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Current perspectives in the epidemiology and control of lymphatic filariasis

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SUMMARY Lymphatic filariasis (LF), a debilitating tropical disease caused by parasitic filarial worms, *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*, remains a significant public health challenge in tropical and subtropical settings where the disease is endemic. The disease affects millions worldwide, leading to severe disability and social stigma. Following the World Health Assembly resolution WHA50.29 in 1997 encouraging Member States to eliminate LF as a public health problem, the Global Programme to Eliminate Lymphatic Filariasis (GPELF) was established in 2000. The establishment of the GPELF paced the way for global eradication efforts, with commitments from non-governmental organizations and Merck donating the drug ivermectin as long as it is needed to control the disease. The advances in the diagnosis and control of LF have shown promising results, including developing novel diagnostic tools, therapeutic agents, and integrated vector management and surveillance strategies. This review explores the latest advances in our understanding of LF epidemiology, transmission assessments, clinical manifestations, and immune response to infection. We further discuss the current state of diagnostic development, treatment approaches, and control

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measures, highlighting the importance of continued research in the fight against this disease.

KEYWORDS lymphatic filariasis, elephantiasis, *Wuchereria bancrofti*

INTRODUCTION

Lymphatic filariasis (LF), also known as elephantiasis, is a neglected tropical disease (NTD) caused by infection with the filarial worms *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*. It is closely linked to poverty, inadequate sanitation, and areas conducive to mosquito breeding, and thus transmitted through the bite of an infected mosquito, mostly of the genera *Anopheles*, *Culex*, *Aedes*, and *Mansonia* depending on the geographic location. It stands as a significant cause of permanent disability worldwide, affecting over 54 million people in 72 endemic countries (1, 2). Approximately 129 million people were estimated to be infected with LF, of which 43 million had clinical disease (3). The disease primarily affects tropical and subtropical regions across Asia, Africa, the Western Pacific, and parts of the Americas. Recent data indicates a declining trend in both prevalence and incidence in several endemic regions, largely attributed to the control measures implemented under the Global Programme to Eliminate Lymphatic Filariasis (GPELF) launched by the World Health Organization (WHO) in 2000 (4). The efforts of GPELF have led to a significant reduction in the number of individuals at risk of LF, from 1.3 billion in 2005 to 850 million in 2021 (5, 6). Furthermore, the program has helped stop the transmission of the disease in numerous countries, with 19 countries being validated by WHO for having eliminated LF as a public health problem (1).

Despite a 74% reduction in global infections since 1997, an estimated 51.4 million people were still infected in 2018 (2). In 2019, it was estimated that approximately 893 million people in 49 countries worldwide were living in areas that require mass drug administration (MDA) to stop the transmission of LF. The disease's burden remains particularly high in certain regions of Africa and Asia, where ongoing transmission and high levels of morbidity are reported (7).

The distribution and prevalence of LF are determined by a complex interplay of environmental, vector, host, and socioeconomic factors, making its elimination a challenging task (8–11). The use of geospatial mapping and epidemiological modeling tools has significantly advanced the field of public health, particularly in identifying populations at risk for diseases, like LF, and optimizing control strategies. These technological advancements have facilitated more precise targeting of interventions, efficient resource allocation, and better outcomes in disease elimination efforts (12–15). Recent advancements in geospatial mapping and epidemiological modeling have been instrumental in identifying at-risk populations and tailoring control strategies accordingly (16–19). However, there remain endgame challenges in the elimination of the disease. The persistence of infection, in districts that have implemented many years of MDA, and logistical challenges in implementing MDA require the need for innovative approaches and sustained commitment to the global eradication effort (7, 20–22).

LIFECYCLE AND TRANSMISSION OF FILARIAL WORMS

The lifecycle of the filarial worms *W. bancrofti*, *B. malayi*, and *B. timori* involves a complex interaction between the human host and the mosquito vectors (Fig. 1). The life cycle begins when a female mosquito feeds on a person (or animal in the case of *Brugia* spp.) who has circulating microfilariae (immature larvae) in the blood. This mostly occurs at night when the parasite density in peripheral blood is highest. *Culex*, *Anopheles*, and *Aedes* mosquitoes are the primary vectors for *W. bancrofti* (23, 24). However, other mosquito species, including *Mansonia uniformis*, *Mansonia annulifera*, *Armigeres subalbatus* (25–27), and *Coquillettidia crassipes* (28), have also been reported as vectors for the transmission of *B. malayi*. *Mansonia uniformis* and *Mansonia annulifera* are also known as vectors of *W. bancrofti* in some areas (29, 30). The timing of mosquito feeding

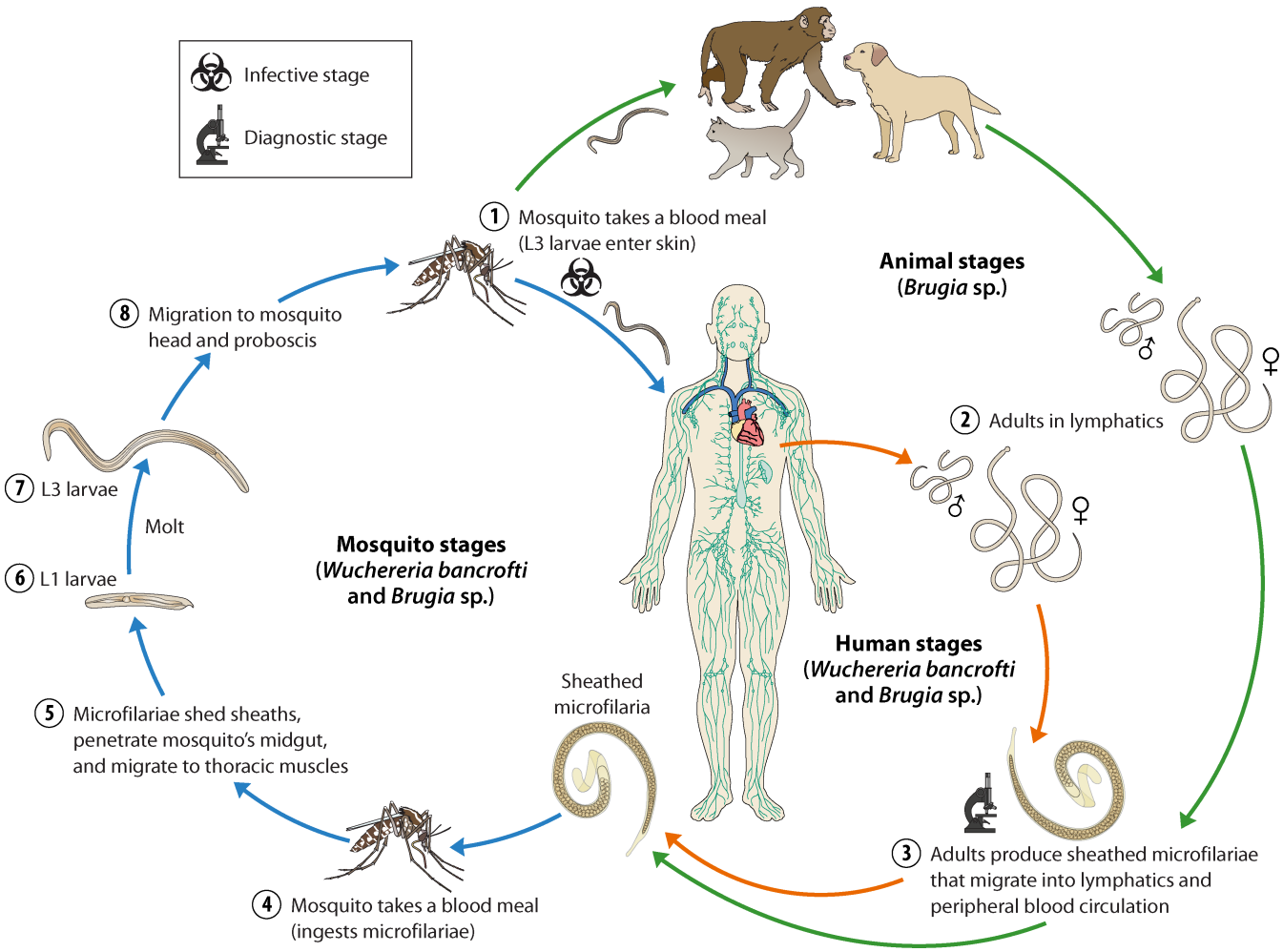


FIG 1 Life cycle of filaria parasites causing lymphatic filariasis. The cycle of *Brugia* spp. can also occur in cats, monkeys, and dogs.

is critical, as microfilariae show periodicity. Their density in peripheral blood varies depending on the time of day, which is adapted to the feeding habits of the local mosquito vector species. Microfilariae of *W. bancrofti* and *Brugia* spp. exhibit a nocturnal periodicity in most regions (31–35), with their concentration in peripheral blood peaking at night when mosquitoes are most active. During the daytime, they accumulate in the small vessels of the lungs, and hence, they are few in the peripheral blood (36). This nocturnal periodicity increases the likelihood of transmission. However, in some South Pacific regions, microfilariae display diurnal periodicity to match the daytime biting habits of local mosquito vectors (34, 37). During a blood meal, the female mosquito ingests microfilariae along with the blood. After ingestion, microfilariae must survive the passage through the mosquito's gut, a critical factor for their development into the next stage (38–41). Factors, such as temperature (42) and the mosquito's cibarial armature (43, 44) and immune defense mechanisms (45–48), are responsible for limiting the number of microfilaria that survive in the mosquito. The surviving microfilariae must then penetrate the mosquito's midgut and migrate to the thoracic muscles to begin their development (48–50).

