Chapter

A New Outlook in Lymphatic Filariasis Elimination in India

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Abstract

In India, human lymphatic filariasis (LF) is the most common vector-borne disease after malaria. It is a roundworm nematode parasitic helminthiases group of diseases under Filarioidea type of infection. The parasites are found in the lymphatic system, damage the system leading to deformities of body organs. Of the eight human filarial parasites, *Wuchereria bancrofti*, *Brugia malayi* and *B. timori* are involved with the lymphatic system. Globally *W. bancrofti* is the most predominant species sharing 90% of the burden. In India, *W. bancrofti* and *B. malayi* are present. The revised control strategy was aimed at a single-dose mass drug administration (MDA) and home-based morbidity management. The Elimination of LF (ELF) was initiated in 2004 in 202 districts which were expanded later in 256 districts after a pilot study in LF endemic districts initiated in 1997. The initial start of ELF campaign was with a single drug, i.e. diethylcarbamazine (DEC), but later in 2007, a combination of two drugs DEC and albendazole (ALB) were given through MDA. Now a third drug ivermectin (IVM) has been added to accelerate the elimination process by 2020 which is the global goal of elimination under Global Programme to Eliminate Lymphatic Filariasis (GPELF).

Keywords: lymphatic filariasis, elimination, *Wuchereria bancrofti*, *Brugia malayi*, diethylcarbamazine, albendazole, ivermectin, DEC-medicated salt, transmission assessment survey, xenomonitoring

1. Introduction

There are eight parasites responsible for filarial infections. Three parasites *Wuchereria bancrofti* (Cobbold 1877), *Brugia malayi* (Brug 1927) and *B. timori* (Partono et al. 1977) are responsible for lymphatic filariasis (LF) that impairs the lymphatic system leading to severe organ deformities leading to social stigma [1–3]. In India, the first two species *W. bancrofti* and *B. malayi* are present. *W. bancrofti* contributes 99.4% of the total burden. It is a roundworm nematode parasitic helminthiasis group of diseases under the Filarioidea type of infection. The main affected organs are legs and genitals causing 'elephantiasis' and hydrocele in males and breast filariasis in females followed by relentless disability causing social stigma. In Indian local language the disease is known as 'Hathipaon'. In India, LF is the second most vector-borne disease after malaria and globally ranks third after malaria and tuberculosis. The World Health Organization (WHO) estimated that LF is found in 81 tropical and subtropical countries with 120 million infected cases and with one billion people at risk; 947 million people are threatened, whereas 40 million people are disfigured by this infection. Four countries India, Indonesia,

Bangladesh (all Asian countries) and Nigeria (Africa) contribute about 70% of the LF infection in the world [4].

In the sixth century BC in his book, *Susruta Samhita*, Susruta mentioned this disease. In the seventh century AD in his memoir, *Madhava Nidhana*, Madhavarakara first described the signs and symptoms of this disease. In 1709, Clarke described 'Malabar legs' from Cochin which is synonymous with elephantiasis. In 1872 in Calcutta (now Kolkata), Lewis first described the microfilariae (Mf) in human blood [5].

LF is distributed in economically challenged countries. *W. bancrofti* is the most predominant species of human filariasis. It was recognized primarily as an urban disease which does not have animal reservoirs. Later it is reported from rural areas also. The parasites develop only in humans and in mosquitoes. But the adult worms may survive for 8–10 years and produce huge numbers of Mf from time to time. This is actually the real challenge in containing the disease.

2. Search methods

We have searched MEDLINE (PubMed) and CAB Abstracts, checked the reference lists of all studies identified by the search, also performed Google Search on specific topics and examined references listed in review articles and previously compiled bibliographies.

3. Genesis and evolution of the elimination of lymphatic filariasis

LF is responsible for deformities and disfigures of potential organs caused by this disease which make social stigma leading to hardship on normal life. Many marriageable persons undergo physical and psychological distress throughout their lives. LF is one of the six infectious diseases identified by the International Task Force for Disease Eradication of the WHO as 'eradicable' or 'potentially eradicable' in 1993 [6]. In 1997, the World Health Assembly resolved to eliminate LF as a public health problem globally [7]. In 2000, the WHO launched Global Programme to Eliminate Lymphatic Filariasis (GPELF). Following the London declaration on neglected tropical diseases (NTDs) in 2012, and consequent on several recent advances on the new knowledge of the pathogenesis, the biology of the parasite, development of better diagnostic tools and treatment strategies of LF, GPELF has an aim to eliminate this disease globally by 2020. India, a signatory to the World Health Assembly resolution, had initially set the target for elimination of filariasis by the year 2015 [4] but later aligned with global target of 2020 which is again to be reset. This programme is based on two components consisting of (i) interruption of transmission to prevent the disease by mass drug administration (MDA) and (ii) alleviation of the morbidity (lymphedema and hydrocele) associated with the disease [8]. Of the two strategies, preventive chemotherapy delivered through MDA has gained prominence as interruption of transmission after the implementation of the GPELF.

