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Lymphatic Filariasis: A systematic review on its morbidity and road to elimination

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Abstract

Lymphatic filariasis is caused by parasitic nematodes transmitted to humans by mosquito bites. It is endemic in tropical and subtropical countries where more than a billion people are at risk of being infected, and some 51 million people are clinically affected. Infective filarial larvae entering human through mosquito bites develops in to adult worm that damages the lymphatic system irreversibly. This lymphatic damage facilitates bacterial infection leading to lymphedema resulting in permanent disfigurement of limbs, and consequent increase in social burden and poverty. Diagnosis based on observing microfilaria in blood and tissue, or serology is widely used. Effective and affordable treatment and mass drug administration by World Health Organization (WHO) have dramatically reduced the incidence of filariasis in most of the endemic countries and many of which have eradicated this disease. This review highlights the epidemiology with emphasis on precision diagnosis, useful treatment and rehabilitation with a view to eliminating this Neglected Tropical Disease (NTD) worldwide by 2030 as planned by WHO.

Keywords: *Lymphatic filariasis, Lymphedema, Mass drug administration, Neglected Tropical Disease (NTD), Diethylcarbamazine*

1. Introduction

Lymphatic filariasis (LF) is a vector borne disease caused by majorly three nematodes within family Onchocercidae including *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*, which are transmitted by mosquitoes. According to World Health Organization (WHO), *W. bancrofti* is responsible for nearly 90% of LF infections worldwide. On the contrary, *B. malayi* is prevalent only in some parts of South and Southeast Asia, and *B. timori* is found only in Indonesia (World Health Organization, 2020). Disease is endemic in 72 countries with more than a billion people are at risk of infection and some 51 million people are clinically affected worldwide (World Health Organization, 2020).

LF is identified as a Neglected Tropical Disease (NTD) by WHO. Chronic symptoms of LF are disfiguring and burdensome, creating social liability and poverty. The epic body therefore set goals for its control and management by year 2030. Considering the Sustainable Development Goals (SDG) 2030 set by United Nations

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(UN), this review summarizes current status of filariasis worldwide, available diagnostic procedures-conventional and modern, recent advances in anti-filarial treatment including conventional practices and their pros and cons, and different control strategies with special emphasis on MDA citing the efforts taken by Bangladesh en route to its elimination.

2. Clinical manifestation

LF begins asymptomatically and develops to elephantiasis. Progression of asymptomatic LF to symptomatic LF is influenced by factors like host's immune response and cumulative acquisition of worms (Freedman *et al*., 1994). Although more than half of filarial infections are asymptomatic, lymphatic abnormalities do develop. A study in India revealed abnormalities in lower limb lymphatics in 63.5% of 52 asymptomatic children (Kar *et al*., 2017).

The most frequent acute clinical signs of LF are Acute Dermato-Lymphangio-Adenitis (ADLA), which are generally accompanied by fever, chills, headache, discomfort in affected region, and vomiting. In severe instances however, there may be toxemia, altered sensorium, and urine incontinence (Shenoy, 2008). ADLA attacks are linked to secondary infections by bacteria, such as group A streptococcus, which cause inflammations of lymph glands (lymphadenitis) and lymph channels (lymphangitis) as they gain access to lymphatics that have been affected and dysfunctional due to filarial infection, resulting in ADLA attacks and afterward lymphedema (Suma *et al*., 1997). Skin lesions established by fungal infection in interdigital spaces, injuries or infections in foot facilitate passage of such bacteria into afflicted limbs (Shenoy *et al*., 1995). Acute attacks become more frequent as disease progress and abet development of lymphedema (Shenoy *et al*., 1998).

