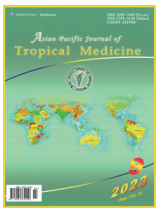

Review Article

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Elimination of lymphatic filariasis: Where do we stand so far?

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ABSTRACT

Lymphatic filariasis (LF), an asymptomatic, acute, and chronic condition in human beings, is the second most common vector-borne disease after malaria. According to the World Health Organization, there are 120 million LF cases detected in 81 tropical and subtropical countries, and one billion people are at risk. Therefore, the Global Program to Eliminate Lymphatic Filariasis was launched in 2000, with the primary objective of stopping LF transmission among all at-risk groups using mass drug administration (MDA), managing morbidities, and preventing LF-related impairments using a minimum treatment package. Additionally, other programs such as epidemiological assessment including National Filaria Control Program and World Health Organization recommended routine and pre-MDA microfilaremia surveys also implemented to stop the LF transmission. The routine filaria surveys were also carried out in around 2 000-4 000 individuals/month throughout the year whereas pre-MDA surveys were also conducted every year in approximately 4 000 individuals in four fixed and four random sites. Furthermore, the Transmission Assessment Survey was also conducted to check the risk of LF among primary school children. Moreover, potential diagnostic methods, systematic surveillance regimes, the Direct Network Report system, and regular trainings and awareness may be also effective in preventing the recurrence of LF. Hence, this review emphasizes the potential advocacy tools and various strategies as well as procedures for monitoring, which could be impactful in eliminating LF.

KEYWORDS: Lymphatic filariasis; Treatment; Challenges; Prospect; Elimination

1. Introduction

One of the six infectious diseases that the International Task Force for Disease Elimination has determined to be "eradicable" or “potentially eradicable” is lymphatic filariasis (LF). As a result, the World Health Organization (WHO) has set LF’s elimination as a priority. The Global Programme to Eliminate Lymphatic Filariasis (GPELF) was established in acknowledgment of the disease’s eradicability to ensure that the World Health Assembly's 1997 resolution (WHA 50.29) to eradicate LF by 2020 was carried out[1]. A spirurid nematode called *Wuchereria* (*W.*) *bancrofti*, which named in honour of Joseph Bancroft and Brazilian-born Dr. Otto Wucherer, is the cause of Bancroftian filariasis. In addition to *W. bancrofti*, *Brugia* (*B.*) *malayi* and *B. timori* also cause LF. Human LF

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is the second most prevalent vector-borne illness in India, behind malaria. According to the WHO, there are 120 million LF cases in 81 tropical and subtropical countries, one billion people are at risk, 947 million people are in danger, and 40 million individuals have permanent disfigurement as a result of this illness[2]. In 50 nations and 863 million people, preventative chemotherapy is needed to halt the spread of illness in 2020. Twenty-five million males with hydrocele and more than 15 million persons with lymphedema were estimated to be affected by LF on a global basis at the time of the baseline estimate[3]. The signs of this disease still affect at least 36 million individuals. It belongs to the Filarioidea class of illness and is a category of roundworm nematode parasitic helminthiases. The parasites, which are located in the lymphatic system, harm the system and cause organ malformations. *W. bancrofti*, *B. malayi*, and *B. timori* are three of the eight human filarial parasites that affect the lymphatic system[4]. These worms, which resemble threads, live in the lymphatic and subcutaneous tissues. Members of various mosquito genera, including *Anopheles*, *Aedes*, *Culex*, and *Mansonia*, are the main vectors for the transmission of these parasites, while the major vectors vary depending on the region. We may alternatively describe it as a mosquito-borne disease that, if left untreated, can cause lymphedema, elephantiasis, and permanent impairment[5].

LF was one of the six infectious illnesses that the International Task Force for Disease Elimination determined to be possibly eradicable out of 94 that assessed. Elephantiasis may occur as a result of an infected mosquito depositing infective larvae onto the skin when biting that quickly enter lymphatics. This ailment causes swelling in the affected area, which causes loss of function and thickened skin , making one seem "like an elephant"[6]. The WHA issued a resolution in 1997 urging the intensification of efforts to eradicate LF as a "public health hazard". As a result, the now well-known GPELF launched in 2000. LF causes excruciating agony and may result in lifelong disability. Some individuals stigmatize LF, and patients deal with social isolation as well[7]. Approximately 50% of the 120 million LF infected persons reside in the South-East Asia Region, with over 63% of the world's 1.34 billion population at risk. Approximately 57% of the projected 5.1 million disability-adjusted life years lost due to LF are borne by this area. LF is prevalent in nine of the nations in this area. Despite the fact that the illness is widespread in 80 countries, India, Nigeria (in Africa), Bangladesh, and Indonesia collectively account for 70% of all cases of LF worldwide[8].

Mature worms blocking and occupying lymphatic channels mostly bring on the disease's varied symptoms. The patient displays a variety of signs and symptoms depending on the kind of filariasis, including elephantiasis, lymphedema, hydrocele, chyluria, chylous diarrhoea, and chylorrhagia[8]. Transmission of LF can be interrupted by providing preventive chemotherapy. This strategy provides annual mass drug treatment of two-drug combination [diethycarbamazine (DEC) and albendazole (Albz)] community-wide with an exception of pregnant women, children younger than 2 years. This mass drug treatment is distributed in all countries except countries where onchocerciasis is endemic[9]. The WHO also recommended MDA to be distributed for at least 5 years with a coverage of at least 65% of the population. The other method for preventing disease spread is vector control[3]. After a successful random trial was carried out in Papua New Guinea, the WHO advised yearly triple medication therapy consisting of Albz, invermectin (IVM), and DEC. This three-drug regimen offers a cost-effective management that shows promise for eliminating LF transmission.

