10 YEARS OF GLOBAL EFFORTS TO ELIMINATE LF: WHERE ARE WE?

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Lymphatic filariasis (LF) is a mosquito-borne parasitic infection responsible for long-term chronic morbidity in the form of lymphoedema, genital pathology (especially hydroceles), recurrent disabling fevers (lymphangitis) and elephantiasis in over 40 million people around the world (Ottesen et al, 2008). Currently, over one billion people are exposed to infection in 81 endemic countries in Asia, Africa, the Western Pacific and some parts of the Americas (World Health Organization [WHO], 2009).

The life cycles of the three human filarial parasites, *Wuchereria bancrofti, Brugia malayi* and *Brugia timori*, involve a human and a mosquito host. Microfilariae (baby worms) released into the blood by lymphatic dwelling adult worms are picked up by human biting mosquito carriers during a blood meal.

Unlike human malaria, which is transmitted only by the *Anopheles* mosquitoes, lymphatic filariasis parasites are carried by five different mosquito genera: *Anopheles*, *Aedes*, *Culex*, *Mansonia* and *Ochlerotatus*. Humans become infected when they are bitten by female mosquitoes containing third-stage infective larvae (L3) that have developed from microfilaria ingested with the blood meal obtained from infected individuals.

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W. bancrofti, which only infects humans, accounts for over 90% of the estimated 120 million cases of lymphatic filariasis worldwide and is the only parasite found in Africa and the Americas, while *Brugia* species are found exclusively in Asia (Michael et al, 1996).

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In 2000 the WHO, in collaboration with other partners (national ministries of health, Governments of the USA, UK and Japan, pharmaceutical companies, e.g. GlaxoSmithKline and Merck & Co., Inc and numerous other donors and non-profit partners, including the Bill and Melinda Gates Foundation and World Bank), launched the Global Alliance to Eliminate Lymphatic Filariasis (GAELF) by 2020 (Ottesen et al, 2008).

The optimism that this target could be achieved resulted from the availability of simple, rapid diagnostic tools, the availability of freely donated drugs by Merck and Co., Inc and GlaxoSmithKline, and the knowledge that in the absence of a non-human reservoir for *W. Bancrofti*, and only minor animal hosts for *B. malayi* (some primates have been found to be infected with *B. Malayi* in Malaysia but they present little or no risk as reservoirs for reinjection of humans; Edison, 1962), lymphatic filariasis transmission could be interrupted by reducing the numbers of circulating microfilaria in the blood through mass drug administration (MDA) to levels not compatible with continued transmission.

The ministries of health of all 83 countries that were endemic in 2000 formed their own national programmes to eliminate lymphatic filariasis through MDA. By the end of 2008, 51 of the 83 previously endemic countries had initiated a programme (WHO, 2009).

The momentum to eliminate lymphatic filariasis has been gathering pace over the past 10 years and funding to control it and other neglected tropical diseases will increase substantially, from $100 million in 2010 to over $200 million in 2011 (Hotez et al, 2009).

The Global Programme to Eliminate Lymphatic Filariasis (GPELF) has expanded MDA coverage from three million people treated in 12 countries in 2000, to more than 497 million in 52 countries in 2008 (WHO, 2009). During that period, the disease was eliminated in China and Korea. Nine countries will probably not require MDA because of a natural decline in transmission intensity that is connected to a history of intense vector control. Nevertheless, 20 endemic countries are yet to initiate MDA and all of them are in Africa, the majority being post-conflict or otherwise fragile states.

Great progress has been made in the Americas and Asia-Pacific regions, where many countries have achieved 100% MDA coverage of all their endemic districts and reduced microfilaria prevalence to below 1% (WHO, 2009).

The majority of the 17 Pacific island countries that were classed as endemic for lymphatic filariasis have now ceased MDA after five rounds and embarked on targeted treatment of high-risk groups, i.e. individual treatment with diethylcarbamazine (DEC) and albendazole. Active surveillance in the 10 countries where MDA has been stopped revealed less than 300 infected individuals.

There is strong evidence that the availability of safe, effective drugs and rapid diagnostic techniques for mapping disease distribution can achieve elimination of lymphatic filariasis (Bockarie and Molyneux, 2009; Molyneux et al, 2009). Clinical improvements in the manifestation of filarial diseases after treatment, such as a reduction in low grade lymphoedemas and hydroceles act as an important catalyst for the general population, encouraging high compliance rates in any MDA programme (Mackenzie et al, 2009).

The main challenge for the next 10 years will be organising and mobilising the financial resources, rather than focusing on those that are conceptual or scientific (for example, new drugs, vaccines, treatment regimens or intervention strategies). There is a continuing need to maintain advocacy of the programme, as it demonstrates success in eliminating a major cause of poverty (Perera et al, 2007). Governments need to recognise LF as a major public health problem that deserves a specific budget line in the ministries of health budgets. Similarly, lymphatic filariasis is globally distributed and the availability of two free drugs (Mectizan®, donated by Merck & Co., Inc and albendazole, donated by GlaxoSmithKline) provides a cost-effective platform for expanded and integrated neglected tropical disease programmes throughout the global tropics.

