



The WHO Collaborating Centre for the Control of Lymphatic Filariasis

Working together

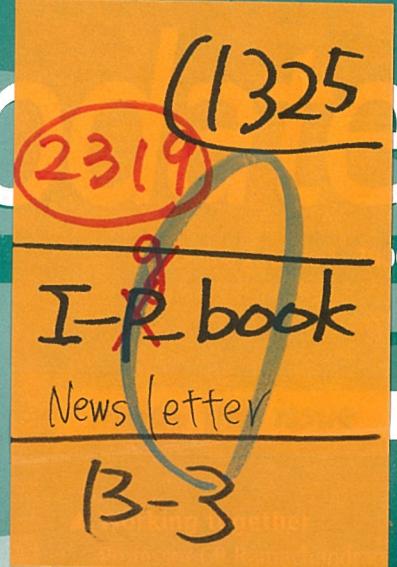
Professor CP Ramachandran

I do hope you enjoy reading this big issue of Filarial Update as we have several interesting articles for you. Dr Maria Neira reports in her article on the announcement of an elimination program for lymphatic filariasis as a public health program. Then from the Liverpool School of Tropical Medicine we have an article from Mark Taylor on his work on *Wolbachia* and from Paul Garner with the Cochrane approach to filariasis systemic reviews. Dr Biswas informs us of a meeting held in India and a workshop held in Cairo and Hans Remme has some interesting news on the important World Health Organization initiative ComDT. Bruce Benton from The World Bank provides us with his recent presentation on the African Program of Onchocerciasis Control. This issue's Regional Update is from Dr Ichimori who has sent us a fact sheet on the outcome of a planning meeting held in Fiji at the end of last year.

As I'm sure you are aware, lymphatic filariasis, a painful and disfiguring disease affecting over 120 million people in 76 endemic countries, has a major social and economic impact and until recently, little if anything could be done to alleviate the suffering and disability caused by the disease. India alone accounts for 41% of the global burden of lymphatic filariasis with an estimated economic loss to the tune of US\$1.5 billion per year. Significant advances have been made in the recent past in understanding both the disease and its control. A start was made in 1997 when the World Health Assembly passed a resolution calling for the elimination of lymphatic filariasis as a public health problem. Since then, through WHO, a global coalition has been formed among many organisations, each with a different mandate but all having a common goal ie. to eliminate lymphatic filariasis as a public health problem from the world.

The disease which affects people physically, mentally and psycho-socially, often the poorest of the poor, has today reached the alarming figure of 120 million infected globally, and nearly 1.1 billion people at risk of infection in 76 endemic countries. These are frightening statistics to all public health workers. However, statistics become a reality when one takes a walk through the villages and shanty towns in endemic countries and visualise people, both young and old, men, women and children walking around with enlarged legs, feet, hands and genitals in addition to other parts of their bodies. The gross clinical symptoms produced by the disease in its chronic stages, viz 'elephantiasis', is the phase dreaded most by every individual infected with filariasis. It cripples them, demoralises them, makes them social outcasts in their own communities and society due to the social stigma and alienation. Today the disease still continues to spread unabated in many parts of the world due to continued unplanned urban and semi-urban development; man-made environmental and ecological disasters and habitats, which continue to enhance mosquito breeding and consequent transmission of the disease. The remarkable advances in diagnosis, clinical understanding, treatment and control of the disease over the past decade has brought to us newer intervention measures that are effective, affordable and sustainable towards the elimination of lymphatic filariasis as a public health problem.

Individually no one organisation can eliminate lymphatic filariasis, but working together as partners and working through Ministries of Health of endemic countries, this can be achieved. Working together we can realise our vision of elimination of the disease by the year 2020 - together we shall conquer!



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Update on Filariasis Intervention Research

Dr Hans Remme, Manager, Task Force on Filariasis Intervention Research, WHO/TDR and Professor Oladele Kale, Former Manager, Task Force on Community-Directed Treatment of Filariasis, WHO/TDR

In 1997 the World Health Assembly passed a resolution calling for "...the elimination of lymphatic filariasis as a public health problem...". Since then the pace of activities towards achieving this goal has increased considerably. Recognising that the effective implementation of filariasis elimination poses major challenges and that research is needed to help resolve the most important problems encountered, the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) has given priority to research on lymphatic filariasis. With the emergence of new treatment regimens, TDR research is increasingly concentrated on developing and testing intervention strategies and finding solutions to implementation problems. One of the main challenges is to deliver single-dose treatment to the populations of endemic communities, and to sustain a sufficiently high treatment coverage for a long enough period to ensure the elimination of filariasis as a public health problem. This is the same challenge facing onchocerciasis control and, because of the many similarities with onchocerciasis, TDR has created a Task Force that addresses intervention research on both diseases together.

In 1997, a Task Force on Community Directed Treatment of Lymphatic Filariasis and Onchocerciasis was created, consisting of independent experts in the scientific disciplines involved. This Task Force has now largely completed its workplan, and it has been succeeded by a Task Force on Filariasis Intervention Research. In this article we will briefly describe some of the most important research findings of the last 12 months for lymphatic filariasis, as well as the results of a recent poll on research needs which has become the basis for a new workplan.

Recent research findings

A multi-country study of drug delivery in lymphatic filariasis has been completed in Africa and India. Community-Directed Treatment (ComDT), in which the community takes responsibility for the organization and execution of treatment of its members, was compared with mass treatment organized and executed by the regular health services (HST).

In the African sites, ComDT achieved very good coverage rates - of 75%-88% of the population above 5 years of age. The coverage achieved by the health services was unsatisfactory, at around 45% - with such a low treatment coverage, elimination will not be feasible. The good performance of ComDT was not unexpected as it has already proved effective in onchocerciasis control. ComDT is now the principal drug delivery strategy in the onchocerciasis control programmes in Africa. However, an important new feature of the filariasis study was the introduction of ComDT to the community through the health services. Researchers only provided initial training to District Health Management Teams, and from then on the district health staff took over without any further external assistance. District health staff were initially sceptical about giving the responsibility for treatment to communities, but after their experience with ComDT they became very positive about this approach. This is an important finding as it indicates how ComDT can be integrated in the health system, and that district health staff can and want to play a central role in ComDT. The full report of the



A Community-Directed Distributor (left) explaining how many tablets to take
(photo: WHO/TDR/Crump)

study is available from TDR. In India, the study produced very different results, with ComDT being equally or less effective in terms of treatment coverage than HST. However, the treatment coverage achieved by the health services, though generally better than with ComDT, was often below the coverage thought to be required for achieving elimination, and further analysis of the data is ongoing to identify factors which may help to improve treatment coverage with HST. One such factor could be compliance with treatment: some 5-15% of all eligibles in the Indian sites received the tablets but failed to swallow them. Such failures were hardly seen in the African sites. The results of the final analysis will be discussed with the National Filariasis Control Programme of India during a workshop to be held in April 2000.

