Elimination of Lymphatic Filariasis:

Roles of Research, International Cooperation, and Participation of Endemic Community Making an Unprecedented Global Program to Eliminate the Neglected Disease into a Reality

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The Global Programme to Eliminate Lymphatic Filariasis (GPELF) inaugurated in 2000 is a unique 'adventure' in a sense that it targets one of the most neglected diseases at a global scale. To accomplish this ambitious program, not only health professionals but community people have been playing an essential role in distributing a huge number of antifilarial drugs. Approximately 500 million people are treated annually worldwide, including numberless 'neglected' people in remote rural areas.

GPELF is said to be one of the most rapidly expanding global health programs in the history of public health. With its cost-effective, systematic mechanism, 60 of 73 endemic countries are conducting national 'mass drug administration' campaign, and 15 of them are now close to the elimination of filariasis.

How can this kind of program be implemented and maintained for more than a decade? What are the achievements and their public health and scientific implications? This review summarizes these topics with emphasis on key researches and field operations which have facilitated this unprecedented program.

Key words: Global Programme to Eliminate Lymphatic Filariasis (GPELF), ICT rapid diagnostic test, diethylcarbamazine (DEC), ivermectin (IVM), mass drug administration (MDA)

What is lymphatic filariasis?

1. Parasite

There are 8 species of filarial parasite that can mature and reproduce in a human body. Three of them (*Wuchereria bancrofti*, *Brugia malayi* and *B. timori*) are called lymphatic filariae because their adults parasitize the lymphatic system. *W. bancrofti* (*W.b.*) is by far the commonest among them (90% of all infected cases), and in this review, *W.b.* is the species of discussion if not specified otherwise. Adult females (9 cm in length) reproduce microfilariae (Mf) (Figure-1A), which are 260 μ m in length, actively motile and circulate in the peripheral blood at night (with some exceptions), and are sucked by vector mosquitos. Mf in the mosquitos develop to infective 3rd-stage larvae (L3s) in about

13-14 days, and then, L3s invade into a new human host during mosquito bites. The life span of adults reproducing Mf is about 5 years¹⁾.

It is known that symbiotic bacterium, *Wolbachia*, parasitizes filarial cells, and is vertically transmitted to progeny (Mf). Without *Wolbachia*, adult filariae cannot survive normally and die eventually. Thus, this bacterium, a kind of rickettsia, can be the target of treatment.

2. Pathology and symptoms

Basic pathology of lymphatic filariasis (LF) is inflammation and disturbance in lymph flow caused by adult worms. The parasitized lymph vessels are dilated and branching with collaterals. The pathogenesis is complicated. Lymphatic endothelial cell growth, proliferation and differentiation are stimu-

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Figure-1 Microfilaria of *Wuchereria bancrofti* (A) and a Japanese case with elephantiasis of the scrotum (B)
[Courtesy of Prof. Yoshito Otsuji]

lated by live adults and their excretory/secretory products, angiopoietins, matrix metalloproteinases, vascular endothelial growth factors (VEGFs), etc.²⁾. In a study with human LF cases, *Wolbachia* is related to the increase of VEGF-C and soluble VEGFR-3 and considered as an important cause of lymphatic pathology³⁾.

Depending on the parasitic site, pathology and duration of infection, lymphedema of limb(s), funiculitis, epididymitis, orchitis, hydrocele, chyluria, etc. will occur. Secondary bacterial infection especially through injuries on the edematous skin will cause acute inflammation with high fever (acute dermatolymphangioadenitis), and the repeated infections may induce thickening and abnormal growth of the skin resulting in disfiguring elephantiasis (Figure-1B). It is also shown that endotoxin-like substance released from *Wolbachia* can induce systemic inflammatory reactions after treatment of *B. malayi* infection⁴⁾.

Mf are harmless in general, but may cause allergic reactions in rare cases (tropical pulmonary eosinophilia).

3. Diagnosis

To detect Mf in the peripheral blood and identify the species morphologically has been the commonest method of diagnosis (finger-prick blood smear method). However, it is cumbersome to collect night blood, make smears and stain with Giemsa.