4. Mass drug administration: scientific background

Before the concept of MDA, the main strategy of LF management was selective treatment by identifying Mf carriers microscopically and/or clinically manifested cases and their treatment with diethylcarbamazine (DEC) for 12 days for individual cure. This strategy was focused on individual level where the people with

low parasitaemia and asymptomatic were left and therefore infection persisted in the community. In the subsequent years, there were significant improvements of LF diagnosis and treatment. Combination of double to triple drugs in single doses has been found to be efficacious than monotherapy. Albendazole (ALB) and more recent ivermectin (IVM) have been added to DEC. Now DEC + ALB is used in the MDA programme, and additionally IVM has been advocated for treating the entire population at high risk [5].

Human pharmacokinetic studies on the two regimens of single-dose drugs have shown that all the three drugs when administered singly or as a partner were well tolerated and safe in both microfilaraemic and non-microfilaraemic cases. Efficacy studies of repeated annual MDAs on different combination drugs of ALB + DEC, ALB + IVM and DEC + IVM indicated significant reductions on Mf rate for long periods [9]. Microsimulation models based on drug coverage, its efficacy and endemicity level of LF have indicated the effectiveness of MDA on ELF. This enabled to assess the number of MDA rounds necessary to achieve elimination [10, 11].

5. Filariasis control initiatives in India

LF is considered one of the NTDs that cause huge deformities and disabilities on the society. India contributes the major burden globally. The initial effort was to establish the concept of controlling the disease. In the concept of its elimination on the line of global initiative, India has made significant progress. In India, LF is caused by two roundworm nematode parasites *W. bancrofti* and *B. malayi* and is transmitted by the mosquito vectors *Culex quinquefasciatus*, *Mansonia annulifera* and *M. uniformis. B. malayi* which contributes to a negligible proportion is present in Kerala, Andhra Pradesh, Odisha, Madhya Pradesh, Assam and West Bengal. In general, Bihar state has the highest endemicity while Goa the lowest [12]. Here a detailed recent account has been enumerated.

5.1 National filaria control programme

After the pilot project in Orissa from 1949 to 1954 and based on its assessment, In India, the National Filaria Control Programme (NFCP) was launched in 1955. The main objective was to control the problem, have effective planning for control measures in endemic areas and also to train health personnel to strengthen the programme. The immediate control measures were mass drug administration of DEC, antilarval measures in urban areas and indoor residual spray in the rural areas. The programme was assessed four times by the assessment committees in 1961, 1971, 1982 and 1995, respectively. In 1961, the assessment revealed the failure of mass DEC administration due to community reluctance and ineffectiveness of insecticidal indoor spray due to the high resistance in the vector, and therefore as per recommendation of assessment committee, recurrent antilarval measures, establishment of new control units in endemic urban areas and provision of disposal of sewage and sullage were instituted. In 1971, the assessment committee recommended the detection and treatment of Mf cases with DEC at a dose of 6 mg/kg per day for 12 days and antilarval measures. Again in 1982, the assessment committee recommended extension of NFCP to rural areas through primary health-care system with 100% central assistance [5]. The fourth assessment in 1995 recommended to launch a project on the eradication of *B. malayi*, integrated vector control for all vector borne diseases, adoption of model bye-laws for effective control of vectors in domestic situation and fresh delimitation survey in rural areas.