Testing the antigen detection test

A multi-country study was done to test the validity of the new filarial antigen detection test (the ICT or card immuno-chromatographic test) under field conditions in endemic countries. Eight countries were involved, three in Africa, three in Asia, one in the Pacific and one in the Caribbean. Sensitivity was tested in 100 mf positives per site and specificity in 100-200 persons from an area without filariasis transmission, e.g. at an altitude which is vector free. The

test had a high sensitivity of 98.9% (96.7-100%) except in the Indian site, where it was 71.9%. The individual Indian readings were later confirmed and a follow-up study is now under way in several Indian sites. The overall specificity of the test was 99.6% and it was high in all sites (97% - 100%). There were only five "false positives", 3 from Ghana (from an urban area) and 2 from Tanzania (from a mountain village), both presumed transmission free areas. The ICT appears to be an excellent test for mapping distribution of the infection in areas where the distribution is not yet sufficiently known to plan treatment.

Rapid mapping

Mapping the distribution of filariasis is a pre-requisite for filariasis elimination, especially in Africa where the distribution is hardly known. A multi-country study was therefore started on Rapid Assessment of the Geographical Distribution of Bancroftian Filariasis (RAGFIL). Following a review of spatial patterns of filariasis in sites for which detailed surveys were available, it was postulated that filariasis foci tend to be large with a diameter of at least 50 km. A rapid mapping method was proposed that uses a spatial sampling grid with 50 km between sampled villages and rapid assessment surveys by hydrocele examination or antigen testing (using the ICT). Spatial analysis techniques are then applied to analyse the spatial correlation pattern and estimate the prevalence contours of filariasis throughout the area to be mapped. Overlay of these prevalence contours with available population data in a GIS allows estimation of the burden of disease. The proposed method was field-tested in 4 countries - Ghana, India, Myanmar and Tanzania - in a study which was completed in 1999. The study showed: (i) a highly significant spatial correlation between sample villages, confirming the existence of large filariasis foci; (ii) the prevalence contours obtained with the 50x50 km grid to be operationally similar to those obtained with a 25x25 km grid, indicating that the 50x50 km grid is adequate for rapid mapping of filariasis; and (iii), a strong correlation between the results obtained with hydrocele examination and with the ICT in 3 of the 4 sites (India being the exception).

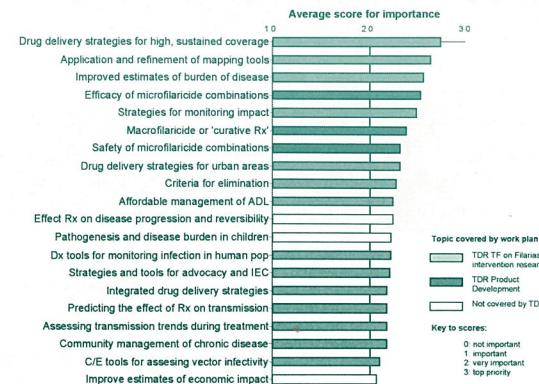
Some other ideas on filariasis mapping had emerged in the meantime, notably the use of the implementation unit - the health administrative unit within which all residents would receive mass treatment - in sampling. A standard method for mapping filariasis in Africa has now been agreed upon which combines the strongest

elements of the different ideas, including the use of the implementation unit as well as the spatial sampling and analysis approach of RAGFIL. A plan for mapping filariasis in Africa has been developed in which it is proposed to implement the mapping in phases. The first phase has started in five West African countries and in Tanzania, and is coordinated by the filariasis elimination unit of WHO with technical support from TDR.

Review of research needs

A review of research needs was undertaken to ensure that the new Task Force workplan addresses the priority research needs as perceived by the many partners involved in the elimination efforts. WHO staff from the control and research departments, and some associated external experts, first made a list of 48 filariasis research needs. This list was subsequently e-mailed to 81 experts in filariasis control and research, requesting them to comment, make additions where required, and score each of the listed items according to current importance for filariasis elimination. Responses were received from some 50% (taking into account group responses), half of whom were from filariasis endemic countries. The respondents considered the list of research needs to be comprehensive. The top twenty needs - those receiving the highest scores - are given in the chart, ranked by average score. A group of WHO staff reviewed the results and suggested who could or should address which priority needs, whether in TDR or elsewhere. TDR has accepted these suggestions and other organizations have also already responded positively.

Priority Research Needs for Filariasis Elimination (Top 20)



New TF workplan

A new workplan for the TDR Task Force on Filariasis Intervention Research was developed on the basis of the identified priority needs, and ongoing research activities were incorporated in this new plan. Drug delivery remains a top priority for the Task Force, but there will be new emphasis on elimination strategies, and on monitoring and evaluation.

The goal of the Task Force will be to develop and facilitate the implementation of cost-effective interventions which meet the requirements of endemic communities, and of onchocerciasis control and filariasis elimination programmes.

The main objectives are:

1. To develop and facilitate the implementation of cost-effective drug delivery strategies for onchocerciasis and lymphatic filariasis.
2. To determine what treatment strategies are required to achieve filariasis elimination, and to develop methods for monitoring and evaluation of filariasis elimination programmes.
3. To develop and apply methods for rapid geographic mapping of disease and of target areas for treatment.

The first meeting of the Task Force will be from 8-11 May 2000. Under discussion will be the specific research activities that need to be generated in order to meet the above objectives. Details will be advertised shortly afterwards. The workplan is available from the TDR Website at www.who.int/tdr/grants/workplans/filaris.htm or from the Task Force manager:

Dr. Hans Remme, Manager,
Task Force on Filariasis Intervention Research,
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Filarial Outlook

Dr Paul Garner, Co-ordinating Editor, Cochrane Infectious Diseases Group,
Liverpool School of Tropical Medicine

Filariasis is not an easy infection to eradicate, and we have a mix of control strategies to tackle the problem, but exactly how effective are they? Most interventions have effects that are not dramatic, and research investigating the comparative advantages of newer regimens and drugs seek relatively small differences in effects against established intervention protocols. Randomised trials are used to evaluate comparative advantages of particular interventions, and it is now accepted that summarising this information should be done scientifically using methods of research synthesis.