Once inside the thoracic muscles, the microfilariae shed their sheaths and develop into the first larval stage (L1) (49, 51, 52). This stage is non-infective and characterized by the larvae beginning to absorb nutrients and grow within the safety of the mosquito's muscle tissues. The L1 larvae soon undergo their first molt to become second-stage larvae (L2) by the fifth to seventh day. This developmental stage is still considered

non-infective and involves further growth and morphological changes that prepare the larvae for their final molt. The most critical development occurs at approximately days 10 to 11 when the L2 larvae molt into the third and final larval stage (L3), which is the infectious stage. This stage is particularly adapted to survive in the human host, and the larvae migrate from the thoracic muscles to the mosquito's proboscis (53–56), positioning themselves to be transmitted during the next blood meal. The entire development process from microfilaria to the infective L3 stage typically takes 7 to 14 days and is dependent on temperature and humidity (41, 52).

When an infected mosquito takes a blood meal from a human, it injects saliva to prevent blood clotting. During this process, the third-stage larvae (L3), which have migrated to the mosquito's proboscis, are deposited onto the skin and then enter the human host through the puncture wound (52). After entry, the L3 larvae navigate through the human host's tissues to reach the lymphatic system (57). Once in the lymphatic system, they mature into adult worms (58). Over the next 6 to 12 months, the L3 larvae develop into adult male and female worms (59, 60). Adult worms can live for 5–7 years, sometimes up to 15 years, in the human lymphatic system (61–64). Adult male and female worms often cohabit in the lymphatic vessels, forming "nests" where they mate (65, 66). Female worms are viviparous, giving birth to live microfilariae (67). Microfilariae are slender, thread-like larvae, measuring between 200 and 300 µm in length (49). These microfilariae are released into the bloodstream, making them available to be picked up by mosquitoes during blood meals, thus perpetuating the transmission cycle. Microfilariae have developed mechanisms to evade the human immune system, which allows them to survive and circulate within the host's bloodstream for extended periods. These mechanisms include molecular mimicry and immune modulation, which help them avoid detection and destruction by the host's immune defenses (68, 69). The presence of microfilariae is often asymptomatic but is crucial for the continuation of the lifecycle, as they must be ingested by mosquitoes to develop further (61). Thus, the lifecycle of *W. bancrofti* and *Brugia* spp. is a remarkable example of parasitic adaptation and efficiency, with each stage finely tuned to exploit both human and mosquito hosts for survival and propagation.

VECTOR SPECIES AND VECTOR–PARASITE TRANSMISSION RELATIONSHIPS

Understanding the species of mosquitoes that act as vectors for LF and their behaviors is crucial for developing effective control and elimination strategies. The primary vectors belong to the genera *Culex*, *Anopheles*, *Aedes*, and *Mansonia*, each exhibiting unique behaviors that influence LF transmission dynamics (23, 70), although other vectors, such as *A. subalbatus* (25–27) and *C. crassipes* (28), also play a role in the transmission of *Brugia* spp.

Culex quinquefasciatus, also known as the southern house mosquito, is a prevalent carrier in urban and peri-urban regions, particularly in tropical and subtropical areas. This mosquito species favors breeding in polluted water and is well suited to human habitats. It is most active in biting during the night, which coincides with the nighttime presence of *W. bancrofti* microfilariae in human peripheral blood (71–73). Various *Anopheles* species, known primarily for their role in malaria transmission, also serve as vectors for LF, particularly *Anopheles gambiae* in Africa. These mosquitoes usually breed in clean, freshwater habitats and display both nocturnal and crepuscular biting behaviors. The involvement of *Anopheles* mosquitoes in LF transmission emphasizes the potential for integrated vector management strategies targeting both malaria and LF (23). *Aedes* mosquitoes, including *Aedes polynesiensis* and *Aedes aegypti*, also play a role in the transmission of LF, especially in the Pacific islands and parts of Asia. *Aedes* species often breed in artificial containers and natural habitats near human dwellings. They are known for their aggressive daytime biting behavior, and their ability to adapt to urban environments presents significant challenges for LF control (74, 75). *Mansonia* mosquitoes are also important vectors of LF (30, 70). These mosquitoes breed in aquatic vegetation and are known for their preference for biting during the early evening. The

ecological niche of *Mansonia* species points to the need for habitat-specific control measures (76, 77). It is important to consider vector competence, biting rates, host preference, and breeding site preferences as key factors that influence the transmission dynamics of LF. Strategies to interrupt transmission, such as insecticide-treated bed nets (ITNs) and source reduction of breeding sites, must take into account these vector-specific behaviors and ecological preferences (78).

The elimination strategy of the GPELF relies on the understanding of the vector–parasite interaction processes, based on which treatment may reduce circulating microfilariae below a threshold level to interrupt transmission by the disease vectors. The strategy is based on research on vector–parasite systems to determine if vectors are effective in picking up and transmitting infection at low microfilaremia levels (10). These vector–parasite combinations are described under the density-dependent processes of "Facilitation," "Limitation," and "Proportionality" (79). In recent years, however, research on these processes has been limited.

Facilitation describes the process where, below a certain microfilariae threshold, designated as Webber's Critical Point (80), the transmission of filaria worms by anopheline vectors cannot be sustained (81–83). Facilitation processes have been observed in anopheline mosquitoes (81, 82). When these vectors ingest infected blood, this, together with the microfilariae, goes through the proboscis as a result of a pumping action by the cibarial and pharyngeal pumps. In some mosquito species, the pumps are lined with denticulate structures (cibarial armature) that can fatally damage passing microfilariae (44). When the mosquito takes a blood meal with low microfilariae density, the cibarial armature substantially reduces the proportion of surviving microfilariae. However, at high microfilariae densities, the cibarial armature becomes masked by a few microfilariae promoting the survival of the others. Thus, at high microfilariae densities, transmission becomes efficient by raising transmission thresholds, which can be more easily achieved through control measures (84). However, there is some evidence that in certain areas, some *Anopheles* species may be exhibiting the process of limitation (85, 86).

Limitation, on the other hand, represents a process in which stable transmission occurs even at low levels of microfilariae, found among *Culex* and *Aedes* mosquitoes (84, 87). Limitation processes occur because the number of parasites per mosquito cannot increase indefinitely. The relationship between mf intake and L3 output is linear at the beginning and then stabilizes or may decrease with higher mf intake due to excessive vector mortality from ingesting too many microfilariae (84). Thus, in terms of Limitation, there is a maximum threshold. Below this threshold, the limited process is considered "over-efficient," and above it, it is deemed "under-efficient" (84). Thus, in the context of Limitation, the ability to eliminate LF is significantly hindered by shifting transmission thresholds to lower values, necessitating greater control efforts.

A third case of non-regulated transmission by vectors, referred to as "Proportionality," leads to a linear relationship of ingested microfilariae by the vector developing to the infective stage. Limitation and Facilitation in vectors cause deviations from this linear relationship (71, 84).

It was important to understand the interactions between vectors and parasites to define the paths to elimination. Studies in Papua New Guinea (PNG) supported the idea that MDA alone could be used to interrupt transmission in regions where *W. bancrofti* is transmitted by *Anopheles* species. These results showed that transmission by *An. punctulatus* was nearly eliminated after 1 year of treatment despite the high infection prevalence in the human population (88). In contrast, in the Polynesian Islands of Moorea and Maupiti, where *Aedes polynesiensis* was the vector, MDA using DEC over a period of 50 years did not eliminate the disease (80).

CLINICAL FEATURES

The development of LF involves intricate interactions between the filarial parasite and the human immune system. Persistent infection can result in serious health problems, such as lymphedema and elephantiasis, due to the immune response and physical

damage caused by the adult worms living in the lymphatic system (89–91). The presence of adult filarial worms in the lymphatic vessels triggers the host immune response, which is primarily characterized by tissue inflammation (90). The body's attempt to kill the worms leads to damage to the lymphatic vessels. Chronic inflammation can result in the thickening of the lymph vessel walls and decreased lymphatic function (92, 93). The ongoing inflammation and immune response cause the lymphatic vessels to dilate and become obstructed, disrupting normal lymph flow (94–96). When there is an obstruction, it can cause a build-up of lymph fluid, known as lymphedema (swelling), which is usually seen in the legs, arms, and genital regions. Repeated episodes of inflammation and lymphedema can lead to fibrosis over time, which is the thickening and hardening of tissues (93, 97, 98). As fibrosis progresses, the skin and underlying tissues thicken, resulting in elephantiasis, a condition marked by severe swelling and skin texture changes that can be disabling. Patients with lymphedema are particularly susceptible to acute secondary bacterial and fungal infections of the skin and lymph system (acute dermatolymphangioadenitis [ADLA]), which can exacerbate the lymphedema and accelerate the progression to elephantiasis (99, 100). Chronic LF can also have systemic effects, including kidney damage (101).

Acute episodes often present as lymphangitis and lymphadenitis, which are inflammatory responses in the lymphatic vessels and nodes, respectively (102, 103). Patients may experience fever, pain, and tenderness along the affected lymph vessels, accompanied by red streaks on the skin and swollen lymph nodes. Acute episodes can also lead to ADLA, acute attacks triggered by bacterial infections in patients with underlying lymphatic damage (104).

Chronic conditions develop over many years of infection and are characterized by irreversible damage to the lymphatic system. Lymphedema, which is swelling due to lymph fluid retention, is initially reversible but becomes permanent over time. It often affects the legs but can also involve the arms, breasts, and genitalia (104). Advanced lymphedema with thickening of the skin and underlying tissues leads to severe swelling and disfigurement (105, 106). Individuals with lymphedema are also prone to recurrent bacterial and fungal infections of the skin and lymphatic system (ADLA), which can exacerbate swelling and pain (105, 107–109). Hydrocele is the accumulation of lymph fluid in the scrotal sac, leading to enlargement. It is the most common chronic manifestation among men in endemic areas (110, 111).

