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Lymphatic Filariasis: Insightful Review of a Neglected Tropical Disease

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Abstract: Lymphatic filariasis (LF), a neglected tropical disease has currently infected at least 51 million individuals globally, disfigured and incapacitated about 36 million and placed over 882 million people at risk of infection. It is a painful and profoundly disfiguring disease that can lead to permanent disability. Victims of the disease do not only manifest physical disability, but suffer psychological, social and financial losses leading to stigmatisation and poverty. Regardless of the fact that LF has burdened the majority of individuals in endemic regions for many years, evidence shows that the disease has been poorly understood and its medical importance underestimated. For the past two decades or so, since the launching of the Global Programme to Eliminate Lymphatic Filariasis (GPELF) by World Health Organization (WHO), there has been an avalanche of research works on the disease. This paper aims to provide a systematic and insightful review of the disease. The paper therefore provides a comprehensive outline of the global burden and distribution of LF, causative agents of human filariasis, life cycle of the parasite, clinical manifestations, diagnosis and control of LF.

Keywords: Anopheles vectors, Albendazole, Elephantiasis, Ivermectin, Lymphatic Filariasis

I. Introduction

Lymphatic filariasis (LF) is a neglected tropical disease caused by three species of lymphatic lodging filarial parasites: *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori* (Centers for Disease Control and Prevention [CDC], 2018; World Health Organization [WHO], 2022). It is a painful and profoundly disfiguring disease representing an important economic burden to many developing countries (WHO, 2014). The disease is the leading cause of physical disability and the second leading cause of long-term permanent and chronic disability after mental illness (CDC, 2013; Ton, Mackenzie & Molyneux, 2015; Zeldenryk *et al.*, 2011).

Wuchereria bancrofti is predominantly responsible for about 90% of all LF cases, whilst the rest of the cases (10%) are caused by *B. malayi and B. timori* (Behera & Panda 2017; WHO, 2022). Bancroftian filariasis is sometimes used to refer to LF infections caused by *W. bancrofti*, while brugian filariasis refers to infections by the *Brugia* spp. (Nutman, 2017; Simonsen *et al.*, 2014). The adults of these parasitic nematodes lodge within the lumen of the lymphatic vessels (CDC, 2018; Mahalingashetti *et al.*, 2014) for an average of 6-8 years, producing millions of immature microfilariae (mf) that circulate in the blood (WHO, 2022).

The vectors of LF are species of mosquitoes belonging to the genera: *Anopheles, Culex, Mansonia* and *Aedes*. These genera alongside *Coquilletidia* and *Ochlerotatus* have been associated to be vectors of the LF parasites (Cano *et al.*, 2014; de Souza *et al.*, 2012).

Ottesen (2000) observed that LF can be eliminated due to its biological nature. Firstly, it is a disease that exclusively affects humans. Secondly, the microfilaria (mf) is unable to multiply its numbers in the vector and finally, the mechanism of transmission is relatively inefficient. Realising the possibilities of elimination of the disease, the World Health Assembly passed a resolution (WHA50.29) in 1997 which requested member states to initiate activities to eliminate LF. This led to the formation of the Global Programme to Eliminate Lymphatic Filariasis (GPELF), launchedby WHO in 2000 with the goal to eliminate LF as a public health problem by 2020 (Ottesen, 2000; WHO 2014). In order to achieve the goal, the GPELF proposed a comprehensive strategy based on two main pillars: (i) interrupting the transmission of LF infection through mass drug administration (MDA) and (ii) alleviating suffering through morbidity management and disability prevention (WHO/GPELF, 2021).

The objective of this review is to summarise the scientific basis of literature relating to LF. The review is divided into six sections corresponding to the major areas of research on LF: global burden and distribution, causative agents of human filariasis, life cycle of LF parasite, clinical manifestation, diagnosis and control. For each of the six sections, some current available literature are reviewed to provide insight into the disease.

II. Methodology

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Search for scientific literature on LF was conducted on Google Scholar and PubMed databases using relevant keywords. Relevant reports from WHO and CDC were also included. Manual scanning was conducted as well. Articles for review were included if they: 1) were written in English language 2) were published between the year 1997 and 2023 with peer-reviewed data 3) explored LF issues related to global burden and distribution, causative agents, life cycle of the parasite, clinical manifestation, diagnosis and control. Articles were excluded from review if they were published before 1997 and do not explore any of the above issues related to LF. From the database search, 500 articles were identified. After initial screening, 200 duplicate articles were deleted. The remaining 300 articles were then screened to locate relevant content. Two hundred and twenty (220) were excluded as they did not meet the inclusion criteria, leaving 80 articles for review. The 80 articles were critically examined and analysed.

It is acknowledged that this review has some limitations. There could have been more papers for review if a review on grey literature and articles in other electronic databases such as MEDLINE (Medical Literature On-Line), CINAHL(Cumulative Index to Nursing and Allied Health Literature), Scopus and ProQuest had been conducted.

Global Burden and Distribution of LF

In 2000, LF was ranked as the second most common vector-borne parasitic disease after malaria and it was prevalent in over 80 tropical and subtropical countries (Wynd *et al.*, 2007).

Currently, the Pan American Health Organization (PAHO) of the WHO recognizes LF as one of the top ten vector-borne diseases that put the population of the Americas at risk (PAHO/WHO, 2014). According to WHO (2014), *W. bancrofti* is predominant in areas with hot and humid climates. It is therefore widespread throughout the tropical regions of Asia, Africa, the Americas and the Pacific (Fig. 1a). *Brugia malayi* is mainly found in Southeast Asia and in areas of south-west India (Fig. 1b), but *B. timori* is only restricted to some islands in Indonesia (Fig. 1b) (Mathison, Couturier & Pritt, 2019; Simonsen, 2008). At the inception of GPELF, global baseline data reveals that, an estimated 120 million individuals are infected, 40 million disfigured and incapacitated and over 1.4 billion people are at risk of infection of LF (Michael & Bundy, 1997; WHO, 2014). Out of the 40 million disfigured and incapacitated, an estimated 15 million people are affected by lymphoedema, which include swelling of the limbs, breasts or genitals, and approximately 25 million men are afflicted with genital swelling, mainly scrotal hydrocele (WHO, 2014). However, recent data acknowledging the impact of 13 rounds of MDA estimated that about 67.88 million people are now infected including 36.45 million mf carriers, 19.43 million with genital hydrocele, and 16.68 million with lymphoedema (Ramaiah & Ottesen, 2014). More recent data from WHO (2023) also reveals that an estimated 51 million individuals are infected and over 882 million individuals in 44 countries are at risk of infection. Though these clinical features are not often lethal, they lead to the ranking of LF as the second leading cause of permanent and long-term disability (CDC, 2018; Zeldenryk *et al.*, 2011).