Human might develop hypersensitivity response known as tropical pulmonary eosinophilia (TPE) to filarial antigens of *W. bancrofti* and *B. malayi* (WEBB *et al*., 1960) with low frequency (<0.5%) in endemic areas (*Lymphatic filariasis/: the disease and its control, fifth report of the WHO Expert Committee on Filariasis*, 1992). TPE is characterized by high eosinophilia levels (>3,000 / μm and may rise as high as 80,000 / μm), asthma-like symptoms and restrictive lung disease (Boggild *et al*., 2004). Antigenic components released by degenerating microfilariae trapped in pulmonary microcirculation elicit an immunological response and eosinophil degranulation, resulting in a severe eosinophilic inflammation affecting lower airways (Nutman *et al*., 1989; and Udwadia, 1975).

Hydrocele, a secondary disorder to LF, is a painless expansion of scrotum in adult males mostly caused by *W. bancrofti* (Debas *et al*., 2015; and Norões and Dreyer, 2010). Migration of adult worm and their persistence in scrotal lymphatic system leads to clogging of lymphatic system and hydrocele. Acute hydroceles are caused by death of filarial worms, which typically occurs after medical treatment. Inflammatory response to dissolving worms causes a temporary lymphatic obstruction (Addiss and Brady, 2007; and Noroes *et al*., 2003). *W. bancrofti* is the most commonly associated filarial parasite with a chronic clinical presentation caused by a dysfunctional hydrocele lymph system as adult worms migrate to scrotal lymphatics and form scrotal nodules (Debas *et al*., 2015; and Norões and Dreyer, 2010).

Lymphedema of limbs is a typical chronic symptom of LF that progresses to elephantiasis. In early stage, damage of limbs by lymphedema is reversible but skin thickens and folds in severe lymphedema, typically with hypertrichosis, black pigmentation, nodules, warty development, intertrigo in webs of toes, or chronic non-healing ulcers (Burri *et al*., 1996).

3. Epidemiology

LF was endemic in 72 countries with an estimated case number of about 198 million people worldwide before Global Programme to Eliminate Lymphatic Filariasis (GPELF) in 2000 was in effect (Figure 1). On the 20th year, although GPELF could not achieve its original goal, 48 out of 72 endemic countries were considered to require MDA in the year 2020. While 8 countries stopped the MDA program, 17 countries eliminated LF resulting in the reduction of the disease burden by 74%, to an estimated 51 million globally (Mathew *et al*., 2020; and *Weekly epidemiological record Relevé épidémiologique hebdomadaire*, 2021) (Figure 1). South East Asian region (SEAR) has the highest burden of LF, estimated more than 36 million cases, that accounts more than 70% of all global cases with around one million lymphedema patients and half a million of hydrocele patients in nine countries (Deshpande *et al*., 2020). According to report of WHO on LF in 2020, although three out of nine endemic countries of SEAR are declared free of LF and one has stopped MDA program, near 500 million people required MDA in SEAR which is 58% of global MDA requirement (World Health Organization, 2020).

African region has the second highest number of LF cases in the world, having more than 10 million cases with 148,115 active lymphedema and around 137,696 hydrocele patients (Deshpande *et al*., 2020). Currently, more than 339 million people of this region requires MDA. Notably, Equatorial Guinea and Gabon, 2 out of 36 endemic countries, however have not started any MDA program (*Weekly epidemiological record Relevé épidémiologique hebdomadaire*, 2021).

