (PCR) to detect filarial DNA in human blood samples (taken at night in areas with nocturnally periodic microfilariae), or molecular xenomonitoring (MX) to detect parasite DNA in pooled mosquitoes or human blood by PCR.[59–61]

The drugs of choice to treat lymphatic filariasis in individual patients are: (1) DEC (often combined with albendazole) given as single-dose treatment (6 mg/kg) if the patient continues to live in an endemic area or is younger than 9 years, or as 12-day course of 6 mg/kg per day; and (2) doxycycline, 200 mg per day for 4 weeks plus ivermectin (or without ivermectin because of the risk of serious adverse events in areas where *L loa* is coendemic). Drugs used in MDA campaigns are: (1) single-dose combinations of ivermectin (100–200 μg/kg) plus albendazole (400 mg) in Africa; and (2) DEC (6 mg/kg) plus albendazole (400 mg) in the remainder of the endemic regions, both distributed for at least 5 years.[1] Of note, DEC must not be applied in areas where onchocerciasis is coendemic because dying microfilariae can cause severe local inflammation in patients with ocular microfilariae.[1] Furthermore, DEC, and to a lesser extent ivermectin, can cause encephalopathy in *L loa*-endemic areas.[62]

DEC is effective against both microfilariae and adult worms.[53] However, a single dose usually does not clear all microfilariae and some adult worms survive. Treatment over 12 consecutive days results in complete microfilariae clearance.[1] Adverse events can occur and are mostly related to the death of adult worms and microfilariae, which can induce systemic inflammation due to the release of endosymbiotic *Wolbachia* bacteria. The adverse effects of ivermectin resemble those of DEC, but are milder because of the slower clearance of microfilariae.[53] Ivermectin and albendazole both effectively reduce the microfilarial load for several months after treatment, and the combination of both drugs prolongs the period of reduced peripheral microfilaremia. Anti-*Wolbachia* therapy using the antibiotic doxycycline results in long-term sterility and eventual death of adult bancroftian worms when administered daily at a 200 mg dose for 4 to 8 weeks.[63] It is also effective in reducing brugian microfilariae when given at 100 mg per day over 6 weeks.[64]

There is no cure for lymphedema, but a series of interventions is available to mitigate and prevent the progression of the swelling.[53] Such methods include keeping the affected limbs clean (to prevent secondary infections), bandaging, regular massage, and exercise and elevation while resting (to stimulate lymph circulation). At present, there are no drug interventions for hydrocele and hence surgery is the only intervention for this advanced form of chronic lymphatic filarial infection.

Control and Prevention

Traditionally, control of lymphatic filariasis was based on the selective treatment of infected individuals detected by mass screening of blood films.[63] In 2000, the Global Program to Eliminate Lymphatic Filariasis (GPELF) was initiated by the WHO as a response to WHA resolution 50.29, which encourages member states to eliminate lymphatic filariasis as a public health problem.[65] Today, the GPELF follows the strategy to (1) interrupt transmission through the annual administration of 2-drug combinations to at-risk communities in endemic areas for at least 5 years, and (2) to alleviate suffering and disease through the promotion of basic measures of hygiene

and skin care to patients with lymphedema, and to provide surgery for men with hydrocele.[66] The GPELF is nowadays part of multi-intervention packages to control neglected tropical diseases by the integration of preventive chemotherapy, vector control, and morbidity management at global, national, and local levels. In 2010, MDA of DEC/ivermectin plus albendazole was implemented in 53 countries. Between 2000 and 2010, more than 3.4 billion treatments were delivered to a targeted population of 897 million people.[39] While the strategy of repeated rounds of MDA indeed resulted in the elimination of lymphatic filariasis in some countries,[39,67,68] others were less successful in halting transmission.[69] It remains to be determined which treatment coverage and duration of MDA (ideally combined with other control measures) are needed to achieve elimination, and to what extent the success of a program depends on the vector and parasite strains, endemicity level, and the drugs applied.[70] It is assumed that MDA must be applied for at least 4 to 6 years[71–73] depending on baseline infection prevalence and transmission intensity,[74] and that coverage should reach at least 80%.[54,75,76] An antigenemia prevalence of 0.1% is proposed as a target for indicating the interruption of lymphatic filariasis transmission by the GPELF.[77,78] Mathematical models are important tools in understanding transmission dynamics of parasitic diseases. Such models have been widely used for the planning and evaluation of control programs such as the GPELF,[70] and might underpin the global strategy to eventually reach elimination of lymphatic filariasis.[79] In a recent statement, the WHO urges its member states to adapt an integrated vector management approach against mosquitoes transmitting lymphatic filariae and malaria.[80] Furthermore, new guidelines on delivering treatment to whole communities, including a protocol for stopping MDA and conducting posttreatment surveillance, will be disseminated from 2012 onwards.[39]

LOIASIS (*LOA LOA*)

Life Cycle and Epidemiology

L loa infections are acquired when infective stages of the parasite actively migrate out of the mouthparts of the vector fly *Chrysops* and enter the biting wound while the fly takes a blood meal.[11]After maturing, the sheathed adult worms live freely in the subcutaneous tissues of humans. Daily, thousands of sheathed microfilariae produced by the gravid female worm are migrating via the lymphatic system to the lung, which serves as a reservoir (see **Table 1**). From there, microfilariae invade the peripheral blood, showing a diurnal periodicity. In rare cases, microfilariae are also found in urine, saliva, cerebrospinal fluid, and other body fluids.[11,81] The *Chrysops* vector is ingesting the microfilariae while taking a blood meal during the day. In the fly the larvae migrate from the gut to the thoracic muscles and from there to the head and proboscis of the fly.

