

Review Article

Elimination of Lymphatic Filariasis: A Neglected Disease of India

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Abstract: In India, human lymphatic filariasis is the most common vector borne disease after malaria. Lymphatic Filariasis caused by nematode worms *Wuchereria bancrofti* and *Brugia malayi* is a major health problem in India, which afflict mostly poor people. The disease leads to disfiguring pathological conditions, severe social stigma, psychological problems and huge economic losses on affected individuals and communities. Filariasis is a major public health problem in India and in spite of existence of the National Filaria Control Programme since 1955, currently there may be up to 31 million microfilaraemics, 23 million cases of symptomatic filariasis, and about 473 million individuals potentially at risk of infection. Over the last 10 years advances have led to new diagnostic / treatment tools and control strategies for filariasis. With the advent of new and easy to implement control strategies, Lymphatic filariasis elimination programs have gained much momentum in the past decade but there are still many challenges that stand in the way of achieving the goal of Lymphatic filariasis free India. A special emphasis has been given on the general hygiene and environmental management of mosquito vectors under the Swachh Bharat Mission (Clean India Movement) and also to provide special incentive under the Ayushman Bharat to make the programme effective and successful.

Keywords: Lymphatic filariasis, *Wuchereria bancrofti*, *Brugia malayi*.

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INTRODUCTION

Filariasis has been a major public health problem in India. The disease was recorded in India as early as 6th century B.C. by the famous Indian physician, Susruta in his book 'Susruta Samhita' [1]. The neglected tropical diseases are a group of 13 major disabling conditions that predominantly affect world's poorest people in Africa, Asia and the Americas. Lymphatic filariasis, caused by filarial nematodes *W. bancrofti* and *B. malayi* and transmitted by mosquitoes, is one of the neglected tropical diseases which is prevalent in 81 tropical and subtropical countries. It is estimated that approximately 1.3 billion world population is at risk of filarial infection. About 129 million people are infected with Lymphatic filariasis and among them 40 million are seriously incapacitated and disfigured. According to World Health Organisation (WHO), Lymphatic filariasis is the second most cause of long term disability after mental illness. One third of people infected with Lymphatic filariasis live in India, one third live in Africa and most of the remainder lives in the Americas, the Pacific Islands and South-East Asia. The burden of Lymphatic filariasis in humans and its impact on socioeconomic aspects has led to the identification of this disease as one of the

priority areas of WHO. In the year 1997, the World Health Assembly at its 50th session passed a resolution (WHA 50.29) to eliminate Lymphatic filariasis globally as a public health problem by the year 2020 [2]. The two main objectives of Global Program to Eliminate Lymphatic filariasis (GPELF) are (1) interruption of transmission of parasite through repeated annual mass drug administration (MDA), using a combination of ivermectin plus albendazole where oncocerciasis is co-endemic with Lymphatic filariasis and diethylcarbamazine plus albendazole where Lymphatic filariasis alone is endemic, to all the people living in endemic area and (2) prevention of Lymphatic filariasis related disability through morbidity management program. GPELF is benefitted by generous donation of drugs Albendazole by GlaxoSmithKline and Ivermectin by Merck and Co., Inc. as long as they are required to eliminate Lymphatic filariasis.

Current Status of Lymphatic Filariasis in India

Lymphatic filariasis is a major health problem in India and is endemic in 250 districts of 20 states/union territories [3]. In India, *W. bancrofti* transmitted by the ubiquitous vector, *Culex quinquefasciatus*, has been the most predominant infection contributing to 99.4% (bancroftian filariasis) of filarial cases. The infection is

prevalent in both urban and rural areas while rest of the infections are caused by *B. malayi* (*brugian filariasis*), which is transmitted by *Mansonia* mosquitoes. Brugian filariasis is mainly restricted to rural areas of Uttar Pradesh, Bihar, Andhra Pradesh, Odhisa, Tamil Nadu, Kerala and West Bengal. The incidence of Lymphatic filariasis in India is very high, currently over 45.5 million people infected with Lymphatic filariasis lives in India and about 553 million are exposed to the risk of infection, of these about 146 million live in urban areas and about 407 million in rural areas. The state of Bihar has highest endemicity of over 17% followed by Kerala (15.7%) and Uttar Pradesh (14.6%). Andhra Pradesh and Tamil Nadu have about 10% endemicity. Goa showed the lowest endemicity of less than 1% followed by Lakshadweep (1.8%), Madhya Pradesh (above 3%) and Assam (about 5%). The seven states namely Andhra Pradesh, Bihar, Kerala, Odisha, Uttar Pradesh, Utrakhand and West Bengal contribute 86% of microfilaria carriers and 97% of disease cases in the country [4].