Many individuals infected with filarial parasites are asymptomatic but may have subclinical lymphatic damage detectable through imaging techniques. Subclinical infection can progress to overt disease or contribute to the transmission cycle of LF (112–114).

Alongside the changes in the lymphatic and associated tissue inflammations, overt signs of LF also include acute and chronic dermatological manifestations (115, 116). In the early stages of infection, patients may experience acute dermatitis, characterized by itching, redness, and swelling of the skin. Calabar swellings may also occur on the arms, legs, or genitals. The inflammation of the lymphatic vessels can result in redness, swelling, and pain in the affected limb (117). Chronic dermatological manifestations exhibit as elephantiasis, the most striking feature of LF characterized by massive swelling of the affected limb, often accompanied by thickening of the skin and subcutaneous tissue (118). Chronic inflammation and obstruction of the lymphatic vessels lead to lymphedema, causing persistent swelling of the affected limb. These eventually result in skin thickening and fibrosis due to the repeated episodes of inflammation and scarring, giving the skin a cobblestone-like appearance. Thickening of the skin can cause hyperkeratosis, leading to a rough, scaly texture (116). Finally, patients may experience pigmentation changes, including hyperpigmentation or hypopigmentation.

CONTROL STRATEGIES

Mass drug administration (MDA)

MDA is the cornerstone of the global strategy to eliminate LF, aiming to reduce the reservoir of infection in human populations (1, 4, 6, 119). Given that infections and exposure to infected vectors within a community often go undetected, MDA is the recommended cost-effective strategy for treating all individuals in endemic areas and preventing further transmission. MDA involves distributing antifilarial medications, primarily diethylcarbamazine (DEC), albendazole, and ivermectin, to all eligible individuals in endemic areas, regardless of their infection status (120). These drugs can effectively kill microfilariae and partly sterilize adult worms, thus reducing the potential for transmission. However, because they do not reliably kill all adult worms, they must be given at least 5 to 6 years to cover the lifespan of the adult worms (121). The WHO recommends conducting sentinel and spot-check community surveys, followed by a transmission assessment survey (TAS), to determine if the infection prevalence has dropped below target thresholds, which would allow MDA to be stopped. After stopping MDA, the TAS is repeated twice over the next 4–6 years (TAS2 and TAS3) to ensure that there is no resurgence of LF infection to levels that would require intervention (1, 122, 123).

Morbidity and management

Before the GPELF, approximately 129 million people were estimated to be infected with LF, of which 43 million had clinical disease, corresponding to a DALY burden of 5.25 million. The total economic burden of LF was estimated at US $5.8 billion annually (3). The morbidity associated with LF includes a wide range of physical and psychosocial consequences resulting from the infection. These manifestations have a significant impact on individuals' quality of life, leading to chronic pain, disability, social stigma, and economic hardship. Understanding the extent of LF morbidity is crucial for developing effective management, support, and preventive measures.

The visible manifestations of LF, such as limb swelling and hydrocele, can lead to stigma, discrimination, and social isolation. Affected individuals may experience decreased marriage prospects, social ostracization, and mental health issues, including depression and anxiety (124–127). LF can also significantly impair an individual's ability to work, leading to loss of income, increased healthcare expenses, and, ultimately, greater poverty. The economic burden extends to families and communities and can hinder socioeconomic development in endemic areas (128–130). The combined physical, social, and economic impacts of LF morbidity severely affect the quality of life of individuals and their families. Chronic pain, limited mobility, and social stigma contribute to a cycle of poverty and disease. The morbidity associated with LF underscores the multifaceted impact of the disease, necessitating comprehensive strategies that address not only the physical symptoms but also the psychosocial and economic challenges faced by affected individuals.

Previous studies have shown that doxycycline improved lymphedema in LF patients (131–133). However, a recent 24-month randomized control trial indicates that while doxycycline is well tolerated, its addition as a 6-week course of doxycycline (200 mg) was not superior to placebo in increasing the improvement associated with hygiene in lymphedema management (134). As such, hygiene remains a critical component in the management of LF morbidity, particularly for individuals suffering from chronic manifestations of the disease such as lymphedema (135–137). Effective hygiene practices can significantly reduce the severity of symptoms and improve the quality of life for affected individuals. Effective hygiene practices include the regular washing of affected areas with soap and clean water to remove dirt and prevent bacterial and fungal infections, drying and moisturizing to prevent cracking and entry of infectious pathogens, keeping nails clean and trimmed to reduce the risk of scratching, which can lead to skin infections, and prompt treatment of infections with appropriate antibiotics to

prevent the progression of symptoms. In addition to the above, physical therapy and exercise are vital for managing lymphedema and improving lymphatic drainage.

Morbidity Management and Disability Prevention (MMDP) services are critical for alleviating the suffering of those already affected by LF and preventing further disability (110). These services include the management of lymphedema and acute episodes of dermatolymphangioadenitis (ADLA), surgical interventions for hydrocele, and physical and psychological support. Effective MMDP can also enhance community participation in LF elimination programs by reducing the stigma associated with LF-related disabilities (138–142). Key components include the following: teaching patients with lymphedema proper skin care to prevent secondary infections and reduce swelling (141), hydrocelectomy as a permanent solution to this debilitating condition (143, 144), and exercises and elevation of affected limbs to help reduce lymphedema volume and improve limb functionality (110).

Improving access to clean water, adequate sanitation, and promoting good hygiene practices are essential for reducing LF transmission (145). WASH interventions also support the management of LF morbidity by preventing secondary infections in individuals with lymphedema (145, 146).

Vector control

Vector control is a crucial component in the strategy to manage and eliminate LF. Effective vector control can significantly reduce transmission rates. There are various strategies and techniques employed in vector control, particularly focusing on mosquitoes due to their role in LF transmission. The first strategy relies on environmental management, a vital aspect of vector control, particularly for reducing the populations of mosquitoes (147–149). This approach involves altering or modifying the environment to prevent vector breeding, reduce vector habitats, and limit human–vector contact. Effective environmental management can significantly decrease the incidence of vector-borne diseases without the recurring costs associated with chemical interventions. Some of the specific strategies and practices within environmental management include source reduction by removing stagnant/standing water (from pots, old tires, buckets, and other containers) where mosquitoes lay their eggs and proper collection and disposal of waste to eliminate water-holding containers from the environment (149–151). Adjusting how water is stored and managed can also significantly impact mosquito breeding. This can be done through the modification of water storage containers, covering water storage containers with lids, or using fine mesh to cover openings to prevent mosquitoes from accessing the water to lay eggs, and adjusting irrigation practices to avoid excessive water standing to reduce mosquito breeding grounds in agricultural settings. Habitat modification is another approach utilized to change the physical environment and make it less suitable for vectors to live and breed (152–154). These can be done through landscaping to ensure better drainage and reduce the accumulation of water, grading lands to promote water run-off, and avoiding heavy underbrush near living areas to decrease mosquito resting and breeding sites, managing the vegetation around water bodies to reduce mosquito populations. Other forms of environmental management can include modifying building designs and construction practices to minimize human–vector contact, such as installing screens on windows and doors that can prevent mosquitoes from entering homes, significantly reducing the risk of disease transmission, and designing buildings to enhance airflow to deter mosquitoes, which prefer calm and sheltered environments to rest and breed (154, 155). In all the above strategies, involving the community in environmental management is crucial for sustained success (156, 157). This can be done through educating the community about how their actions can impact mosquito breeding, and teaching them ways to modify their environment can empower residents to take charge of reducing vector populations. Organizing regular community-led clean-up drives to clear litter and potential mosquito breeding sites can foster community spirit and enhance public health.

Insecticides

The most common approach to vector management is using chemical insecticides to kill or repel vectors. Insecticides are the cornerstone of chemical control strategies. These are usually formulated to kill adult mosquitoes or larvae. Commonly used adulticides include pyrethroids (e.g., permethrin, deltamethrin), organophosphates (e.g., malathion, temephos), and carbamates (158, 159). Larvicides are targeted at mosquito larvae to prevent them from maturing into adults. Examples include insect growth regulators (e.g., methoprene) (160), microbial larvicides like *Bacillus thuringiensis israelensis* (Bti) (161, 162), and organophosphates (e.g., temephos) (163, 164). The effectiveness of chemical control depends significantly on the method of application. Indoor residual spraying (IRS) involves the application of long-acting insecticides on the walls and other surfaces of houses and buildings where mosquitoes are likely to rest (165, 166). IRS is particularly effective against mosquitoes that enter dwellings to feed. Space spraying involves the application of insecticides in outdoor or indoor spaces to reduce mosquito populations quickly (167, 168). It can be conducted using handheld sprayers, truck-mounted equipment, or even aerial applications in large-scale operations. Larvicidal treatments apply larvicides to water bodies where mosquitoes breed (169–171). This can be done manually for small water bodies or mechanically for larger areas. A major challenge to chemical management is the development of insecticide resistance among mosquito populations (172–174).

Personal protection

Personal protection measures are also crucial in reducing human exposure to disease vectors (175–177). These measures are particularly important where environmental and chemical controls might not be fully effective or accessible. However, it is also worth noting that some personal protection methods rely on the use of chemicals. Effective personal protection can significantly decrease the incidence of mosquito bites, thus reducing the risk of disease transmission. Some of the personal protection methods include the use of insecticide-treated nets (ITNs), one of the most effective personal protection measures (178–180). ITNs provide a physical barrier that prevents mosquitoes from biting individuals while they sleep. The insecticide impregnated in the nets also kills or repels mosquitoes upon contact, increasing the protective effect. ITNs are widely used in malaria-endemic regions and are also effective against LF vectors. Their use is promoted in all LF endemic areas, particularly where night-biting vectors are prevalent. Topical repellents applied to the skin or clothing can also deter mosquitoes from landing and biting, offering personal protection when outdoors or in areas where ITNs and IRS are not feasible. The most effective repellents contain DEET, picaridin, or IR3535 (181–184). These chemicals are safe for human use and provide long-lasting protection against mosquito bites. Wearing clothing that covers most of the body can also significantly reduce mosquito bites. This is particularly important during peak biting times. Spatial repellents and mosquito traps offer additional protection by reducing the number of mosquitoes in an area, thereby reducing the risk of bites. Finally, modifying activities to reduce exposure to vectors, such as avoiding outdoor activities during peak mosquito biting times, typically dusk and dawn, can also serve as an effective personal protection strategy.