BinaxNOW[®] Filariasis is an immunochromatographic (ICT) card test to detect circulating filarial antigen. It has been used widely due to its high sensitivity and specificity, ease in handling in the field and very quick result (10 minutes). However, this test is effective only for *W. b.* For *Brugia* spp., the different ICT test to detect *Brugia*-specific IgG4 antibody (Brugia Rapid test) is used⁵⁾.

4. Treatment

Antifilarial drugs used in GPELF are diethylcarbamazine (DEC), ivermectin (IVM) and albendazole (ALB). In LF only endemic areas, the combination of DEC at 6 mg/kg and ALB at 400 mg is given once a year as a single dose. In parts of Africa, where LF is co-endemic with onchocerciasis, another filariasis caused by *Onchocerca volvulus*, a single dose of IVM (150–200 µg/kg) and ALB (400 mg) is used, because DEC may cause severe adverse reactions with the *Onchocerca* infection.

In GPELF, the annual mass drug administration (MDA) is repeated minimum 5 times. MDA is a unique treatment scheme: all people at risk, including infected and non-infected people living in the endemic areas, are included, except ineligible people like very young children, pregnant women, etc.

Treatments of clinical cases with lymphedema/elephantiasis and hydrocele are variable depending on available health services. WHO's program for

morbidity management and disability prevention (MMDP) puts emphasis on local hygiene to prevent bacterial and fungal infections. For example, washing affected limb(s) with soap and clean water, and following drying up with a cloth is the principal measure, and exercise and elevation of the affected limb to drain congested lymph fluid are essential supportive measures. Antibiotics are necessary for severe fever cases with bacterial infection. Hydrocele is treated surgically^{6) 7)}.

It is reported that doxycycline (DOX), which selectively destroys *Wolbachia* endosymbiont, eventually kills adult filariae, reduces plasma concentration of VEGF-C and soluble VEGFR-3, and improves lymphatic pathologies³⁾.

5. Epidemiology

A 1997 paper by WHO listed 73 LF endemic countries in the world. *W.b.* only was endemic in 65 countries, *B. malayi* was co-endemic with *W.b.* in 7 countries and *B. malayi* only was endemic in Republic of Korea. All *B. malayi* endemic countries are in Asia⁸⁾. It was estimated that there were a total of 119 million infected cases globally (106 million *W.b.* cases and 13 million *B. malayi* cases). India and Sub-Saharan Africa accounted for 43% and 38% of the total global cases, respectively. China had 5.5 million cases, occupying 5% of the global total. The number of clinical cases with hydrocele or lymphedema was 43 million in total. As a whole, the prevalence in the 0–4 year age group was the lowest (0.5%), which gradually increased up to 4.2% in the 45–59 year group. Males had 1.7 times more cases than females⁹⁾. *B. timori* infection was reported only on several islands in Indonesia¹⁰⁾.

The global elimination program must have reduced the burden of filariasis significantly in the past 14 years. However, the baseline epidemiological figure (120 million infected people) has been still surviving in recent WHO documents.

GPELF: the background of establishment, activities and achievements

1. Outline of the GPELF

The 50th World Health Assembly held in May 1997 resolved to eliminate lymphatic filariasis from the world. The “elimination” is to control the clinical manifestations so that the disease is no longer

considered a public health problem. Operationally, a certain level of infection prevalence (threshold) was fixed, below which no more transmission would occur after stopping MDAs (Mf prevalence of <1%, revised in 2011¹¹⁾).

The GPELF was inaugurated in 2000 with the target to accomplish the elimination by 2020. The two strategic aims are (i) to interrupt transmission using MDAs (repeat a minimum of 5 times), and (ii) to alleviate suffering and disability by providing access to basic care for people with symptoms such as lymphedema and hydrocele.

The magnitude of GPELF can be recognized by the estimation that a total of 1.4 billion people have to be treated annually, covering 120 million infected people and nearly 1.3 billion non-infected people living in the endemic areas.

Each endemic country organizes the national program to eliminate LF and carries out mapping of endemic areas to be treated, MDAs (registration of people, drug delivery and evaluation of treatment coverage), and follow-up surveys to confirm the effects of MDAs. More recently, after successful MDAs in an increasing number of countries, a more systematic transmission assessment survey (TAS) has been implemented to decide when to stop MDA and, further, to confirm the elimination¹¹⁾.