2. Geographical distribution of lymphatic filariasis

The distribution of filariasis is closely linked to the distribution of its mosquito vectors, which are most active in warm and humid conditions. The disease is most prevalent in areas with poor sanitation and hygiene, where there are high mosquito populations and a high incidence of mosquito bites. In addition, certain species of mosquitoes are more efficient at transmitting the disease than others, and the prevalence of these species can also impact the distribution of filariasis[10]. LF is considered as a Neglected Tropical Disease (NTD) as per the London declaration on NTDs in January 2012. LF caused predominantly by *W. bancrofti* and *B. malayi*. *W. bancrofti* is prevalent in many tropical and subtropical regions of the world, particularly in Africa, Asia, and South America. In South America, filariasis is found in countries such as Brazil, Guyana, and Suriname. In Africa, filariasis is endemic in many countries, particularly in West and Central Africa. Some of the countries with the highest burden of filariasis in Africa include Nigeria, Democratic Republic of Congo, and Ghana[11]. It occurs throughout the tropics with majority in Asia and is currently endemic in sub-Saharan Africa excluding the southern portion of the continent, Madagascar, several Western Pacific Island nations and territories, and parts of Caribbean[12]. In Asia, the disease is endemic in many countries, particularly in the Indian subcontinent, Southeast Asia, and the Pacific Islands. Some of the countries with the highest burden of filariasis in Asia include India, Indonesia, and the Philippines[8]. The *B. malayi* parasites are confined to areas of east and south Asia, especially India, Malaysia, Indonesia, the Philippines and China[13]. Small foci of *B. timori* infections were also found in Indonesia. It affects 120 million people in 72 countries worldwide with four endemic countries in the Americas: Haiti, Dominican Republic, Guyana, and Brazil[14]. Approximately 45.5 million LF-infected people come from South-East Asia and India[15].

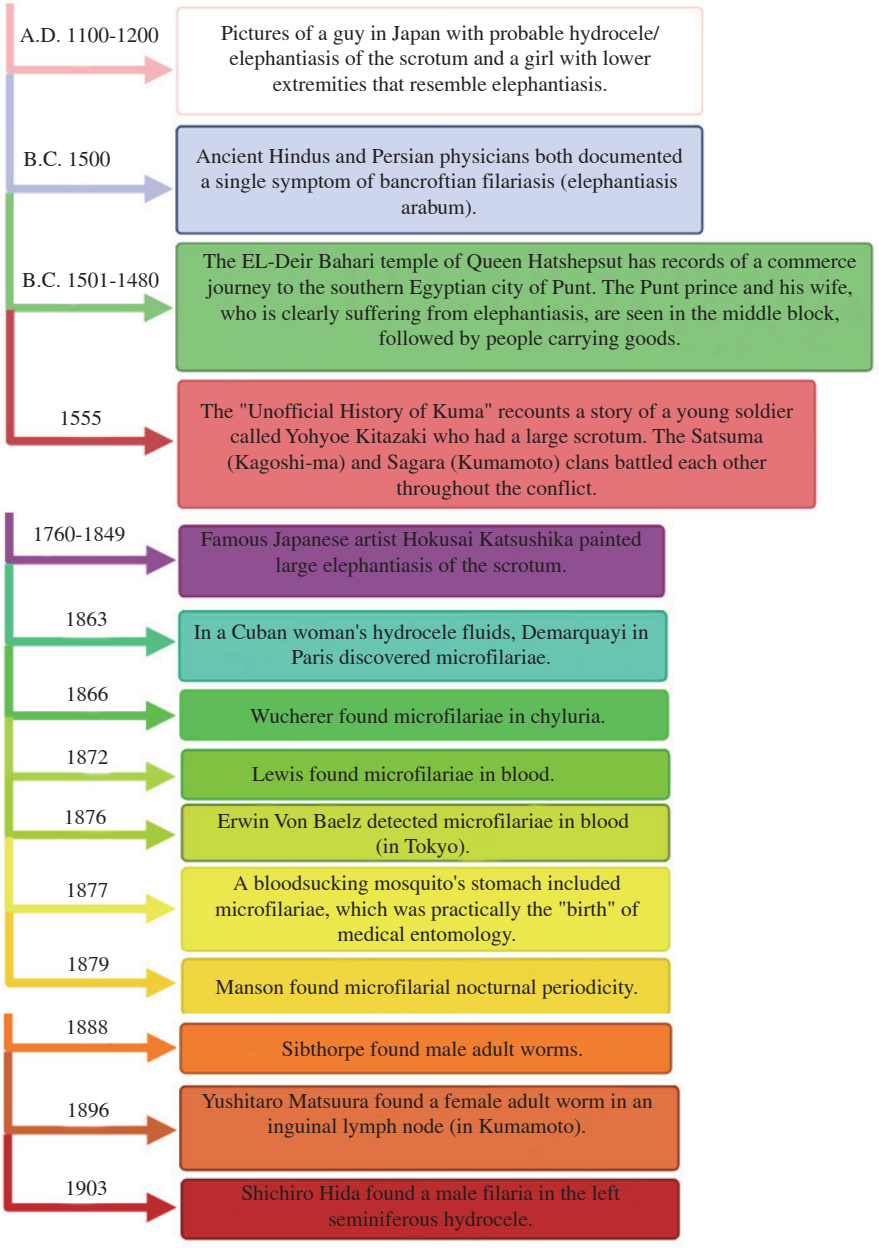

Figure 1. Early scientific milestones in the history of filariasis disease from A.D. 1100-1200 to 1903. This figure depicts the advancement in diagnosis of lymphatic filariasis on the basis of microfilariae characteristics.

3. Ancient history

Although “filariasis” was not a name used in ancient Chinese medical literature, early Chinese traditional medicine manuals, the earliest of which were written in 600-700 B.C., did include symptoms that were comparable to LF signs. A thorough description of symptoms resembling the manifestations of LF, such as filarial acute lymphadenitis/lymphangitis (ADL), lymphedema/ elephantiasis, chyluria, and hydrocele, was recorded during the Sui Dynasty in the 610 A.D. General Treatise on the Cause and Symptoms of Diseases by the renowned ancient physician Chao Yuanfang[16]. Dr. Patrick Manson noted that in 1872, elephantiasis of the scrotum occurred in Xiamen, which is located south of the Fujian Province. In 1876, he provided descriptions of *W. bancrofti* microfilariae (Mf), sheath Mf, and a female adult. He discovered in 1877 (Figure 1) that there were more Mf examined at night than during the day. By studying two instances every three hours over the course of 23 days in 1881, Dr. Manson was able to prove once more that microfilariae only manifested themselves in the bloodstream at night. At the same year[16], Rennie further established the periodicity of the night in Fuzhou, the center of the Fujian province. While conducting research to establish the link among Mf and elephantiasis between 1878 and 1882, Dr. Manson discovered that the *Culex quinquefasciatus* (*C. quinquefasciatus*) was the intermediary host and vector of Mf[17]. In addition to Dr. Manson's research, international doctors also published some data regarding the prevalence of

