Elimination of lymphatic filariasis in South East Asia

Expanding treatment options alongside ensuring high coverage of mass drug administration can accelerate progress in elimination of lymphatic filarisis, say **Sabine Specht and colleagues**

Lymphatic filariasis is a tropical disease that affects about 70 million people worldwide.[1] It is caused by infection with the parasitic nematodes *Wuchereria bancrofti*, *Brugia malayi*, or *Brugia timori* and is transmitted through mosquitoes. Chronic infection causes lymphatic dysfunction, resulting in progressive, irreversible swelling of the limbs and genitals (box 1). Filarial induced lymphoedema is the second leading cause of disability in the world, accounting for about two million disability adjusted life years lost.[1] The associated social stigma often causes mental health problems and poverty because of loss of employment.[1]

The third sustainable development goal calls for elimination of neglected tropical diseases, including filariasis, by 2020. Sixty three per cent of the population at risk of lymphatic filariasis and 50% of the people infected worldwide live in South East Asia. India alone harbours 40% of the world's burden of disease.[2] The region has made considerable progress towards elimination, yet several challenges remain. We present an overview of the global efforts to eliminate filariasis and progress made in South East Asia, and discuss key priorities.

Global elimination efforts

The World Health Organization launched the global programme to eliminate lymphatic filariasis in 2000. This programme comprises two key strategies: mass drug administration to prevent infection, and management of morbidity and prevention of disability.

Mass drug administration

Mass drug administration entails annual distribution of diethylcarbamazine in combination with albendazole for a minimum of five years in an endemic area.[3] These drugs are mainly microfilaricidal. The goal is to achieve a coverage of more than 65% of the population. It is based on the premise that repeated mass drug administration will reduce the microfilaria density in the community and thus halt transmission and new infections. Up to 2015, the programme has provided more than 6.7 billion treatments to over 850 million people at least once in 66 countries. Mass administration is estimated to have cured or prevented up to 96 million new cases of lymphatic filariasis and averted more than $100bn of lifetime economic loss.[4] Since 2000, the number of cases of filarial induced hydrocele has declined by about 49% to 19.4 million, and the number of cases of filarial induced lymphoedema by 23% to 16.7 million.[4]

Managing chronic disease

Long term care is important to prevent and treat chronic manifestations of filariasis. Treatment for lymphoedema includes good hygiene (regular washing with soap and water; skin and nail care), use of topical antibiotics or antifungal agents, exercise, and appropriate footwear. Providing a basic package of care to manage morbidity has been shown to reduce the frequency of acute attacks of adenolymphangitis that drive the progression of lymphoedema.[5,6]

Microfilaricidal drugs have little benefit in infected individuals with lymphoedema and hydrocele.[7] A recent trial involving 105 children with filariasis in India showed a possible benefit in reversing lymph dilation early in the course of disease,[8] and a few observational reports have also noted a benefit.[9,10] Further evidence is needed on their role in preventing the development of lymphoedema and associated disfigurement.

Monitoring impact

The number of people requiring mass drug administration fell from 1.41 billion in 2011 to 856 million in 2016.[1] It is expected that mass administration will no longer be required when the prevalence of infection has been reduced to low levels, such as microfilariae in <1% of the population or antigenaemia in <2% of the population.[11]

After five effective rounds of mass drug administration, a school based transmission assessment survey is conducted. Antigen levels are recorded in 6-7 year old children in the endemic area using a filariasis test strip. If the levels meet cut-off criteria suggesting transmission has been arrested, mass drug administration can be stopped and surveillance used

KEY MESSAGES

- Mass administration of microfilaricidal drugs has reduced new infections of filariasis
- Current challenges include management of patients with chronic manifestations, such as lymphoedema and hydrocele, and the uneven prevalence, with persisting transmission hotspots
- New drugs and regimens that kill adult worms (eg, triple therapy) and alleviate lymphoedema can help accelerate elimination efforts

