The end of lymphatic filariasis?

Many programmes to improve health in poor countries are struggling to meet their targets, but as **Moses Bockarie** and **David Molyneux** report, elimination of lymphatic filariasis has a real chance of success

When the British physician Patrick Manson incriminated mosquitoes as vectors of *Wuchereria bancrofti* in China in 1877, it was the first time that an insect had been associated with the active transmission of an agent of any human or animal disease. The minute filarial worms (microfilariae), were, however, first observed as blood parasites by another British physician, Timothy Lewis. A *BMJ* report in 1870 records he had noticed microfilariae in the urine of patients.[1] Manson had read Lewis's work and postulated that the worms lived in the lymphatic system, and that like other similar parasites, the females produced larvae viviparously. His curiosity about the fate of the microfilariae led to the discovery that they were transmitted by mosquitoes.

Lymphatic filariasis is a major cause of acute and chronic morbidity of humans in tropical and subtropical areas of Asia, Africa, the western Pacific, and some parts of the Americas. Over 20% of the world's population live in areas where they are at risk of infection with filarial parasites. An estimated 120 million people are infected in at least 83 endemic countries, with 91% of cases caused by *W bancrofti* and the remainder by *Brugia malayi* and *B timori*.[2]

Uniquely among vector borne infections, lymphatic filariasis can be transmitted by five genera of mosquito (*Anopheles, Aedes, Culex, Mansonia,* and *Ochlerotatus*). Human infection occurs when the third stage (L3) infective larvae escape from the mosquito's proboscis on to the skin and penetrate at the site of the bite. The larvae migrate to the lymphatic system, where they mature into adult male and female worms. As Manson suspected, adult females release live microfilariae. Concentrations of microfilariae in the blood show periodic variation, peaking at the time when the dominant vector mosquito bites.

Greater financial commitment is crucial for a global programme targeting over a billion people in 83 countries

Despite being one of the most debilitating conditions in the world, lymphatic filariasis has escaped the attention of mainstream health policy because it is not generally fatal and is restricted to tropical and subtropical countries, where it mainly affects poor people.[3] Around 41 million people have visible symptoms, including lymphoedema, genital pathology (especially hydroceles), and elephantiasis.[4] A further 76 million have hidden infection, most often with microfilariae in their blood and hidden internal damage to their lymphatic and renal systems. About 44 million infected patients have recurrent infections and abnormalities of renal function.

Elimination programme

In 1997, the World Health Assembly passed a resolution urging member states to strengthen activities toward eliminating lymphatic filariasis by 2020. In 2000 the Global Alliance to Eliminate Lymphatic Filariasis was formed as a partnership to support national elimination programmes in endemic countries (www.filariasis.org) and WHO launched its Global Programme to Eliminate Lymphatic Filariasis. Optimism that elimination can be achieved lies in the availability of safe, single dose, two drug treatment regimens capable of reducing microfilaraemia to near zero levels for one year or more, along with remarkable improvement in techniques for diagnosing the infection. Vector control, which is logistically challenging, is desirable but not required to interrupt transmission.

Nevertheless, the elimination campaign has its own challenges. Because lymphatic filariasis is not a fatal disease and does not threaten the developed world, there is less political motivation, finance, and engagement of politicians than for diseases such as malaria, tuberculosis, polio, and AIDS. Greater financial commitment is crucial for

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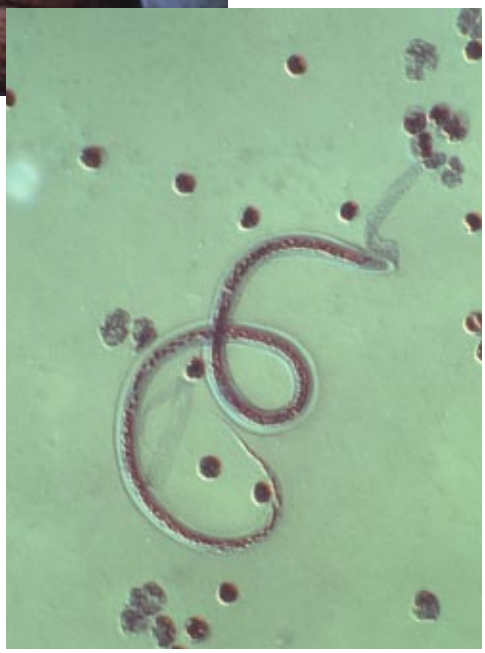
a global programme targeting over a billion people in 83 countries. A further challenge in implementation is to persuade people who have no symptoms to take the tablets.