Symptoms and Socio Economic Burden

Symptoms of Lymphatic filariasis can be divided into three basic disease stages namely (a) asymptomatic (b) acute and (c) chronic. Asymptomatic microfilaraemia is often regarded as a non-disease because the individuals concerned have no idea that their blood contains large numbers of microfilariae and this situation may persist for decades without any progression to clinical disease. Most of the signs and symptoms of filariasis are caused as a consequence of the adult worms living in the lymph system. Tissue damage caused by the worms restricts the normal flow of lymph fluid resulting in swelling, scarring, and infections. The most common manifestation of acute filariasis is adeno-lymphadenitis (ADL), which is characterized by intense lymphangitis, lymphadenitis and reddening of the overlying skin. The worst symptoms of the chronic disease generally appear in adults, include persistent lymphoedema of arms and legs, hydrocoel, elephantiasis of genital organs, chyluria (milky urine) and tropical pulmonary eosinophilia. In addition, Lymphatic filariasis also causes internal damage to the kidneys [3].

Chronic filarial infections have serious social, psychological and economic effects. The massive swelling of the limbs and disfigurement due to lymphoedema interferes with the day-to-day activities

of the sufferers and reduces their productivity resulting in low income and long term poverty. The problem becomes more intense, if the patient is major income earner of the family. In rural areas, where agriculture is the primary source of livelihood, incidence of Lymphatic filariasis affects the agricultural activity of farmers leading to poor harvest, loss of livelihood and food insecurity. It is estimated that the total disability adjusted life years lost in India due to this disease are around 2.06 million, resulting in an annual wage loss of \$ 1 billion [5]. Lymphatic filariasis also exerts a profound social burden on patients as the chronic manifestations of this disease such as lymphoedema of the limbs, breasts and external genitalia cause social stigmatization of the patients and prevent them from playing their role in society.

Life Cycle and Pathogenesis

Human filarial nematode worms have a complicated life cycle, which requires both a vertebrate host and a blood sucking arthropod vector (Figure-1). Human is the definitive host and arthropod vector is the intermediate host. There are no intervening free living stages. Microfilariae are picked up by arthropod vector during their feeding on the infected person. Inside the intermediate host these microfilariae lose their sheath and migrate rapidly to the thoracic muscles where they develop into first stage larvae and subsequently into third stage larvae and migrate through the haemocoel to the mosquito's proboscis. These third stage larvae require human host for their further development. The third stage larvae enter into the human host during a blood meal by an infected mosquito and penetrate into the blood capillaries. Inside human host third stage larvae molt to fourth stage larvae in approximately 4-6 weeks. Within nine months they molt again to the sexually mature juvenile adult stage. The adult filarial parasites reside in the lymphatics, where they can live upto 15 year. The worms have and estimated active reproductive span of 4-6 years. The female worms measures 80 to 100 mm in length and 0.24 to 0.30 mm in diameter, while the shorter males measure about 40 mm by 0.1 mm. The mature adult male and female parasite mate and produce millions of very small immature larvae known as mf that find their way into the blood circulation. These mf measures 244 to 296 μ m by 7.5 to 10 μ m, which are sheathed and have nocturnal periodicity. These are essentially pre-larval stages, which will not undergo further development until taken into the haemocoel of the intermediate host.