Box 1: Course of lymphatic filariasis

- Adult filarial parasites reside in the lymphatic vessels of an infected person for up to eight years and produce thousands of first stage larvae (microfilaria)
- Mosquitoes of the genera *Aedes*, *Anopheles*, *Culex*, and *Mansonia* ingest microfilaria during blood meals from humans and these develop into an infective larval stage
- Larvae enter humans through the wound made by a mosquito, where they migrate and settle in the lymphatics to mature into adult worms and complete the cycle
- Lymphatic dysfunction in response to the parasites provokes severe morbidity, including progressive, irreversible swelling of the limbs (elephantiasis) and genitals (hydrocele) with acute adenolymphangitis or acute secondary bacterial infection
- Infection often occurs early in childhood in endemic areas, but clinical signs appear much later. Once triggered, symptoms may progress even after the parasites have died, being sustained by opportunistic bacterial and fungal infections

instead. Transmission surveys are repeated after one and two years. If these are successful, the region can be validated for certification of elimination. If transmission is still ongoing on assessment, mass drug administration has to be continued.

Progress in South East Asia

South East Asian countries are at different stages of implementation of the global elimination programme (table 1). In 2016, the region achieved mass drug coverage of 60.7% of the population in endemic areas.[1] Sri Lanka, Thailand, and Maldives have achieved the criteria for elimination of lymphatic filariasis. Bangladesh has stopped mass drug administration and is presently under surveillance.[1]

A guiding example in the region is Sri Lanka's Anti Filariasis Campaign, in which three rounds of diethylcarbamazine were followed by five annual rounds of diethylcarbamazine in combination with albendazole distributed in all eight endemic districts between 2002 and 2006. Two post-drug administration surveillance assessments were conducted in 2011-13[12] and repeated in areas with continued transmission in 2016. All but three areas showed strongly reduced disease transmission, and it is expected that the incidence will fall to zero without further mass drug administration.[13]

Remaining challenges

Some countries that have completed five annual rounds of mass drug administration are now struggling with suboptimal results on the transmission assessment survey. Elimination efforts have proved challenging in larger countries such as India, with 256 districts involved. Full implementation has not been achieved, and continued transmission is noted in surveys. As such, elimination may not be feasible by 2020 using currently available tools.[14]

Efforts to maintain high mass drug administration coverage must continue. Factors that can interfere with maintaining sufficiently high coverage include insufficient political will, inadequate health infrastructure, logistical issues, systematic non-compliance, and the risk of drug resistance. Recrudescence of infection owing to migration of infected people into areas with interrupted transmission presents a major challenge to elimination efforts.

Next steps

Surveillance

The Sri Lanka experience shows the importance of robust surveillance after mass drug administration to identifiy remaining transmission hot spots. The spatial distribution of lymphatic filariasis where one community may be non-endemic but a neighbouring village has a 30% prevalence makes it particularly difficult to obtain representative data, and success rates may be overinterpreted. In the past, prevalence of lymphatic filariasis was longitudinaly captured in large geographical areas to reduce surveillance costs. Smaller units compensate for spatial prevalence and are more sensitive for detecting persistence or resurgence of lymphatic filariasis.

Using a point-of-care antibody test in combination with xenomonitoring (the detection of parasites in mosquitoes) has been shown to be more sensitive than the antigen testing currently used for detecting low level transmission.[12 13] Such focused elimination strategies are costly, however, and must be weighed against the costs of upscaling or re-starting mass drug administration if transmission persists.[15] A tipping point may be reached, at least in some areas, where test and treat (that is, treatment only of those diagnosed as infected) is likely to become more cost effective, even if it requires 5-10 day treatment instead of a single dose yearly for 5-10 years.

Morbidity management

Morbidity management is even more challenging and must be continued in endemic communities even after mass drug administration has stopped, because affected patients remain in these communities. An accurate assessment of filarial cases has proved difficult. Severe lymphoedema is under-reported in Africa,[16] while reporting from South East Asia has increased over the past few years.[1]

Health systems should be strengthened to deliver a minimum package of care to all affected individuals, with a goal of achieving complete geographical coverage. WHO has developed a toolkit for managing morbidity and preventing disability for endemic countries that must be integrated into primary healthcare alongside continuing mass drug administration. Training will further support patients to continue care and to improve their quality of life.