Integrated vector management

Integrated vector management (IVM) is a strategic and rational approach to vector control that combines various methodologies and practices to manage vector populations effectively (185, 186). IVM aims to reduce and manage vector densities to levels where they no longer pose significant risks to public health. This approach is crucial in the control of diseases, such as malaria and LF, where multiple vector species are involved, and environmental, social, and economic factors play significant roles. IVM is based on several key principles that ensure its effectiveness and sustainability.

These include utilizing data on local vector ecology, disease transmission, and socioeconomic conditions to tailor vector control strategies appropriately; combining chemical, biological, environmental, and mechanical control methods along with public health interventions to manage vector populations; ensuring that the methods employed provide the maximum possible benefit in terms of disease control for the resources invested; and focusing on methods that are environmentally sound and socially acceptable, reducing reliance on any single type of control measure such as insecticides. IVM incorporates the various vector control components described above, coupled with the need for local capacity building, monitoring and evaluation, and research and development. While it offers a comprehensive approach to vector control, several challenges can impact its success, including the availability of resources and the need for intersectoral coordination, public awareness, and compliance (187, 188).

Vector control strategies play a critical role in the fight against lymphatic filariasis (LF), serving as essential complements to MDA efforts. Vector control complements MDA by directly reducing vector density and human–vector contact (78, 189, 190). Methods include the use of insecticide-treated bed nets (ITNs), indoor residual spraying (IRS) (185, 191, 192), and environmental management (193) to eliminate mosquito breeding sites. These methods have proven effective, especially when tailored to local vector species and their behaviors. Integrated vector management involves coordinating the use of multiple vector control strategies and integrating LF control efforts with other vector-borne disease control programs (185, 186). This approach maximizes resource efficiency and the impact on vector populations, contributing to the broader goals of public health. Vector control measures are crucial in reducing the transmission of LF. Integrating LF vector control with control programs for other vector-borne diseases can enhance the overall effectiveness and cost efficiency of these interventions.

IMMUNOLOGY

The immunology of LF involves a complex interplay between the human immune response and filarial parasites. Understanding these interactions is crucial for developing vaccines, diagnostic tools, and new treatments. The immune response to filarial infection is characterized by both an innate and adaptive response, with immunomodulation by the parasite to ensure its survival. The innate immune response involves the immediate, non-specific response to the filarial parasites. Key players in the immune response include macrophages, dendritic cells, neutrophils, and natural killer (NK) cells. These cells detect parasite antigens through pattern recognition receptors (PRRs) and trigger an inflammatory response to eradicate the infection (194). The adaptive immune response is more specific and involves the activation of T and B lymphocytes. LF is associated with a mixed Th1/Th2 response, with a significant role played by regulatory T cells (Tregs) and Th2 cells in controlling inflammation and preventing tissue damage. This response results in the production of antibodies by B cells, particularly IgG4, which is elevated in chronic LF and may play a role in immune tolerance to the parasite (195). The immune response to infection also plays a role in the development and modulation of inflammatory response associated with acute disease resulting in overt symptoms in some infected individuals and not others (196).

The immune response biomarkers for LF are crucial for understanding how the body responds to infection and for developing diagnostic and monitoring tools. These biomarkers, such as specific antibodies, cytokines, and immune cells, can show exposure to filarial parasites, the severity of infection, and the body's immune status. They provide valuable information about disease progression and the effectiveness of treatment interventions (194). The body's production of antibodies in response to an infection is essential for diagnosing and understanding the immune-related aspects of the disease. Studying these responses has resulted in the creation of serological tests that can identify particular antibodies to filarial antigens, showing exposure to the parasites (197–200). The cytokine response in LF-infected individuals can also provide insights into the disease's pathogenesis and the host's immune status (194, 201, 202). The cytokine

profiles in LF-infected individuals provide valuable insights into the host's immune response to infection with filarial parasites. Pro-inflammatory cytokines play a critical role in the immune response to LF, influencing both disease progression and the severity of symptoms. Research into pro-inflammatory cytokines, such as IFN-γ, TNF-α, and IL-1β, has provided insights into their roles in the development of LF and their potential as targets for therapeutic intervention (203–205). The Th2 cytokines are commonly linked to chronic infection and the regulation of inflammatory responses. These cytokines, such as IL-4, IL-5, IL-9, and IL-13, play a role in controlling antibody production, eosinophilia, mast cell growth, and the activation of alternatively activated macrophages, which are key components of the immune response to LF (194, 203, 206, 207). Regulatory cytokines, including IL-10 and TGF-β, play crucial roles in controlling inflammation, preventing tissue damage, and promoting parasite survival by inducing tolerance or suppressing effector immune mechanisms (207–210). These profiles reflect the complex interplay between pro-inflammatory, anti-inflammatory, and regulatory cytokines that can influence disease progression, symptom manifestation, and the efficacy of treatment interventions (194, 201, 202). Understanding cytokine dynamics is crucial for elucidating the pathogenesis of LF and for developing targeted therapeutic strategies.

T-cell subsets play an equally important role in the immune response to LF. The balance between different T-cell subsets, such as Th1, Th2, Th17, and regulatory T cells (Tregs), is crucial in determining the outcome of the infection. It influences whether an individual will develop chronic disease symptoms, remain asymptomatic, or successfully clear the infection (204, 211–213). Th1 cells are pivotal in orchestrating the immune response against intracellular pathogens through the production of pro-inflammatory cytokines such as IFN-γ and TNF-α. In the context of LF, Th1 cells play a crucial role in mediating the immune response (203, 204, 214, 215), which can influence disease progression, pathology, and the efficacy of treatments. Understanding the role of Th1 cells in LF is essential for developing more effective interventions and vaccines. Th2 cells are a subset of CD4+ T cells that produce cytokines such as IL-4, IL-5, IL-9, and IL-13. These cytokines are crucial for antibody production, eosinophil activation, and mast cell growth. They help mediate immune responses that limit tissue damage from infection while potentially allowing chronic infections to persist (194, 203, 207, 215). Th17 cells, characterized by their production of interleukin-17 (IL-17), are crucial in host defense against extracellular pathogens and have been less extensively studied in the context of LF compared to other T-cell subsets (216–218). However, their involvement in immune responses to various parasitic infections suggests they could also play a role in LF, particularly in inflammatory aspects of the disease. Regulatory T cells (Tregs) maintain immune homeostasis and prevent autoimmune diseases by suppressing excessive immune responses (195, 205, 206). In the context of LF, Tregs play an essential role in modulating the host's immune response to the filarial parasites (204). Tregs help control the inflammatory reactions associated with the infection, potentially facilitating parasite survival while preventing severe pathology.

Filarial parasites have evolved mechanisms to evade and modulate the host's immune response, allowing them to survive for years. They release excretory–secretory products that can induce regulatory immune responses, suppress T-cell proliferation, and divert the immune response toward a Th2 and Treg profile (60). This immunomodulation can lead to a state of antigen-specific tolerance or hypo-responsiveness in the host, contributing to the chronicity of the infection. The clinical manifestations of LF, such as lymphedema and hydrocele, are primarily the result of the host's immune response to the parasite rather than direct parasitic damage. Chronic immune activation and inflammation in the lymphatic system lead to lymphatic dysfunction and fibrosis. The balance between protective and pathological immune responses plays a crucial role in disease progression and severity (205).

Understanding the immune evasion strategies of filarial parasites is critical for vaccine development. Identifying antigens that can elicit a protective immune response without causing harmful inflammation is a major focus of research. Several potential vaccine

candidates have been identified, but the development of an effective vaccine remains a challenge due to the complexity of the immune response to filarial infection (219). The immunology of lymphatic filariasis highlights the intricate dance between the human immune system and filarial parasites, underscoring the challenges in managing and eliminating this disease. The ongoing research into the immunopathogenesis of LF is crucial for developing new therapeutic and preventive strategies. (ChatGPT was used for ideation for the Immunology section of the paper.)

Protective immunity

Despite prolonged exposure in endemic regions, a subset of individuals remains uninfected or asymptomatic, suggesting the role of protective immunity (220). It is known that many individuals presenting overt clinical symptoms are usually microfilariae negative (118). While the exact etiology facilitating the development of pathologies, such as lymphedema and hydrocele, remains unclear, vascular endothelial growth factors (VEGFs) have been implicated (131, 221). Thus, the protective immunity in LF involves a balance of innate and adaptive immune responses, including innate cell activation, Th1/Th2 polarization, antibody-mediated responses, and immune regulatory mechanisms. Protective mechanisms may also likely vary based on the lifecycle stage of the parasites (222, 223).

The innate immunity serves as the first line of defense against filarial infection. Pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), recognize pathogen-associated molecular patterns (PAMPs) on filarial antigens, initiating immune responses (224). Macrophages and dendritic cells process filarial antigens and release pro-inflammatory cytokines, which activate downstream responses (225–227). Eosinophils contribute to larval killing via degranulation and release of cytotoxic granules, including major basic protein (228, 229), while natural killer (NK) cells mediate early responses by producing interferon-gamma (IFN-γ), enhancing macrophage activation (230).