2. Why lymphatic filariasis was selected as a target of the global elimination?

In 1980, WHO proudly declared the eradication of smallpox. Thirteen years later, the International Task Force for Disease Eradication (ITFDE) selected 6 eradicable or potentially eradicable diseases after reviewing more than 90 diseases¹²⁾. They are dracunculiasis, poliomyelitis, lymphatic filariasis, mumps, rubella, and taeniasis/cysticercosis. Here the “eradication” was defined by the task force as “reduction of the worldwide incidence of a disease to zero as a result of deliberate efforts, obviating the necessity for further control measures.” Lymphatic filariasis was selected as a potentially eradicable one, and it will be enlightening to know how well LF meets the ITFDE selection criteria of eradication.

Scientific feasibility (Criteria [1] to [3])

[1] Epidemiological vulnerability

Transmission efficiency of lymphatic filaria is

very low in several respects. First, as a matter of fact, the parasite does not multiply in mosquitos and humans. Second, in the vector, a large majority of Mf cannot develop to infective larvae (L3s)¹³⁾, though mosquito species and other factors could influence the result. Thirdly, the majority of L3s released on the human skin during mosquito bites cannot penetrate the skin and reach to the human tissues for further development, and furthermore, it takes > 8 months for L3s to mature, mate and reproduce in human body¹⁴⁾. Finally, the parasite does not have animal reservoirs, indicating that treatment of humans can reduce the source of infection. Relatively easy diagnosis of LF infection is another advantage for elimination/eradication.

[2] Effective way of treatment

DEC has been the most effective antifilarial drug since it was introduced in 1947. It was also shown to be safe for use in mass chemotherapy. Before the mid-1980s, several studies had confirmed that annual single-dose DEC treatment at 6 mg/kg could reduce Mf count by 80–90% 12 months after treatment^{15)–17)}, indicating that a large scale chemotherapy in endemic areas is feasible. On another front, DEC, which is tasteless, odorless and heat-resistant, was shown to be effective when mixed with cooking salt and taken daily at a very low dosage. The DEC-medicated salt was employed successfully in China as a simple and safe mass treatment of a large population¹⁸⁾. Fortunately, no drug resistance has been confirmed with DEC so far.

IVM, which had been used for onchocerciasis mass treatment before GPELF was implemented, was tested for LF treatment, and the efficacy to kill Mf and the safety were confirmed^{19) 20)}.

[3] Demonstrated feasibility of elimination

Elimination of filariasis had been reported in several Asian countries. In Japan, the disease was highly endemic especially in the southern parts. The government-supported nationwide control initiative started in 1962 with DEC mass treatment (including Mf positive people only), and successfully eliminated the infection by around 1978²¹⁾.

In China, there are many success stories²²⁾. For example, in Shandong province, the antifilariasis campaign in 1970–1983 based on various DEC

regimens, including DEC-medicated salt, successfully reduced mf rate to < 1% throughout the province by 1983, and follow-up studies revealed further decline of the rates, even to 0% in many study sites without DEC treatment²³⁾. In Korea, *B. malayi* was endemic countrywide with 3 major foci, including Jeju island. Extensive DEC treatments in 1960s – early 70s successfully reduced the infection and in the mid-1980s, it was considered that filarial transmission had been almost ceased except in groups of islands in the southwestern part of Korean Peninsula²⁴⁾.

Political will/Popular support (Criteria [4] to [7])

[4] Perceived burden of the disease

LF is a disease of global scale. The number of patients enduring physical and mental suffering from lymphedema/elephantiasis and hydrocele was estimated to be 43 million, and LF was ranked by WHO as the second important cause of permanent and long-term disability²⁵⁾. Acute filarial fever also incapacitates infected people and causes a vast loss of working days. Thus, economic loss due to the disease is huge: in India alone, it was estimated that a minimum of US\$ 842 million were lost to patients and households/year from treatment costs and loss of working days²⁶⁾.

[5] Cost of eradication

Any eradication program should cost tremendously. However, this cost can be balanced by the benefit the eradication will bring about, which can also be enormous due to its scale. In India, the above mentioned economic loss (US\$ 842 million) was estimated to be far more costly than carrying out dozens of annual MDA with DEC. On the other hand, there was a favorable environment for a LF elimination program: Merck & Co. was donating IVM for onchocerciasis mass therapy in West Africa since 1986 (Mectizan[®] Donation Program), and community people were supporting the drug distribution.