5.2 Diethylcarbamazine-medicated salt

Mass treatment with DEC-medicated salt at community level has been used in a number of places as a control measure for lymphatic filariasis. In India this regimen was initiated as pilot projects in 1968–1969 in Uttar Pradesh and Andhra Pradesh. This showed very encouraging results. A recent review from 11 communities from China, India, Taiwan, Tanzania and Haiti on DEC-medicated salt in high-endemic districts and also in *B. malayi* areas opined high impact of this strategy which may be an end game for LF elimination. In 1976–1977 the distribution of 0.1% DEC-medicated salt was distributed in a population of 25,000 in Lakshadweep Island. There was an 80% reduction on Mf rate and 90% on circulating Mf after 1 year. Similarly, 0.2% salt conducted in Karaikal, Puducherry, showed 98% reduction on Mf [13]. A recent study on DEC-fortified salt (0.2%) and iodine for the elimination of diurnally sub-periodic *W. bancrofti* in Andaman and Nicobar Island showed encouraging results. Community coverage of >90% resulted in the reduction of Mf rate from 2.27 to 0.14% in the DEC-salt-arm (<1% in all the villages) and 1.26 to 0.74% (>1% in 4 out of 14 villages) in the MDA-arm. Antigen prevalence reduced to zero from 1.0 (DEC-salt + MDA-arm) to 6.3% (MDA-arm) in 2–3 years old, 1.2 to 3.6% from 2.9 in the DEC-salt-arm and 4.5% in the MDA-arm among 6–7 years old [14]. However, studies have indicated that it has to be used in specific situations [15].

5.3 Improved diagnosis of lymphatic filariasis

There are several methods for the diagnosis of LF. The microfilariae can be detected directly through blood smear examination, membrane filtration method, DEC-provocative test and quantitative buffy coat methods. Other methods are polymerase chain reaction (PCR), ultrasonography, lymphoscintigraphy (LSG), X-ray diagnosis and also hematology [16].

Circulating microfilariae can be detected by examining thick smears (20–60 µl) of finger-prick blood. Based on the periodicity of the microfilariae, blood samples are collected either at night hours or during daytime (in Andaman Nicobar Islands where *W. bancrofti* is transmitted by Aedes). The method is cheap and feasible at individual and community levels for mapping the endemicity of lymphatic filariasis and monitoring of MDA activities [17]. It has been observed that blood smear preparation on the micro-slides is a cumbersome process. Alternatively though not recommended in the programme, the finger-pricked whole blood (50 µl) can be collected in citrate–phosphate-dextrose (CPD) solution charged (25 µl) in 1.5 ml microfuge tubes. The tubes can be kept in +4°C freezer and can be examined within 48 hours. CPD-mixed whole blood (20 µl) are drawn by micropipette and placed in a micro-slide. The blood is smeared on the micro-slide and examined under10× microscope when the blood is wet. In positive samples, live moving parasites can be seen easily. This is a very simple method and can be easily executed. If needed, the dry smears can be stained for future reference.

The Filariasis Test Strip (FTS) of Alere (now Abbott Diagnostics) is a rapid diagnostic test recommended for mapping, monitoring and transmission assessment surveys (TAS) for the qualitative detection of *W. bancrofti* antigen in human blood samples. Now, the FTS has replaced the Binax Now filariasis immunochromatographic test (ICT), which also detects the same antigen in blood samples. The Brugia Rapid point-of-care cassette test (BRT) manufactured by Reszon Diagnostics is recommended for use during TAS to detect IgG4 antibody against *Brugia spp.* in human blood samples [17].

5.4 Mass drug administration its coverage and impact

In India, in the initial process of ELF, a district-level survey in 2000 revealed that of the 289 districts, 257 were endemic for LF [18]. In 2002, the National Health Policy had set the interim goal for the elimination of this disease in India by the year 2015 [19]. To support GPELF by raising funds and helping in various other ways, a global coalition was forged among 43 different donors constituting the Global Alliance to Eliminate Lymphatic Filariasis (GAELF). One of the partners GlaxoSmithKline has volunteered to supply the total quantity of albendazole tablets required to eliminate LF globally, free of cost [20]. The DEC tablets needed for the programme in India is being supplied by the central government [19].

In 2004, the elimination of LF programme was launched on June 5 in 202 districts of 15 states and 5 union territories. However, based on the experience of MDA in June 2004 when high temperature prevailed in most of the places, the date of 'National Filaria Day' was changed to November 11 in consultation with the states. To promote and create awareness on LF, this date was observed as 'National Filaria Day' since then. In the beginning, DEC was introduced under the MDA programme and, in 2007 ALB, was added with DEC as a global strategy. Gradually 255 districts were brought under MDA, and the assessment in 2013 indicated that 203 districts out of 255 had reported microfilaria rate <1% [21–24]. The number of districts reporting Mf rate below 1% increased to 222 and in 53 districts where MDA was withdrawn as halt in transmission was indicated. A transmission assessment survey (TAS) was qualified for 68 districts. The remaining districts were struggling to achieve the goal, making the MDA twice in a year [25].