Infected people need to take two drugs once a year for five to seven years to ensure interruption of transmission. In areas where lymphatic filariasis is coendemic with onchocerciasis (river blindness) the recommended regimen is ivermectin 200 µg/kg plus albendazole 400 mg; elsewhere, the regimen should be diethylcarbamazine 6 mg/kg plus albendazole 400 mg.[5] The drugs are in tablet form and have a long shelf life at room temperature.

The elimination programme aims to reach 80% population coverage yearly, for at least five years in order to interrupt transmission of the parasite.[6] GlaxoSmithKline has donated albendazole and Merck has donated ivermectin to treat both lymphatic filariasis and onchocerciasis, so drug cost is not a barrier to participation. Awareness campaigns have used the safety, efficacy, and ancillary benefits of ivermectin and albendazole to improve compliance with mass drug distribution. These drugs are also effective against soil transmitted helminths, which are a common problem that mothers in endemic areas know affects their children's physical and intellectual development, and ivermectin is active against scabies and head lice.

In delivering treatment, high priority is given to achieving full coverage of communities at risk, which may be states, provinces, districts, subdistricts, towns, or villages. Endemic communities are identified using rapid diagnostic tools such as the immunochromatographic card test.[7] Mass drug administration campaigns either deliver drugs to individual homes or dispense them from a fixed station that is easily accessible. Campaigns may be organised as a national day or over a few days. This approach is built around the use of community volunteers and strong social mobilisation and information, education, and communication strategies. Many national elimination programmes in Africa have adopted the community directed intervention strategy that was developed for ivermectin distribution to control onchocerciasis.[6] In this model each community takes the lead role in planning, implementing, and assessing its local drug delivery strategy. It relies on community volunteers to distribute the drugs.

Manson's discovery that *W bancrofti* required a mosquito host to complete its life cycle suggested that the disease may be eliminated by controlling the vectors. Vector control is particularly attractive for lymphatic filariasis because, unlike malaria, the parasite does not multiply in the mosquito vector and only continuous exposure to bites of many infected mosquitoes maintains the infection in humans. Vector control alone, through indoor residual spraying, has interrupted transmission of the disease in Solomon Islands[8] and Togo where *Anopheles* mosquitoes are the only vectors.[9] Recent studies have shown that insecticide treated bed nets are more effective than spraying in reducing transmission of malaria,[10] and the same may be true for lymphatic filariasis. In communities where filariasis mosquitoes are a biting nuisance, the noticeable effect of vector control might help to gain community support for integrated control programmes that include drug treatment.



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Larval stage of the parasitic worm *Wucheria bancrofti*

Signs of success

In its first eight years the Global Programme to Eliminate Lymphatic Filariasis delivered 1.9 billion treatments to individuals living in 48 of the 83 endemic countries.[11] Thirty two million disability adjusted life years have been averted since the programme was initiated in 2000. The 310 million treatments to the children and women of childbearing age have also significantly reduced intestinal helminths, onchocerciasis, lice, scabies, and other conditions, particularly anaemia.[12 13]

The programme has been successful because the disease mapping tools are simple and applicable in remote field settings.

However, even with donated drugs, mass drug administration requires resources; characteristically middle income countries have made the most progress. China became the first country declared to have eliminated the disease, followed by the Republic of Korea in March 2008.[14] South East Asia has the highest burden of disease, with 859 million people at risk, but all nine endemic countries in the region have initiated mass drug administration programmes and four (India, the Maldives, Sri Lanka and Thailand) have reached full geographic coverage. In 2007 alone, 63.6% (546 million) of the target population received treatment.[14]

In Africa, where all 39 endemic countries are low income economies, only 15 were implementing mass drug administration in 2007.[14] Of the 382 million people at risk in the region only 47 million (12.3%) were treated. Resources for scaling up in poor countries is the key to achieving global elimination by 2020.