L loa is endemic in the rainforest and some savannah areas of Central and West Africa, where several million people are infected.[81] The *Chrysops* flies live in and around forested and muddy areas, on the edges of water reservoirs, and in dying or rotting vegetation.[82] People at highest risk of infection are those living and working in such areas during the day, as *Chrysops* is day-biting. The prevalence of infection increases with age.[81]

Clinical Features and Associated Burden

As for other filarial infections, most people infected with *L loa* show no disease symptoms. A specific sign of *L loa* infection is the Calabar swelling, a subcutaneous edema of allergic type, often associated with localized, migrating or generalized itching (see

Box 3). Calabar swellings appear and disappear spontaneously at irregular intervals and can be observed on any part of the body, but typically occur in the limbs near the joints, which may render movement difficult and painful.[11] The swellings may be caused by antigenic material, for example, microfilariae released by adult female worms, or by larvae that migrate away from the biting wound after infection.[11,81] Other clinical signs can develop within a few months after infection but are often not overt for more than a decade. *L loa* is also known as the African eyeworm, because adult worms migrating under the skin are sometimes seen while passing the conjunctiva of the eye, often without other clinical symptoms. Migration of the adult worms may cause severe pain and inflammation in the eye and might result in blindness. Occasionally adult *L loa* have been detected in various other parts of the body including the testes, kidneys, and heart.[11] Although the burden of loiasis seems to be considerable in some areas of Central Africa, it has never been quantified, and hence no DALY figures are available (see **Table 2**).

Diagnosis and Treatment

L loa microfilariae can best be detected in blood samples taken between 10:00 and 14:00.[83,84] The classic method to determine infection and intensity is to count microfilariae in thin or thick blood films prepared from a defined volume of blood that has been stained with Giemsa. The sheath of *L loa* microfilariae stains only poorly with Giemsa. If microfilaremia is low, concentration techniques including sedimentation or filtration of blood may be required.[11] A PCR for species-specific DNA also exists, which is perhaps the most accurate technique for individual diagnosis of loiasis.[11] The interpretation of specific clinical signs, such as the Calabar swelling, or the detection of adult worms when they cross the subconjunctiva or sclera of the eye, is straightforward.

Adult *L loa* can be surgically extracted from the eye. For this purpose, the eye needs to be anesthetized and the worm extracted with forceps through a small incision in the conjunctiva.[81] To systemically kill adult worms and microfilariae, DEC administered at a dose of 8 to 10 mg/kg per day for 3 weeks is the standard treatment.[3] Caution is needed when administering the drug, because DEC can cause serious adverse reactions such as encephalitis and retinal hemorrhage, especially when the microfilarial load is high.[85] Alternatively, the anthelmintic drugs ivermectin, albendazole, and mebendazole have been shown to have microfilaricidal effects.[11,81] However, serious adverse events after ivermectin treatment have been reported: high *L loa* microfilaremia is statistically significantly associated with serious adverse reactions in people treated with ivermectin in the context of onchocerciasis control programs.[48] Observed adverse events include functional impairment for more than 1 week after treatment or microfilariae in the cerebrospinal fluid, causing coma. Occurrence of encephalopathy following albendazole treatment of highly filaremic *L loa* cases has been reported.[62,86] In patients presenting with high microfilarial load, anthelmintic treatment with albendazole (2 $\times$ 200 mg/d) for 21 days is recommended to slowly lower the microfilaremia.[3,62,86] Anti-*Wolbachia* (ie, doxycycline) treatment is ineffective against loiasis because *L loa* does not host the bacteria.[1]

Control and Prevention

There are currently no specific control programs targeting *L loa*. Onchocerciasis and lymphatic filariasis control programs cannot be implemented in regions in Central and West Africa where *L loa* is coendemic, because of the serious adverse reactions (namely encephalopathy) caused by ivermectin in patients coinfected with *L loa*.[87] For example, in onchocerciasis-endemic communities where more than 20% of the

population also has loiasis, the risk of severe adverse reactions is considered to be unacceptably high. To predict whether loiasis is present at high levels in a community targeted for onchocerciasis control with ivermectin, the application of a simple questionnaire (Rapid Assessment Procedure for Loiasis, or RAPLOA) that assesses the history of visible worms moving in the lower part of the eye is recommended.[88,89]

MANSONELLOSIS (*MANSONELLA PERSTANS*)

Life Cycle and Epidemiology

M perstans filariasis is widespread in the tropics but still is one of the most neglected of the tropical diseases.[12] The larvae of *M perstans* are transmitted through the bite of tiny infected midges of the genus *Culicoides* (see **Table 1**). The larvae develop into adult worms that live in serous cavities and mesentery as well as retroperitoneal tissues. Unsheathed microfilariae released by the female adult parasites are carried through the blood stream; no periodic patterns of their presence in peripheral blood vessels have been observed.[90] Female midges ingest the microfilariae while taking their blood meal. In the vector, the larvae molt most likely twice before the infective stage is reintroduced into the human definitive host.