5.5 Transmission assessment survey

TAS is a tool designed to know whether or not transmission is interrupted by MDA. In case, the transmission has been interrupted; the prevalence of circulating antegenaemia among children born after initiation of MDA should be below critical threshold, so that the transmission of disease is no longer sustainable and future generation will be free from this disease. Before TAS, it should be ensured that all implementation units (IUs) have had at least five effective MDAs with >65% of population coverage and each of sentinel, spot and additional spot sites had achieved <1% Mf rate [26].

China and the Republic of Korea have declared to have eliminated lymphatic filariasis as a public health problem in 2007 and 2008, respectively. According to the WHO, 81 endemic countries were reduced to 72 requiring MDA. Out of the 72 countries, 15 have been declared to have eliminated LF as a public health problem. These countries are Togo, Egypt, Maldives, Sri Lanka, Thailand, American Samoa, Cambodia, Cook Islands, Marshall Islands, Niue, Palau, Tonga, Vanuatu, Viet Nam and Wallis and Futuna [26].

Another six countries, namely, Malawi, Brazil, Bangladesh, Kiribati and Lao PDR have stopped MDA and are under post-MDA surveillance. Recent report indicates that two countries Kiribati and Yemen have eliminated LF [17]. Out of the remaining, 5 have not yet started MDA, 32 have fully scaled up MDA and 14 thought to be started and MDA is yet to be scaled up fully [26].

6. Discussion

Now India is on a critical phase for ELF facing serious challenges. The main challenge is the implementation of MDA with improved actual drug compliance so

as to cover >80% at-risk population. It is required to have continued IEC activities, community engagement and all-round support [27]. It is really a huge operational and logistical challenge to cover about 650 million populations for the MDA programme.

In June 2018, in the 10th GPELF meeting at New Delhi, India, the government of India launched Accelerated Plan for Lymphatic Filariasis Elimination (APELF). A triple-drug therapy or IDA (IVM, DEC and ALB) along with community engagement has been planned for accelerating the LF elimination in India [28, 29]. As a pilot project, IDA has been rolled out successfully across four districts in India. These districts are Arwal in Bihar (20 December 2018), Simdega in Jharkhand (10 January 2019), Nagpur in Maharashtra (20 January 2019) and Varanasi in Uttar Pradesh (20 February 2019). A total of 8.07 million people out of 10.7 million vulnerable people (75.4%) were benefitted with the IDA medicines. The IDA approach is to be scaled up in all endemic districts to eliminate LF by 2021. It is expected that with triple-drug combination, if effective, actual drug compliance is achieved; the MDA districts may qualify for TAS and also clear the TAS successfully.

Another important issue is asymptomatic cases in children age group. In some endemic areas, about 30% of children have acquired LF by the age of 4 years either with the presence of Mf or *W. bancrofti* antigen in their blood [30]. Similarly, in a *B. malayi* area in Kerala, asymptomatic Mf has been demonstrated in children through LSG [31]. LF parasites in human do not have animal reservoirs. But human dirofilariasis, i.e. zoonotic transmission to human, cannot be ruled out. This thing should be kept in mind after successful ELF in human [32]. There are other issues of management of acute and chronic filariasis cases and treatment of adenolymphangitis (ADL) cases with antibiotics since the majority of acute episodes are bacterial origin. The APELF provides free morbidity management and disability prevention services through kits and corrective surgeries [28].

Vector surveillance is another important tool to facilitate in instituting vector control measures as well as to assess the infection in vectors in the areas. Xenomonitoring, in other words, the presence of Mf larvae in vector mosquitoes, is a method to assess the effectiveness of the post-MDA and TAS. Specific PCR technique is applied [33]. Recently Khatri et al. screened the presence of *W. bancrofti* L3-specific *Ssp1* gene in trapped mosquitoes by PCR in certain districts in Maharashtra and Karnataka. This indicated that MDA needed to be strengthened [33]. Scaling up xenomonitoring is a big challenge in existing infrastructure with weak strength of skilled entomologists. At present IVM has been planned to introduce in all LF endemic districts in India covering many districts endemic for malaria also. IVM introduction in context of malaria control is towards targeting their vector populations [34]. It is important to assess the impact of other coexistent diseases in the same eco-endemic regions [35].

7. Conclusion

India is on a very strong ground to achieve lymphatic elimination [19]. Several efforts are now in place. The total disability-adjusted life years (DALYs) lost due to LF is around 2.06 million, resulting in an annual wage loss of US $811 million [36]. 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 [37].

Conflict of interest

The authors declare no conflict of interest.

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