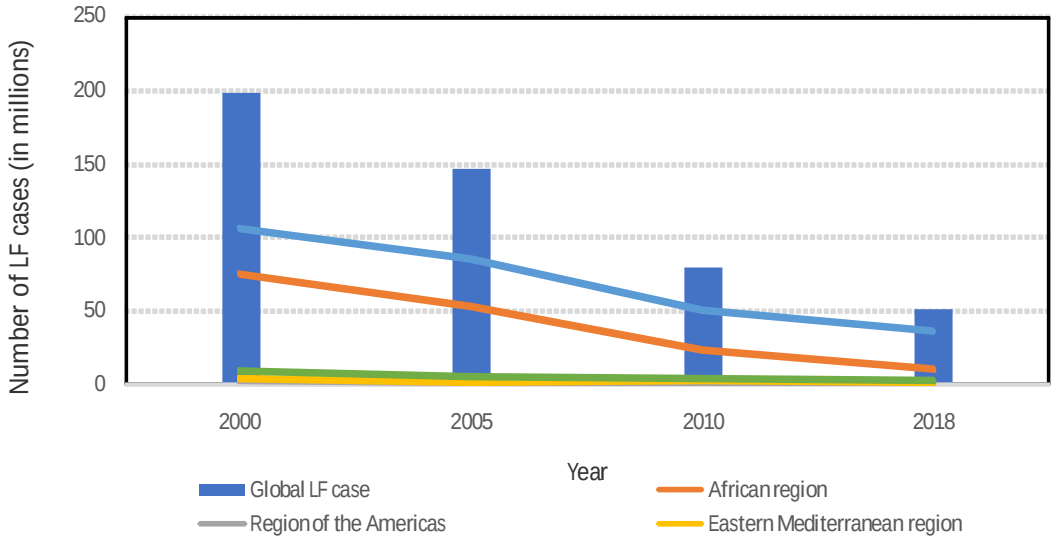

Figure 1: LF cases in WHO region

4. Diagnosis

Strategy of diagnosing and treating filarial infections varies depending on geographic location and availability to medical resources, and depends on a combination of clinical, radiographic, and laboratory diagnostic techniques ("CDC - Lymphatic Filariasis - Resources for Health Professionals," 2017; and Centers for Disease Control and Prevention, 2017a, 2017b). In endemic areas, objectives of early diagnosis are minimizing long-term illness consequences, monitoring, and treatment of infection. While diagnosing, it is important to establish patient's history of vector exposure because short periods of exposure, such as visiting an endemic area will not lead to high levels of microfilaria, as opposed to prolonged exposure, such as living in an endemic region. There are various techniques for diagnosing LF:

Microfilariae detection: Identification of microfilariae in peripheral blood on dyed thick and thin blood films has long been used to diagnose most filarial nematode infections. Considering microfilariae's periodicity, venous blood is collected when microfilaria levels are maximum, for example, a night time is preferred for *W. bancrofti* and *Brugia* spp, while day time is suitable for *Loa loa*, a filarial nematode that causes loasis (Mathison *et al*., 2019; and Nanduri and Kazura, 1989). Capillary blood from periphery exams, which contain more microfilaria from *W. bancrofti* and *Brugia spp* than venous blood can be performed through finger pricks in addition to venous blood samples (Global Health, 2017; and Nanduri and Kazura, 1989). Microfilariae detection was extensively utilized in endemic regions across the world until development of immunological tests. Major disadvantages of this method are its periodic nature and the fact that it only works till lymphedema develops (Mendoza *et al*., 2009).

Serologic Assays: An array of serological techniques targeting either antigen or antibodies is developed on field for diagnosis of LF including Enzyme Linked Immunosorbent Assay (ELISA), Luciferase Immuno Precipitation System (LIPS) and multiplex bead assay and Immune-Chromatographic Test (ICT) to avoid inconvenient night sampling.

Detection of antigen: First commercial *W. bancrofti* antigen test kit was based on monoclonal antibody Og4C3 (Trop-Ag *W. bancrofti* ELISA kit, JCU Tropical Biotechnology Pty Ltd, Queensland, Australia); it detects Circulatory Filarial Antigen (CFA) in ELISA (More and Copeman, 1990; and Weil *et al*., 1997). This test results negative for patients of *Onchocerca volvulus* and *B. malayi* (Harnett *et al*., 1999; and More and Copeman, 1990).

Although, this test can detect circulating antigen in 94–100% microfilaria carriers with high specificity, it is not used in regular diagnosis for its high cost (Harnett *et al*., 1999; and Nicolas, 1997). On the contrary, a rapid ICT based assay, filariasis card test that uses mAb AD12.1 takes only 5–15 min to complete without any specialized equipment and gives comparable results to ELISA at low cost, hence is popularly used for diagnosis (Weil *et al*., 1987, 1997). *B. malayi* has no antigen detection-based test used in routine diagnosis of LF (Harnett *et al*., 1999). Multiple ELISA-based detection tests were developed to detect antigen of *O. volvulus* from blood and urine with specificities varying from 86% to 98%; as they corroborate high incidence of false positive, these methods are not used in regular diagnosis (Cabrera *et al*., 1989; Mbacham *et al*., 1992; and Schlie-Guzmán and Rivas-Alcalá, 1989).