[6] Synergy of eradication efforts with other interventions

Most of the helminthic infections can be cured easily by taking medicine, but hundreds of millions of people continue suffering from them. A program to eliminate LF globally is a real challenge to such

gloomy reality in the history of health services. If successful, the implication will be tremendous: based on the experiences obtained, all neglected diseases will be re-evaluated and new challenges can be organized to combat the problems. In fact, later in 2005, WHO set up the Department of Neglected Tropical Diseases (NTDs), and now NTDs are a big health topic, for which government agencies, NGOs, companies, etc. have been collaborating²⁷⁾.

[7] Necessity for eradication rather than control

LF is not a fatal disease and drug treatments can prevent the infection. The disease may even disappear as living conditions improve. Considering misery of clinical cases being ignored, it would be reasonable to start elimination program quickly rather than preparing for eradication, which is much more challenging.

3. Achievements by GPELF

First of all, it was confirmed that 5 rounds of annual MDA could reduce Mf load in the endemic population significantly: Of 68 pre-selected sentinel sites to monitor treatment efficacy, the MDAs reduced the Mf prevalence to zero in 43 (63%) sites. During the first 8 years of GPELF (2000–2007), a minimum of 570 million individuals in 48 endemic countries were treated, or accumulated

total of > 1.9 billion doses were given through annual MDAs. These treatments reduced LF transmission progressively, and stopped new infections. As a result, it was estimated that 6.6 million newborns had been protected from contracting filariasis, and this would prevent 1.4 million hydrocele and 0.8 million lymphedema cases in their lifetimes. Also, 9.5 million infected but subclinical cases were protected from developing a total of 6 million hydrocele or 3.5 million lymphedema. Altogether, an estimate of 32 million DALYs (Disability Adjusted Life Years) were averted²⁸⁾.

The economic impact of the first 8 years of GPELF was also analyzed. It was estimated that US\$ 21.8 billion of direct benefit would be gained over the lifetime of 31.4 million individuals treated, which include children born into areas freed of LF transmission, and already infected people benefitted from the program. In addition, the health systems of endemic countries could save US\$ 2.2 billion. It is concluded that GPELF is an excellent investment in global health²⁹⁾. This owes much to generous donation of antifilarial drugs by pharmaceutical companies.

WHO summarized the achievements at the halfway point of the program, covering the years from 2000 to 2009³⁰⁾. In this report, the number of endemic countries is 83. China and Korea declared the elimination in 2007 and 2008 respectively. Of

*Before 2009, some countries such as India used only DEC for MDA.

[Source: ref. No. 32]

Figure-2 No. of people receiving treatment through mass drug administration (MDA) for lymphatic filariasis and number of countries delivering MDA, 2000–2012

remaining 81 endemic countries, 68 had completed mapping of endemic foci, and 10 of the 68 were considered unnecessary to implement MDA due to extremely low transmission levels. In 2009, 53 countries were implementing MDA and 37 of them have completed 5 or more rounds of annual MDA (nationwide or partially). Meanwhile, the progress of morbidity management program was delayed. Only 27 endemic countries had implemented the program.

According to the latest WHO report on GPELF³¹⁾, in 2013, out of the 73 endemic countries, 60 have started implementing MDA, and 15 of them have moved to the post-MDA surveillance phase, which is the first step toward declaring the elimination.

ALB and IVM are well known drugs for soil-transmitted helminthiasis (STH). Between 2000–2007, GPELF concomitantly treated 56.6 million children and 44.6 million women-of-childbearing age, improving nutritional status, anemia, and other health conditions²⁸⁾. After this evaluation, the treatment data between 2009 and 2011 show that approximately 500 million people were treated annually, implying enormous impact of MDAs not only on LF but STH-related health problems (Figure-2)³²⁾.