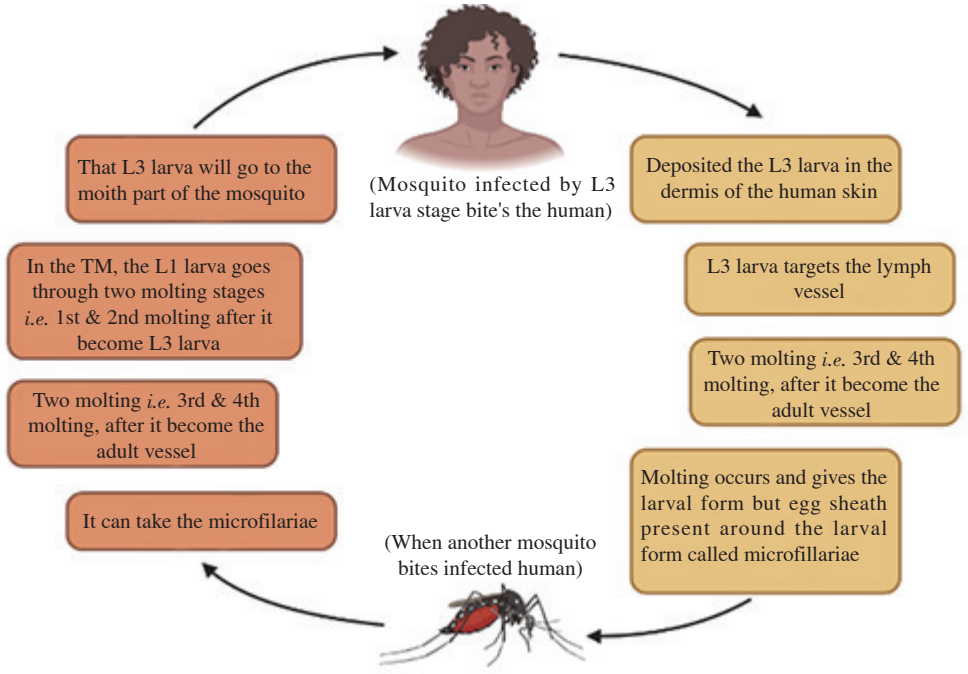

Figure 2. Lifecycle of lymphatic filariasis undergoes different stages during the maturation between two human host and mosquitos.

bancroftian filariasis in China. Whyte discovered that the illness, which occasionally resulted in eosinophilia, was prevalent in the Chaozhou, Guangdong area. During the 20 years that Maxwell was a doctor in Fujian, he noted that filariasis was often discovered in the eastern part of the province[16].

Filariasis, also known as elephantiasis, is indeed a serious public health issue in India. While it is true that Susruta, a renowned Indian physician from ancient times, described the symptoms of filariasis in his book "Susruta Samhita," it was not until the 19th century that the filarial worm identified as the cause of the disease. Timothy Lewis, a British surgeon working in Calcutta, identified the first case of human filariasis in 1866. Since then, efforts have been made to control and eliminate filariasis in India through measures such as mosquito control, mass drug administration, and public health education. While progress has been made, filariasis remains a significant public health issue in certain parts of the country[18]. The Nation's National Filaria Control Program established in 1955 with the goal of defining the issue and implementing control measures in endemic regions. The massive rise in filariasis over the past forty years is due to the failure of control programs[19]. There may be as many as 31 million Mf, 23 million symptomatic filariasis cases, and around 473 million people who are at risk of infection in the nation[6]. LF causes severe psychological distress in those who are infected and significantly hinders socioeconomic growth (annual loss estimated at $1 billion)[20,21].

4. Life cycle

The life cycle of the filarial worm is complex and involves two hosts: humans and mosquitoes. The adult filarial worms reside in the lymphatic system of humans, while the immature worms, called microfilariae, circulate in the blood. When a mosquito bites an infected human, it ingests microfilariae, that develop into infectious larvae within the mosquito's body. The infectious larvae are then transmitted to a new human host when the mosquito bites again. The most serious kind of filariasis is LF, often known as elephantiasis because the adult worms targets the lymphatic system. *Culex*, *Mansonia*, and *Anopheles* mosquitoes are responsible for transmitting it[8].

The life cycle of the filarial worm can be broken down into several stages (Figure 2).

(i) Transmission of disease: Mosquitoes infected with microfilariae when they bite an infected human.

(ii) Development: The microfilariae develop into infectious larvae within the mosquito's body over a period of several days.

(iii) Infection: When the infected mosquito bites a human, it introduces third-stage filarial larvae onto the skin, where they penetrate into the bite wound. The larvae migrate through the hemocoel to the mosquito's prosbocis and can infect another human when the mosquito takes a blood meal[5].

(iv) Migration: The larvae migrate to the lymphatic system and develop into adult worms over several months.

(v) Reproduction: The adult worms mate and produce

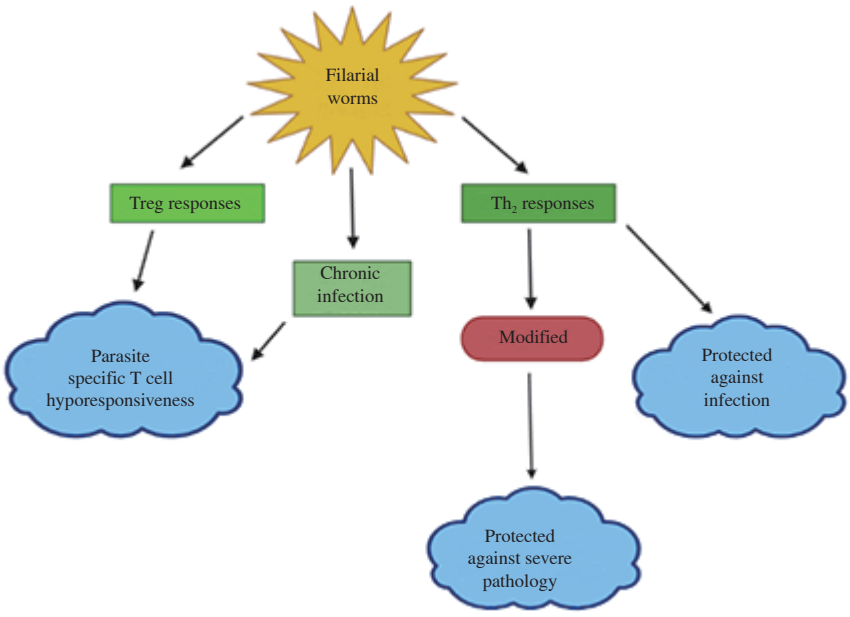

Figure 3. Immune responses in filarial infection. When filarial worms enter into human, the Th2 started responding against worm, leading to generation of cytokines such as IL4, IL-25 and IL-3, that protects human against infection. Th2 response also produces different cytokines such as IL-10, IL-19 and IL-24. Which also protect human against severe pathology. T-regulatory cells (Tregs) response causes specific T-cells hyporesponsivness against parasites.

microfilariae, that circulate in the blood and can be detected through blood tests.