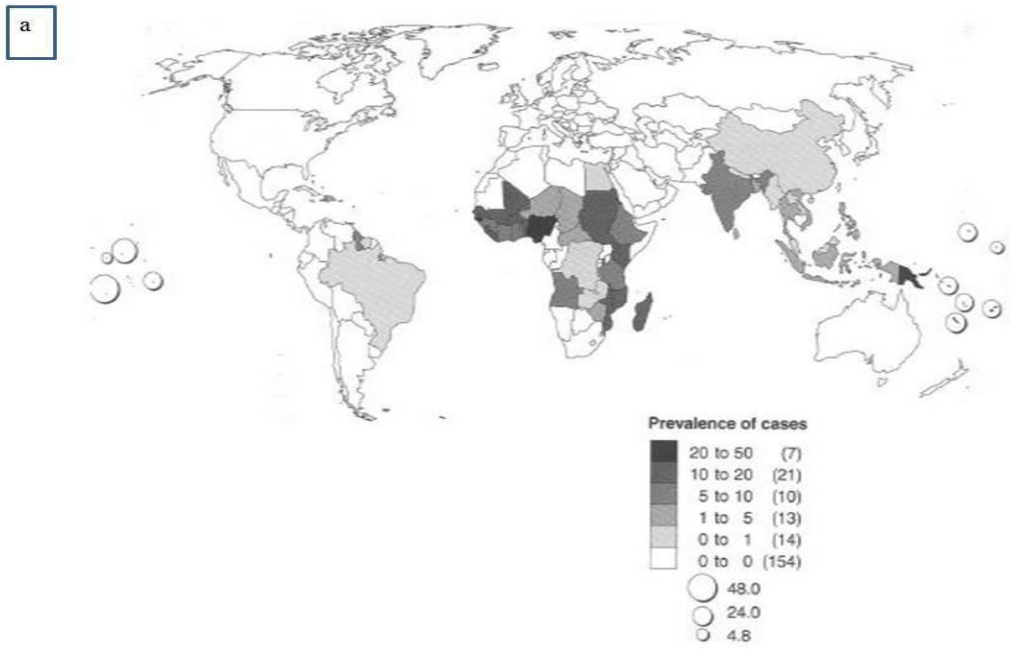

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Figure 1a: Geographical distribution of bancroftian filariasis based on the crude Global Burden of Disease (GBD) estimates. Circles denote the corresponding prevalences (%) estimated for the various Pacific Islands and vary in size proportionately with the prevalence of each island. The figures in brackets indicate the number of countries.

Source:(Michael & Bundy, 1997).

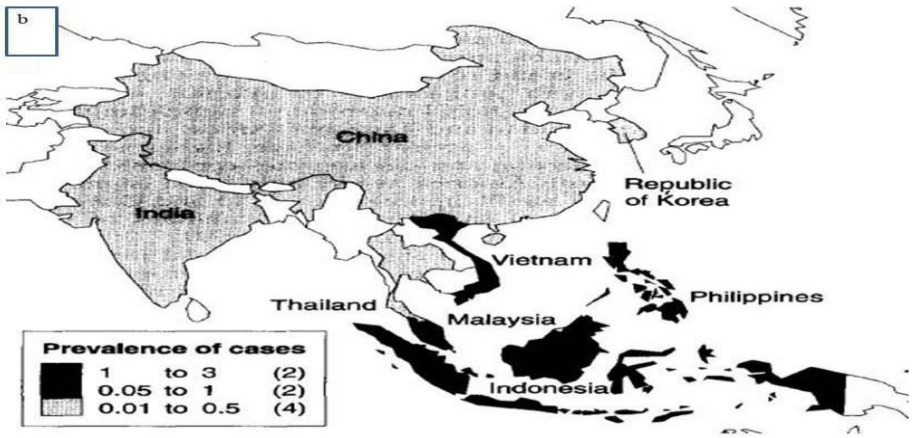

Figure 1b: Geographical distribution of brugian filariasis based on the crude GBD estimates. The figures in brackets indicate the number of countries.

Source: (Michael & Bundy, 1997).

Causative Agents of Human Filariasis

Filariasis is caused by vector-borne nematodes (roundworms) that are parasitic in nature. Depending on the species, adult filariae may inhabit the lymphatics, blood vessels, subcutaneous tissues, connective tissues or serous membranes of body cavities. The adult females produce microfilariae which normally lodge in the bloodstream or the skin and they are transmitted from person to person by dipteran vectors (Nutman, 2017; Simonsen, 2008). Eight species of filarial parasites (nematodes) infect humans: *Onchocerca volvulus, Loa loa, Mansonella streptocerca, M. perstans, M. ozzardi, Wuchereria bancrofti, Brugia malayi* and *Brugia timori* (Ash & Orihel, 2007; Nutman, 2017).

However, the first three parasites (*O. volvulus, L. loa, M. streptocerca*)affect the subcutaneous tissues. *Mansonella perstans* and *M. ozzardi* affect the serous cavity of the abdomen while the last three parasites (*W. bancrofti, B. malayi* and *B. timori*) affect the lymphatics and are responsible for the morbidity associated with LF.

Wuchereria bancrofti (fig. 2 and 4) is the most widespread and responsible for about 90% of all LF cases in the world (WHO, 2023). *Brugia malayi* (fig. 3 and 4) is mainly limited to Southeast Asia and South-west India, but *B. timori* (fig. 5) is restricted to some islands in Indonesia (Mathison, Couturier & Pritt, 2019; Simonsen, 2008).