Researchers working in trials of filarial interventions will be well aware of the problems investigating benefits and harms, and these will face the reviewers. Measures of impact on transmission and disease are not easy to interpret; adverse effects are often important and not easily quantified; and impacts require interventions across whole communities. These challenges make it even more important to get on top of existing trial data.

The Lymphatic Filariasis Support Centre at the Liverpool School of Tropical Medicine, co-ordinated by Professor David Molyneux, is working closely with the Cochrane Infectious Diseases Group to summarise evidence from trials to help fine tune programmes. The Cochrane Infectious Diseases Group has over eighty contributors, six editors, and 10 years of experience in summarising diseases

relevant to the tropics in filariasis control. The reviewing process will include wide consultation at the protocol stage - the materials and methods section of the review - working closely with experts, searching carefully for relevant unpublished materials, and contacting researchers where additional data are required.

We've just started the work by consulting with WHO and others, assembling a register of trials, and now seek a full time research associate with good quantitative skills (preferably with experience in systematic reviewing) to work with us in Liverpool for two years. There will also be a number training fellowships for individuals from developing countries to develop protocols and reviews in particular areas that interest them. Applicants from women in developing countries are encouraged as they are under-represented in Cochrane Review Groups.

Further information on the Cochrane Infectious Diseases Group is on the web site at www.liv.ac.uk/lstm or by contacting Reive Robb, Liverpool School of Tropical Medicine, Pembroke Place Liverpool L3 5QA (e-mail reive@liv.ac.uk). Details of the Research Associate post are with Eileen Tedford, the Personnel Officer (e-mail emt@liv.ac.uk), and people interested in the training fellowships should contact Joan Fahy, Filariasis Initiative Co-ordinator (e-mail fahy@liv.ac.uk).

Global Program Starts Up!

Dr Maria Neira, Director, Department of Control, Prevention and Eradication, Programme on Communicable Diseases, World Health Organization

The first people in communities where lymphatic filariasis is endemic have now received anti-parasitic drugs as part of the programme to eliminate LF as a public health problem.

On January 20th 2000, at a scientific meeting in London hosted by the Royal

Society for Tropical Medicine and Hygiene, it was announced that Nigeria, Egypt and Samoa were the first countries to initiate programmes to eliminate lymphatic filariasis as part of the LF Global Alliance.

The principal strategy of the programme is to interrupt transmission of infection by treating the entire at-risk population

through community-wide mass drug administration (MDA) programmes.

Community-wide MDA entails the co-administration of two safe and effective oral anti-parasite drugs to members of endemic communities, once-a-year, for at least four to six years. The drugs have the power to interrupt transmission of

infection, thus sparing the next generation from LF. This co-administration of drugs is either albendazole (donated by SmithKline Beecham) and Mectizan, (donated by Merck & Co., Inc.) or albendazole and diethylcarbamazine (DEC). Mectizan, will be given in areas of Africa where onchocerciasis (river blindness) is also endemic; DEC will be used in all other locations where onchocerciasis is not co-endemic. DEC can also be administered as DEC-fortified table/cooking salt.

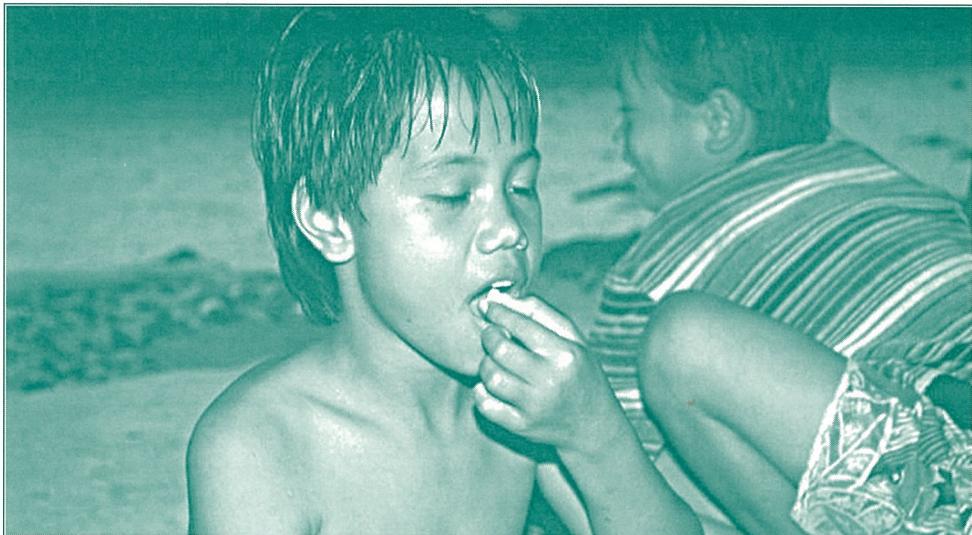
American Samoa, Egypt, the Philippines and Samoa have started the co-administration of anti-parasitic drugs to endemic communities, while Nigeria is preparing to administer mass drug co-administration early in 2000.

It is anticipated that a second wave of countries will begin their programmes later this year. These countries include the Cook Islands, Federated States of Micronesia, French Polynesia, Ghana, Tonga, Togo and Vanuatu, which are hoped to be the next countries to start a programme, beginning implementation this year and expanding to cover the whole country within two years.

How Country Programmes will work

National governments and organisations working with governments are driving elimination efforts forward. A Lymphatic Filariasis National Task Force will be set up in each endemic country to develop and monitor the implementation of the national plan of action. Whenever possible, NGOs and other partners should be part of this Task Force. Applications for drug donations should be made on an annual basis to the appropriate drug donation approval committees, within the framework of the national plans.

Each year the LF National Task Force should review progress on the national plan and this report should form the basis for re-application of additional drug supply.