Antibody detection: Antibody detection assays for LF was not well explored until development of ELISA and Radioimmunoassay (RIA) as they compensated for major drawback of most filarial antigen detection tests, the cross reactivity (Hamilton, 1985). Initially studied recombinant antigens from *B. malayi, W. bancrofti* had specificity issues (Dissanayake *et al*., 1992; Harnett *et al*., 1999; and Theodore *et al*., 1993). An ELISA (CDC; Atlanta, GA) for IgG4 antibodies against recombinant Bm14 antigen has showed relatively high sensitivity (92%) and specificity (99%) in detection of *B. malayi* infection (Chandrashekar *et al*., 1994; and Won *et al*., 2018). Recently developed Wb123-based IgG and IgG4 LIPS assays can detect *W. bancrofti* infection with 100% sensitivity and 98% to 100% specificity (Kubofcik *et al*., 2012; and Won *et al*., 2018). Such detection assays can give accurate result in a relatively short time that makes them suitable for epidemiological surveys however, requirements of specialized equipment and trained personnel as well as high cost thwart its use in regular diagnosis.

X-ray and Ultrasound detection: Characteristic movement of living adult filarial worms of *W. bancrofti*, known as "filarial dance sign" in scrotal lymphatics is detected using ultrasonography having a 7.5 or 10 MHz probe(Arid, 2021; Panditi *et al*., 2016; and Singh *et al*., 2019). This method is suitable only for asymptomatic males with microfilaremia, and not useful once lymphedema develops (Freedman *et al*., 1994). *B. malayi* parasite can be detected in lymphatics of thigh, epitrochlear region, axilla, and popliteal fossa but not in scrotal lymphatics (Mendoza *et al*., 2009; and Shenoy *et al*., 2007). X-ray can identify calcified remains of the worms in the tissue, however its use is limited as it only detects dead adult worms (Mendoza *et al*., 2009).

Polymerase chain reaction (PCR) assay: PCR as well as Real Time PCR-based diagnosis of LF are available with primers mainly targeting multiple repeat sequences in chromosomal DNA (Dissanayake *et al*., 1991; Fischer *et al*., 1999; McCarthy *et al*., 1996; Rao *et al*., 2006; and Williams *et al*., 1988). These techniques can be applied for blood and urine, from where parasites can be detected and differentiated (Ximenes *et al*., 2014). A very sensitive and specific PCR detection method, based on a highly repeated DNA sequence of *W. bancrofti* (SspI repeat) was developed in 1996 by Zhong *et al* (Nuchprayoon, 2009; and Zhong *et al*., 1996). However, it showed less sensitivity when compared to Og4C3 antigen-based ELISA assay in an epidemiological study in Thailand (Nuchprayoon *et al*., 2001). A semi-nested PCR that can detect as little as 0.001 fg of *W. bancrofti* DNA in blood sample produced 100% positive results on serum and urine samples collected from participants with positive in ICT card test (Kanjanavas *et al*., 2005; and Ximenes *et al*., 2014). Hha1 repeat based PCR assay can detect *B. malayi* infection with high sensitivity and specificity (Williams *et al*., 1988). Real Time PCR assays are available for both brugian and bancroftian filariasis (Nuchprayoon, 2009). Nuchprayoon *et al* developed an assay to differentiate filarial parasite at species level for *W. bancrofti, B. malayi, B. pahangi, D. immitis,* and *D. repens* making useful to diagnose and differentiate parasites in endemic areas with multiple causative agents and this assay consists of a PCR followed by RFLP analysis based on first internal transcribed spacer (ITS1) along with flanking 18S and 5.8S rDNA (Nuchprayoon *et al*., 2006; and Nuchprayoon *et al*., 2005).