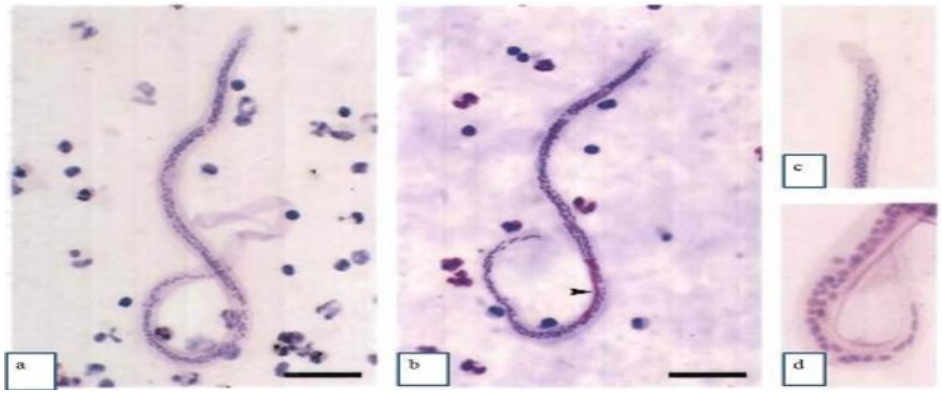

Figure 2:*Wuchereria bancrofti* microfilaria in heamatoxylin (a, c, d) and Giemsa (b) stains.Image reprinted from Bench Aids for the diagnosis of filarial infections. Copyright World Health Organization 1997.

Source: http://www.dpd.cdc.gov/DPDx/HTML/PDF Files/Wbancrofti Lloa benchaid who.pdf

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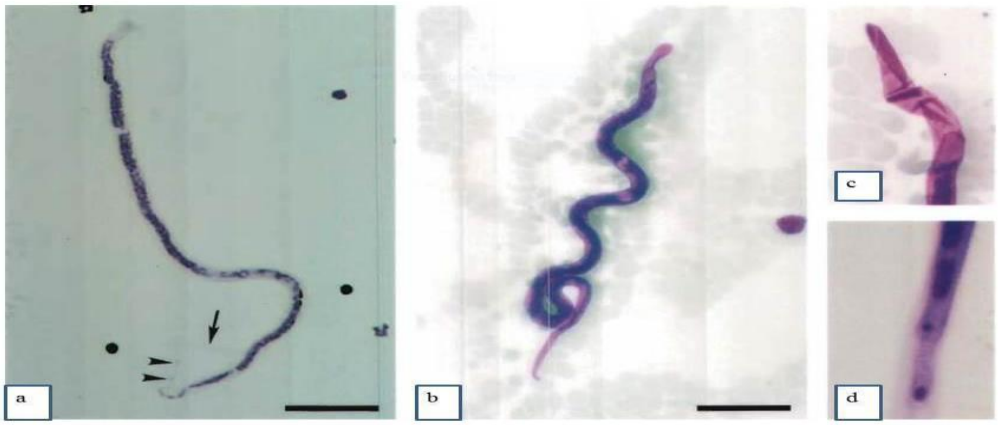

Figure 3: *Brugia malayi* microfilariae in heamatoxylin (a) and Giemsa (b-d) stains. Image reprinted from Bench Aids for the diagnosis of filarial infections. CopyrightWorldHealthOrganization1997.

Source:http://www.dpd.cdc.gov/DPDx/HTML/PDF_Files/Brugia benchaid who.pdf

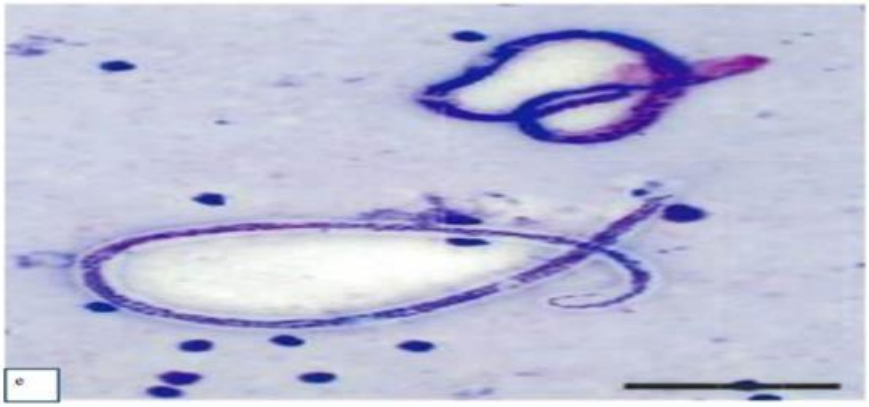

Figure 4:*Brugia malayi* (upper) and *W. bancrofti* (lower) microfilariae in the same field of Giemsa-stained blood film (e). Image reprinted from Bench Aids for the diagnosis of filarial infections. Copyright World Health Organization 1997.

Source: http://www.dpd.cdc.gov/DPDx/HTML/PDF_Files/Brugia benchaid who.pdf

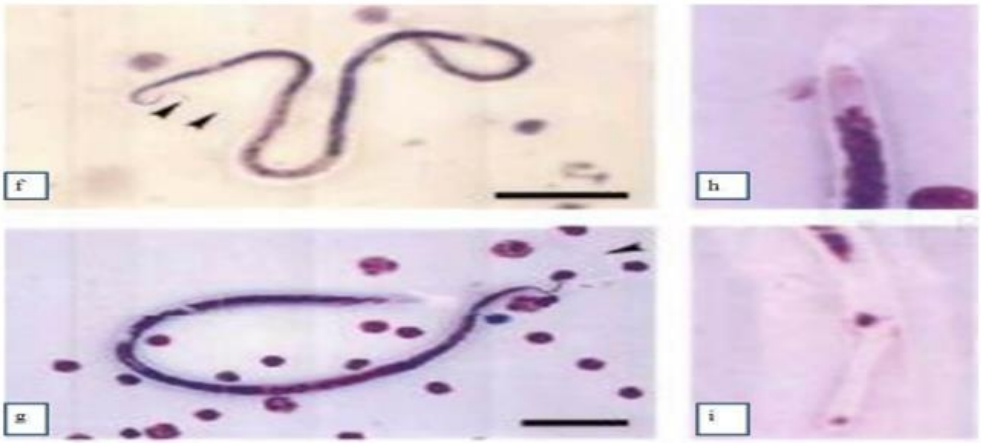

Figure 5: *Brugia timori* microfilariae in heamatoxylin (f) and Giemsa (g-i) stains. Image reprinted from Bench Aids for the diagnosis of filarial infections. CopyrightWorldHealthOrganization1997.

Source:http://www.dpd.cdc.gov/DPDx/HTML/PDF_Files/Brugia benchaid who.pdf

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The Life Cycle of LF Parasite

The parasite, *W. bancrofti* has biphasic life cycles in two hosts. It has a definitive human host and various genera of mosquitoes (vector) as intermediate hosts. Mosquito species belonging to the *Anopheles, Culex, Aedes, Mansonia, Coquillettidia* and *Ochlerotatus* genera are carriers of the LF parasites (de Souza *et al*, 2012; Manguin *et al.*, 2010). The life cycle of the parasite is illustrated in fig. 6. The development of the parasite in the mosquito takes a minimum of 10-12 days under optimal conditions, mainly temperature (Paniker & Ghosh, 2017; Scot, 2000).