Drug administration

First Countries to Administer Anti-Parasitic Drugs

Egypt has a total population of 65 million with the total population at risk of lymphatic filariasis estimated as 3.5 million. Currently, it is estimated that 150,000 people are infected with the disease. In November 1999 the Ministry of Health treated over 7,000 individuals at risk under a pilot project, with the co-administration of DEC and albendazole. Egypt will initiate its national campaign of single annual mass drug administration with DEC and albendazole covering the entire at risk population in August 2000. Following four-to-six years of programme implementation, LF infection is expected to fall below the level where new infection can occur. The impact of mass drug administration will be monitored at sentinel sites for interruption of transmission.

The biggest challenge for Egypt will be to achieve and maintain a high level of drug coverage. A sustained health education campaign is being undertaken to try and meet this challenge and to encourage the continued political will that can make the programme a success. The Egyptian programme is supported by WHO and the Arab Fund for Economic and Social Development, a regional development institution established in 1971 at the initiative of the Arab League. Other Arab Fund member countries include Algeria,

Bahrain, Djibouti, Egypt, Iran, Jordan, Kuwait, Lebanon, Libya, Mauritania, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates, and Yemen.

Samoa has a total population of 170,000, and the whole population is at risk from LF. The entire country was covered in 1999 and this process will be repeated in 2000. It is estimated that Samoa will be free of LF infection by the year 2005. The biggest challenge for Samoa is social mobilisation to achieve high coverage.

Nigeria has a total population of 118 million with 80 million estimated to be at risk of LF infection. The number currently infected is estimated to be around 25 million. Nigeria is the country with the second largest burden of LF (after India) with approximately 8% of the world's at-risk population. Areas of Nigeria are also endemic with river blindness. Various organisations have been working on river blindness control in Nigeria for many years and adding an LF elimination programme to this work poses special challenges. Albendazole was delivered to Nigeria in late 1999 to initiate the programme and the first treatments are expected in early 2000. The challenge for Nigeria will be to achieve and sustain a high level of drug coverage in synergy with the river blindness control programme. The Nigeria LF programme is currently supported by WHO and The Carter Centre which is working with the Ministry of Health to initiate a

programme in central Nigeria's Plateau and Nasarawa States. The WHO and the Carter Centre are also assisting Nigerian health authorities in gathering data for the nation-wide elimination programme.

The Launch of an International LF Support Centre

The UK Government's Department for International Development (DFID) was the bilateral donor to pledge funds for the programme to eliminate lymphatic filariasis. This is in recognition of the close correlation between this disease and poverty as part of its aim to halve the proportion of people in extreme poverty by the year 2015. DFID has taken a lead in supporting this initiative. Funds will be used to establish an LF Support Centre at the Liverpool School of Tropical Medicine, with additional funds provided by SmithKline Beecham. The Liverpool School has been actively involved in research and training in both LF and onchocerciasis for many years. Additional DFID funds will be provided to WHO and for operational activities supported through the Liverpool Centre.

International Training Centre

The inauguration of an International Training Centre in Lymphatic Filariasis took place at the Federal University of Pernambuco, Brazil, on 25 October 1999. This inauguration represents a major milestone for the global lymphatic filariasis elimination program as it offers hope for the millions of people who suffer from the disease and for people who live in filariasis-endemic countries, who remain at risk of acquiring lymphatic filariasis. The first International Training of Trainers course in Lymphoedema Management will take place in Recife in May/June 2000. The Centre will focus on morbidity control with a team co-ordinating the development of a variety of training courses.

Clinical Update

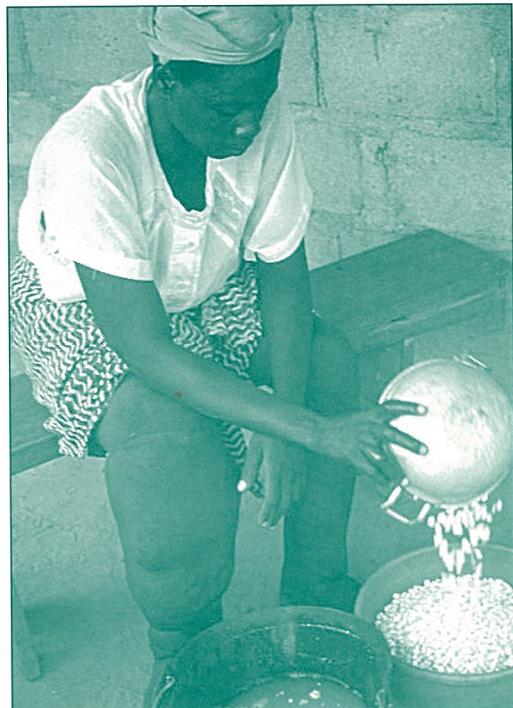
SmithKline Beecham, Merck and Co., Inc., and WHO collaborated to complete the documentation of the safety assessment of the co-administration of albendazole with Mectizan® or DEC. The results were released in November 1999, and showed that there were no serious adverse events or safety concerns identified in either non-LF infected or LF infected individuals, including cases with overt lymphatic disease. The addition of albendazole to treatment regimen did not increase the frequency or intensity of adverse events seen over that when the microfilaricidal drug, DEC or ivermectin is used alone. Following this safety assessment, it has been recommended that national programmes for community wide distribution should be initiated with an initial phase of active surveillance.

The Future

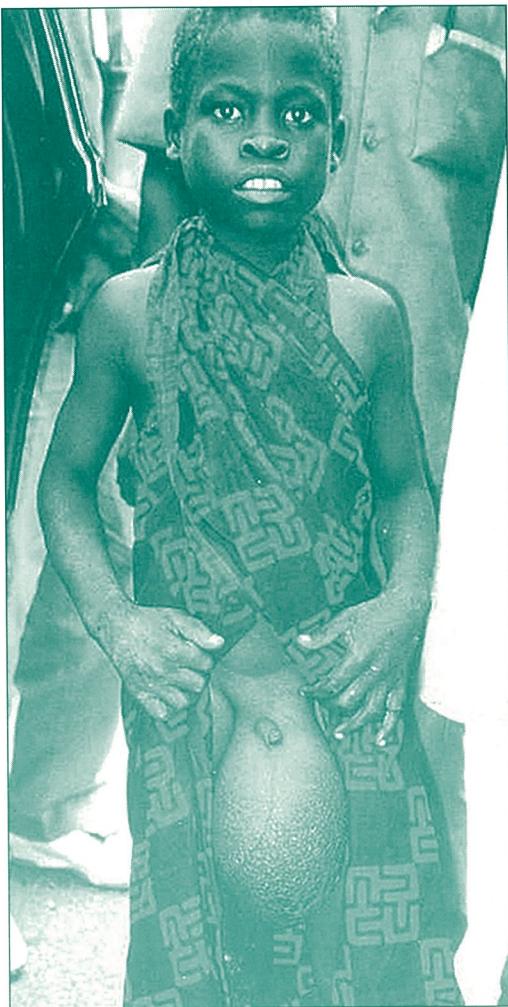
The programme has continued to grow in strength with additional backing from a number of other organisations becoming involved, for example, the Governments of Belgium, Italy, and Spain, and other private sector partners. It now represents an extraordinary coalition of partners working towards the global elimination of LF. Further partners are continually sought. The first meeting of the Technical Advisory Group of experts was held on 2-3 May, followed by the first meeting of the Global Alliance of Partners on 4-5 May in Santiago de Compostela, Spain.