The adaptive immune system, on the other hand, provides long-term immunity and involves T- and B-cell responses. *Th1 responses*, driven by IFN-γ and IL-12, are associated with parasite clearance and protection in resistant individuals (211), while *Th2 responses*, characterized by IL-4, IL-5, and IL-13, promote antibody production and eosinophil activation. However, excessive Th2 responses may contribute to chronic infection (198). B-cell and antibody responses initiated through immunoglobulin G (IgG) and immunoglobulin E (IgE) antibodies target filarial antigens, mediating antibody-dependent cellular cytotoxicity (ADCC) (231–233).

Immune regulation and natural resistance

Chronic filarial infections often result in immune tolerance, characterized by regulatory T cells (Tregs) and anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta (TGF-β) (234, 235). Eosinophils play a crucial role in the immune response against LF, particularly during the larval stages of the parasite (236). These granulocytes are recruited to infection sites by cytokines, such as interleukin-5 (IL-5) and eotaxins, which are produced in response to Th2-dominated immune responses (198). Additionally, eosinophils mediate antibody-dependent cellular cytotoxicity (ADCC) by binding to IgE and IgG antibodies coating the parasite through their Fc receptors, facilitating larval killing (237). Despite their protective role, eosinophils are also implicated in pathological inflammation associated with chronic infections, as their prolonged activation can contribute to tissue damage and fibrosis in lymphatic vessels (238). Understanding the dual role of eosinophils in immunity and pathology is essential for designing therapies that enhance their protective effects while mitigating collateral damage.

DIAGNOSIS

The accurate diagnosis of LF is crucial for effective disease management, control programs, and for monitoring and evaluating elimination efforts. The diagnostic

landscape for LF has evolved significantly, incorporating traditional methods alongside advances in molecular diagnostics and imaging techniques. The traditional method for LF diagnosis involves the microscopic examination of blood samples for the presence of microfilariae. Blood is collected during the night to coincide with the nocturnal periodicity of microfilariae in the peripheral blood of infected individuals. There are two main methods for preparing blood samples for microscopic examination as follows: the thick blood smears and concentration techniques (239, 240). For the thick blood smears, a drop of blood is spread on a slide to create a thick layer, which is then dehemoglobinized, stained, and examined under a microscope. The concentration techniques, such as Knott's method or filtration through a membrane, are used to concentrate microfilariae from a larger volume of blood, increasing the sensitivity of detection (240–242). Microscopy is widely used in endemic areas for the initial diagnosis of LF and for monitoring the effectiveness of treatment and control programs. It provides a direct means of observing the parasite, offering definitive proof of infection. The distinguishing morphological characteristics for the microscopic diagnosis of *W. bancrofti*, *B. malayi*, and *B. timori* are presented in Fig. 2 below. These species can be distinguished based on the measurements of various body characteristics of the microfilarial forms, such as the number and position of caudal nuclei, length and width of microfilariae, cephalic space, and the presence or absence of a sheath. However, this method has limitations in sensitivity, especially in low-endemicity areas or in individuals with low-level infections (243). It also requires skilled personnel to accurately identify microfilariae among blood cells. Furthermore, the need for nighttime blood collection to match the nocturnal periodicity of microfilariae poses logistical challenges.

The advent of circulating antigen detection tests for LF marked a significant advancement in the disease's diagnosis and management. These tests, primarily targeting *W. bancrofti* infections, have become integral in identifying both symptomatic and asymptomatic carriers, thereby facilitating prompt intervention and reducing transmission rates. The inception of antigen detection tests arose from the necessity for a diagnostic method that surpassed the sensitivity and specificity limitations inherent in microscopic examination of blood for filarial larvae. This need led to the development of the immunochromatographic test (ICT) in the 1990s, a significant leap forward due to its rapid, point-of-care utility, operable without specialized lab facilities (243). Following the ICT, the Filariasis Test Strip (FTS) was introduced (244, 245), offering logistical improvements over the ICT, such as better usability, cost effectiveness, and less stringent storage conditions, making it highly suitable for mass epidemiological surveys and monitoring within LF elimination initiatives. The evaluation of these diagnostic tools has consistently demonstrated their high sensitivity and specificity in identifying *W. bancrofti* infections. A study by Weil and Ramzy (199) emphasized the FTS's heightened sensitivity compared to the ICT, especially in low prevalence settings, underscoring its importance to the

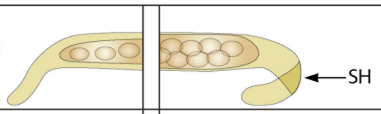
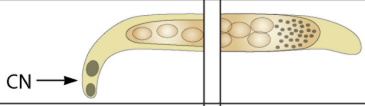
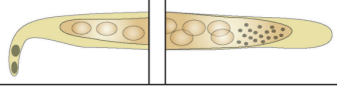
	Posterior ends / Anterior ends	Body characters			
		Length	Width	Cephalic space	Length-width ratio
Wuchereria bancrofti		309-347 µm	5.30 µm	4.10 µm	1:1
Brugia malayi		205-240 µm	4.00 µm	7.50 µm	1:9:1
Brugia timori		265-323 µm	4.40 µm	13.00 µm	3:1

FIG 2 Differentiation of different species of microfilariae on the basis of the presence or absence of caudal nuclei (CN) and sheath (SH).

GPELF's success (199). Other studies have contributed to the development of recombinant antigen-based antibody assays, significantly enhancing the diagnostic landscape for filarial infections (246, 247).

Several immunodiagnostic tests have been developed to detect filarial antigens or antibodies. The Circulating Filarial Antigen (CFA) test (243), such as the Og4C3 ELISA (248) and the Alere Filariasis Test Strip (FTS) (244), detects antigens released by adult worms, offering high sensitivity and specificity. These tests do not depend on the timing of blood collection, making them more convenient and suitable for large-scale screening. Polymerase chain reaction (PCR)-based methods have significantly improved the sensitivity and specificity of LF diagnosis. PCR and real-time PCR can detect filarial DNA in blood, skin snips, and mosquito vectors (249). These molecular tools are particularly valuable for detecting low-level infections, confirming eradication in elimination programs, and studying the transmission dynamics.

The Og4C3 assay represents a pivotal advancement in the fight against LF. The development and application of the Og4C3 assay, which detects CFA in human blood, have significantly improved the diagnosis and surveillance of this disease. The Og4C3 assay utilizes a monoclonal antibody (Og4C3) that specifically targets a soluble antigen released by adult filarial worms, making it a powerful tool for identifying *W. bancrofti* infections, even in asymptomatic individuals. This assay's introduction marked a significant improvement over previous diagnostic methods, offering higher sensitivity and specificity and the ability to perform large-scale screenings essential for LF elimination programs. The development of the Og4C3 assay in the early 1990s (250) represented a breakthrough in LF diagnostics, establishing the basis for using monoclonal antibodies to detect CFA, a game changer in the disease's management and control strategies. Significant evaluations of the Og4C3 assay have demonstrated its utility, reliability, and effectiveness (248, 251, 252), highlighting its role in supporting LF elimination efforts by providing a means for accurate disease surveillance. However, the Og4C3 assay faces challenges, particularly regarding its implementation in resource-limited settings. The requirement for specialized laboratory equipment and trained personnel can limit its use. Moreover, the assay's cost may be prohibitive for widespread application in endemic countries. Additionally, while highly effective in detecting *W. bancrofti* infections, the Og4C3 assay does not differentiate between active and past infections, which is vital for accurately assessing ongoing transmission and the impact of intervention measures.

Developed in the 1990s, the ICT card test rapidly became a cornerstone in LF diagnosis and surveillance (243). It offers a simple, rapid, point-of-care tool for detecting CFA from *W. bancrofti*, facilitating mass screenings, and supporting decision making in MDA programs. Its introduction marked a significant advancement over previous diagnostic methods, such as microscopic examination of blood smears, which were labor intensive, less sensitive, and limited by the nocturnal periodicity of the microfilariae. The development and widespread adoption of the ICT were instrumental in the GPELF. This test allowed for more accurate mapping of LF endemic areas, assessment of MDA program effectiveness, and provided a means to certify elimination in various regions. Studies have underscored the ICT's critical role in these global efforts, demonstrating its high sensitivity and specificity for *W. bancrofti* infection (199). Despite its advantages, the ICT for LF is not without challenges. First, it requires a cold chain. The test's specificity to *W. bancrofti* means it is not applicable for detecting *Brugia* species infections. Furthermore, the cost and logistical challenges associated with deploying ICTs can limit their use in resource-poor settings. Finally, the test's reliance on the detection of antigens from adult worms means it cannot differentiate between past and current infections, potentially leading to an overestimation of infection prevalence post-MDA. Following treatment, antigen levels typically decline, but the duration of antigen positivity depends on several factors, including the efficacy of treatment, longevity of adult worms, and sensitivity of the diagnostic assay. Antigen levels often remain detectable for several months to years after treatment. This persistence occurs because the antigens are

produced by adult worms, which may survive temporarily despite treatment, or due to the slow clearance of antigens after worm death. Studies show that CFA declines gradually but may remain detectable for up to 1–2 years post-treatment, even when no live microfilariae are present (199, 243, 253, 254). The duration of antigen positivity also varies based on the treatment administered. For example, diethylcarbamazine and ivermectin target microfilariae but are less effective in killing adult worms, leading to prolonged antigenemia. Combination regimens with albendazole may accelerate the decline in antigen levels by enhancing adult worm clearance (255).