The periodicity of most *W. bancrofti* mf bloodstream appearance coincides with the peak feeding activity of the local vectors (WHO, 2013). This adaptation increases their likelihood of onward transmission. The periodicity of *W. bancrofti* mf is nocturnal, with peak concentrations in the peripheral blood around midnight (WHO, 2014). This periodicity is determined by a biological rhythm that is innate in the microfilariae but influenced by the circadian rhythm of the host (Nutman, 2017; Simonsen, 2008).

The adult worms live in the lymphatic vessels of the human host. The adult female *W. bancrofti* is viviparous and measures 80-100 × 0.25 mm with the male measuring about 40 × 0.1 mm (CDC, 2018). The adult *Brugia* spp. have only half of this dimension. Microfilariae are produced from ova in the uterus of the female worm. Microfilariae are surrounded by a loose sheath and measure on average 200-250 µm long and 5-7 µm wide (Nutman, 2017). During a blood meal by the female mosquito, mf are ingested and the sheaths are broken in the mosquito abdomen. Some of the parasites pass through the abdominal wall of the mosquito and migrate to the thoracic muscles, where they differentiate into first-stage larvae (L_1). The larvae grow and moult into sausage shaped second-stage larvae (L_2). They subsequently moult again to produce highly active infective third-stage larvae (L_3) (Rajasekaran *et al.*, 2017). Mature infective larvae then migrate to the head region within the labium (mouthpart) of the mosquito from where they enter the skin of the human host, probably through the puncture site made by the proboscis of the vector when it takes its blood meal.

The transmission of filarial worms is highly inefficient and requires many successful bites from infected mosquitoes (Bartholomay, 2002; Davis *et al.*, 2019). The L_3 develop to fourth-stage larvae (L_4) as they migrate through the human body to the lymphatic vessels and lymph nodes, where they develop into adult worms in about a year and mate (CDC, 2018). Female worms produce many sheathed mf which appear in peripheral blood at night between 10PM-2AM reaching a peak about midnight (nocturnal periodicity) (CDC, 2018; Simonsen, 2008).

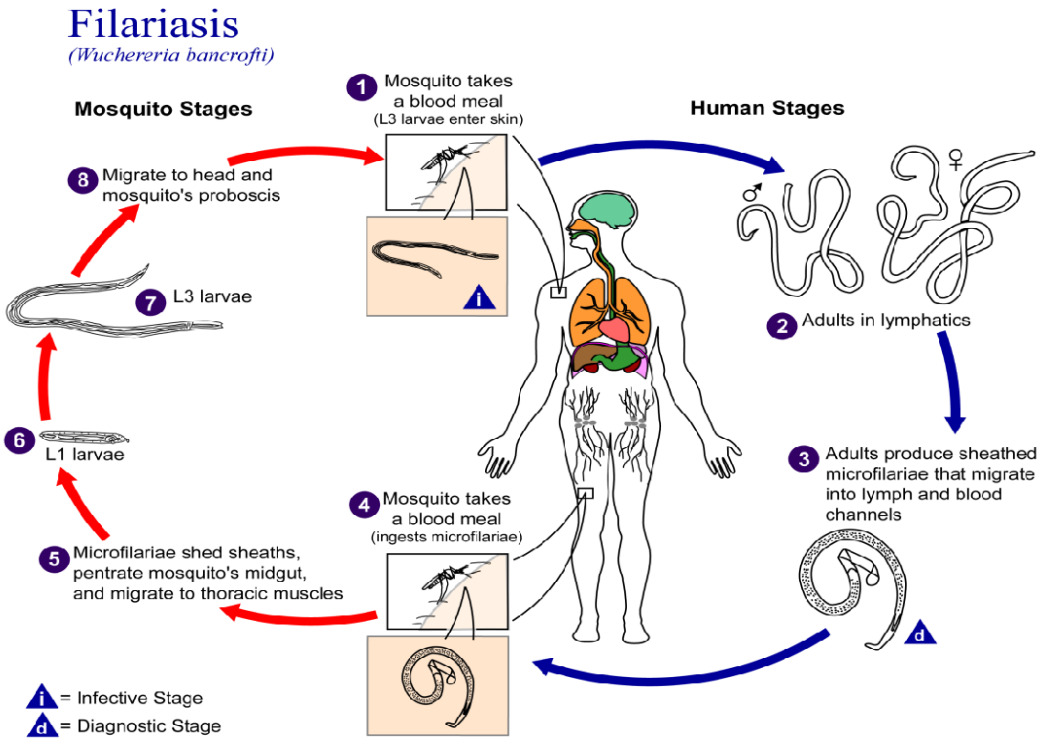

Figure 6: The life cycle of *W. bancrofti* showing the various developmental stages of the parasite in the vector and the vertebrate host.

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Source: US Centers for Disease Control and Prevention, 2019. http://phil.cdc.gov/phil/home.asp

Clinical Features of LF

Lymphatic filariasis is described by a wide spectrum of clinical and subclinical disease manifestations (Wynd *et al*., 2007). Rajasekaran *et al.* (2017) established that the clinical manifestations of LF can be classified into: endemic normal, clinically asymptomatic infection, acute clinical disease and chronic pathology.

Endemic normal refers to individuals in an endemic community that may be asymptomatic and amicrofilariaemic. Such individuals would not show any clinical symptoms of LF. These include individuals who have not been sufficiently exposed to the infection, individuals with prepatent infection or adult worm infection without microfilaraemia, and individuals who have cleared the infection through chemotherapy (Simonsen, 2008). In this case, laboratory diagnostic techniques are not able to determine whether such individuals are infected or free.

Asymptomatic infection relates to individuals in the endemic community that may be asymptomatic but microfilariaemic. These individuals may have circulating mf in their peripheral blood but would not show any clinical symptom of LF. Such individuals may remain microfilaraemic and asymptomatic for many years (Simonsen, 2008). They are important reservoirs for the transmission of the disease.

Considerable proportion of individuals may also be symptomatic and microfilaraemic. Such groups of individuals may show either acute disease manifestation or chronic pathology because of the presence of mf in the bloodstream.

Behera, Das & Panda in their study observed that only about one-third of infected individuals in endemic communities will develop clinical symptoms of the infection while the rest will remain asymptomatic (Behera, Das & Panda, 2017).