As the endgame — the elimination or interruption of LF transmission — approaches for the many endemic countries where MDA has been successful, there is an urgent need to develop new strategies to help those countries embarking on similar programmes. Many of these are post-conflict countries with limited human resource capacity and poor health service infrastructure.

Community-directed interventions

Community-directed treatment with ivermectin has been the cornerstone of the success of the African Programme for Onchocerciasis Control (APOC) (Amazigo, 2008a). Onchocerciasis is a parasitic disease caused by the filarial worm *Onchocerca volvulus* and is transmitted through the bites of infected blackflies of the *Simulium* species, which carry immature larval forms of the parasite from human to human. It is a major cause of blindness.

The capacity of many endemic African countries to deliver primary healthcare to the rural poor has been severely affected by recent conflicts.

In many parts of Africa, where lymphatic filariasis is co-endemic with onchocerciasis, governments that have been working with APOC are aware of the effectiveness of rolling out drug delivery programmes for community ownership (Amazigo, 2008b). Trained healthcare workers play a supervisory and technical role through the provision of professional expertise and conducting household and community surveys to ensure programme requirements are met.

The capacity of many endemic African countries to deliver primary healthcare to the rural poor has been severely affected by recent conflicts. Indeed, the majority of the 20 endemic countries yet to initiate MDA for lymphatic filariasis have recently been affected by strife of one kind or another — these include Angola, Central African Republic, Chad, Cote d'Ivoire, Democratic Republic of the Congo, Ethiopia, Guinea, Liberia, Mozambique and Sudan.

With the experience gained from community-directed treatment strategies in resource-poor settings, WHO has developed a pro-poor strategy for health service delivery in countries challenged by conflicts and poor infrastructure. This integrated approach, called Preventive Chemotherapy and Transmission Control, is characterised by large-scale interventions that provide antihelminthic drug treatment for the integrated control of multiple neglected tropical diseases, including lymphatic filariasis, onchocerciasis, schistosomiasis and soil-transmitted helminthiasis (WHO, 2006). This approach requires the delivery of good-quality medicine, either alone or in combination (DEC or ivermectin alone, or either drugs in combination with albendazole), to as many people as possible at regular intervals until transmission has been interrupted. In the case of soil-transmitted helminths (commonly known as intestinal worms), there is a continuing need to maintain delivery of medicines to ensure a continued reduction in morbidity in younger age groups. The long-term solution to the problems of soil-transmitted worm infections will be improved water and sanitation.

The availability of safe and effective medication for use in MDA, and low cost rapid diagnostic tools for mapping and accessing the impact of MDA on disease prevalence and distribution, makes this a non-discriminatory strategy that can result in rapid effects. In the years between 2000 and 2008, over two billion treatments of the anti-filarial drug albendazole were administered to approximately 570 million individuals living in 51 of the 83 initially lymphatic filariasis-endemic countries through MDA (Ottesen et al, 2008; WHO, 2009). There is also a developing consensus on the recognition of Preventive Chemotherapy and Transmission Control as a critical platform for scaling up malaria interventions, particularly bednets and antimalarial drugs (Molyneux et al, 2009).

The strategy used by the GPELF to combat lymphatic filariasis is a once-yearly, single-dose, two-drug regimen. The goal is to reach 80% population coverage each year for at least five years, in order to

interrupt transmission of the parasite. The number of annual treatments required to interrupt transmission of *Anopheles*-transmitted lymphatic filariasis may be reduced with an increase in the use of long-lasting insecticide-treated bednets (Bockarie et al, 2009).

Co-endemicity with Loa loa

Reports of serious adverse events associated with MDA for lymphatic filariasis are uncommon (Gyapong et al, 2005). However, in recent years serious adverse events associated with ivermectin treatment used to combat onchocerciasis, such as progressive neurologic decline and encephalopathy within a few days of taking ivermectin (Kamgno et al, 2009), have caused some concern. One of the major causes of serious adverse events is co-endemicity with Loaiasis, a filarial disease of the skin and eye caused by the nematode worm Loa loa (Kamgno et al, 2009).

This has warranted some careful reviews to improve programme delivery because these adverse events can result in life-threatening encephalopathy and even death.