5. Treatment

Lymphatic filariasis patients may present an asymptomatic infection. Acute and chronic manifestations and ADLA lead to elephantiasis which is incurable disfigurement of body parts specially limbs and genitals. Proper treatment of LF is necessary to prevent such complications and further spread of this illness. WHO recommended drugs include Diethylcarbamazine (DEC), Ivermectin, and Albendazole. These can be used for MDA programs too.

Diethylcarbamazine (DEC): DEC is effective in controlling all kinds of filarial parasites including *L. loa* and onchocerciasis (Mendoza *et al*., 2009; and Tisch *et al*., 2005). The recommended dose is 6 mg / kg of body weight (Global Health, 2017; and Kazura *et al*., 1993) which is effective for lowering microfilariae levels in blood, and

the impact lasts for a year. MDA of DEC has successfully reduced not only microfilarial infections, but also its prevalence more than 50% in South India (Yuvaraj *et al*., 2008). Because of immune response to dying microfilariae, or lipopolysaccharide released from endosymbiotic *Wolbachia* spp, DEC usage may induce minor and self-limiting side effects such as fever, headache, myalgia, sore throat, or cough (Mendoza *et al*., 2009). These reactions are more severe with onchocerciasis and loiasis which might require antipyretic or anti-inflammatory treatment.

Ivermectin (IVM): Ivermectin, a synthetic macrocyclic lactone molecule is used as a broad spectrum antiparasitic drug to treat a variety of parasitic diseases such as LF, onchocerciasis and loaiasis, as well as scabies, pediculosis, demodecidosis, and strongyloidiasis (Mendoza *et al*., 2009). A single dosage of IVM at 150–400 mg / kg body weight quickly reduces the amount of microfilaria in blood, for example, 90% of bancroftian filariasis (Cao *et al*., 1997; and Tisch *et al*., 2005). However, efficacy is temporary because IVM only kills microfilaria not adult worms, hence repeated course is necessary (Mendoza *et al*., 2009; and Tisch *et al*., 2005). Although in Cameroon, encephalopathy and neurologic decline were reported in only 1.83% of 50,929 patients after IVM treatment, in most cases side effects are mild and temporary (Mendoza *et al*., 2009; and Twum-Danso, 2003).

Albendazole (ALB): Albendazole is a broad-spectrum anthelmintic drug that only kills adult filarial worms. ALB is prescribed at doses of 400 mg twice daily for two weeks resulting in gradual decrease in microfilarial levels over the next six months (Gyapong *et al*., 2005; and Tisch *et al*., 2005).

Anti-wolbachial therapy: *Wolbachia* bacteria and filarial parasite have a symbiotic relationship. Use of antibiotics such as doxycycline against *Wolbachia* is a new strategy found effective against both bancroftian and brugian filariasis. Doses of doxycycline could be 200 mg / day in a 4-to-8-week course. A 4-week course in Ghana demonstrated 80% reduction of microfilariae of bancroftian filariasis patients (Debrah *et al*., 2007). A randomized trial of doxycycline treatment for *B. malayi*-mediated LF in Indonesia yielded 98% reduction of *Wolbachia* loads after four months, and a microfilaremia reduction up to 87% after one year (Supali *et al*., 2008).

Combination therapy: Drug combinations are increasingly being used for treating LF in endemic areas. A single dosage of DEC in conjunction with either ALB or IVM was found more effective than DEC alone. In a randomized community-based trial in Papua New Guinea, reduction up to 91.1% in microfilarial intensity was evidenced in a combination therapy than with DEC alone that reduced 57.5% cases (Bockarie et al., 1998). Furthermore, yearly transmission potential fell from 75.7 to 98.8% in areas receiving combination treatment, compared to 75.6 to 79.4% in those receiving DEC alone (Bockarie *et al*., 1998). A single ALB dose plus IVM has the most sustained effect on microfilaremia (Ismail *et al*., 1998). This combination effectively reduced microfilarial prevalence to 87·8% of the baseline at 7–12 months post-treatment (Beach *et al*., 1999). Combination of DEC and ALB appears to have the highest macrofilaricidal impact (Ismail *et al*., 1998). Doxycycline, in combination with DEC and ALB has also been proven effective in decreasing microfilaremia (Supali *et al*., 2008; and Turner *et al*., 2006).