M perstans is endemic in rural populations living in sub-Saharan and in northern South America and the Caribbean, often in areas where *L loa*, *O volvulus*, and *W bancrofti* coexist. Infection prevalences are often very high (80–100%) in endemic areas, even among children.[12] In general, the prevalence and intensity of infection with *M perstans* increase with age, hence peak levels are observed in the adult population. Men usually are more likely to be infected than women.[12]

Clinical Features and Associated Burden

Little is known about the outcome of *M perstans* infections. As for other filarial infections, most infected people remain asymptomatic. The variety of symptoms attributed to *M perstans* infections include angioedema, arthralgia, fever, headache, pruritus, skin eruption, serositis, neurologic manifestations, ocular or palpebral pruritus, visual impairment, and chest pain (see **Box 3**).[90,91] Allergic reactions resembling the 'Calabar swellings' seen in *L loa* infections have been reported. The clinical outcomes are most likely related to the presence of adult worms in the serous body cavities and not to the microfilariae.[12]

Diagnosis and Treatment

Unsheathed microfilariae of *M perstans* can be detected by microscopic examination of peripheral blood samples taken at any time. When the microfilariae are present in high numbers, they can be easily detected and identified in thick or thin blood films stained with Giemsa.[12] Another technique for the quantitative detection of *M perstans* is the examination of fixed finger-prick blood samples in a counting chamber under a microscope.[92] However, because of the small size of the microfilariae and their unsheathed nature, they are more difficult to recognize than the larger sheathed microfilariae of other species.[12] Various concentration techniques have proved valuable for *M perstans* diagnosis in an experimental context.[12]

Drugs effective against other filariae such as DEC, ivermectin, albendazole, and mebendazole have limited efficacy against *M perstans*.[91] An effective, fast-acting, tolerable therapy that is easy to administer still needs to be identified.[12] In a recent trial, doxycycline, given at a daily dose of 200 mg for 4 to 8 weeks, was shown to be effective in reducing microfilaremia.[90] The therapy suppressed microfilariae for

36 months after treatment, suggesting that doxycycline has an effect on adult worms as well.[90]

Control and Prevention

Currently, there are no large-scale programs for the control of mansonellosis. Because of the insensitivity of *M perstans* to antifilarial drugs applied in onchocerciasis or lymphatic filariasis control programs, the species tends to persist in populations targeted by those programs. Data on the long-term impact of such programs on *M perstans* are conflicting.[12] A combination therapy of ivermectin plus albendazole, as used for MDA targeting lymphatic filariasis and onchocerciasis, failed to show marked decreases in *M perstans* microfilaremia.[92]

SUMMARY

Filarial infections can result in highly debilitating and irreversible disease outcomes, both physically and psychologically.[1,93,94] Despite filariae not being transmitted in Europe and North America, travel clinics must be aware of infections in patients who have spent an extended period of time in endemic areas, and handle cases carefully. With the exception of doxycycline, classically applied antifilarial drugs (DEC, ivermectin and albendazole) are able to kill microfilariae, but have only limited effects against adult worms.[33,43] These agents can thus reduce the transmission of the parasites in endemic areas but are not able to mitigate disease symptoms. Moreover, they often cause severe adverse reactions resulting from strong immune reactions to dying microfilariae, and must hence be applied with care.[1] Filariasis control programs targeting vectors and treating at-risk communities have successfully been implemented over the past decades in many endemic countries and have been able to reduce new or repeated infections.[1,33,36] However, continuous interventions and rigorous monitoring are still required in most (formerly) endemic places to avoid resurgence of transmission as well as physical damage and chronic disease. The development of diagnostic tools that reliably detect and differentiate prepatent, patent, and postpatent infections, as well as new, safe, and efficacious drugs that permanently sterilize or kill adult worms, are essential for progress in filariasis control and ultimately achieving the goal of elimination. The Bill & Melinda Gates–funded Death to Onchocerciasis and Lymphatic Filariasis (DOLF) project, commenced in 2010, aims at developing and validating improved treatments (new drugs and optimized treatment regimens) to eliminate onchocerciasis and lymphatic filariasis also in *L loa*–endemic areas. The ancillary benefit of repeated rounds of MDA using ivermectin and albendazole on soil-transmitted helminthiasis is also being evaluated. This program might become a pathfinder for operational research, paving the way from control towards integrated control and elimination of multiple neglected tropical diseases.

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