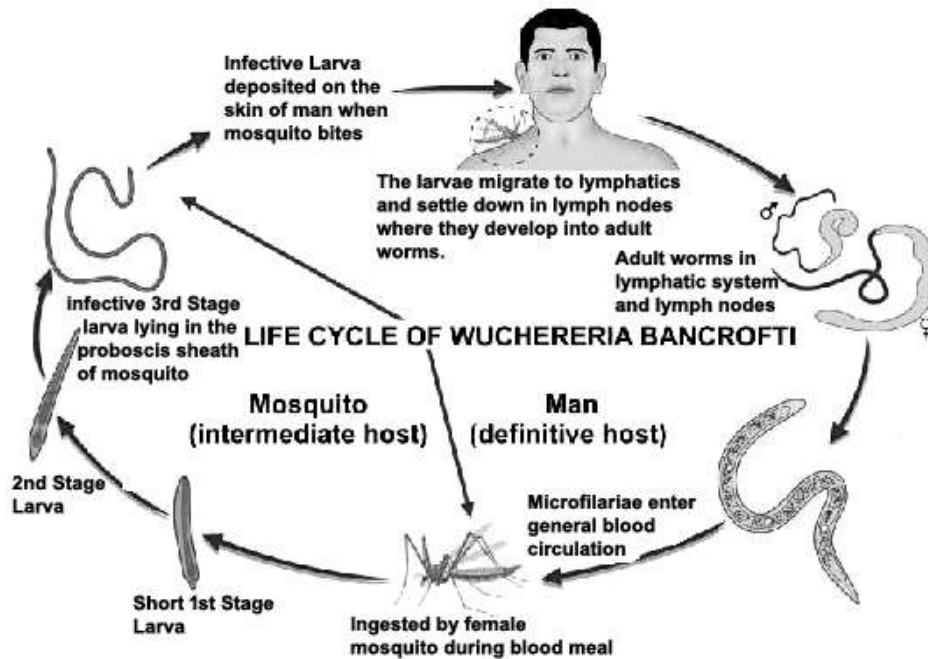


Fig-1: Life Cycle of Filarial Parasite

Present Scenario of Lymphatic Filariasis Elimination in India

Considering the impact of Lymphatic filariasis on the affected population, National Filaria Control Program (NFCP) was launched in India in 1955 with the objective of delimiting the problem and to undertake control measures in endemic areas. Initially NFCP activities were mainly confined to urban areas, which were implemented through 206 control units and 199 filaria clinics. However, the program was extended to rural areas in 1996 in 13 districts of 7 endemic states through annual mass drug administration (MDA) with single dose of diethylcarbamazine, covering 41 million populations. The program was scaled up to cover a population of 77 million in 2002 with the administration of diethylcarbamazine alone in 19 districts and combination of diethylcarbamazine and albendazole in 11 districts [6]. In 2002, the National Health Policy has set the goal of elimination of Lymphatic filariasis as a public health problem in India by 2015. For achieving this goal, mass drug administration with annual single dose of diethylcarbamazine (6 mg/kg body weight) for five or more years to all the population vulnerable to filariasis, excluding pregnant women, children below 2 years of age and seriously ill persons, was launched in 2004 targeting about 468 million populations from 202 districts. It was also proposed to observe National Filaria Day every year from 2004 in all endemic districts. The coverage of mass drug administration has been reported to be 72.6%, 79.84% and 83.67% respectively in the year 2004, 2005 and 2006 respectively. From 2007, the program was scaled up to cover the entire population of 590 million in all 250 endemic districts. Administration of ALB (400 mg alongwith diethylcarbamazine (DEC) was included in mass drug administration from 2008 onwards. Besides

MDA another pillar for elimination of Lymphatic filariasis is morbidity management, which includes home based management of lymphoedema cases by simple washing and surgical intervention for hydrocele cases.

Major Problems and Challenges for Disease Control

With the advent of new and easy to implement control strategies, NFCP has gained much momentum in the past decade but there are still many challenges that stand in the way of achieving the goal of Lymphatic filariasis free India. It is evident from number of studies that some MDAs work better and more efficiently than the others [7, 8]. The major challenge of MDA is that it requires very high treatment coverage and compliance (>85%) sustained for consecutive five years, which is believed to be average reproductive life of adult worms, for achieving transmission interruption of the disease in endemic areas [9]. However many MDAs have struggled to attain this required level of coverage was found below the optimum levels in spite of several rounds of MDAs with social mobilization in Tamil Nadu [10] and Andhra Pradesh states [11]. The study conducted in Bihar district of Karnataka showed that only 62.3% coverage and 60.4% compliance could be achieved with MDA, which was much below the expected national standard [12]. The other study in Paschim Midnapur district of West Bengal over a two year period from 2009 to 2010 also indicated low coverage (84.1% in 2009 and 78.5% in 2010) and compliance (70.5% in 2009 and 66.9% in 2010) [13]. Similar findings of low compliance ranging from 32.7% to 76.2% were also observed by other studies across India [14, 15]. Some of the main reasons, which were cited for insufficient coverage and compliance include: lack of knowledge