Acute disease conditions

Acute adenolymphangitis (ADL) is the acute form of the disease (WHO/GPELF, 2021). ADL may occur in both early and late stage infections and it is the first clinical manifestation of LF (Rajasekaran *et al*., 2017).ADL, is characterized by episodic attacks of malaise, fever and chills, and by the appearance of enlarged painful lymph nodes draining the affected part, usually the lower limb, followed by an acute, warm and tender swelling. The episodes usually resolve spontaneously after about a week, and may recur several times within a year (Simonsen, 2008). Regression of the swelling to a normal state after an ADL attack of the leg is commonly followed by unnecessary shedding of the outer layer of the skin (Dunyo *et al*., 1998).

ADL, also referred to as acute filarial disease (Simonsen, 2008) was distinguished into two distinct clinical syndromes by Dreyer and his colleagues: acute filarial lymphangitis (AFL) and acute dermato-lymphangioadenitis (ADLA) (Dreyer *et al.,* 1999). In some situations, healthcare workers may occasionally find it difficult to distinguish between ADLA and AFL (WHO/GPELF, 2021).

AFL is caused by the death of the adult worms, either naturally or after treatment with chemotherapy (Behera, Das & Panda, 2017; Pfarr *et al.,* 2009).AFL manifests itself as a circumscribed inflammatory nodule or cord centered on degenerating adult worms, with lymphangitis spreading in a descending (centrifugal) fashion. It usually has a mild clinical course and rarely causes residual lymphoedema (Simonsen, 2008).

ADLA, on the other hand, is provoked by secondary bacterial infection with group A streptococcus (Behera, Das & Panda, 2017). It develops in a reticular or circumferential pattern, and is clinically similar to erysipelas or cellulitis (Simonsen, 2008). Symptoms of local pain and swelling, as well as fever and chills, are present (Addiss & Brady, 2007). In LF endemic communities, ADLA occurs much more commonly than AFL (Dreyer *et. al.,* 1999). Recurrent attacks of ADLA play an important role in the progression of lymphoedema leading to elephantiasis (Addiss & Brady, 2007; Behera, Das & Panda, 2017). ADLA requires antibiotic therapy (WHO/GPELF, 2021).

Chronic disease conditions

In the year 2000, WHO estimated that more than 40 million individuals suffer from chronic forms of the disease (hydrocele, lymphoedema and elephantiasis) caused by the filarial worms and approximately 25 million men globally exhibit urogenital manifestations of LF and over 15 million people are plagued with lymphoedema (WHO, 2014). Currently, after 13 years of MDA programme, Ramaiah & Ottesen (2014) estimated that there are 67.88 million cases of LF that include 36.45 million mf carriers, 19.43 million hydrocele cases, and 16.68 million lymphoedema cases. Chronic disease is incapacitating, leading to limitation in the duration and capacity to work and responsible for the socioeconomic burdens of isolation and poverty for victims (Ramaiah *et al.,* 2000; WHO, 2023).

Hydrocele is the most common chronic presentation of LF and occurs in only males (Mackenzie *et al.,* 2008). *Wuchereriabancrofti* is the only lymphatic filarial parasite that induces genital diseases (DeVries, 2002; Yonder & Pandey, 2023).

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Hydrocele is a source of psychological, social, marital and economic challenges to the victim (WHO, 2023). This condition results following the accumulation of clear, straw-coloured, fluid in the sac surrounding the testicles. The onset may not accompany acute episodes, or it may be preceded by one or more attacks of funiculitis or epididymoorchitis. Following early acute episodes, the swelling around the testes usually disappears completely, but over the years the tunica vaginalis (sac surrounding the testis) becomes thickened and there is progressive enlargement of the hydrocele. Most cases are unilateral, but bilateral hydrocele, often with different sizes on the two sides, is not uncommon (Simonsen, 2008). Rarely, the fluid may have a milky appearance if lymph from a ruptured lymphatic vessel pours into the hydrocele to form a chylocele (Simonsen 2008).

Lymphoedema and elephantiasis (fig. 7) are the best known clinical manifestations of the disease (Mackenzie *et al.*, 2008). Lymphoedema leading to elephantiasis mostly affects the limbs. Though it may also affect the penis, breast, vulva and scrotum, it is uncommon. Lymphoedema is simply tissue swelling and it results from the accumulation of lymph in the tissues at the infected parts of the body. Elephantiasis progresses from lymphoedema of the affected body parts due to obstruction of the lymphatic drainage (Cheng *et al.* 2006; Palumbo, 2008). This results in skin/tissue thickening.

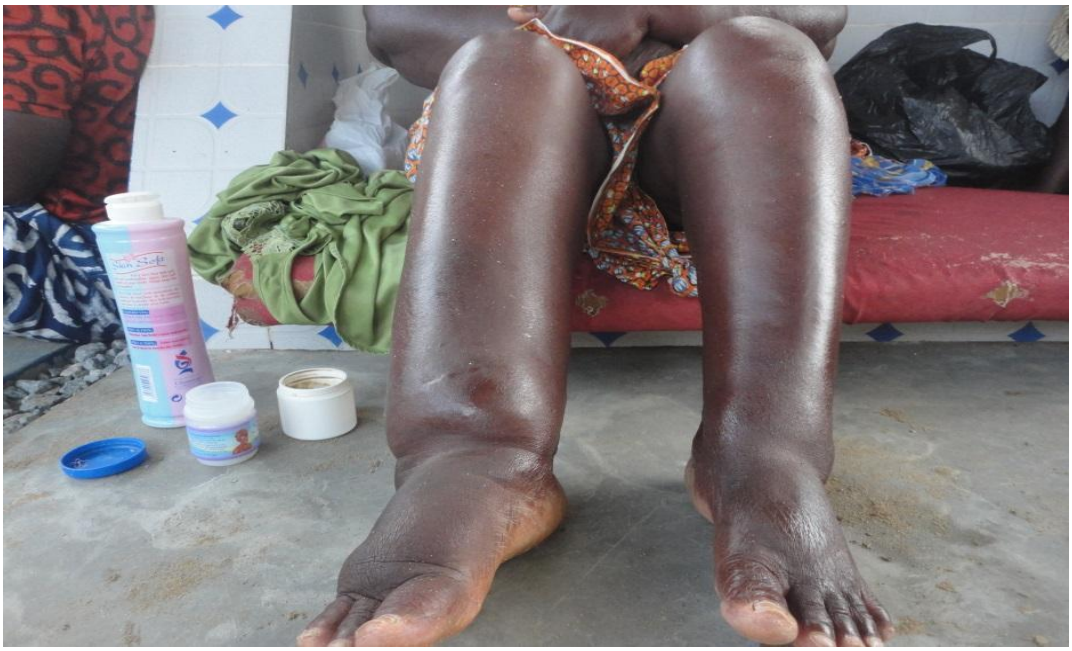

Figure 7: Lymphoedema of the leg.