To achieve lymphatic filariasis elimination in Africa, this co-endemicity of *W. bancrofti* and Loa loa in central Africa will need to be addressed. This will require further research to test new drug regimens (including single high doses of albendazole) or alternative treatment regimens (including biannual treatment schedules). Albendazole is an effective anti-filarial agent whose precise optimal dosage in MDA regimens has yet to be determined — even at the single, low 400mg dose used for treating most intestinal helminth infections, it decreases *W. bancrofti* microfilaraemia progressively over the course of 6–12 months (Gyapong et al, 2005). Higher doses may reduce microfilaraemia more rapidly and the low microfilaria levels sustained for much longer periods. Recent studies have shown that a much higher 1000mg dose of albendazole is well tolerated in cancer patients (Pourgholami et al, 2010).

W bancrofti, *B. malayi* and *B. timori* are host to *Wolbachia*, a bacterial endosymbiont which is essential for their growth, development, embryogenesis and survival. *Wolbachia* is, however, not present in Loa loa. An alternative anti-filarial treatment, doxycycline, which exploits the symbiosis between the nematode (worm) and the *Wolbachia* bacteria, is showing promise as a treatment option for areas where lymphatic filariasis is co-endemic with Loa loa. Treatment of bancroftian filariasis with doxycycline results in the long-term sterility and eventual death of these adult worms (Taylor et al, 2005).

A drug discovery and development programme (A-WOL, http://www.a-wol.com) based at the Liverpool School of Tropical Medicine is developing an anti-wolbachia therapy that is compatible with MDA. The A-WOL programme aims to provide a product pipeline and drug portfolio that will optimise the use of existing drugs and prioritise the development of novel drugs and combinations for use in future control and treatment of filariasis.

Synergies with vector control

Evidence exists that the widespread use of insecticide-treated bednets may have an added effect on the reduction of lymphatic filariasis transmission through vector control (Bockarie et al, 2009). Transmission of lymphatic filariasis may have been interrupted in the Gambia, São Tomé and Príncipe and Togo, which have the highest coverage rates for insecticide-treated bednets in West Africa (Bockarie et al, 2009). In these three countries, MDA has been either stopped or considered unnecessary. There is no evidence of ongoing transmission in Costa Rica, Suriname or Trinidad and Tobago, where indoor residual spraying was performed for a limited period during the malaria eradication campaigns of the 1970s, and no imported cases have been reported in these countries since 2000 (WHO, 2009).

Vector control efforts aimed at malaria eradication during the 1960s and 1970s did not achieve the desired targets in many parts of Africa and the Asia-Pacific region. However, the transmission of lymphatic filariasis was interrupted in parts of Togo, Solomon Islands, Papua New Guinea and Indonesia, where *Anopheles* mosquitoes were the major carriers of the filarial parasite (Bockarie et al, 2009). Effective vector control would be an important supplementary approach to expedite interruption of transmission.

Data management in resource-poor settings

Disease mapping, routine surveillance and the monitoring and evaluation of programmes play a central role in both achieving and determining the success of MDA implementation. This involves the collection and reporting of both laboratory and demographic data.

However, collecting reliable standardised data in developing countries is often impeded by a lack of data management infrastructure, including desktop and handheld computers, network connectivity and expertise in information technology. Most data is entered and collected using paper forms, which has drawbacks such as inefficient collection, transcribing errors and long delays before the data is available — this can all result in delayed reporting to donors and other partners.

The rapid growth of a mobile phone infrastructure in developing countries provides unique opportunities to address gaps in the collection and reporting of health data from the peripheral health level, i.e. community. Such data could potentially be collected more reliably, less expensively and more rapidly using a mobile phone platform. In addition, a new generation of mobile phones (smartphones) means that the collection of complementary data, including Global Positioning System (GPS) co-ordinates, photographs, video and barcode scans, are now possible (Aanensen et al, 2009). Data can be submitted by smartphone directly to a database, which can be analysed using web-based applications such as Google Maps or Google Earth. Georeferencing and visualisation of such data can allow district programmers to identify particular at risk or low coverage areas in need of targeted resources, and can help answer associated operational research questions. In this regard,

data from other sources can be also displayed, such as rainfall patterns, locations of roads and water sources or disease risk maps, which would not otherwise be accessible at the peripheral health level.

Monitoring is not just an exercise in gathering data and reporting back to a higher level, it can also inform managers of the status of their programmes. Data can be requested and displayed on smartphones *via* the web, thereby informing programme managers on the ground. The Centre for Neglected Tropical Diseases (CNTD) in the Liverpool School of Tropical Medicine is piloting a smartphone-based monitoring and evaluation framework for the collection of data in mapping, routine surveillance and monitoring and evaluation of neglected tropical disease programmes in selected African countries.

Conclusion

Coordinating an integrated approach to neglected tropical diseases involving public and private institutions in unstable countries is a huge challenge (Hotez et al, 2009). Many of the stakeholders are sporadically funded and require separate reporting systems.