about the disease and the program among the endemic population, inconsistent drug distribution, inadequate training of health workers and their reluctance in drug distribution, lack of supervised dosing, fear of side effects of drug, incapability of health personnel to convince people, who feel healthy and have no sign of disease, for drug consumption and absence of recipients of drugs at the time of MDA [16, 17]. In addition, MDAs have also been affected by inadequate supply of drug, insufficient time for MDA implementation and storage of health workers, and repeated postponement of MDA. It has been seen that inadequate compliance is a major impediment to elimination campaign as the non-compliant persons remain microfilaremic and act as a reservoir of infection and plays very important role in resurgence of disease [18-20]. The other challenge to the elimination program is the dearth of anti-filarial drugs, currently DEC alone or combination of albendazole (ALB) and DEC is distributed in MDA programs. These drugs are principally microfilaricidal and are not able to kill adult worms and provide only partial benefit to the patient. Moreover, there prolong use for number of years to prevent the build-up of mf from the surviving adult worm has raised the concern about emergence of resistance [20, 2].

Future Perspective

The success of elimination program depends on sustained and sufficient compliance with MDA rather than MDA coverage. Most of the studies in India indicated that MDA was restricted to tablet distribution only and the major issues of implementation in compliance, in health education, social mobilization, morbidity management and the logistics were not been given due attention. Some imperative steps are therefore urgently needed to improve strategy of MDA implementation through cooperation and coordination of government officials, local health workers, non-governmental organizations and community volunteers. The reluctance of health personnel or drug distributors (DDs) to strictly adhere to the national guidelines for program implementation, which has been cited as the main cause of low compliance and coverage in most of the studies, warrants some strategic changes in drug delivery mechanism so that drug can be best delivered to the mouth of endemic population. Further, current MDA programs should be supplemented with educational intervention and motivational activities at national level as well as at community level so that maximum number of persons can be informed about cause, transmission and elimination strategy for Lymphatic filariasis. As DDs interact directly with the population living in endemic areas therefore emphasis should be given on recruitment of well trained, motivated and enthusiastic DDs, who can convince the people for drug consumption. For training of health workers educational camps must be organized at national level with the involvement of educational institutes. More importantly, drug consumption should be monitored directly by the health workers as

insufficient compliance leads to recurrence of microfilaraemia in the affected individuals and also place the community under risk of filarial infections, which in turn necessitates more rounds of MDA and additional fund for the implementation of program. Vector control has played important role in filariasis control in some programs but it has been given very low priority in India. Therefore, in situation where transmission interruption is not possible through MDA alone the role of integrated vector management as a potential supplementary strategy needs to be explored. Further, adequate monitoring and surveillance is also required to determine the new foci in non-endemic areas as these can serve as sites for fresh infection. Though, many research studies discussed here have failed to implement MDAs successfully but they provide some important clues for the development of more effective drug delivery strategies [2, 21].

Furthermore, drugs for Lymphatic filariasis are taken for years therefore in consideration of threat of emergence of drug resistance also to overcome the well-known deficiencies of the existing drugs, policies should be made to create more funds for research and development of new, safe and more effective anti-filarial drugs and vaccines. Despite huge detrimental effects on affected individuals and communities, Lymphatic filariasis is given very low priority and in fact the disease has escaped the attention of planners and policy makers because of low mortality rate and its association with poverty. The NTDs including Lymphatic filariasis occurs mostly among people living on less than \$2 per day. The big pharmaceutical companies do not take initiative to embark on research and development activities for Lymphatic filariasis because of low profit as the people who need new vaccine and treatments the most can never afford to pay for it. The analysis of the outcomes of pharmaceutical research and development over the past 25 years revealed that out of 13,000 chemical entities marketed between 1975 and 1999, only thirteen were for (Neglected Tropical Diseases)NTDs, of these only three combinations of Ivermectin (IVM) plus ALB; IVM plus doxycycline and ALB plus DEC were registered for LF. With an impressive growth of healthcare industry in the past decade, India has emerged as an innovative developing country which has the capacity of producing its own drugs, vaccines and diagnostics. Therefore, India urgently needs new strategy to stimulate drug research and development program for NTDs through the establishment of public-private partnership of leading government institutions and biopharmaceutical companies [22, 21, 23].