Recognising the need for economic empowerment and more resources in the poorest countries, the US increased its commitment to controlling neglected tropical diseases from $15m for 2008 to a total of $350m over the next five years. In July 2008, the G8 leaders meeting in Japan called for efforts to control or eliminate neglected tropical diseases to be reinvigorated "by expanding health system coverage, alleviating poverty and social exclusion as well as promoting adequate integrated public health approaches, including through the mass administration of drugs." In September 2008, the British government committed £50m to the control of neglected tropical diseases. In January this year, the Global Network for Neglected Tropical Diseases (www.globalnetwork.org) announced that it has received $34m from the Bill and Melinda Gates Foundation to step up the global advocacy efforts to prevent and treat these diseases. If this momentum is maintained lymphatic filariasis could be eliminated by 2020. Lymphatic filariasis is the core disease in integrated neglected disease programmes throughout the world and is the key platform given the availability of the donated drugs and their wide spectrum efficacy and safety.

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Chylous urine (1870)

Mr. T. R. Lewis had opportunities of making an examination of the urine of a patient in the General Calcutta Hospital under the care of Dr. Lyons, who had been suffering from the condition known as chylous urine for about a month, together with pain in the right testicle, and great emaciation, in spite of good food and a good appetite. As the colour closely resembled many rice-water stools, he carefully examined it, and was repaid in a way he had not anticipated. It was albuminous to the extent of about one-fourth of its bulk, slightly acid, with a specific gravity of 1.015. Ether caused a separation into two layers—a clear urine-like fluid containing oil-molecules, and a white homogeneous mass consisting of minutely molecular *débris*. Before the addition of reagents, the fluid under the microscope so closely resembled the condition of a cholera stool just described, as not to be distinguishable from it—yellowish-green cells, some hyaline, some granular, some protruding a tongue-like prominence, and others with the contained plasma puckered in various ways. A few of the larger corpuscles were seen to shift themselves (like amoebae) a distance fully their own diameter, the shape altering at the same time. At first he doubted that they really were blood-cells, as the extent of variation in size was considerable. The fluid very quickly gelatinised in the test-tube; indeed, it frequently does so in the patient's bladder, giving rise to stoppages during micturition. He had not seen cholera discharges spontaneously gelatinise, although such a condition is said to occur. A portion of the coagulated mass (which, when stirred, closely resembled a lump of moist gluten) was teased on a slide with needles, and examined. It consisted of fibrillae studded with blood—granular cells, scarcely differing from those seen in the flakes of cholera discharge, except, perhaps, in being more universally granular. They seemed to present more of the character of pus-cells. In the midst of this fibro-albuminous matter, several *embryos of a round worm* were discovered every time the urine was examined. A careful sketch of a large one, after the addition of acetic acid, is given. In the course of a few minutes, when the sketch was nearly completed, a *caudal bursa* became visible under the influence of the acid. "When first seen," says Mr. Lewis, "I thought they were some detached filaments of a fungus, judging from the hyaline structureless appearance presented. After a time, however, a few of them were observed to move very slowly, when all doubt as to their nature was at an end. It will not be surprising that the existence of these was not suspected, when we consider that fully two hundred of the larger size could pass abreast through a very small pin-hole, an orifice not exceding the fiftieth of an inch in diameter, as may be verified by a simple calculation. Perhaps this fact may help to throw some light on a very obscure disease, of which little is known beyond the symptoms, although frequently met with in some parts of the world; and, indeed, may perhaps account for its localisation to such places as the West Coast of Africa, where, I am told, it is by no means a rare malady. As the mature worm still retains a hold on its victim, being perhaps safely lodged in the kidney and I have not seen an embryo of this kind before, nor yet a drawing—I must leave to a more experienced helminthologist to decide to what species of nematode it belongs."

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