Important researches and operations contributed for the successful execution of the global program

1. Annual single-dose treatment with DEC

Before the mid-1980s, it was almost the must to give DEC at 6 mg/kg, 12 times to make the total dosage of 72 mg/kg^{33) 34)}. In practice, this was a very difficult regimen to carry out in most endemic countries. Several earlier studies reported very high efficacy of a single dose DEC at 6 mg/kg, that is, the mean Mf count reduced by 91.4% in Brazil¹⁵⁾, 80% in French Polynesia¹⁶⁾ and 94.4% in Samoa¹⁷⁾ when assessed 12 months after treatment. A report from Fiji compared a course of 5 annual MDAs at 6 mg/kg (total dosage 30 mg/kg) with a 28-dose DEC treatment spread in 2 years at 5 mg/kg (total dosage 140 mg/kg), and obtained 87% reduction in Mf prevalence in the former scheme and 93% reduction in the latter³⁵⁾. The practical value of annual single-dose treatment had been accepted gradually by the mid-1990s^{36)–38)}, and now the

annual scheme is the most important basis for the global elimination program.

2. MDA by community members

MDA has a definite advantage: time-consuming and costly night blood surveys to identify infected people are not necessary. On the contrary, a huge number of people have to be treated: a total of 1.4 billion people globally. How can MDAs be carried out when many endemic communities are in remote areas without established health services? This is a very serious problem especially in sub-Saharan Africa.

An epoch-making study was carried out in 1995–96 in 5 African countries, where onchocerciasis is endemic, and annual MDAs with IVM were conducted by the onchocerciasis control programs. Using a total of 153 villages, the study compared two different methods of drug distribution: one designed by community people and the other designed by experienced program staff. The study revealed that the community-designed treatment, carried out by drug distributors selected by each community, was not only feasible but more efficient than the program-designed one³⁹⁾. It is probable that people are more motivated when they can decide and act themselves than they were instructed what to do by outsiders. Community directed treatment with ivermectin (CDTI) has become the platform for onchocerciasis control, and the system has been adopted in LF elimination and other mass treatment programs in Africa particularly. The drug distributors have evolved gradually into reliable health manpower in remote areas, and are playing essential role in distributing vitamin A supplement, anti-malarial bednets, anti-helminth drugs, etc.⁴⁰⁾.

3. Donation of antifilarial drugs by pharmaceutical companies

The stable supply of drugs is the most crucial requirement for the global program, and it is the most costly process too. Two pharmaceutical companies helped in removing the barrier. In 1998, SmithKline Beecham (GlaxoSmithKline since 2001) started collaboration with WHO, and donating ALB for GPELF free of charge for as long as it is needed for the elimination program²⁷⁾. As mentioned before, the combination of ALB adds extra

significance to GPELF: each MDA cures highly endemic intestinal parasites.

The next year, Merck & Co., Inc. decided to donate IVM for African LF programs, where onchocerciasis is co-endemic. Donation of DEC by Eisai Co., Ltd. (Japan) has given an additional strong impetus for GPELF. The delivery started in October 2013, and the company is to donate 2.2 billion DEC tablets in 2013–2020.

4. Immunochromatographic (ICT) antigen test for the diagnosis of filariasis

A convenient rapid diagnostic test had been awaited to facilitate GPELF activities. ICT Filariasis test (ICT Diagnostics, Australia) to detect circulating *W.b.* antigen appeared just in time for the global program⁴¹⁾. To make accurate diagnosis in the daytime in only 15 minutes was a kind of miracle for field workers. For more than a decade, the rapid diagnostic test (presently BinaxNOW[®] Filariasis card test is used) has been playing a key role in GPELF: prior to MDAs, it is prerequisite to delineate the target areas for the treatment, and collect accurate pre-treatment base-line data. After MDAs, the effects have to be monitored and evaluated. The test has been particularly valuable in areas where diagnostic capability is not sufficient.

5. Morbidity control based on basic hygiene

People or even doctors used to believe that lymphedema/elephantiasis is incurable or too difficult to treat. Bacteriological and careful clinical studies broke down the ‘superstition’. The studies found that repeated bacterial infections are the cause of worsening lymphedema^{42)–44)}. This finding has led to an unforeseen new morbidity management program based on simple hygiene to prevent the bacterial infections: washing the swollen leg with soap and water⁶⁾. The method is not only a remedy for the cursed symptom but an entry into interactions between the sufferers, who are isolated and often depressed, and family/community members, who can now take care of the patients.