EDITOR'S NOTE

We hope to publish a report of this landmark meeting in the next edition. As of May 2000, 44 countries are in process of developing applications to commence LF programs. Seventeen countries have completed the application process for donated drug(s) and are commencing Stage 1 programs. (Regional breakup is WPRO 10; AFRO 5; SEARO 0; AMRO 1; EMRO 1). Sixteen additional countries are actively in the process of developing applications for donated drugs to commence their LF programs.



Above: Lady with Elephantiasis



Above: Boy with Hydrocele.



Annual International Development Presentation: African Program of Onchocerciasis Control and other Development Programs

A World Bank Perspective

Dr Bernhard Liese and Mr Bruce Benton

James Cook University
Townsville, Australia
18th February, 2000

"Let me get into the story of the program. We have two riverblindness programs in Africa. One was established in 1974, the West African Onchocerciasis Control program.

Robert MacNamara, who was President of the Bank at that time went on his first trip to Africa and saw the disease firsthand. He went to what was at the time Upper Volta (now Burkina Faso) and he saw hundreds and hundreds of people being led around by sticks or on long ropes, who were blind. He thought to himself 'you know, there's no way this whole subregion of Africa can be developed unless we get a handle on this disease. So, is there a way to control it?' He got together with some French scientists and they convinced him there was a way to control it. He came back to the Bank Board, convinced them to establish an international fund, and that's what got the program launched. Nine donors came on board at that time.

Riverblindness, by the way, is also called onchocerciasis so I will use these terms interchangeably. The second program, the one that I launched in 1995, covers the rest of Africa where the disease remains

endemic. Ninety-nine per cent of the world's cases of onchocerciasis or riverblindness exist in Africa. So, if we can eliminate onchocerciasis in these thirty countries, we have essentially eliminated it everywhere in the world. There is a little bit in Latin America, but it's less than one percent.

The burden in Africa – about 120 million people are at risk of the disease in these thirty countries and twenty million people are infected. The disease is caused by a parasite, which is transmitted by a blackfly from person to person. The blackfly bites, picks up a microscopic parasite from someone who has the disease, then continues on and bites someone else and injects that parasite into the body of another person who may not have the disease. That microscopic parasite then develops into an adult worm, which is about three feet long and lives in the human body for fourteen years.

During those fourteen years that adult worm produces millions and millions and millions of microscopic worms which gradually fill up the body. In the process, they cause unbearable itching, and this is

unimaginable unless you have got the disease – I mean, there's no way I can fathom it except to imagine what it would be like to have millions and millions of microscopic worms migrating through your skin all day long and all night. These people can't function during the day and they can't sleep at night. They sit around and scratch themselves with stones and sticks and even machetes, and people have been known to commit suicide just because of the itching. One of the other manifestations is highly disfiguring skin disease, which affects particularly women in their late teens and early twenties. Frequently their families and their husbands abandon them because of the unsightly skin disease which develops. Then, finally, blindness. Once blindness occurs it is a permanent state; it cannot be reversed. Before blindness hits, you can reverse many of the manifestations of the disease. The average onset of blindness is thirty-five years of age, so these people are in what would otherwise be their most productive stage of life. Because they are blind they depend on their families and actually sap productivity from the economy because they are dependent on others who care for them.

At the stage in which 60% of the adult population in a village becomes blind from the disease, usually that village is abandoned because it can no longer survive economically. The village may be dependent upon fishing or agriculture, both of which require water nearby. It was not uncommon back in the 1970's for as many as 60% of the adult population to become blind and therefore these villages were abandoned. People would move upcountry and onto plateaux, where they would overpopulate land. Degradation of the soil would occur, leading to declining productivity. So, a lot of fertile areas were abandoned because of the severity of the disease.

This was what MacNamera came across as a way of controlling the disease – vector control, or spraying the blackfly breeding sites with environmental safe insecticides. Two French scientists convinced him that if you could spray the breeding sites of the blackfly in those eleven countries in West Africa and prevent the flies from reproducing for fourteen years, then all of the adult worms would die out in the population and the disease would be eliminated. So, this was a theory, which hadn't been tried. The program was launched and, in fact, vector control worked. Not immediately, but in time it did work. It was very, very effective. This was the first health program the Bank had supported. It was the first program to establish an ecological committee, which monitored the impact of the spraying of insecticides on the environment to make sure that there was no long-term environmental damage. What they're using now is a biological agent called *Basillus thuringiensis*, which is the same as they're using for gypsy moths in the US. It's harmless for the environment but it does the job.

Then in '87 came a drug called ivermectin, or Mectizan. Merck and Company came up with this pill which was almost a miracle drug in the sense that two pills (dependant on the person's weight) kill off 95% of the microscopic worms in the body with virtually no side effects. Merck decided to give this drug free of charge for as long as needed to as many as need it to eliminate riverblindness in Africa. I can

come back to why Merck decided to do this, but a lot of people were skeptical at the time – why would a pharmaceutical company give out this drug for free? Essentially there was no market there. They either had to withhold it and let people go blind, or give it out for free and be a good corporate citizen. They decided to do the latter, which was really the first major donation by a pharmaceutical company in the developing world. Since then there have been a number of others.