Source: Field Data (2014).

Clinical Diagnostic Techniques

Several diagnostic tools exist for the detection of LF. Current existing techniques employed in the LF control programmes in various endemic regions include detection of circulating filarial antigen (CFA), detection of mf, detection of anti-filarial antibodies and detection of parasitegenomic DNA in mosquito and human blood samples.

Detection of Circulating Filarial Antigen (CFA)

This method is conveniently used to detect molecules shed by the adult worms or mf (Wamae & Njenga, 2008). The immunochromatographic test (ICT) and the Og4C3 enzyme linked immunosorbent assay (ELISA) are the two commercially existing techniques that detect CFA. These diagnostic tests have been confirmed by Weil *et al.* (1997) that they are very convenient for daytime diagnostic examination and also offer higher sensitivity and specificity.

An ELISA test kit uses Og4C3, a monoclonal antibody, to identify this LF parasite (Rocha *et. al.*, 2009; Pani *et. al.*, 2000). With this test, as little as 100 µl plasma samples from the test individual is required.

The ICT rapid card test is specific for *W. bancrofti* CFA. One hundred microliters (100 µl) of finger- pricked blood is added to the sample pad of the card. The pad contains a gold-labelled polyclonal anti-filarial antibody that binds antigen from the blood. When the card is closed, the pad touches a nitrocellulose strip. The antibody-antigen complexes move along the strip and are trapped by an immobilised anti-filarial monoclonal antibody (AD12.1) in the strip's coating. The result is read after 10 minutes, and appears as a pink test line (in case of a positive test) next to a control line that appears in all valid cards (fig. 8). Thus, blood samples from

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antigen negative individuals show one pink line, whereas those from antigen positive individuals show two pink lines (Wamae & Njenga, 2008).

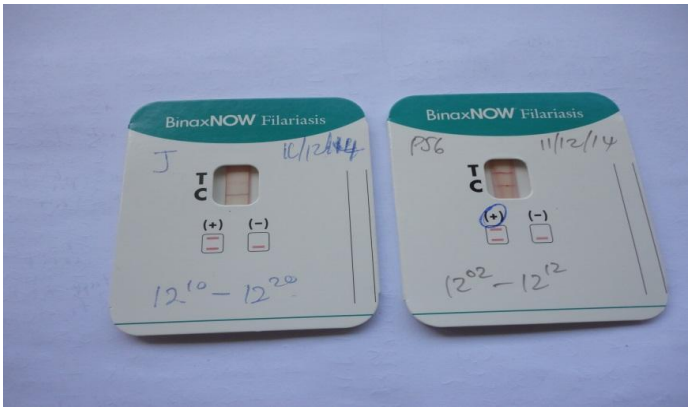

Figure 8: ICT cards used for LF detection. The left ICT card shows negative results for LF infection, while the right card shows positive results.

Source: Field data (2014).

Detection of microfilariae

This technique involves direct demonstration of mf in peripheral blood. Though this method is traditional, it is still relevant to the success of GPELF. The mfs of *W. bancrofti* have nocturnal periodicity (Simonsen, 2008) and therefore the blood samples for diagnosis are collected at night.

Thick blood smear method

The Giemsa stained thick smear is the most frequently used method for diagnosis of mf. Twenty to sixty microlitres (20-60 µl) of blood sample is applied on a clean microscopic glass slide and dried overnight before dehaemoglobinization and subsequent fixation and staining (Wamae & Njenga, 2008). Microscopy is later employed for the morphological identification of mf. McMahon *et al.* (1979) and Pani *et al.* (2004) identified two limitations of this method; low sensitivity due to small volume of blood sample used and loss of mf during the dehaemoglobinization step.

Knott's concentration method

This method is very sensitive in detecting mf (Knott, 1939). Here 1 ml of venous blood collected in a tube containing anticoagulant is mixed with 10 ml of 2% formalin. The mixture is left for at least 15 minutes before centrifugation. The supernatant is discarded and the remaining sediment examined for mf as a wet smear on a microscope glass slide. A drop of 1% methylene blue may be added to the sediment to aid examination. Individuals with elevated levels of gamma globulin may have a large amount of sediments, thus making the Knott's concentration method difficult to perform because of the longer time required in examining the specimen (Wamae & Njenga, 2008).

The membrane filtration technique

In this method 1- 5 ml of venous blood collected in a tube containing anticoagulant is first mixed with a solution to lyse the erythrocytes and then filtered through a 5 µM pore size Nucleopore filter. The filter is carefully held between plastic supports within a leak – proof reusable filter holder. After filtration, the filter is removed using forceps and placed on a glass slide for examination and counting of mf under a microscope (Wamae & Njenga, 2008). One limitation of the membrane filtration technique is that the blood sample must be processed immediately after collection otherwise the filters may get clogged, thus preventing the blood specimen from passing through with the potential of even contaminating the user (Dickerson *et al.*, 1990; Wamae & Njenga, 2008). The difficulty of getting venous blood as most endemic communities are reluctant to give is another drawback to this technique. Also, a trained phlebotomist is required for the blood collection process (Wamae & Njenga, 2008).

The counting chamber method

This diagnostic technique also detects mf directly in peripheral blood. For this technique, 100 µl of finger-prick or venous blood is collected and transferred to a tube containing 900 µl of 3% acetic acid (Simonsen *et al.*, 2014). The acetic acid serves as a preservative as well as a lysing solution for the erythrocytes (Wamae & Njenga, 2008). In the laboratory, the blood specimen is transferred to a Sedgewick-Rafter chamber and examined directly for mf under a compound light microscope (Kanamitie *et al*,

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2017). The Sedgewick-Rafter counting chambers are available in plastic and glass versions. The glass chambers are durable but expensive (Wamae & Njenga, 2008). A major drawback of the plastic chamber identified by Wamae & Njenga (2008) is that it easily gets scratches which under the microscope may appear as mf. They also identified two advantages of the counting chamber technique in the quantification of mf. These include the relative convenience of the counting chamber technique because the acetic acid preserves the blood samples which can be stored for later examination in the laboratory. Also, there is little chance of losing mf during processing because the blood specimen is transferred directly into the counting chamber for examination. Studies conducted by Agbolade & Akinboye (2005) disclosed a higher microfilaraemic sensitivity of the counting chamber technique than the thick blood smear technique. This finding is in consonance with earlier reports by Denham *et al.* (1971) and McMahon *et al.* (1979).