(vi) Transmission: When an infected mosquito bites an uninfected human, the cycle repeats again.

The life cycle of the parasite can take several years to complete, and the symptoms of the disease can take years to manifest. Prevention and control efforts for filariasis focus on interrupting the transmission cycle through mosquito control, mass drug administration, and public health education[22].

5. Diagnosis of lymphatic filariasis

The currently available methods for identification of *W. bancrofti*, causing filiriasis are (a) identification of Mf using microscopic study on smear of blood from the patients at night time. Because the periodicity of the parasite helps in its accurate detection, (b) identification of circulating filarial antigen (CFA) in blood, and (c) identification of filarial DNA utilizing molecular biology polymerase chain reaction (PCR) tool[23]. Of these, the most widely used method is CFA identification in blood, since, it has more sensitivity and specificity, and easy to uses, which can be done in blood samples drawn from patients at any time of the day. The CFA antigen tests based on enzyme-linked immunosorbent assays or radioimmune assays. Furthermore, lateral flow assay is also established by Australian diagnostic manufacturing company ICT Diagnostics, that can be used in the field during assessment survey. Also, it does not depend upon blood drawn at night or day time[23]. Recently, Filarial Test Strip has been developed, that can be utilized as monitoring and surveillance tool for LF[23].

6. Immunological aspects of lymphatic filariasis

The intricate life cycles of all human filarial nematodes involve an insect vector; mosquitoes transmit *W. bancrofti* and *B. malayi*. When a mosquito bites a person, infectious larvae (L3) are deposited in the skin and the infection process begins[24]. Early research on immune responses in LF revealed that, endemic normal individuals (without parasites clinical symptoms) as well as from people with lymphedema (without circulating filarial antigenemia) proliferated vigorously and produced detectable levels of cytokines to filarial parasites. At other hands, people with circulating Mf showed impaired filarial-specific lymphoproliferative responses and cytokine (IL-2 and IFN-γ) (Figure 3). The T-helper (Th2 -type) cell is responsible for inducing the immune response against filarial parasites, which results in the production of a cascade of cytokines including IL-4, IL-5, IL-9, IL-10, and IL-13 (Figure 3), the antibody isotypes IgG1, IgG4 (in humans), and IgE, as well as increased populations of eosinophils and alternatively activated macrophages[4,24]. It was established that dendritic cells and macrophages are responsible for the first T-cell contact, which results in the development of the Th2 response[24]. Recent research has demonstrated that ILC2 are increased in both mouse models of

filarial infections and human filarial infections, and they frequently release large amounts of IL-5 and IL-13 before the initiation of traditional Th2 responses[25]. ILC2 may thus be crucial in directing the development of the Th2 response in filarial infections. Over the course of the infection, eosinophils, alternatively activated macrophages, adaptive and natural regulatory T cells, and other cell types influence these classic Th2 responses[26]. Regulatory T cells (Tregs) are T-cells that regulates or suppress the immune reactions against self and foreign antigens. Tregs also plays an important role in the immunity to tumors and other pathogens[27,28]. Hence, Tregs may also be very impactful in fighting against filaria worms (Figure 3).

During filarial infections, macrophage presentation with CD4+ cells stimulates the latter to cause the production of cytokines (IL-3, IL-4, IL-9) to activate mast cells, as well as IL-5 for eosinophils and IL-4 to cause the secretion of IgM (acute), IgG (chronic), and IgE anti-bodies from plasma cells. IgG antibodies (IgG1, IgG4, and IgM) and their Fab fragments can bind to the filarial worms' surface antigens. In order to eliminate parasite membranes, effector cells like macrophages and eosinophils use an antibody-dependent cytotoxicity, either by producing nitric oxide, secreting perforins, or secreting various lytic enzymes. In order to continue clearing parasites, IgE's immunological function necessitates mast cell degranulation, which releases eosinophil and neutrophil chemotactic factors. IgG1 can be protective against *B. malayi* whereas IgG4 can be a sign of *W. bancrofti* infection. Eosinophils and neutrophils also produce platelet-activating substances, which in turn trigger the development of a clot that may prevent filarial worm movement.

7. Various strategies for treatment of lymphatic filariasis

The adult worms and microfilariae, which cause LF, are killed by medications used in its therapy. DEC and Alb, which are frequently administered together, are the medications that are frequently used to treat LF. Few drugs for LF treatment have mentioned below.

(ⅰ) Drugs: Although less powerful, DEC can also kill adult worms in addition to microfilariae. Although DEC is often administered as a single dosage, a course of treatment may be necessary[29]. Albendazole is effective against other parasitic infections and can kill mature worms. When used with DEC, it can greatly lessen the microfilariae burden and stop additional lymphatic system damage[30].

(ⅱ) Surgery: In some instances, surgery may be necessary to relieve swelling brought on by LF and stop additional harm to the lymphatic system[31].

(ⅲ) Management of complications: Complications from LF may include bacterial infections, skin abnormalities, and lymphedema, which can make patients disabled. Appropriate medical care such as antibiotics, wound care, and physiotherapy can manage these consequences[32].

The damage to the lymphatic system may not be able to be undone. However, treatment for LF can stop more damage from happening and lessen the severity of symptoms. The disease can also be stopped from spreading using preventive measures including applying insect repellent, dressing safely, and sleeping under a mosquito net.