New treatment and control options

Expanding the toolbox to prevent and treat filarial infections will help progress towards elimination. Beneficial effects of bednets have been reported from areas with Anopheles transmission and persistent lymphatic filariasis in Papua New Guinea, where infection is transmitted by indoor biting mosquitoes. The use of impregnated bednets as well as treatment has been suggested for remaining lymphatic filariasis hot spots.[17 18]

New drugs enabling reversal of lymphoedema would be highly beneficial. This has also become imperative in view of sustainable development goal 3.8, which targets individual wellbeing and thus calls for individual cure and not merely epidemiological "control as a public health problem."

Since the adult worm confers pathology in lymphatic filariasis, the ultimate goal for a new drug is to kill or sterilise adult worms. A pilot study in 24 patients showed a possible sterilising effect with the addition of ivermectin to the existing treatment regimen (diethylcarbamazine with albendazole). A single dose triple drug therapy (ivermectin in combination with diethylcarbamazine and albendazole) achieved almost total clearance of microfilaraemia at 36 hours. This effect was sustained in all patients at one year (12 patients) and half the patients at two

Table 1 | Implementation of mass drug administration for lymphatic filariasis in South East Asia, 2016[1]

Country	Mass drug administration	Total population requiring treatment	Reported No of people treated	National coverage (%)
Indonesia	Started, not scaled up to all endemic districts	61 617 614	43 783 064	71.1
India	Scaled to all endemic districts	337 024 378	187 492 171	60.7
Myanmar	Scaled to all endemic districts	36 023 429	31 867 477	88.5
Nepal	Scaled to all endemic districts	13 434 920	8 980 509	66.8
East Timor	Scaled to all endemic districts	1 167 242	778 346	66.7
Bangladesh	Stopped, under surveillance	—	—	—
Thailand	Eliminated	—	—	—
Maldives	Elimination validated	—	—	—
Sri Lanka	Elimination validated	—	—	—

years, compared with the usual two drug regimen, where 11 of 12 patients tested positive for microfilaria at one year.[19] The triple drug therapy could accelerate interruption of transmission by reducing the number of annual rounds of mass drug administration required to achieve the elimination target. Two to three rounds of treatment with ivermectin in combination with diethylcarbamazine and albendazole may be sufficient to reduce community microfilaraemia to below the threshold level, rather than five to six rounds of dual therapy.[20 21] This would be particularly useful to accelerate progress in countries left behind through delays in mapping or initiation of mass drug administration. In 2017, WHO provisionally approved the use of triple drug therapy to interrupt transmission of lymphatic filariasis infection, and guidelines have been released for its use in Asia, where onchocerciasis and loiasis are not endemic.[22] India is currently preparing to start the triple drug therapy as part of an accelerated national programme.

Two trials from Africa have shown a positive effect of a six week course of doxycycline in reducing lymphoedema severity in the early stages in patients with filariasis[23 24] beyond that seen with improved hygiene alone. This improvement was independent of current filarial infection.[24] Currently, five multicentre placebo controlled trials are being conducted (three in Africa and two in Asia) and will provide evidence to determine whether doxycycline can be included as an adjunct therapy for morbidity management. Understanding its effect on the adult worm and microfilaria will help inform its use in reducing transmission as well.

To expand the toolbox for anti-filarial drugs, the Drugs for Neglected Diseases initiative, together with its partners from academia and industry, is developing new anti-wolbachial and direct acting drugs. Two of these, emodepside and ABBV-4083, are orginal or modified veterinary drugs and are now in phase I development for use in humans; several others are in the drug pipeline. While these drugs will be developed primarily for use against onchocerciasis, for which apart from doxycycline no safe macrofilaricide exists, their indication may extend to include lymphatic filariasis as well.

However, it has also become clear that higher efficacy drugs do not compensate for low coverage. Decision makers must assess the feasibility of, and rationale for, investing in new strategies for elimination of lymphatic filariasis, taking into consideration the costs of the programme to ensure wide coverage. Successful elimination of lymphatic filariasis will depend on more than monetary investment. Going forward, political will and continued public engagement and community ownership will be critical.[25]

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