The FTS was developed to improve upon the ICT (245). Its ease of use and high sensitivity make it suitable for field conditions, especially in resource-limited settings. Studies have shown that the FTS is highly effective in detecting low levels of filarial antigenemia, which is crucial for identifying infections in areas with declining prevalence due to successful MDA programs. One key study by Chesnais et al. (256) evaluated the FTS in various endemic settings, highlighting its superiority over other diagnostic tests and its utility in post-MDA surveillance to confirm the elimination of LF transmission (256). Despite its advantages, the FTS faces challenges, including the possible cross-reactivity in areas co-endemic with loiasis (257) and the need for improved specificity in differentiating between active and past infections. Recently, a new rapid test detecting *W. bancrofti* CFA, the STANDARD Q Filariasis Antigen Test (QFAT), has been developed as a simple card format by SD Biosensor, South Korea, with promising results to address some of the challenges with the FTS (258, 259).

Serological tests have also been developed for the diagnosis of LF. These tests detect antibodies against filarial antigens, indicating exposure to the parasites. Unlike tests for CFA that indicate current infection, serological tests can identify both current and past infections, making them valuable tools for assessing transmission dynamics, especially in children, and evaluating MDA program effectiveness. The development of serological tests for LF has been aimed at enhancing disease surveillance and elimination strategies. One of the notable advancements is the use of recombinant antigen Bm14 assays, which have shown promising results for their specificity and sensitivity in detecting LF exposure (260–263). The Wb123 test is another serological assay designed to detect antibodies against the Wb123 antigen of *W. bancrofti* (264). The Wb123 antigen was identified through genomic and proteomic analyses as a potential marker for LF exposure due to its specificity to *W. bancrofti*. Serological tests face challenges, including the differentiation between past and current infections and the potential for cross-reactivity in areas endemic to other parasitic diseases. Moreover, the interpretation of seropositivity in low-transmission settings remains a challenge for elimination programs. Ongoing research aims to refine these tests for better specificity and sensitivity and develop strategies for their use in conjunction with other diagnostic methods. The development of multiplex assays capable of detecting antibodies against multiple filarial species is also underway, which could streamline LF surveillance efforts.

The identification of new markers for the diagnosis of LF is a dynamic area of research, pivotal to advancing global efforts. Recent studies have focused on identifying unique molecular and protein markers that are expressed by adult worms and their microfilariae. These markers include DNA, RNA, and proteins that are specific to LF parasites and can be detected in human blood or tissue samples. Advances in sequencing technologies have facilitated the identification of genomic sequences unique to *W. bancrofti*, *B. malayi*, and *B. timori*. This has led to the identification of DNA sequences specific to these parasites, which can be targeted for diagnostic purposes. For example, PCR assays have been developed for detecting parasite DNA in human blood and mosquito samples (249, 265–268). The detection of parasite-specific DNA in blood samples using PCR-based methods represents a promising approach for diagnosing LF, including in individuals with low parasite loads (269). The detection of circulating cell-free parasite DNA (cfDNA) is a relatively recent advancement that offers a non-invasive, highly sensitive method for identifying infections (270, 271). This approach involves identifying fragments of DNA released into the bloodstream by the parasites responsible for the disease. The presence

of cfDNA from these parasites can indicate an active infection, potentially before the appearance of microfilariae or CFA.

Antigenic proteins play a crucial role in the diagnosis of LF. The discovery of antigenic proteins expressed by filarial worms has led to the development of serological tests (199). Proteins such as Wb123 (197) for *W. bancrofti* and Bm14 (263) for *Brugia* species have been utilized in ELISA and RDTs, offering improved sensitivity and specificity over traditional methods. Examples of antigenic proteins include the WbSXP-1 (272), a recombinant antigen derived from *W. bancrofti*, which is used in serological tests to detect antibodies against *W. bancrofti*, indicating exposure to the parasite; the Bm14 (261, 263) originating from *B. malayi*; and the Og4C3 (200, 248) detecting a carbohydrate antigen expressed by adult *W. bancrofti*. The identification and utilization of antigenic proteins, such as WbSXP-1, Bm14, and Og4C3, have revolutionized LF diagnostics, supporting global efforts toward disease elimination. These advances in serological testing facilitate more effective surveillance, early detection, and assessment of intervention impacts, marking critical steps forward in the fight against LF.

Ultrasound imaging has been instrumental in visualizing live adult worms in the lymphatic vessels, a condition known as "filarial dance sign" (FDS) (273, 274). This non-invasive technique provides direct evidence of infection and is particularly useful in endemic areas for assessing disease prevalence and the efficacy of treatment interventions. Lymphoscintigraphy is also used to assess lymphatic system dysfunction in individuals with lymphedema or hydrocele (275–277). While not a direct test for LF, it helps in diagnosing and managing lymphatic damage and understanding the pathogenesis of disease manifestations. However, using the filaria dance sign for diagnosis is challenging, and its efficacy may be dependent largely on the expertise of the individual doing the ultrasound.

Diagnosis methods for LF have progressed from conventional microscopy to more advanced molecular and imaging techniques, enhancing our ability to detect and manage the disease. As elimination efforts progress, these diagnostic tools play a pivotal role in confirming the absence of transmission and guiding public health interventions.

TREATMENT AND CONTROL

Chemotherapy

Treatment of LF aims to eliminate infection, manage symptoms, and prevent the progression of disease-related morbidity. It encompasses a combination of antifilarial drugs, morbidity management, and preventive measures. Recent advances have significantly improved treatment outcomes, particularly in the context of global elimination efforts. MDA is the cornerstone of the global strategy to eliminate LF, aiming to reduce the reservoir of infection in human populations (1, 4, 6, 119). Since infections and exposure to infected vectors within a community often go undetected, MDA is the recommended cost-effective strategy for treating all individuals in endemic areas and preventing further transmission. MDA involves the distribution of a combination of the antifilarial drugs albendazole, ivermectin, and diethylcarbamazine (DEC) to all eligible individuals in endemic areas, regardless of their infection status (120). These drugs are the cornerstone in the global fight against LF and have been extensively studied in clinical trials, both individually and in combination, to determine their efficacy and safety in reducing the burden of filarial infection.

Albendazole is a benzimidazole derivative used as an anthelminthic drug to treat a variety of parasitic worm infestations (278–282). It is often used in combination with either ivermectin or DEC to enhance efficacy against LF. Albendazole disrupts the function of microtubules and fumarate reductase and, as a result, selectively and irreversibly inhibits glucose absorption. This leads to a decrease in glycogen storage in the parasite's tegumentary and intestinal cells, causing immobility, motor paralysis, and eventual death (283, 284). Ivermectin was discovered from *Streptomyces avermectinius* in 1973 by Satoshi Omura (285). It is widely used in MDA programs, particularly in Africa, where it is co-administered with albendazole to control onchocerciasis as well as LF. It

is believed to be a selective positive allosteric modulator of glutamate-gated chloride channels found in nematodes and insects (286). In filarial worms, ivermectin paralyzes and kills the microfilariae and inhibits the release of new microfilariae from adult worms. Studies have shown that ivermectin is highly effective in reducing microfilarial density in the host and has a prolonged effect on preventing their resurgence (287–290). It is less effective against adult worms, which necessitates its use in annual or biannual MDA programs to maintain its impact on transmission. Further, its use is contraindicated in areas co-endemic with *Loa loa*, due to the severe adverse reactions in patients also infected with *L. loa* (291–293). DEC has been the backbone of LF control efforts in many regions before the wider adoption of ivermectin and albendazole (294–297). DEC directly kills microfilariae and some adult worms by acting on the parasite signaling pathways (298–300). DEC is highly effective in reducing microfilariae in the blood and has been used in both individual treatment and community-wide MDA (294, 297). Its use is limited in areas co-endemic with onchocerciasis and loiasis due to severe adverse reactions in patients also infected with *Onchocerca volvulus* and *Loa loa* (301–305).

The combination of these drugs has been the subject of extensive research to optimize LF treatment regimens. The combination of albendazole with ivermectin or DEC has been shown to be more effective than any single drug regimen (7, 255, 306–310). These trials have demonstrated that albendazole, when combined with ivermectin or DEC, is effective in significantly reducing microfilariae load in the blood, aiding in the disruption of transmission cycles. The combination therapies have a synergistic effect, reducing both the microfilariae load and the longevity of adult worms. The evaluation of these drugs through clinical trials has significantly influenced global health policies, leading to the adoption of these drug combinations in the GPELF (10, 119). These drugs are effective in killing microfilariae and some adult worms, thereby reducing transmission potential. The WHO recommends conducting sentinel and spot-check community surveys, followed by a transmission assessment survey (TAS), to determine whether the infection prevalence has fallen below target thresholds, allowing MDA to be discontinued. TAS is then repeated twice over the next 4–6 years after stopping MDA (TAS2 and TAS3) to ensure there is no resurgence of LF infection to levels that would necessitate intervention (1, 122, 123).

While albendazole, ivermectin, and DEC remain the mainstay of MDA programs for the elimination of LF, there is a continual search for new drugs. These new drugs aim to overcome the limitations of current treatments, such as the development of drug resistance (311–313), the need for prolonged treatment regimens, and the lack of efficacy against adult worms in some cases (314, 315). Emodepside is a novel anthelmintic agent with shown effectiveness against a variety of parasitic worms in veterinary medicine (316–319). Recent studies are investigating its potential application in humans, particularly given its efficacy in targeting adult worms, which are typically more challenging to eliminate with current LF treatments (318, 320). Flubendazole, a benzimidazole drug, is primarily used for gastrointestinal infections caused by nematodes (321). Recent formulations have been developed for improved efficacy against filarial infections (322). While not new drugs, tetracycline and doxycycline have been repurposed for LF due to their ability to target *Wolbachia*, a bacterial endosymbiont of filarial worms that is essential for their fertility and survival (323, 324). These antibiotics effectively eliminate *Wolbachia* populations within the worms, leading to reduced reproduction and survival of the worms. Moxidectin (currently evaluated against onchocerciasis) and other antiparasitic agents are other drugs being trialed to assess their safety and tolerability in combination with other drugs (325, 326).