DEC plus Alb is one of the principal regimens that the WHO recommends to treat LF. The two medications combine to kill the disease-causing adult worms and microfilariae. The precise mode of action of the medications conventionally used for treatment of LF is not entirely known[33]. The combination of two medications works incredibly well to lessen the burden of microfilariae and stops additional harm to the lymphatic system. In endemic locations, it has been demonstrated that using DEC and Alb together considerably lowers the prevalence of LF. The twofold medication regimen for LF has the following salient characteristics:

•Dosage: To eradicate LF, DEC and Alb are often administered in conjunction once a year for at least five years.

•Safety: The majority of individuals tolerate the dual medication regimen safely and well. However, it could result in minor side effects like nausea, vertigo, and headaches.

•Efficacy: It has been demonstrated that the two-drug regimen is quite successful at lowering the microfilariae burden and halting further harm to the lymphatic system[1].

•Accessibility: The two-drug regimen is practical for usage in situations with limited resources because it is inexpensive and simple to administer.

The periodic mass treatment by single-dose DEC is a new tactic that is being implemented by numerous national-level programmes for the elimination of LF. Since adult filarial worms are crucial for the pathogenesis of LF, it is thought that a yearly mass therapy stops the spread of the disease. This raises the need for effective macrofilaricidal drugs. DEC is the only drug with a potent macrofilaricidal activity and few adverse effects. Additionally, it has been found that giving Alb enhances its effect on fully developed filarial worms[34]. In order to evaluate the impact of two annual single-dose MDA of DEC plus Alb on Mf and antigenemia, and diethylcarbamazine (DEC) alone in the other arm, a study on the community-based elimination of LF was conducted, which revealed that in children[35], the reduction in antigenemia level following a dosage of DEC of 72 mg/kg was reported to be 40.7% and 32.5% respectively for DEC+Alb and DEC alone[36]. Two mass medication administrations are observed to minimize the frequency

Table 1. The single dose, two drug treatment regimens.

Name of drug	Dosage	Days	Effective against	Peak level	Reference
Diethycarbamazine, derivative of piperazine, antiparasitic drug	6 mg/kg/day	12	Bancroftian filariasis	Readily absorbed by oral administration with blood peak levels after 1-2 h, half-life 2-12 h	[3,38,39]
		6	*Brugia* spp. filariasis		
Invermectin 80: 20 mixture of avermectin b1a and avermectin b1b	200 μg/kg		Many parasites, ectoparasites except for hookworm, reduce microfilaraemia	Readily absorbed, peak levels after 3-4 h, half-life 28 h	[40,41]
Albz, Benzimidazole carbamate	400 mg	6-12 months	Decrease *Wuchereria bancrofti* microfilariae	Poorly absorbed 1%-5%, half-life 8.5 h, peak level after 2-3 h	[42]
			Active against human veterinary parasites, particularly helminths		
Albz	400 mg		Reduction in microfilariae level observed. Shown similar pharmacokinetics profiles when given in combination or individually		[43]
Diethycarbamazine	6 mg/kg				
Albz	400 mg		Used on *Wuchereria bancrofti* microfilariae to assess the outcomes. No pharmacokinetics profiles between these two drugs		[44]
Invermectin	200 μg/kg				

of microfilaremia. When DEC+Alb was used, Mf was observed to decrease by 54% and 62%, respectively, compared to 26% and 37% when using DEC alone. It may be concluded that Albz provided real benefits when combined with DEC as opposed to DEC alone. With the use of Albz, MF is decreased by a factor of two[37].

7.1. Triple drug therapy for lymphatic filariasis treatment

A combination of Alb plus DEC plus IVM, is known as IDA, whereas IA represents IVM plus Alb or DEC plus Alb. Latest research demonstrated that triple therapy (IDA) administered as a single dosage is more effective in clearing blood of microfilaria than dual therapy (IA) in LF[45,46]. The present double medication therapy, which consists of DEC and Alb, was designed to be more effective, so the triple drug therapy was created to achieve the same. It has been demonstrated that the triple medication therapy is more effective at stopping the spread of the disease and lowering microfilarial burden. Additionally, it might hasten the elimination of LF in regions where it is endemic. The triple medication therapy for LF has the following salient characteristics[47].

(ⅰ) Dosage: IVM, DEC, and Alb are the three drugs that make up the triple medication therapy, which is administered once a year for at least three to five years[30].

(ⅱ) Efficacy: It has been demonstrated that the triple medication therapy is very successful at lowering the Mf load and stopping the spread of LF. Additionally, it might hasten the elimination of LF in regions where it is endemic[1].

(ⅲ) Safety: It has been established that the triple medication therapy is secure and generally well-tolerated by patients. However, it could result in minor side effects like nausea, vertigo, and headaches[48].

(ⅳ) Accessibility: The triple medication therapy is practical for usage in places with low resources because it is inexpensive and simple to administer[48].

The efficacy of the triple medication therapy in lowering the prevalence of LF in endemic areas is currently being examined in a number of clinical trials. If it is successful, it could replace other LF treatments and help the campaign to end the illness worldwide[48]. Millions of doses were given through LF elimination efforts, and the medications employed in the IDA regimen have a large margin of safety. A recent literature analysis, however, revealed that mild to moderate side effects are frequent with LF therapy regimens[49].

8. Control and management of lymphatic filariasis

The goal for LF elimination is to eliminate the transmission of the parasitic disease from person to person and to control and ultimately eliminate the morbidity and disability associated with the infection. This is typically achieved through a combination of strategies, including mass drug administration (MDA) of antifilarial drugs to entire at-risk populations, improved sanitation and vector control measures, and increased access to diagnosis and treatment for those who are infected[50]. The World Health Organization (WHO) has set a goal to eliminate LF as a public health problem by 2030. This goal is known as the GPELF and is a collaborative effort involving multiple stakeholders, including national governments, international organizations, and communities affected by the disease[51]. The strategy is to implement MDA in endemic areas, with a target of at least 65% coverage in order to interrupt transmission of the