Detection of anti-filarial antibodies

Early research on LF diagnosis proposed that detection of anti-filarial IgG4 antibody has higher specificity for filarial infection (Lal & Ottesen, 1998; Jaoko *et al.*, 2006). According to Wamae & Njenga (2008), selected recombinant proteins developed from filarial cDNA libraries have been identified for further research. This is as a result to get more specific antigens for antibody-detection based diagnostic tests (Lammie *et al.*, 2004). Itoh *et al.* (2001) also confirmed that an ELISA that detects filarial-specific IgG4 antibodies in urine has been designed. Wamae & Njenga (2008) reported that the assay has high sensitivity (96%) and specificity (99%). Also urine samples are easier to collect than blood samples.

Detection of *W. bancrofti* DNA

This is a molecular identification technique that involves the use of Polymerase Chain Reaction (PCR), Real-time quantitative PCR and Loop-Mediated Isothermal Amplification (LAMP). The identification of a *W. bancrofti* repeated DNA sequence has facilitated the design of a PCR based assay capable of detecting *W. bancrofti* genomic DNA in human blood (Zhong *et al*., 1996; Zulch *et al.*, 2020) and in mosquito vectors (Chanteau, 1994; Zulch *et al.*, 2020). The PCR is an enzyme-catalysed biochemical reaction in which a small quantity of a specific DNA segment is amplified into large quantities, using two oligonucleotide primers, and a DNA polymerase (Mullis, 1990; Yao *et al.*, 2021).

Laney *et al*. (2010) have successfully developed an assay that specifically detects the infective stage of *W. bancrofti* in mosquitoes. The assay detects an L3-activated mRNA transcript by reverse-transcriptase PCR (RT-PCR). The assay can also be used to detect any of the larval stages of *W. bancrofti* in pooled vector mosquitoes.

An alternative to PCR in detecting *W. bancrofti* DNAis the Loop-mediated isothermal amplification (LAMP) (Takagi *et al.*, 2011). Under isothermal conditions, the LAMP technique amplifies DNA with great specificity, sensitivity, and rapidity (de Souza *et al*., 2014; Poole *et al.*, 2012). Amplification and detection of genes can be completed in a single step, by incubating the mixture of samples, primers, DNA polymerase with strand displacement activity and substrates at a constant temperature. It provides high amplification efficiency, with DNA being amplified 10^9–10^{10} times in about 1 hour. The resulting product is a turbid solution (fig. 9), indicative of product amplification. Sample confirmation can therefore be done visually (de Souza *et al.*, 2014).

Unlike PCR technology in which the reaction is carried out with a series of alternating temperature steps or cycles, LAMP is carried out at a constant temperature, and does not require a thermal cycler. Takagi *et al.* (2011) highlighted that the LAMP method is superior to PCR in terms of running cost and demonstration time.

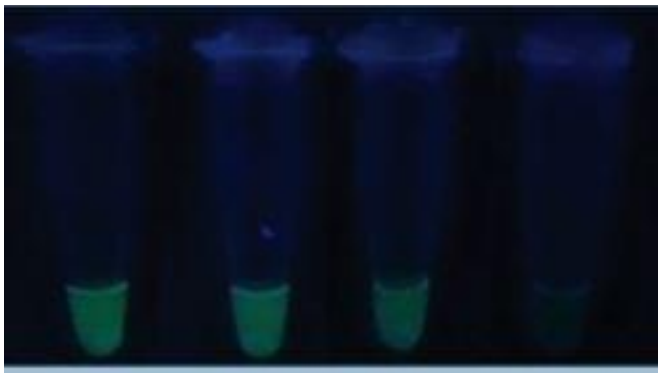

Figure 9: Products of samples after Loop-Mediated Isothermal Amplification. Positive samples fluoresce green while negative samples remain dark.

Source: (Poole *et al.*, 2012).

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Control of Lymphatic Filariasis

The goal of the GPELF was to eliminate LF as a public health problem by 2020. The programme has two principal pillars in achieving the goal. First, interruption of the transmission of LF parasite through chemotherapy (use of antifilarial drugs) to all at risk populations. Second, the programme is geared up to manage morbidity and prevent disability among individuals affected by the disease (Ottesen 2000; WHO/GPELF 2021).

Transmission control

The approach to disease transmission control can either target the use of antifilarial drugs or vector control to break the transmission cycle.

Use of antifilarial drugs (chemotherapy)

Lymphatic filariasis elimination programme involves annual MDA of a single-dose treatment of a combination of two antifilarial drugs to the entire eligible population living in areas where the disease is endemic (defined as areas where the prevalence of microfilaraemia or antigenaemia is ≥ 1%) (WHO/GPELF, 2014). The purpose of the chemotherapy is to reduce circulating mf in the blood to a minimum threshold in the human population such that the vectors exhibiting 'facilitation' may not be able to ingest and enhance the development of mf and therefore transmission would be halted. This is achieved through the oral administration of single dose of two drug-regimens; 6 mg/kg of body weight diethylcarbamazine citrate (DEC) + 400 mg albendazole or 200 µg/kg of body weight ivermectin + 400 mg albendazole (Ottesen 2000; WHO, 2014). The treatment combination of ivermectin and albendazole is used in areas where onchocerciasis is co-endemic (Taylor, Hoerauf & Bockarie, 2010; WHO/GPELF, 2023). This combination produces sustained complete clearance of mf for 15 months (Edi *et al.*, 2019; Ismail *et al*. 1998).Though the use of DEC remains the main treatment drug in most endemic countries, it is not recommended in areas where onchocerciasis and loiasis are co-endemic due to the severe side effects in people infected with *Lao lao* (Bockarie *et al*., 2013; WHO, 2023). In those endemic communities, ivermectin and albendazole or one drug regimen of ivermectin alone is required for administration (WHO, 2000; WHO, 2023). DEC is very effective against microfilariae and adult worms. DEC lowers the mf levels in the peripheral blood even in a single annual dose and continues this effect even after one year (Jambulingam *et al*., 2016; Kazura *et al*., 1993). Though DEC kills the adult worms, it does not have direct action on the parasite, but it mediates through the immune system of the host (Maclean *et al*., 2019). Ivermectin directly acts on mf but has no action on adult worms (Reaves, 2018). Albendazole is an anti-helminthic that kills adult worms but has no action on mf (Abuelenain *et al*., 2022; Jayakody *et al*, 1993).