The WHO recommends using a triple therapy combination of ivermectin (I), diethylcarbamazine (D), and albendazole (A) or IDA for MDA against LF in specific settings (327). In 2022, IDA was administered to 34.3 million people across 13 countries (1). The WHO recommends assessing the impact of IDA after two effective rounds in most settings. Impact surveys in Egypt, Papua New Guinea, São Tomé and Príncipe, and Timor-Leste have shown that IDA can reduce microfilaremia below the target threshold

in settings where endemicity was low at the start of IDA, fewer than four two-drug MDA rounds had been previously delivered, and more than 65% of the total population received IDA (1).

The need for new treatments that are effective against adult worms (macrofilaricidal) has prompted the search for new drugs (328–330). Repurposing drugs already approved for other uses is a promising strategy because the safety profiles of these drugs are well-known, which can accelerate the process from discovery to application (60). For example, drugs that inhibit proteases have been examined for their potential to inhibit similar enzymes in filarial worms (331–333). Many filarial worms also contain symbiotic bacteria called *Wolbachia*, which are essential for the worm's fertility and survival. Research into adjunctive therapies, such as the use of doxycycline to target *Wolbachia* (endosymbiotic bacteria essential for filarial worm survival), has shown promise in reducing adult worm viability and interrupting disease transmission (323, 324, 334). This approach has shown efficacy but requires prolonged treatment durations, prompting the search for more potent and shorter-course therapies. Research on new macrocyclic lactone, moxidectin, with enhanced activity and safety profiles, is ongoing to expand the arsenal against adult worms (325).

Vaccines

Despite significant control efforts through mass drug administration, the development of a vaccine offers a promising long-term solution for eradication. Several works suggest that vaccine-based control is possible against human LF infections (335–337). However, the vaccine research for LF is complex due to the parasite's lifecycle and the immune evasion strategies it employs. Thus, vaccine development for LF is still in the exploratory phase, with several antigens being studied for their efficacy and immunogenicity. As such, there are currently no effective vaccines available to control LF. Several subunit candidate vaccine antigens have been tested in laboratory animals with varying results (69, 338–343). Other traditional methods, such as live attenuated pathogens, were also attempted to develop a vaccine against LF (344, 345). As multicellular organisms, the parasites responsible for LF produce a large array of host modulatory molecules, making the development of a single antigen vaccine against this infection challenging.

Recombinant protein vaccines represent a promising approach in the fight against LF, targeting specific proteins expressed by the filarial parasites (346–348). These vaccines aim to induce an immune response that prevents the parasite from establishing infection or reduces the parasite load, thereby mitigating disease transmission and severity. Among the notable recombinant protein vaccine candidates that have shown potential in preclinical studies are those that target *Wolbachia* (349–353) and Tetraspanin (TSP) (354–358). *Wolbachia* are intracellular bacteria that symbiotically reside within many filarial nematodes (334, 359, 360). The bacteria are crucial for the parasite's fertility and survival, making them an attractive target for vaccine development. *Wolbachia* surface protein (WSP) elicits an immune response that can disrupt the lifecycle of the filarial parasite (350, 352, 359, 361). Vaccinating with WSP can lead to an immune attack on the *Wolbachia*, subsequently impairing the parasite's ability to reproduce and survive. Studies have demonstrated that immunization with *Wolbachia* translation initiation factor-1 (Wol TI IF-1) can reduce the microfilariae load in animal models (353). Tetraspanins, on the other hand, are a family of proteins that play critical roles in cell signaling, membrane fusion, and pathogenesis in a variety of organisms (362, 363). In filarial nematodes, Tetraspanins are located on the surface of the infective larval stage and involved in the parasite's invasion of the host (355, 358). Tetraspanin-based vaccines aim to induce antibodies that block these proteins, thereby preventing the larvae from successfully invading the host tissues (355, 358). This blockade can potentially stop the lifecycle of the parasite at a critical early stage. Experimental vaccines targeting TSP-2 have shown promise in eliciting strong immune responses that confer partial protection against filarial infection in animal models. These immune responses are characterized by high levels of specific antibodies that can neutralize the infective larvae.

DNA vaccines also represent an innovative approach to combat LF (364, 365). DNA vaccines work by introducing genetically engineered plasmids containing the DNA sequence of a target antigen from the pathogen of interest (366–368). Once administered, typically via injection, the host's cells uptake the DNA, express the encoded antigen, and present it on their surface. This antigen presentation stimulates both humoral (antibody mediated) and cellular immune responses, particularly involving helper and cytotoxic T cells. DNA vaccines have several benefits over traditional vaccines, including the stability of DNA, ease of production, and the ability to induce a broad range of immune responses (369). Additionally, DNA vaccines do not involve live pathogens, which enhances their safety profile. However, the efficacy of a DNA vaccine largely depends on the choice of antigen. For LF, antigens that have shown promise in preclinical studies include *B. malayi* abundant larval transcript-2 (BmALT-2) and *B. malayi* small heat shock protein (BmHSP) (370–372). Several potential vaccine candidates were identified by screening a phage display cDNA expression library of the *B. malayi* parasite with sera from immune individuals (373). The administration of each of the candidate vaccine antigens as a DNA, protein, or prime boost vaccine resulted in different degrees of protection (338). In a study describing the development of a multivalent DNA-based vaccine on BmALT-2 and BmHSP, challenge experiments using third-stage infective larvae of *B. malayi* in a mouse model suggested that nearly 90% protection can be achieved using the multivalent formulation in a DNA prime protein boost approach (372). The vaccination regimen induced significant IgG antibody responses, and spleen cells of vaccinated animals produced significant amounts of IL-4. The results also showed that a multivalent vaccine formulation of BmALT-2 and BmHSP could represent an excellent vaccine for LF, and significant protection can be achieved against a challenge infection with *B. malayi* in a mouse model (372).

Developing a vaccine for LF involves deep understanding of the immune responses elicited by filarial infections and how these responses can be manipulated to achieve effective and lasting immunity. The immunological landscape of LF is complex, as the parasite has evolved numerous strategies to evade and manipulate host immune mechanisms. The immune evasion strategies are initiated with the communication between the invaded parasites and parasite-derived molecules, with the Toll-like receptors (TLRs) present on the surface of the antigen-presenting cells (APCs) (374). The innate immune response is the first line of defense against filarial worms and involves cellular components such as macrophages, neutrophils, and dendritic cells. These cells recognize pathogen-associated molecular patterns (375) on the worms and initiate an inflammatory response aimed at eliminating the parasites. NK cells also play a role in the early immune response by producing cytokines that help regulate the activity of other immune cells (230, 375, 376). The humoral and cellular responses also need consideration. Filarial infections typically induce a strong Th2-dominant humoral response, characterized by high levels of IgG and IgE antibodies (377–379). These antibodies are crucial for targeting microfilariae and adult worms for destruction by the immune system. However, the worms often evade these responses through molecular mimicry and immune modulation. For the cellular response, T cells are vital in the immune defense against LF (380–382). The balance between different T cell subsets (Th1, Th2, Th17, and Treg) influences the outcome of the infection and the host's ability to control or clear the parasite.

STRATEGIES FOR MONITORING AND EVALUATION

Transmission assessment surveys

Transmission assessment surveys (TAS) are critical components of the GPELF, designed to evaluate whether the transmission of LF has been reduced to levels where it is no longer sustainable, and MDA can be stopped (123, 383). TAS are conducted following several rounds of effective MDA, serving as a key tool for program managers to make evidence-based decisions on stopping treatment in an area. The primary objective of TAS

is to determine the absence of new infections among children, who serve as a proxy for the general population's exposure to LF transmission. TAS typically involves testing a representative sample of children, usually aged 6–7 years, from endemic areas using ICT cards or antigen rapid tests, which detect CFA indicative of *W. bancrofti* infections (123). TAS is conducted based on specific epidemiological criteria, including the completion of at least five rounds of effective MDA with coverage exceeding 65% of the total population (383). The timing and design of TAS are carefully planned to accurately assess the interruption of LF transmission, taking into consideration the pre-MDA prevalence of the disease and other local epidemiological factors. The results of the TAS guide program managers in deciding whether to stop MDA in a given area. A finding of CFA prevalence below a critical threshold in the tested cohort indicates that transmission has likely been interrupted. However, if the threshold is exceeded, it suggests continued transmission, necessitating additional rounds of MDA and possibly other interventions. TAS has been successfully deployed in many countries. As of 2022, 5,254 TAS have been conducted globally, with 10 countries no longer requiring MDA, as well as several other implementation units in disease-endemic countries (1).

Following a successful TAS, post-MDA surveillance is essential to detect any potential resurgence of LF transmission (384). This ongoing surveillance involves periodic re-assessment using TAS or other suitable epidemiological tools to ensure that the gains achieved through the elimination program are sustained over time (385, 386). Despite the success of TAS in guiding LF elimination efforts, challenges remain, such as ensuring sufficient sensitivity and specificity of diagnostic tests, addressing logistical issues in conducting surveys, and interpreting results in the context of co-endemic diseases (387).

Molecular xenomonitoring

Molecular xenomonitoring (MX) is a surveillance technique used to detect pathogens in vector populations, such as mosquitoes, to infer the presence and intensity of human infections in a given area. It is particularly useful in programs aimed at eliminating diseases such as LF and onchocerciasis (388, 389). This method involves the detection of pathogen DNA or RNA in the arthropod vectors that transmit the disease, providing a non-invasive way to monitor infection rates and assess the effectiveness of control measures. For LF, MX involves the collection and analysis of mosquito populations to detect filarial DNA, typically from *W. bancrofti* or *Brugia* spp. (249, 390, 391). This method is used to assess the transmission dynamics of filariasis, especially in areas where MDA programs are ongoing or have stopped.