6. Ultrasonography in LF study

Live and moving adult filariae in the human lymphatics were visualized with ultrasonography and was named ‘filaria dance sign’⁴⁵⁾. This technique has opened the new way for researches on

pathology, pathogenesis, diagnosis and treatment⁴⁶⁾. The dance sign is particularly valuable to judge whether adult worms are alive or dead after treatment⁴⁷⁾, and can be utilized in the development of a new drug capable of killing the adults in a human body. As will be discussed later, GPELF has been eager to find such a drug.

Recent and future researches/operations

1. Diagnosis

ICT card tests to detect *W.b.* antigen (Binax NOW[®] Filariasis) have been an indispensable tool for the global program, but with some inconveniences: short shelf life under tropical climate, false positive results if not read at the indicated time, and high cost. Long efforts to improve the antigen test have finally produced a new generation product, Alere Filariasis Test Strip (Alere Scarborough, Inc.), which has a longer shelf life at ambient temperature, and reported to be more sensitive and easier to read results⁴⁸⁾. It is expected to be employed soon in GPELF and will facilitate the transmission assessment surveys (TAS).

There are other immunodiagnostic methods developed for the filariasis elimination activities. They are not used in GPELF presently, but have practical significance in that they may become useful tools in near future. In order to know filarial transmission to humans, *W.b.* infective larva (L3)-specific antigen Wb123 is used to detect IgG antibody with luciferase immunoprecipitation system. The Wb123-based assay is useful to detect exposure to *W.b.* infection, or possible transmission levels, and also it has been shown to have a very high specificity to exclude other species of filarial infection⁴⁹⁾. The Wb123-based diagnosis has been modified to a lateral-flow strip format for rapid diagnosis⁵⁰⁾.

A RT-PCR detecting L3-specific cDNA is also reported⁵¹⁾. This technique can be applied to study the infectivity status of vector mosquitos.

Non-invasive sample collection may be valuable to obtain acceptance by people particularly in areas with a very low infection rate, or at the stage of confirming elimination. In this regard, ELISA to detect recombinant SXP-1 *W.b.* antigen-specific IgG4 in urine has been employed successfully in several countries^{52) 53)}. A latex agglutination test to

detect SXP-1-specific IgG4 in urine is also reported, with which visual diagnosis is possible⁵⁴⁾. However, the present urine tests crossreact with other filarial parasites, and cannot be used as they are in Africa where different species of filarial parasites are endemic.

2. Treatment

Antifilarial drugs are categorized into microfilaricide (killing Mf) and macrofilaricide (killing adults). DEC is known to have stronger macrofilaricidal effect than ALB and IVM, but even DEC can kill only about a half of parasitic adults⁵⁵⁾.

Macrofilaricidal effect is crucial in the elimination program, because the adults surviving after MDAs can be a source of Mf for continuous transmission and will hinder clinical improvements. Thus without a potent macrofilaricidal drug, the elimination schedule will be protracted.

Flubendazole, which is used for intestinal nematodiasis, is known to have a strong macrofilaricidal effect. Studies are going on for use in GPELF and for onchocerciasis control⁵⁶⁾. A recent study with rats showed embryotoxic activity⁵⁷⁾. Moxidectin is another drug under extensive evaluation. With human subjects of onchocerciasis, 8 mg dosage was safe and showed much stronger microfilaricidal effect than IVM. However, the macrofilaricidal effect was not conclusive⁵⁸⁾.

Outside GPELF, the use of doxycycline (DOX) as macrofilaricide has been reported. The treatment requires a long period (200 mg/day for 4–6 weeks), but this is the most effective way to remove adult worms so far: more than 80% of them were killed when judged 24 months after treatment⁵⁹⁾. This treatment has a significance in that the antibiotic destroys *Wolbachia* endosymbiont and then indirectly kills adult filariae. It is observed that DOX induced extensive apoptosis of adult germline cells, embryos and somatic cells of Mf with *B. malayi*⁶⁰⁾.

DOX, as a result of killing adults, can improve lymphedema, and hydrocele. This is another reason anti-*Wolbachia* chemotherapy draws attention⁶¹⁾. It is reported that 'Anti-*Wolbachia*' (A · WOL) consortium has screened 2,664 registered drugs and obtained 9 compounds which are more potent than DOX. One of them, minocycline is under efficacy trial with *Onchocerca volvulus*-infected humans in Ghana. Other basic studies are also going on⁶²⁾.