Management and surgical treatment of lymphedema: Lymphedema is an irreversible condition for which there is no known treatment. In the early stages of lymphedema characterized by occasional swelling and acute attacks of lymphangitis, treatment with anti-filarial drugs was shown just prophylactic for patients (Dreyer *et al*., 2001). As skin-folding develops, patient requires additional treatment to prevent ADLAs which was mostly related to secondary bacterial infection (Suma *et al*., 1997). Proper hygiene of the infected areas is important to prevent ADLAs, that can be accomplished by washing the affected area with soap and water twice a day; keeping the area dry; clipping nails; and trying to prevent or promptly treat any local injuries or infections (Ciocon *et al*., 1995; Dreyer *et al*., 2001; and Palumbo, 2008). Resting legs at elevated position, use of an elastocrepe bandage, or tailor-made stockings, exercise, massage of affected limb and heat treatment can provide relief and may prevent further swelling progression (Chang *et al*., 1989; Dreyer *et al*., 2001; and Palumbo, 2008).

Surgery for lymphoedema of limb can be classified into two main types: bypass procedures and debulking operations (Tiwari *et al*., 2002). Although men showed less improvement than women after debulking operations, overall, bypass procedures have showed promising outcome (Miller *et al*., 1998; and Tiwari *et al*., 2003).

6. MDA en route to LF Elimination

LF is an NTD that affects a large number of people in impoverished community. Chronic symptoms of LF are disfiguring and burdensome, accounting for an estimated 5.25 million disability-adjusted life-years (DALYs)

and at least US$ 5.7 bn in yearly economic loss (Mathew *et al*., 2020). International Task Force for Disease Eradication (ITFDE) listed LF as one of six infectious illnesses designated as "eradicable" or "possibly eradicable". GPELF was formed with two goals in mind: limit spread of LF by MDA and relieve suffering of afflicted patients through morbidity management and disability prevention.

On the 20th year, although GPELF could not achieve the set goals, it could able to eliminate LF in 17 countries, stop MDA program in eight countries while 48 countries continued its operation out of 73 endemic countries by the year 2020 with 86.3% of implementation units (IU) achieving effective coverage globally (*Weekly epidemiological record Relevé épidémiologique hebdomadaire*, 2021). Since 2000, more than 8.6 billion treatments were administered to over 925 million individuals worldwide (*Weekly epidemiological record Relevé épidémiologique hebdomadaire*, 2021) resulting in the reduction of incidence by 74%, to an estimated 51 million (Mathew *et al*., 2020). 649.1 million persons were out of MDA, representing a 43% reduction from the total population living in IUs that were considered endemic, indicating continued progress in effect towards achieving SDG goal 3.3 (World Health Organization, 2020). Population receiving MDA in 2020 was 863.2 million, with 358.8 million persons treated (41.6%), a 34% decrease from 2019 owing to COVID-19 pandemic (*Weekly epidemiological record Relevé épidémiologique hebdomadaire*, 2021; and World Health Organization, 2020).

South East Asian region (SEAR) has the largest LF burden, with just India accounting for more than half of the world LF burden in 2020 (Figure 2) (Kapa and Mohamed, 2021; and *Weekly epidemiological record Relevé épidémiologique hebdomadaire*, 2021). SEAR nations formed National Programs to Eliminate LF (NPELF), with 2020 as target date. By 2020, 91.8% of IUs achieved effective coverage and three countries including Maldives, Thailand and Sri Lanka were declared free of LF and Bangladesh been under post MDA surveillance (Figure 2).