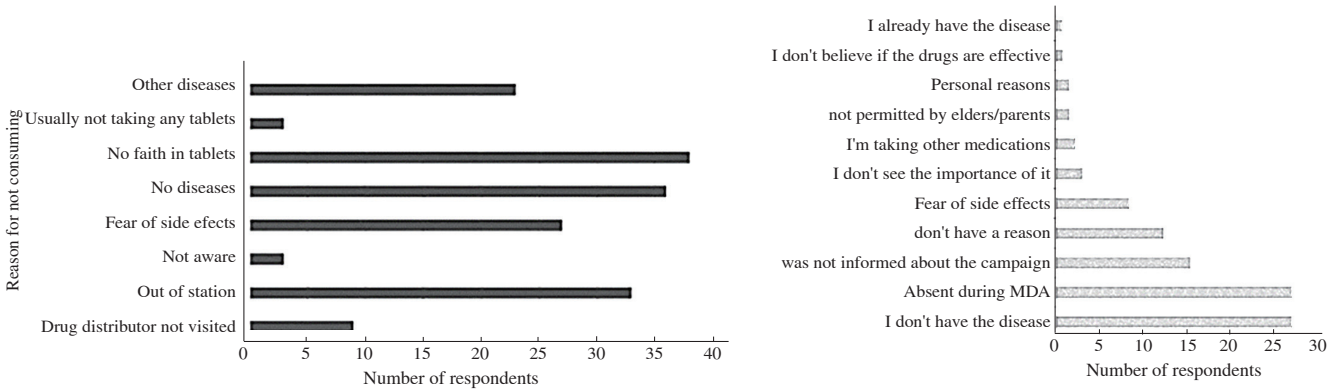

Figure 4. Reason for non-compliance to anti-filarial drugs. Various factors are responsible, where patients does not consume medications for the treatment of filarial infection.

parasite. In addition, efforts are being made to improve morbidity management and disability prevention for those already infected with the disease[52].

"For India LF is not a neglected disease, but a priority disease for elimination" by Dr Mansukh Mandaviya. The goal is "Let us aim to eliminate LF by 2027, three years ahead of the global target, through the five-pronged roadmap" as stated by Union Minister for Health & Family Welfare Dr Mansukh Mandaviya[53]. The Accelerated Plan for Lymphatic Filariasis Elimination (APELF) was introduced by the Indian government in June 2018 during the 10th GPELF conference in New Delhi, India. To speed up the LF elimination in India, a triple-drug treatment known as IDA (IVM, DEC, and ALB) has been designed. If the triple-drug combination is successful in achieving real drug compliance, it is anticipated that the MDA districts will be able to apply for and pass the transmission assessment survey[2].

8.1. Approach towards the control of lymphatic filariasis

In order to achieve the objectives, the Indian government expanded hydrocelectomies in hospitals and Community Health Centres and began a nationwide MDA programme in endemic regions in 2004. Only 202 districts might have been covered in 2004 with a 72.6% coverage percentage.

•The number of districts was increased, and in 2007 all 250 recognized LF endemic districts (now 256 due to bifurcation) were brought under MDA. About 650 million people in the country are at risk of LF, and 257 districts (one of which was added in 2019) have been brought under MDA.

•About 500 million of such people qualify for MDA. The percentage of the people covered by MDA increased from 73% in 2004 to 87.33% in 2019.

•In 2019, MDA had been implemented in 151 districts in India. The Triple Drug Therapy (IDA) implementation programme has been approved by the MoH & FW for five specific districts, including Arwal (Bihar), Simdega (Jharkhand), Varanasi (Uttar Pradesh), Nagpur (Maharashtra), and Yadgir (Karnataka), where it has been effectively executed[54]. In December 2019, Uttar Pradesh adopted IDA in eleven additional districts. Gujarat's Tapi district began adopting IDA in January 2020.

•In December 2019, Uttar Pradesh adopted IDA in eleven additional districts. Arwal district in Bihar observed the second phase of IDA on January 7, 2019, while Tapi in Gujarat adopted IDA in January 2020.

•Several States and UTs have engaged in extensive social mobilization during MDA, including political and opinion leaders, decision-makers, local authorities, and the general public. For high-level advocacy, the Hon. Union Health Minister officially opened the United to Eliminate Lymphatic National Symposium Filariasis on October 30, 2019 at Pravasi Bharatiya Kendra in New Delhi[55].

9. Challenges in eliminating lymphatic filariasis

Although, there is more worldwide support for LF elimination, some crucial concerns still need to be handled before it can be eliminated from India. There are several obstacles to controlling and eliminating filariasis in India, including:

•Poor sanitation and hygiene: Poor sanitation and hygiene practices can contribute to the spread of filariasis, as they allow mosquitoes to breed in stagnant water, increasing the risk of infection.

•Limited access to healthcare: Many people in India do not have access to healthcare facilities or cannot afford treatment, making it difficult to diagnose and treat filariasis.

•Limited awareness and education: Lack of awareness and education about filariasis can lead to misconceptions and stigmatization, making it difficult to implement effective prevention

and control measures.

•Resistance to mass drug administration: Mass drug administration (MDA) is a key strategy for controlling filariasis, but resistance to the drugs used can reduce its effectiveness.

•Co-infection with other diseases: Co-infection with other diseases such as malaria and dengue can complicate the diagnosis and treatment of filariasis.

Drug administration is hindered by unavailability of drug distributors, lack of faith in tablets, unavailability of respondents, and fear of side effects (Figure 4A). The different types of difficulties and obstacles has been explained in Figure 4B. Kulkarni *et al*, has performed the evaluation of the coverage and compliances using MDA against LF, in a northern Karnataka district, in India[56,57]. The data suggested that the prevalence of asymptomatic occurrences in children is another crucial problem. 30% Of youngsters in some endemic areas in India have either contracted LF or have blood antigens for Mf or *W. bancrofti*[58]. Similar to this, asymptomatic Mf in children has been shown using LSG in a *B. malayi* endemic region of Kerala[59]. Human LF parasites lack animal reservoirs. After successful ELF in humans, this should be kept in mind[60]. Since the majority of acute episodes are of bacterial origin, there are additional concerns regarding the management of acute and chronic filariasis cases as well as the use of antibiotics in the treatment of adenolymphangitis (ADL) cases. Through kits and corrective operations, the APELF offers free morbidity management and disability prevention treatments.

Two-thirds of infected people do not exhibit any outward signs of LF, but may have immune suppression or renal dysfunction[61]. Although LF does not usually result in death, the debilitating symptoms brought on by this illness can have a substantial impact on carrying out everyday duties and engaging in social interactions. Those who suffer from debilitating illnesses can lessen pain and avoid secondary infections by maintaining strict cleanliness standards, such as bathing the afflicted body parts with soap and water[62]. Due to the impairment it causes in endemic places, the issue of LF is crucial to public health. Economic damage brought on by LF affects healthy persons who would otherwise contribute to economic progress because they become disabled[61,63].