The target set by GPELF in 2000 to eliminate Lymphatic filariasis as a public health problem globally by 2020 will not be achieved by then. Despite setbacks due to COVID-19, WHO will accelerate work to achieve this target by 2030. New global estimates suggest a 74% reduction in the number of infected

people since the start of GPELF. The new, ambitious targets for 2030 are that 80% of endemic countries have met the criteria for validation of elimination as a public health problem, with the remaining 20% under post-treatment surveillance, meaning that MDA will no longer be required.

GPELF aims to reduce the prevalence of infection below target thresholds and to alleviate the suffering of people affected by lymphoedema and hydrocele, the chronic manifestations of the disease. The recommended essential package of care for managing lymphoedema and hydrocele should be available in 100% of districts where people are living with these manifestations. This goal is aligned with the aims of universal health coverage to leave no one behind by 2030. Reporting of Lymphatic filariasis morbidity improved again in 2019, showing that countries are addressing this aim and planning services for people affected by the disease.

In 2019, 538.1 million people were treated for lymphatic filariasis (LF) in 38 countries that implemented mass drug administration (MDA) of populations at risk of the disease, as recommended by the World Health Organization (WHO). Seventeen countries achieved the criteria for elimination of LF as a public health problem; Kiribati, Malawi and Yemen were the latest to be acknowledged by WHO. The Global Programme to Eliminate Lymphatic Filariasis (GPELF) has delivered over 8.2 billion cumulative treatments to more than 923 million people since 2000. The treatments target the parasites in the blood of infected people and prevent the risk of transmission in the community. Infections have been brought to such low levels in some areas that 649.1 million people no longer require MDA for this debilitating parasitic disease.

Risks to Success

In 2017, WHO published a new guideline on alternative MDA regimens to eliminate LF and recommended a combined regimen of ivermectin, diethylcarbamazine citrate and albendazole (IDA) to accelerate the impact of MDA on transmission of the parasites. In 2019, IDA was used to treat 45.2 million people in 11 countries. In India, IDA was extended from four to 16 districts to treat more than 41 million people. Currently, only six of 17 countries validated as having eliminated Lymphatic filariasis as a public health problem report surveillance activities. Without robust post-validation activities, transmission can remain undetected and the number of infections can resurge to previous levels. Countries are willing to conduct surveillance and remain vigilant, but programmes require clear guidance and resources. Additional research and better diagnostics are necessary to design more detailed, standardized methods for surveillance.

CONCLUSION

In spite of high morbidity, Lymphatic filariasis remains neglected and understudied as compared to other infectious diseases such as tuberculosis, HIV/AIDS and malaria. Because of the extent of disease problem and its negative impact on affected individuals, some concrete steps should be initiated soon to remedy this gruesome disease. These include to:

1. Motivate the community to participate in the MDA program by raising general awareness about the cause and transmittance of the disease
2. Educate the communities about cleanliness as inadequate sanitation creates numerous breeding sites for the mosquitoes that transmit the disease
3. Earmark the funds for research and development of new, safe and affordable treatment regimens, most important macrofilaricidal drugs
4. Plan and implement MDA program systematically and efficiently to the entire country within a timeframe without any inconsistency so that required level of coverage and compliance could be achieved
5. Generate resources importantly consistency funding for proper functioning of MDAs.

In addition, the elimination programs must focus on morbidity management and disability prevention, so that the diseased persons could be able to live self-dependent and respectful life. Furthermore, tremendous efforts are also required by policy makers, program manager, governmental and non-governmental organizations, health workers, community volunteer and individuals residing in endemic areas for the accomplishment of MDAs leading to the success of NECP. Though the filarial elimination program in India have geared up a lot during the past decade to make its presence felt worldwide, the Indian government needs to act swiftly in a time-bound manner if it has to achieve the target of eliminating Lymphatic filariasis in the country. India is on a very strong ground to achieve lymphatic elimination. Several efforts are now in place. The total disability adjusted life years (DALYs) lost due to Lymphatic filariasis is around 2.06 million, resulting in an annual wage loss of US \$2.06 million, resulting in an annual wage loss of US \$811 million. A special emphasis has been given on the general hygiene and environmental management of mosquito vectors under the Swachh Bharat Mission (Clean India Movement) and also to provide special incentive under the Ayushman Bharat to make the programme effective and successful.

Conflict of Interest: The authors declare no conflict of interest.

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