When we started the program in West Africa in 1974, 60% or more of the people living in those communities had the disease. The situation as of three years ago is that we have pretty much eliminated the disease in West Africa with the exception of Sierra Leone. With the fighting that has been going on for the last seven years, we haven't been able to control the disease there. In the southeastern corner of the area there's still some active disease, but that is expected to be eliminated in the next two to three years. The program will be brought to a conclusion in 2002. Only Sierra Leone will be left. Probably we will have a separate Bank project, which will focus on Sierra Leone to eliminate the disease there and prevent the disease from spreading to other parts of West Africa. Then we will have eliminated the disease in West Africa, but not all of Africa of course.

This has opened up arable land – 25 million hectares of arable land, which is fertile land near rivers. There is a lot of spontaneous resettlement moving back into the area. Those 25 million hectares that opened up as a result of controlling the disease, by the way, provide enough food to feed 17 million people a year. So, it's had a substantial development impact far beyond the health effects.

To sum up on the success of OCP: we have 34 million people in that area now fully protected from the effects of that disease. We've prevented 600,000 cases of blindness. 25 million hectares of land have been opened up. We estimate that the program has had an Economic Rate of Return of 25%. This may not mean much to you, but as a result of increased labor productivity by preventing people from

going blind, and the increased arable land which the people can use to produce, this program has resulted in production which, for every dollar invested in the program, has led to a flow of economic benefits which yields 20% per annum, which is very good. The average for a Bank project is about 14%.

The new program, APOC, covers nineteen countries. The objective here is to rid the remainder of Africa of the disease. We had to develop a different strategy here. We couldn't use vector control. The area was too widespread and flying helicopters around that area would have been enormously expensive. Furthermore, many of those areas are forested, and you can't get under the canopy of trees to reach the blackfly breeding sites. So, we're relying solely on the drug, and we're doing it through communities. We're actually giving communities responsibility for designing their own method of delivering the drug and delivering it themselves and keeping track of how it's delivered. This allows them to take ownership in controlling the disease, and hopefully drug distribution will be sustained over a long period of time – a long enough period of time to eliminate the disease in these other countries in Africa.

Remarkable progress has been achieved under this second program. We've got 61 projects now going in 13 countries treating 32 million people per year. We've achieved this within a period of four years. The only countries we're not operating in now are Angola, primarily because of a civil war that's been going on there for a long time, and Congo, where again there is civil disturbance. Remarkably, we have been able to get into Sudan, and although the North and the South are fighting each other, we are delivering the drug in both the Northern areas and the rebel areas. We're able to do this with former US President Jimmy Carter's assistance; he arranged a cease fire there in order to get the program going, and it's continued to function very effectively. We're about the only program that's really operating throughout that country.

This is a huge development partnership, and this is the first time the Bank has

really launched into a partnership like this. The Bank has always made loans for individual countries. Now we're pulling together partners that can offer certain comparative advantages which, when put together, result in a synergistic result much greater than if they operated independently. The partnership is, of course, the countries and the communities within those countries. We've got 25 donors, six of which have just come on this last year. We've got the private sector, Merck, which we estimate will donate a billion tablets over the life of the program, and that value will run in the hundreds of millions of dollars. We have about 30 Non-Governmental Organizations working with us now. There's a Non-Governmental Organization in every project. They're largely North American or European, and there are some local ones as well. These are organizations that are close to the ground, they know the people, they can help us train the communities and those who deliver the drug in the communities, and they've added great value to the program.

There are a couple of precedent-setting benefits to this program. One is that it is establishing a model of global partnership, which we think can be used to address other major disease control problems and maybe go beyond the health area itself. There are, as you know, huge disease problems in Africa – AIDS, malaria – which can't be addressed on a country-by-country basis. You've got to have a global partnership, and you've got to go about it on a regional basis. The other is that we've established a basis for establishing other disease-control interventions within Africa's rural areas, because onchocerciasis is primarily a disease which exists at the end of the road, in the poorest rural areas in which there are no other services. We can now begin to tag onto the distribution of the drug for riverblindness some other disease-control efforts.

To sum up on the financing, we've completely financed the West African program. We have \$560 million dollars that have been mobilized over the past 25 years, and that's enough to bring the program to a conclusion by 2002. For the other one, APOC, we have an \$8 million

gap over the next two years, but I think we're making headway and, with luck, we'll get through it. Then we'll have another phase to go. Once we're through that second phase, which runs through 2007, that will eliminate the disease on the continent.

So, OCP and APOC are rapidly progressing toward eliminating the disease throughout Africa, alleviating poverty for millions of Africans (and these are really the poorest of the poor), strengthening community-level health care in the rural areas, and establishing a model of global partnership. Now just a word on what can be done to add-on another disease. The same drug, ivermectin or Mectizan, is the most effective drug against what is called elephantiasis, or lymphatic filariasis. This is also caused by a parasite, transmitted by a mosquito, which blocks the lymphatic channels, and it causes horrendous difficulties for those who are infected: stigma, total disability. As I said, the mosquitoes transmit a parasite, parasites develop into adult worms, block the lymphatic channels, and this is the kind of swelling that you get, often in the genital areas, sometimes the limbs. These people just hide away. They're outcasts. There are many, many more than we probably have been able to estimate, simply because the disease often effects the genital areas and is a taboo subject. They don't talk about it and do their best to hide it. So, we're trying to bring this out into the open and address it.

The disease burden of elephantiasis is, in fact, greater than onchocerciasis. You've got 120 million people in 80 countries in the world affected with the disease. Forty-four million have visible signs of the disease, and 20% of the world's population is at risk. Lymphatic filariasis is the fourth leading cause of permanent disability in the world. Africa has a third of the cases. Most of the other cases are in South Asia, on the Indian sub-continent. As for the burden in Africa, we've got 43 million people infected, which is more than twice the number of people infected with riverblindness, in 37 countries. It is interesting, though, that these are almost the same countries where onchocerciasis exists. We estimate that the burden of this

disease causes a loss of almost \$2 billion in productivity in Africa per year due to the disabling effects alone. Children are also affected; they can get the disease as young as two years old.

If you look at a map of the overlap between riverblindness and lymphatic filariasis you'll see that's it's almost exactly the same countries; every country that's endemic with riverblindness in Africa is endemic with lymphatic filariasis. As I said, the same drug works equally effectively against both, and it's given free. So now we have the opportunity of eliminating two diseases. By using the donation of ivermectin from Merck, and there is another donation from SmithKlein Beecham for albendazole, and together the combination of ivermectin and albendazole is very effective in halting transmission of this disease. That's what we're aiming at. There is another aspect of it, and that is how do you treat the people who are already affected? That can be done through hygiene and use of antibiotics, and we have to incorporate that into the program eventually, because it's an important part of addressing the entire problem.