Additionally, the disease can be quite stigmatizing for those who experience persistent, incapacitating symptoms that limit social connections[64,65]. Visible LF symptoms, such as lymphedema of the limbs, breasts, and genitalia, have significant social repercussions[65,66]. Because LF is a neglected illness, communities at risk for it do not receive the same attention in terms of health education as groups at risk for diseases like HIV/AIDS and TB, which are better recognized[62].

9.1. Spacio–temporal effect of lymphatic filariasis vectors

Numerous mosquito species can transmit LF and aid in continued transmission. *A. arabiensis*, *A. gambiae*, *A. merus*, *A. melas*, and *A. funestus* are examples of *Anopheles* species that are LF vectors (Table 1). Due to its widespread distribution throughout sub-Saharan Africa, quick larval development, and other behavioral characteristics, *A. gambiae* s.s. is regarded as one of the most effective vectors[67]. Because of its extensive geographic spread and adaptable behavior, *A. arabiensis* is especially noteworthy[68]. Additionally, *Culex* (*Cx.*) *quinquefasciatus* is an important vector widespread across the world and more prevalent in urban regions near residential areas[69]. *Cx. quinquefasciatus* thrives in locations containing decomposing organic matter such as access pits and pit latrines[69]. In urban areas, LF vectors like *Cx. quinquefasciatus* are crucial. Due to the *Cx. quinquefasciatus* vector's propensity for thriving in congested cities with subpar sanitation and sewage systems, *W. bancrofti* has shown a high potential for urban transmission[70]. Urban areas used to receive less attention, whereas rural areas were the center of LF elimination campaign, research, and control activities[71]. The feeding habits of vectors and choice of habitat have a significant influence on the transmission of LF. In Tanzania, recent research by Derua and colleagues[71] found that the relative number of mosquito species in the *A. gambiae* complex has changed. Previously, *A. gambiae* s.s. was the most prevalent vector, but researchers noticed a change in mosquito composition where *A. arabiensis* became the dominating vector in the complex[71]. Because *A. arabiensis* mosquitoes differ from *A. gambiae* s.s. in their feeding and resting habits, this result may have an effect on local vector control programmes and change intervention tactics for lowering the mosquito population. Data from 2012 showed a significant change in composition, with *A. arabiensis* accounting for 76.8% of the sampled vector population and *A. gambiae* experiencing a sharp decline. *A. gambiae* s.s. and *A. arabiensis* were nearly equally dispersed at 39.2% and 41.9%, respectively, during the previous survey period[71]. Similar results were found in a research conducted in Moshi, Tanzania, which revealed that 99.3% of the *Anopheles* species and 79.5% of the overall mosquito population were *A. arabiensis* mosquitoes[72]. A rise in *A. merus* population create more issues for control initiatives. Also, the concept on feeding and resting habits of some disease vectors play an important role in designing the tool for vector control tools. The livestock, *i.e.*, cattle acts as a host and provide blood meal for some vectors. Therefore, the availability of cattle may influence the transmission of parasites in human. For example, the higher number of livestock could provide enough blood meals for the vectors, and may reduce occurrence of vectors biting to humans. At other hand, higher number of cattle could increase

the accessibility of blood meals for mosquitoes, that may help in its longer survival, lead to higher risk of parasite transmission[73]. Hence, feeding and resting habits of mosquito affects in controlling with insecticide-treated materials and larvicide[73,74]. The presence of the *A. merus* and *A. arabiensis* vectors has an impact on vector management initiatives as well as broader LF elimination initiatives[62]. According to analysis, if local transmission patterns are not taken into account, the WHO-recommended MDA method would probably fail[75]. Two threshold values that are crucial for LF elimination are the worm breakpoint and the threshold biting rate[76]. The proper threshold biting rate and worm breakpoint required to stop transmission in a certain population can be found using mathematical models[77]. However, results from one location might not be generalizable to another place since threshold values vary throughout groups. In order to establish precise threshold values, mathematical models must be fitted to site-specific infection data[76]. As more Mf are consumed, the output of infectious larvae declines, a process known as limitation. As a result, at high Mf densities, the production of infective larvae per vector declines. Limiting vectors are very effective at maintaining transmission even at low Mf levels. By lowering transmission thresholds, limiting processes undermine elimination attempts and force more intense control measures to be taken[78]. There have been instances of this mechanism in *Culex* mosquito populations. In regions where LF transmission is prevalent, compensator is a crucial addition to MDA[79]. However, if vector control measures do not successfully lower mosquito populations, the development of pesticide resistance among different LF vectors will put the success of control efforts in jeopardy.

Climate change also has an effect on LF transmission dynamics since LF transmission is directly impacted by seasonal fluctuations in temperature, rainfall, and humidity. Due to variations in climatic factors like temperature and rainfall that affect the habitats for breeding vectors, *W. bancrofti* transmission in some places may vary significantly across a very limited geographic region[80]. There may be a direct relationship between seasonal trends and mosquito numbers and species proliferation, which may have an effect on LF transmission dynamics. Along with the aforementioned mosquito activities, it is also crucial to take into account human behavior and how it affects the dynamics of transmission. The implementation of an effective elimination campaign might be significantly hampered by noncompliance with medication regimens. It has been predicted that between 65 and 80 percent of the population has to receive treatment over the course of four to six years in order for elimination to take place[81]. Reducing patient noncompliance and identifying those who refuse to take their prescription are crucial for universal elimination.

9.2. Strategy to overcome lymphatic filariasis

Mass drug administration and vector control are two important strategies to control LF.