Nevertheless, the chances of success are promising because the tools are simple and many African leaders have long been committed to a community-directed approach through their association with APOC. APOC, which has been the architect of the community-directed approach to filariasis control, has built a strong and productive working relationship with the health ministries in various endemic countries. It has been highly successful in post-conflict and fragile states where few other disease control programmes targeting neglected tropical diseases exist (Amazigo, 2008b; Hotez et al, 2009).

The WHO director general and the organisation's department of neglected tropical diseases represent a clear point of leadership. The dominant funding organisations, The Bill and Melinda Gates Foundation, United States Agency for International Development (USAID) and the UK Department for International Development (DFID) are also committed to an integrated approach.

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In September 2008 following announcements of support for neglected tropical diseases from President Bush and The Bill and Melinda Gates Foundation, the UK Secretary of State for International Development, Douglas Alexander, announced a £50 million commitment to neglected tropical diseases over the five-year period 2009–2014. The DFID, through the CNTD at Liverpool School of Tropical Medicine, is now supporting 10 endemic countries in Africa to reduce the prevalence of lymphatic filariasis and progress towards elimination of the disease. This will be achieved through capacity strengthening, operational research and advocacy. JL

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References

Aanensen DM, Huntley DM, Feil EJ, al-Own F, Spratt BG (2009) EpiCollect: linking smartphones to web applications for epidemiology, ecology and community data collection. *PLoS One* **4(9)**: e69–8

Amazigo U (2008a) The African Programme for Onchocerciasis Control (APOC). *Ann Trop Med Parasitol* **102 (Suppl 1)**: 19–22

Amazigo U (2008b) Engaging the community: an interview with Uche Amazigo by Brown Hannah. *PLoS Negl Trop Dis* **2(7)**: e268

Bockarie MJ, Molyneux DH (2009) The end of lymphatic filariasis? *Br Med J* **338**: 1686

Bockarie MJ, Pedersen EM, White GB, Michael E (2009) Role of vector control in the global program to eliminate lymphatic filariasis. *Annu Rev Entomol* **54**: 469–87

Edison JFB (1962) Epidemiology and treatment of infection due to *Brugia malayi*. *Bull WHO* **27**: 529–41

Gyapong JO, Kumaraswami V, Biswas G, Ottesen EA (2005) Treatment strategies underpinning the global programme to eliminate lymphatic filariasis. *Expert Opin Pharmacother* **6(2)**: 179–200

Hotez PJ, Fenwick A, Savioli L, Molyneux DH (2009) Rescuing the bottom billion through control of neglected tropical diseases. *Lancet* **373(9674)**: 1570–75

Kamgno J, Pion SD, Mackenzie CD, Thylefors B, Boussinesq M (2009) Loa loa microfilarial periodicity in ivermectin-treated patients: comparison between those developing and those free of serious adverse events. *Am J Trop Med Hyg* **81(6)**: 1056–61

Mackenzie CD, Lazarus WM, Mwakitalu ME, Mwingira U, Malecela MN (2009) Lymphatic filariasis: patients and the global elimination programme. *Ann Trop Med Parasitol* **103(Suppl 1)**: S41–51

Michael E, Bundy DA, Grenfell BT (1996) Re-assessing the global prevalence and distribution of lymphatic filariasis. *Parasitology* **112(Pt 4)**: 409–28

Molyneux DH, Hotez PJ, Fenwick A, Newman RD, Greenwood B, Sachs J (2009) Neglected tropical diseases and the Global Fund. *Lancet* **373(9660)**: 296–7

Ottesen EA, Hooper PJ, Bradley M, Biswas G (2008) The global programme to eliminate lymphatic filariasis: health impact after 8 years. *PLoS Negl Trop Dis* **2(10)**: e317

Perera M, Whitehead M, Molyneux D, Weerasooriya M, Gunatilleke G (2007) Neglected patients with a neglected disease? A qualitative study of lymphatic filariasis. *PLoS Negl Trop Dis* **1(2)**: e128

Pourgholami MH, Szwajcer M, Chin M, Liauw W, Seef J, Galettis P, Morris DL, Links M (2010) Phase I clinical trial to determine maximum tolerated dose of oral albendazole in patients with advanced cancer. *Cancer Chemother Pharmacol* **65(3)**: 597–605

Taylor MJ, Makunde WH, McGarry HF, Turner JD, Mand S, Hoerauf A (2005) Macrofilaricidal activity after doxycycline treatment of Wuchereria bancrofti: a double-blind, randomised placebo-controlled trial. *Lancet* **365(9477)**: 2116–2121

World Health Organization (2006) Preventive chemotherapy in human helminthiasis. WHO, Geneva. Available online at: http://whqlibdoc.who.int/publications/2006/9241547103_eng.pdf [accessed 8 March, 2010]

World Health Organization (2009) Global programme to eliminate lymphatic filariasis. *Wkly Epidemiol Rec* **84(42)**: 437–444