Drug resistance is a serious problem for GPELF⁶³⁾, which will continue for 2 decades. Although DEC resistance has not been reported, with *Onchocerca volvulus*, protracted control programs have already induced possible IVM resistance⁶⁴⁾. As for albendazole resistance, in Burkina Faso, benzimidazole resistance-associated mutation is detected in Mf of *W. b.* more frequently after ALB plus IVM treatments⁶⁵⁾.

One of the two strategic aims of GPELF is to alleviate suffering and disability by providing access to basic care for people with symptoms. This aim has not been attained. Effective treatments are available, but most of the sufferers live far away from hospitals. Patients with leg edema may have to work barefoot in the field or bush, or they may not get enough clean water to wash the affected limb daily. These are big challenges for GPELF.

3. Integrated vector management and preventive chemotherapy

Vector management

The elimination of LF has been executed under GPELF, and malaria control under the Global Malaria Programme. However, in a large part of Africa, LF and malaria are co-endemic and *Anopheles* mosquitoes transmit both of the diseases. So, if the two programs are integrated in an effective manner, substantive merits can be expected operationally and financially. For example, the two programs may coordinate and rationalize the distribution of insecticide-treated mosquito nets and indoor residual spraying⁶⁶⁾.

In relation to integrated vector management, several recent studies put a focus on IVM as one of possible vector control agents for malaria: the drug administered for LF/onchocerciasis can kill *Anopheles* mosquitoes when they suck blood from treated humans^{67) 68)}.

Preventive chemotherapy

In sub-Saharan Africa, IVM is used for LF and onchocerciasis, which are often co-endemic. To rationalize the treatment, the WHO Regional Committee for Africa agreed, in 2013, to coordinate MDAs for LF (under GPELF) and onchocerciasis (under African Program for Onchocerciasis Control)²⁷⁾.

Large-scale, periodic and single-dose mass chemotherapy similar to the MDA for LF has been employed as a control strategy for several NTDs, i.e.,

schistosomiasis, soil-transmitted helminthiasis (STH), and trachoma. Albendazole is distributed in GPELF, and also in school-based deworming programs to treat STH. This may be coordinated relatively easily. In Mali, a preliminary trial to integrate MDA for LF (with IVM and ALB) and trachoma control with azithromycin is reported⁶⁹⁾. The coadministration of the 3 drugs was reported to be safe.

Although the integration is most essential in the long run, the implementation may not be simple. Careful and methodical processes seem to be necessary for successful integration⁷⁰⁾.

4. Co-infection of *Loa loa* filaria with lymphatic filaria in Africa

Loa loa is another species of filaria endemic in 10 countries of Central and West Africa⁷¹⁾. *Loa* infection with very high Mf counts (>30,000 Mf/1 ml of blood) causes serious side effects such as encephalopathy and death when Mf are killed with IVM. Thus, in *Loa* endemic areas, MDAs for LF cannot be implemented without detailed information on *Loa loa*. In fact, 6 of 13 countries which have not started the MDA yet are with co-endemic loiasis. This is a big concern for GPELF whose target of elimination is the year 2020.

To avoid the severe reactions of treatment, a fine-resolution distribution map of loiasis and co-endemic LF (and onchocerciasis) is essential, but to create such a map is often not easy⁷²⁾. Under the specific setting, in which LF, loiasis and malaria are co-endemic, but there is no onchocerciasis, ALB 400 mg twice/year mass treatment for 5 years plus integrated vector management is recommended for LF elimination⁷³⁾. A single dose of ALB at 400 mg is reported to be effective against *W.b.*^{74) 75)}.

In GPELF, research work has been playing a crucial role: the adoption of annual single-dose MDA and the development of ICT rapid diagnostic test contributed greatly to the swift global deployment of the program. Intensive efforts are being made to develop macrofilaricides, which can shorten the duration of program, prevent/improve clinical symptoms, and counteract drug resistance problem. However, there are some challenges remaining before the completion of the program: MDA has not been implemented yet in 13 countries, and morbidity management activities are still

lagging. Also, integration or coordination of different programs has to be accelerated. Despite these, GPELF with more than a decade-long solid experience will be able to overcome them, achieve the elimination of long-neglected disease of LF, and set a precious precedent for public health program.

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