While MX is a powerful tool, it faces significant challenges related to sensitivity, specificity, assay optimization, sample collection, and processing (249, 390, 391). One of the primary challenges for the sensitivity of MX is the typically low parasite load in vector species, such as mosquitoes, which can make it difficult to detect pathogen DNA. This issue is exacerbated in post-MDA settings where parasite levels are reduced significantly. The sensitivity of the molecular assays must be high enough to detect very small amounts of DNA. The sensitivity of MX also depends heavily on the optimization of molecular assays, including PCR. Factors, such as primer design, PCR efficiency, and the type of molecular target (e.g., multicopy vs single-copy genes), all affect the sensitivity of detection. Suboptimal assay conditions can lead to false negatives, particularly in areas with low transmission. Finally, the method of collecting, storing, and processing vector samples can also affect sensitivity. Improper handling can degrade DNA, while inefficient extraction methods can fail to recover sufficient genetic material for detection.

Vector collection and processing are fundamental components of MX for LF. The accuracy of disease monitoring heavily relies on effective vector collection and the subsequent processing of these specimens to detect the presence of filarial DNA. The methods for collecting mosquitoes for LF studies are crucial and need to be tailored to the behavior and habitats of the specific mosquito species involved in transmission (392, 393). Strategic placement of traps is guided by ecological and epidemiological data to maximize capture rates and ensure representative sampling of the vector population

(394). Other aspects, such as transport and storage, species identification and sorting, DNA extraction, and quality control, are all important for effective MX (395).

Recent advances in MX for LF have focused on the development of sensitive and specific detection methods (396–398), the trialing of methods for the collection of large numbers of mosquitoes (393, 399), and the use of mosquito excreta in detecting infection (396, 400). Despite these achievements, the challenges of data interpretation remain, especially in establishing a direct correlation between pathogen presence in vectors and actual human infection rates (401). While positive MX results indicate that vectors are carrying the pathogen, this does not always translate directly to ongoing transmission or current human infections, especially in post-MDA settings where human infection rates may have significantly declined. Recent reviews of longitudinal studies do indicate that, within a given study area, there is a strong linear relationship between MX rate and mf prevalence (R2 = 0.78, $P < 0.001$), thus presenting the potential as a tool for detecting communities where LF is present and as a predictor of human mf prevalence (401).

The role of modeling

Modeling the transmission dynamics, impact of control strategies, and potential pathways to elimination of LF provides invaluable insights for public health decision making and program implementation. Mathematical and computational models help predict the course of the disease under various intervention scenarios, evaluate the cost effectiveness of control measures, and estimate the time required to achieve elimination targets. These models are crucial tools in the global effort to eliminate LF as a public health problem. Transmission models of LF incorporate the complex life cycle of the filarial worms, human–mosquito interaction, and the impact of MDA on reducing microfilaremia in human populations (402, 403). These models are used to estimate the threshold levels of treatment coverage and duration necessary to interrupt transmission. The models account for variables such as vector species, biting rates, and microfilariae development rates within mosquitoes. Models simulating the impact of MDA on LF prevalence highlight the importance of achieving high treatment coverage and compliance over successive rounds (404). These models have been instrumental in guiding the GPELF by providing evidence for the efficacy of different drug regimens and the need for integrated vector management to achieve elimination goals. Morbidity models estimate the burden of disease, including the incidence of acute attacks and the prevalence of chronic conditions such as lymphedema and hydrocele. Economic models use these estimates to calculate the cost effectiveness of various intervention strategies, highlighting the economic benefits of LF elimination beyond the health impacts, including increased productivity and reduced healthcare costs (405). As countries achieve elimination targets, models help design surveillance strategies to detect and respond to potential resurgence. These models evaluate the sensitivity and specificity of diagnostic tests, the optimal frequency and scale of surveillance activities, and the risk factors associated with LF reintroduction (406). While modeling provides critical insights, it also faces challenges, including the need for accurate data on infection prevalence, vector dynamics, and drug efficacy. Another limitation is that current models fail to account for potential future population shifts/immigration (407), which can result in the re-introduction of infection into areas that have successfully eliminated the infection with MDA. Future models aim to incorporate factors affecting susceptibility to infection and drug resistance, climate change impacts on vector distribution, and the integration of LF programs with other neglected tropical disease initiatives (17). Modeling plays a crucial role in the strategic planning and evaluation of LF elimination efforts, offering insights into the dynamics of disease transmission, intervention impacts, and the pathways toward achieving and sustaining elimination goals. These models continue to evolve, incorporating new data and methodologies to address the challenges of LF elimination in diverse epidemiological settings.

CURRENT CHALLENGES IN ELIMINATION

Despite significant progress in the fight against LF, several challenges remain that hamper global elimination efforts. Addressing these challenges requires innovative strategies, interdisciplinary collaboration, and sustained commitment from global health communities. Emerging reports of reduced efficacy and potential resistance to the standard antifilarial drugs may pose a challenge (311–313). Continuous monitoring of drug efficacy, developing new antifilarial compounds, and exploring alternative treatment regimens are critical steps to overcome this challenge. Achieving high coverage in MDA campaigns is essential for the success of elimination programs (408, 409). However, operational challenges, including logistical issues, inadequate healthcare infrastructure, and difficulties in reaching remote or conflict-affected areas, can impede the delivery of MDA and other control measures (410–412). Community hesitancy, due to lack of awareness or fear of adverse reactions from treatment, can also lead to low participation and compliance rates in MDA campaigns (21, 22, 413). Enhancing community education, engagement, and trust-building activities is vital for improving compliance and achieving high coverage. In many settings, TAS failures have also been reported, indicating possible resurgence of the disease in those implementation units (414–419). LF is often endemic in areas with a high prevalence of other parasitic diseases, such as malaria and soil-transmitted helminthiasis (420). Co-infections can complicate diagnosis, treatment, and control efforts. Integrated approaches to manage multiple parasitic diseases simultaneously are needed. As countries approach elimination, robust surveillance systems are required to detect, report, and respond to new LF cases and potential outbreaks. Developing sensitive, specific, and cost-effective diagnostic tools for use in post-elimination surveillance is a challenge. Climate change impacts, such as altered rainfall patterns and temperatures, can influence mosquito vector populations and distribution, potentially expanding the geographic range of LF (421, 422). Understanding and incorporating climate change impacts into control and elimination strategies are emerging challenges. A recent scoping review of the impact of climate change on vector-borne NTDs concluded that more collaborative and standardized modeling efforts are needed to understand better how climate change will, directly and indirectly, affect malaria and NTDs (423). These challenges underscore the complexity of eliminating lymphatic filariasis. Addressing them requires a coordinated global effort, innovation in treatment and surveillance strategies, and a commitment to tackling the socioeconomic determinants of health.

Repurposing existing drugs for new therapeutic uses is an attractive strategy as it can significantly reduce the time and cost associated with drug development. However, this comes with several challenges, particularly in terms of efficacy, safety, regulatory approvals, and market incentives (424, 425). First, there are challenges with drug efficacy as drugs initially developed for one condition may not be effective against another due to different underlying biological mechanisms. Effective repurposing requires a deep understanding of the pathophysiology of both the original and new diseases (426, 427). Further, the dose that is effective for the original indication may not be appropriate for the new use, and finding the right dosage can require extensive clinical trials, which can diminish the cost and time benefits of drug repurposing. Then, there may be safety concerns as drugs may exhibit side effects not observed in their original use due to different patient populations, dosing regimens, or interactions with other diseases (424, 425). The long-term impacts may also not be fully understood for the new indication, especially if the drug was originally intended for short-term use. Regulatory and approval challenges may also prevent effective repurposing (428). Even if a drug is already approved for one use, obtaining approval for a new indication requires demonstration of safety and efficacy through additional clinical trials. Regulatory bodies, like the Food and Drug Administration, require changes in labeling for new uses, which can be a complex process. In some cases, potential repurposing opportunities may be missed due to insufficient scientific research or infrastructure to properly evaluate the drug's potential for new indications (429–431). Sharing and accessing data regarding

drug efficacy and safety can be difficult, particularly when proprietary interests are at stake or when data silos exist within the pharmaceutical industry. For LF, the steps of developing new drugs are particularly challenging (432, 433). While a few drugs are available for use in veterinary practice or human medicine for other indications, there is a need for further investigations in humans (434). The process is complicated by the fact that early drug discovery pipelines are poorly populated, and macrofilaricide discovery and development remains highly challenging, coupled with the lack of animal models, especially *for W. bancrofti* (434).

Developing vaccines against LF also comes with many challenges, including (i) lack of suitable animal models, (ii) complex life cycle of the parasite, (iii) complicated immune responses by humans against nematodes, and (iv) limited evidence and information to prove and characterize natural protective immunity in animals as well as in humans (435). Harnessing the immune response for vaccine development also comes with challenges (436). First, there is immune evasion by the parasite. Filarial worms produce a variety of immunomodulatory molecules that dampen the immune response, including those that induce regulatory T cells (Tregs), which suppress other immune responses (374). Thus, overcoming these evasion strategies is critical for a successful vaccine. Chronic infections can also lead to an immunotolerant state (437, 438), where the host immune system becomes less responsive to the parasites. A successful vaccine must break this tolerance and reinvigorate the immune response. Then, there is the need to induce protective immunity (439, 440). The vaccine must also promote long-term immunological memory to ensure protection over many years, considering the long lifespan of the worms. Filaria-specific IgE antibodies can also induce anaphylaxis (441), and the use of antigens against which LF-endemic populations are not IgE sensitized should be carefully considered.

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