Kanamitie *et al*. (2017) hypothesized the impact of biannual treatment on the parasitological indicators of LF with ivermectin and albendazole, and observed that the strategy is very useful in reducing the prevalence of LF in areas of persistent transmission.

These antifilarial drugs are usually given by mass administration for 4-6 years, until adult filarial worms have reached the end of their reproductive lifespan. In endemic areas where MDA coverage is poor or where transmission is very severe, MDA may have to be longer in order to ensure interruption of transmission (WHO/GPELF, 2013).

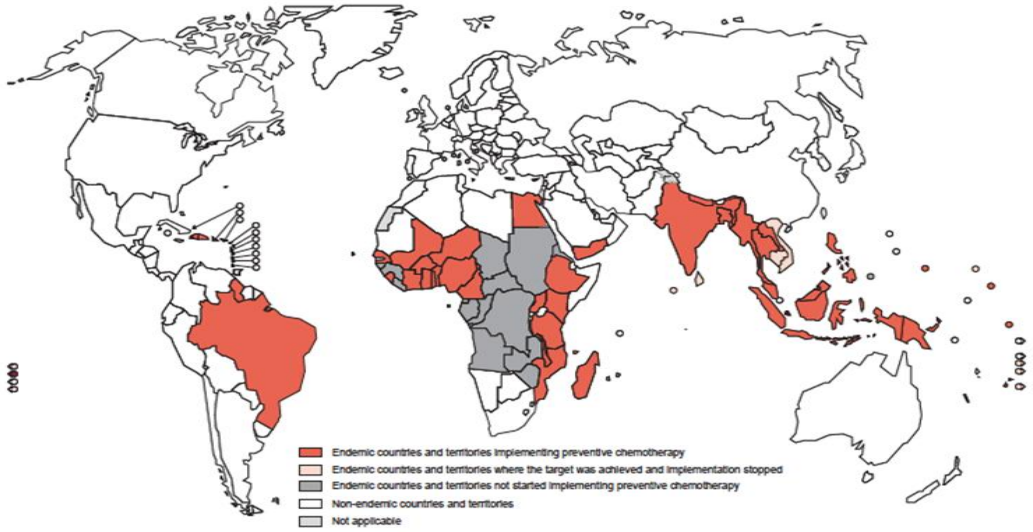

Figure 10: Distribution and status of mass drug administration for lymphatic filariasis worldwide, 2011.

Source**:** (WHO/GPELF, 2013).

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Vector control

The World Health Organization has recommended vector control to other strategies appropriate for the prevention, control, elimination and eradication of neglected tropical diseases (WHO/GPELF, 2012). WHO strategy for LF elimination was based primarily on chemotherapy until vector control was recommended in 2012. The effect of vector control on LF transmission is now being appreciated (Bockarie *et al*, 2009).

There are new improved techniques for enhancing the efficacy of vector control which include the use of insecticide-treated materials (ITMs), residual spraying and the use of floating layers of expanded polystyrene beads (EPBs) (Jabeen *et al.*, 2017).The use of ITMs for malaria control also serves as a control measure for LF transmission since both diseases are transmitted by the same vector (WHO, 2021). The use of EPBs creates a physical barrier to egg-laying adult *Culex* while suffocating larvae and pupae (Jabeen *et al.*, 2017; Sunish *et al*., 2002). These and other techniques have enabled the elimination of the disease in Japan, Taiwan, Solomon Islands, South Korea and some parts of China (De-Jian *et al.*, 2013; Tada, 2011, Webber, 1991).

Disease (Morbidity) management

To manage morbidity and decrease the disability caused by LF, the principal strategy focuses on decreasing secondary bacterial and fungal infection of individuals whose limbs and genitals have already been compromised by filarial infection (Ottesen, 2000; WHO/GPELF, 2014). Secondary infections caused by bacteria or fungi are the main pathogenic determinant of worsening the conditions of lymphoedema and elephantiasis (Ottesen, 2000; Chlebicki & Oh, 2014).

It has been recommended that the maintenance of personal hygiene by regular washing of elephantoid limbs with antibacterial soap and the application of antibiotic topical ointments, exercise, wound care and wearing comfortable shoes reduces the incidence of acute attacks and the advancement of elephantiasis (Dreyer *et al*., 2002; WHO/GPELF, 2021).The wearing of suitable foot wears, keeping the nails and toes clean, treating of wounds with medicated creams, elevating the limbs at night and regular physical exercise with low-intensity movement of the joints are the recognized methods proposed by the GPELF in managing lymphoedema and elephantiasis (WHO, 2013). Surgical operation for men with hydrocoele is also an element of morbidity control recommended by the GPELF (WHO/GPELF, 2021).

III. Conclusion

The launching of the GPELF for the last two decades has seen an avalanche of studies on lymphatic filariasis. LF is a neglected tropical disease caused by mosquito-borne filarial worms and prevalent in tropical and sub-tropical regions of Africa, Asia, Western Pacific and some parts of the Americas. Clinical features of LF infection can either be asymptomatic or symptomatic. Symptomatic individuals may show either acute or chronic disease manifestations. In the case of acute infection, victims suffer from symptoms such as enlarged painful lymph nodes, fever, warm and tender swelling and skin exfoliation while chronic lymphatic filariasis is characterised by chronic lymphoedema of the limbs and breasts, elephantiasis and hydrocele. For treating active LF infection, DEC plus albendazole or ivermectin plus albendazole is recommended. DEC is very effective in treating microfilariae (microfilaricidal) and adult worms, ivermectin is very efficacious against microfilariae while albendazole is very helpful in clearing the adult worms only. Opportunistic bacterial and fungal infections are the main pathogenic determinants in the progression of lymphoedema and therefore morbidity management is recommended as well. Morbidity management efforts within the GPELF have focused on basic hygiene, skin care, use of antibiotics, exercise and physiotherapy to reduce the incidence of ADLA and prevent progression of lymphoedema. Surgical repair is also targeted for hydrocele.

Despite the overwhelming research evidence regarding the disease, there is still much to be learnt. Some basic questions regarding possible development of drug resistance to ivermectin and albendazole have been asked. There is the need for additional research to establish the possible development of drug resistance to ivermectin and albendazole in LF endemic areas following several years of MDA.

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