So, integration of lymphatic filariasis control into the onchocerciasis framework is feasible and cost-effective. We're starting to see what we can do to combine the two. It's estimated that successful control by integrating the two would result in a rate of return of 27% from today to the year 2029 – a very high rate of return. As I said, we're beginning right now. In fact, about 50% of the work in my office right now is on lymphatic filariasis, not riverblindness. So that is the story of the riverblindness and lymphatic filariasis control programs. We hope to be able to eliminate these two diseases in the next decade. Not before I retire, unfortunately, but within the coming decade. Thank you very much."

Mr. Bruce Benton, Manager, Onchocerciasis Coordination Unit, Africa Region, The World Bank

Filarial nematodes: a bug's life?

Dr Mark Taylor, Liverpool School of Tropical Medicine

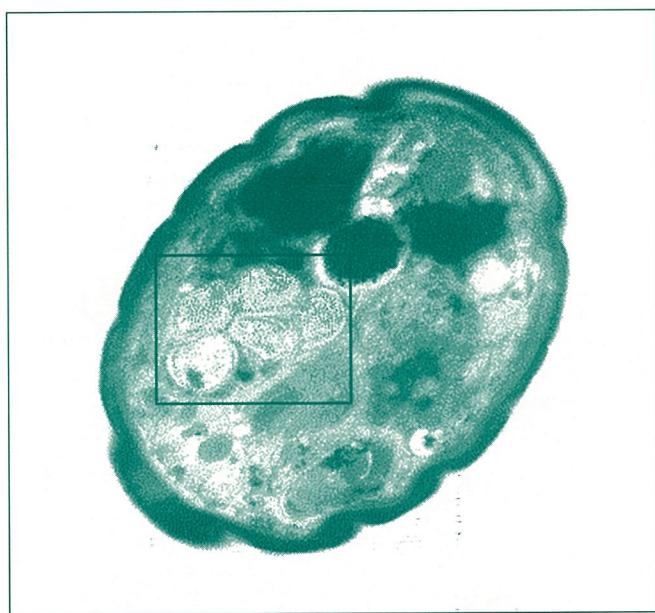
A new and exciting advance in filariasis research is the discovery that filarial parasites appear to have evolved a mutualistic association with their endosymbiotic bacteria *Wolbachia*. Although we have known since the mid 70's that filarial nematodes are infected with intracellular bacteria, it is only recently that new technological advances and experimental studies have shown that the symbionts play an important role in the biology of filarial parasites and contribute to the pathogenesis of filarial disease¹.

The first surprise came when molecular phylogenetics was used to identify the bacteria as members of the rickettsial group of bacteria *Wolbachia*². This group of bacteria was previously known only in insects and other arthropods, with the impressive ability to manipulate the reproductive activity of their hosts to

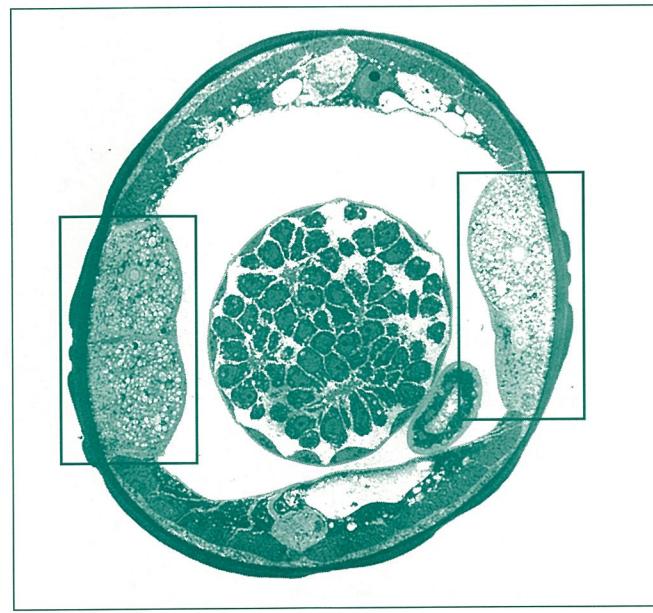
enhance transmission. Further studies have shown that the majority of filarial nematodes, including those pathogenic in humans, are ubiquitously infected with bacteria throughout the species geographical distribution. All developmental stages and individual worms appear to be infected with transmission maintained through vertical transfer via the egg¹.

Next, studies were carried out to see if antibiotic treatment could 'cure' nematodes of their bacteria, and in doing so affect the viability of the nematode. Several studies in animal models confirmed that long-term treatment with the anti-rickettsial drugs, tetracycline and rifampicin, lead to the clearance of bacteria with profound consequences on the embryogenesis, fertility and development of the nematode³. Notably in a cattle model of onchocerciasis, oxytetracycline therapy given at intervals for several months

resulted in adulticidal activity with the complete disappearance of nodules⁴. Encouraged by the promise of filaricidal activity of antibiotic therapy, clinical trials in Ghana have shown that in humans infected with *Onchocerca volvulus*, a 6 week course of doxycycline resulted in a sustained reduction in bacteria accompanied by potent embryotoxicity, leading to a prolonged suppression of microfiladermia following ivermectin treatment⁵. Further studies in animal models and clinical trials on onchocerciasis and lymphatic filariasis are underway to optimise antibiotic treatment regimes and evaluate the prospect of antibiotic targeting in the control of other human filarial parasites. Other important questions to address include: 1) Does antibiotic treatment have any effect on transmission to insect vectors? 2) Why does it take so long to observe adulticidal activity following clearance of the bacteria? 3) Does long-term antibiotic therapy for other



Wolbachia in a microfilaria of *Wuchereria bancrofti* (affected area shown in box)



Wolbachia bacteria in an adult *Onchocerca ochengi* (affected areas shown in boxes)

infections, such as TB and leprosy, have any effect on concurrent filarial infection? and 4) What is the effect of combination therapies of antibiotic and anti-filarial drugs?

Another area in which *Wolbachia* appear to play an important role is in the pathogenesis of filarial disease. In studies on *Brugia malayi*, the characterization of parasite-derived inflammatory stimuli found that endotoxin or lipopolysaccharide (LPS) derived from *Wolbachia* was the major activator of pro-inflammatory responses induced directly by the parasite⁶.