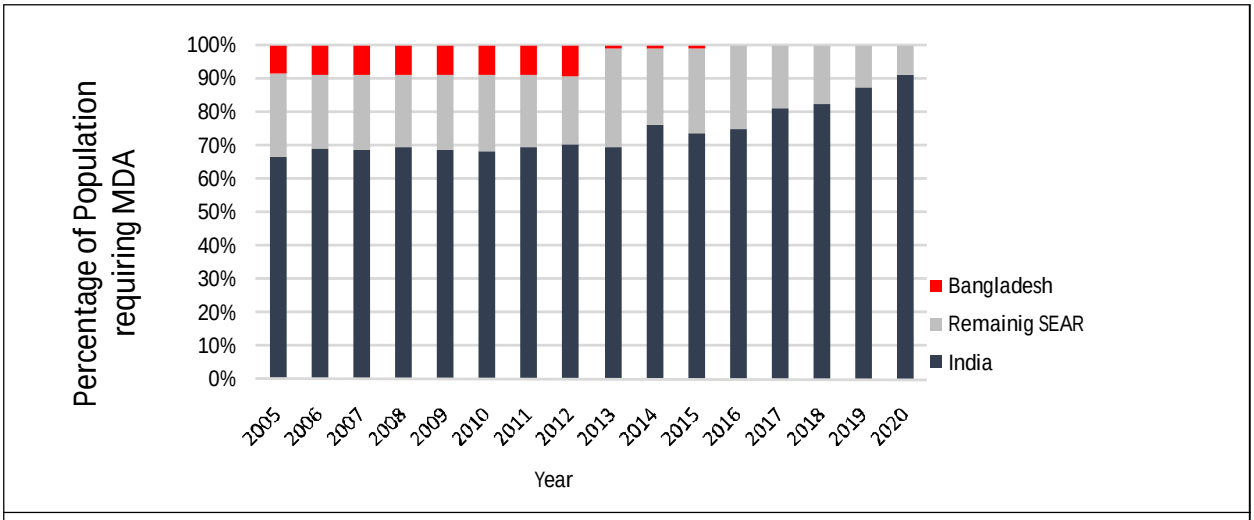

Figure 2: Comparative analysis of Population requiring MDA in South East Asian region, India and Bangladesh

Bangladesh strategy for eliminating LF: Bangladesh was formerly one of the countries having the largest number of LF victims. Despite being a low- to middle-income country, Bangladesh shines out in SEAR due to the best practices implemented by the NPELF. Filariasis Elimination Program was launched on 9th November, 2001 with implementation of the first MDA (Khanum *et al*., 2013). Each of 19 endemic districts was designated as an IU for MDA targeting around 35 million people. By 2010, LF program effectively gave at least three rounds of MDA to each of the 19 endemic districts, with 12 districts getting more than six rounds of MDA, totaling more than 150 million doses to the target population (Hafiz *et al*., 2015; and Shamsuzzaman *et al*., 2017). Transmission Assessment Surveys (TAS) 1 was implemented in five districts in 2011, and by 2016 all endemic districts were under TAS1, and MDA program in all IUs was terminated following satisfactory achievement (Shamsuzzaman et al., 2017; and *Weekly epidemiological record Relevé épidémiologique hebdomadaire*, 2021). Second round of TAS (TAS2) was implemented from 2013 to 2018 (Kapa and Mohamed, 2021). Its third round (TAS3), scheduled to be completed by 2020 was interrupted due to COVID-19 pandemic, however survey duration was extended to 2021 (*Weekly epidemiological record Relevé épidémiologique hebdomadaire*, 2021).

7. Conclusion

Despite the fact that, GPELF's 2020 aim was not met, the globe has made remarkable progress toward LF eradication and has already lowered disease burden dramatically. Both MDA and TAS were halted due to Covid-19 pandemic that specifically postponed 167 surveys in SEAR alone until 2021. Despite a catastrophic global pandemic, progress was achieved throughout GPELF in 2020, and in order to meet NTD road plan objectives for 2030, WHO is pushing countries to continue MDA and TAS utilizing enhanced MDA delivery systems, as well as extend access to necessary treatment for lymphedema patients.

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