(ⅰ) Mass drug administration (MDA) and integrated approach: The most effective way to control filariasis is through MDA, which involves administering antifilarial drugs to entire at-risk populations. The drugs kill the microfilariae and prevent the adult worms from producing more microfilariae, thus reducing transmission. Since the WHO introduced the GPELF in 2000, endemic nations around the globe, including India, have adopted a twin-pillar strategy-prevention through MDA using a combination of two anti-filarial drugs (DEC and Albz), and providing morbidity management and disability prevention services to those affected by the disease[82]. The APELF, which was introduced in 2018 as part of India's renewed commitment to elimination, was followed by the gradual rollout of IDA therapy as part of increased elimination efforts. India effectively implemented IDA in four districts by the end of February 2019, including Arwal, Simdega, Nagpur, and Varanasi in Maharashtra. Out of 10.7 million disadvantaged persons, 8.07 million people (75.4%) benefited from the IDA drugs. Launching the National Vector Borne Disease Control Program's (NVBDCP) United to Eliminate LF conference in New Delhi. To enhance the caliber of MDA rounds, strategies like Triple Drug Therapy or IDA (IVM, DEC, and Alb) with stronger programme delivery and extensive community participation are necessary[83]. A comprehensive approach that combines MDA, vector control, and health education has been shown to be effective in reducing filariasis transmission and controlling the disease[84].

(ii) Vector control: Since filariasis is transmitted by mosquitoes, vector control measures such as the use of insecticide-treated bed nets, indoor residual spraying, and larval control can help reduce mosquito populations and prevent transmission[85].

Examples of these specified approaches for the elimination of malaria include the progressive control pathway for FMD[86]. In the Western Pacific, where LF was first eradicated in the 1900s, progress has been made in reducing prevalence as well as gaining useful knowledge for estimating current worldwide efforts. The Pac ELF and GPELF initiatives assisted endemic nations in their efforts to eradicate LF globally by using standardized management and monitoring measures. It was estimated that LF infection would be eliminated from half of the endemic countries by 2020. Additionally, by 2020, the majority of the endemic nations had stopped receiving MDA. It was observed that between 2000 and 2018, the requirement for MDA in the western pacific area decreased by 72%[87].

Many locations have tried community-level mass treatment with DEC-medicated salt as a LF control strategy. In India, trial

programme for this regimen were started in the states of Uttar Pradesh and Andhra Pradesh in 1968-1969. In Andaman and Nicobar Island, recent research utilizing DEC-fortified salt (0.2%) and iodine for the elimination of diurnally sub-periodic *W. bancrofti* showed promising results. The Mf rate decreased from 2.27% to 0.14% in the DEC-salt-arm (1% in all the villages) and from 1.26% to 0.74% (>1% in 4 out of 14 villages) in the MDA-arm as a result of community coverage of >90%. Data from the eleven groups utilizing DEC salt treatments were gathered and analyzed using Bayesian data model assimilation techniques in order to evaluate the LF transmission models. This medication has helped eliminate LF in a few areas of Africa, Central America, and Asia[16,88]. During the salt therapy, the prevalence of community Mf dropped from 8.89% to 0.63%, and no new infections appeared during the course of the next 10 years[89]. Compared to the other examined therapies, DEC medicated salt consistently reduced Mf prevalence upto 1% in endemic regions.

10. Conclusion and future prospect of lymphatic filariasis elimination

Millions of individuals worldwide suffer from lymphatic filariasis, often known as elephantiasis, a parasitic illness. It results in persistent swelling and impairment and is brought on by nematode worms with the appearance of threads that inhabit the lymphatic system. By 2030, the illness is expected to be eradicated as a public health issue because of the Global Programme to Eliminate Lymphatic Filariasis (GPELF). However, there are a number of barriers and challenges in reaching this objective. The first difficulty is the disease transmission cycle's complexity, which includes a number of worm species as well as vector mosquitoes. Because of this, it is challenging to control LF spread using conventional public health techniques like mass drug administration (MDA). The second issue is that some places, especially those that are isolated or afflicted by war, do not have easy access to medical care. This indicates that a large number of people do not receive the treatment they require to either prevent or treat the illness, which encourages its spread. Another barrier is the poor knowledge of LF and the stigma associated with complications, which can cause a delay in identification and treatment[90]. The illness may spread more widely because many afflicted individuals may feel too humiliated or embarrassed to seek medical attention. In addition, there is a dearth of funds and resources for research and the creation of innovative cures and prevention methods. This makes it challenging to create new methods and instruments to handle the problems associated with curing the condition. Despite these difficulties, progress has been made in the control of LF. Over 800 million persons in endemic regions have received more than 7 billion treatments since the GPELF was founded in 2000. Over 70% fewer individuals are now afflicted, and numerous nations have managed to completely eliminate the illness as a public health issue. In summary, eliminating lymphatic filariasis is a complex and difficult aim, yet it is being accomplished. Continued efforts and funding for research, treatment, and preventive initiatives are required to get beyond the remaining challenges and accomplish the elimination target.

Inaccessible animal reservoirs, disruption of the pathogen's life cycle, clinical demonstration or laboratory-based testing to confirm cases, and low environmental persistence are only a few biological methods that must be used to eradicate illness[91]. There must be preventative measures, such as vaccination shots, efficient medications, or behavioral modifications. Both the vaccine's effectiveness and cost must be considered. To achieve the elimination, each of these conditions must be met. The future prospects for LF control are encouraging, with ongoing efforts aimed at eliminating the disease as a public health problem. Here are some of the prospects for LF elimination[92]:

•Elimination of the illness: The WHO has established a deadline of 2030 for the complete elimination of LF as a public health issue. This objective calls for expanding the use of mass drug administration, enhancing vector control, and taking additional steps to stop the spread of the illness. Research is still being done on new medications and vaccines that could treat LF. Alternatives to current treatments that are more potent and less harmful might be provided by these procedures[93].

•Improved diagnostics: To detect and keep track of LF infections, better diagnostic technologies are required. Point-of-care diagnostics, for example, could assist increase the precision and timeliness of diagnosis, making it simpler to focus interventions[94].

•Increased awareness: Increased knowledge about LF can lessen stigma and enhance access to care. There are initiatives undertaken to increase understanding of the illness and its effects, particularly in afflicted communities[95].

•Integration with other programs: It may be possible to combine efforts to combat LF with those to combat malaria and other neglected tropical diseases. This might result in more effective resource management and improved community health outcomes[96].

Overall, while LF remains a significant public health challenge, there is reason to be optimistic about the future prospects for eliminating the disease and improving the lives of those affected by it.

Conflict of interest statement

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Authors' contributions

S.K. and K.K.C. designed, supervised the study, analyzed data, and corrected the manuscript, A.S. and S.K. searched the literature and wrote the manuscript, D.D., V.Y. and A.P. critically reviewed the manuscript. All authors A.S., S.K., D.D., V.Y., A.P., K.K.C., and S.K. contributed to the final version of the manuscript.

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