Ongoing studies have also shown that in Brugian filariasis, *Wolbachia* are released into the blood following the death of parasites and are associated with severe inflammatory adverse reactions following DEC chemotherapy (Taylor et al unpublished). The release of *Wolbachia* following drug-induced or natural elimination is therefore likely to contribute to acute inflammatory responses associated with the death of parasites.

The chronic release of bacteria and/or inflammatory mediators may also contribute to the development of chronic pathologies through the induction of tolerance in innate immune responses. The potential damage of acute inflammation on lymphatic tissues and the suppression of innate immunity would favour the establishment of the opportunistic infections often associated

with chronic pathology in lymphatic filariasis. The targeting of bacteria with antibiotics, in addition to having effects on embryogenesis and worm viability, may prevent the onset of chronic pathology and reduce severe adverse reactions to filarial chemotherapy. Although many more studies are required to investigate the full potential of antibiotic therapy in anti-filarial and anti-pathology treatment, the prospect of a novel target, treatable with drugs which are readily available in many endemic communities make *Wolbachia* an attractive candidate for the future control of filariasis.

Ongoing research will hopefully begin to unravel the nature of the association between bacteria and nematode. Is the effect of antibiotic therapy on embryogenesis due to an essential function provided by the bacteria, or does this reflect a form of mating incompatibility as observed in insect *Wolbachia*? Can nematodes be 'cured' of their bacteria and regain viability and fertility? Having only recently rediscovered this symbiosis we will soon know the complete genome sequence of *B. malayi Wolbachia*, together with those of its relatives in fruit flies and other arthropods⁷, which will provide valuable information to begin to answer some of the questions raised here. The combination of an intriguing biological association in parallel with the potential for clinical intervention should ensure that *Wolbachia* will encourage further

mutualistic symbiosis between pure and applied research on filariasis.

1. Taylor, M.J. & Hoerauf, A. (1999) *Wolbachia* bacteria of filarial nematodes. *Parasitology Today* 15, 437-442.
2. Sironi, M. et al (1995) Molecular evidence for a close relative of the arthropod endosymbiont *Wolbachia* in a filarial worm. *Molecular and Biochemical Parasitology* 74, 223-227.
3. Taylor, M.J. et al (2000) *Wolbachia* a bacteria of filarial nematodes: a target for control? *Parasitology Today* 16, 179-180.
4. Langworthy et al (2000) *Macrofilaricidal* activity of tetracycline against the filarial nematode, *Onchocerca ochengi*: elimination of *Wolbachia* precedes worm death and suggests a dependent relationship. *Proceedings of the Royal Society of London (series B)* in press.
5. Hoerauf et al (2000) Endosymbiotic bacteria in worms as targets for a novel chemotherapy in filariasis. *The Lancet* 355, 1242-1243.
6. Taylor et al (2000) Inflammatory responses induced by the filarial nematode *Brugia malayi* are mediated by Lipopolysaccharide-like activity from endosymbiotic *Wolbachia* bacteria. *Journal of Experimental Medicine* 191, 1429-1435.
7. Bandi, C. et al (1999) *Wolbachia* genomes and the many faces of symbiosis. *Parasitology Today* 15, 428-429.

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Report from Geneva

Dr Gautam Biswas

The South-East Asian Region held an informal consultation from the 23 – 25 February at Bhubaneswar in Orissa, India. Programme managers at national and regional levels from India, Bangladesh, Thailand, Indonesia, Maldives, Myanmar and Nepal participated along with lymphatic filariasis experts from the region and also WHO staff from HQ and the Regional Office. The consultation lead to the

finalisation of a regional plan to eliminate lymphatic filariasis from South-East Asia. On April 17 and 18, a workshop was held in Cairo on the Elimination of Lymphatic Filariasis from the Eastern Mediterranean Region. The workshop was attended by national focal points from Egypt, Yemen, Pakistan, Iran, Oman and The United Arab Emirates.

REGIONAL UPDATE

PacELF

Elimination of Lymphatic Filariasis in the Pacific

What is PacELF?

PacELF is a regional collaborative approach in eliminating filariasis by the year 2010 - ten years before global elimination is achieved! PacELF represents the 22 islands and territories in the Pacific region. Through the introduction of new tools and the efforts of a coordinating body, PacELF is the first attempt at an elimination of a vector borne disease in a regional area.

Why is a coordinated approach needed in the Pacific?

There are now two new tools to help eliminate filariasis:

- the combination of drugs - DEC and albendazole; and,
- the recent development of antigen test kits.

These tools however are not enough. Coordinating resources is important if elimination is to be achieved within a region. Most islands and territories in the region are small. They have few resources to manage a disease elimination program and small populations. Working together, the islands and territories can share resources including information and help each other implement a comprehensive regional strategy. Most of the Pacific Islands and territories have low prevalence of filariasis. Eliminating the disease completely by 2010 is achievable.

Eliminating filariasis in one country may help in the short term, but because of migration, people travel from island to island frequently. Elimination in one country is not enough as the disease may spread from one country to another. We have to work together.

What is the background for the elimination of filariasis?

- In May 1997, the World Health Assembly called for the elimination of lymphatic filariasis as a public health problem globally by 2020.
- In March 1999, Ministers and Directors of Health endorsed the development and implementation of a comprehensive strategy to eliminate lymphatic filariasis in all 22 Pacific Island countries and territories.
- In June 1999, the World Health Organization and the Secretaries of the Pacific Community sponsored a meeting of public health practitioners and others working in the field of filariasis in the Pacific. Participants nominated members of the Coordinating Body.

- In December 1999, members of the Coordinating Body discussed and agreed to the outline of PacELF at its first Coordinating Body meeting.

Where is PacELF home (HQ)?

PacELF regional office (PacELF HOME) is located in MATAIKA HOUSE; National Centre for Scientific Services on Virology and Vector Borne Diseases, Suva, Fiji.

How can I get more information about PacELF?

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Call for Articles for Filarial Update

If you have an article you feel would be useful for people involved in the control of lymphatic filariasis or perhaps some news from a meeting you would like to share, please contact the editors or e-mail: Brenda.Turner@jcu.edu.au
Facsimile: + 61 7 4781 6336

We would love to hear from you and welcome your feedback.