Meeting Report

CONSULTATION TO ACCELERATE ELIMINATION OF *BRUGIA MALAYI* TRANSMISSION IN INDONESIA AND MALAYSIA

13–15 December 2016
Kota Kinabalu, Malaysia

World Health Organization

WORLD HEALTH ORGANIZATION

REGIONAL OFFICE FOR THE WESTERN PACIFIC

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MEETING REPORT

CONSULTATION TO ACCELERATE ELIMINATION OF *BRUGIA MALAYI* TRANSMISSION IN INDONESIA AND MALAYSIA

Convened by:

WORLD HEALTH ORGANIZATION
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NOTE

The views expressed in this report are those of the participants of the Consultation to Accelerate Elimination of *Brugia malayi* Transmission in Indonesia and Malaysia and do not necessarily reflect the policies of the conveners.

This report has been prepared by the World Health Organization Regional Office for the Western Pacific for Member States in the Region and for those who participated in the Consultation to Accelerate Elimination of *Brugia malayi* Transmission in Indonesia and Malaysia, Malaysia from 13 to 15 December 2016.

CONTENTS

Keywords:

Brugia malayi / Elephantiasis, Filarial – prevention and control / Filariasis /

Indonesia / Malaysia

SUMMARY

Lymphatic filariasis (LF) is caused by three types of filarial worms, of which *Wuchereria bancrofti* is responsible for 90% of cases, with *Brugia malayi* causing most of the remainder of cases globally. *B. malayi* is still endemic in the Western Pacific and South-East Asia regions, including Malaysia and Indonesia.

The national programme to eliminate LF was launched in Malaysia in 2001 and in Indonesia in 2002. Since then, mass drug administration (MDA) has been implemented annually in Malaysia, leading to the majority of endemic areas already stopping MDA and undergoing post-MDA surveillance. However, selected areas in Borneo Island continue to show persistent transmission of *Brugia malayi* even after nine rounds of MDA. In Indonesia, MDA is gradually scaling up to a nationwide level but in many endemic areas in Borneo Island MDA has started only recently.

In the consultation, potential causes of persistent transmission of *Brugia malayi* in Indonesia and Malaysia and results of the relevant studies to date was extensively discussed, including possible contribution of zoonotic transmission, the presence of a population sub-group with non-compliance to MDA, such as migrants and ethnic populations, lower efficacy of preventive medicines, quality of diagnostic tests and interpretation of results and possible drug resistance.

Malaysia was congratulated for progress in achieving elimination threshold in the majority of implementation units (IUs), the quality and extent of monitoring impact and proactive response in the few areas of remaining infection. Indonesia was congratulated for rapid scale-up of MDA in all endemic districts through the National Lymphatic Filariasis Elimination Campaign (BELKAGA), progress with transmission assessment survey (TAS) implementation, and commitment to investigation and response in failed TAS districts.

The recommended programmatic actions for Malaysia included implementation of enhanced MDA in implementation units where TAS or pre-TAS has failed, consistent use of the Brugia Rapid™ in the surveys, reinforcement of quality assurance of diagnosis in terms of sample collection and reading of slides/tests and implementation of mini-TAS in non-endemic implementation units surrounded by or adjacent to endemic implementation units where persistent transmission is currently observed.

More information is needed to understand possible contribution of zoonotic transmission to human infection. A case control study is considered as a first step to compare animal infection in households with and without infected persons.

1. INTRODUCTION

1.1 Meeting organization

The Consultation to Accelerate Elimination of *Brugia malayi* Transmission in Indonesia and Malaysia was held from 13 to 15 December 2017 in Kota Kinabalu, Malaysia. Eight participants attended the consultation from Indonesia and Malaysia, six temporary advisors, and 11 observers from selected state health offices in Malaysia and partner agencies.

1.2 Meeting objectives

The objectives of the consultation were to:

(1) discuss potential causes of persistent transmission of *Brugia malayi* in Indonesia and Malaysia and the results of relevant studies to date; and

(2) determine the immediate and medium-term programmatic actions and operational research priorities to address this issue.

2. PROCEEDINGS

2.1 Opening session

Datuk Dr Lokman Hakim Bin Sulaiman extended a warm welcome to all consultation participants to Sabah. He highlighted that the lymphatic filariasis (LF) control programme in Malaysia has a long history and has been well supported by the Ministry of Health and the Institute of Medical Research (IMR). The endemic areas have shrunk during the last few decades due to extensive control efforts supported by research. When the LF Elimination Programme (LFEP) was launched in 2003, following the launch of the Global Programme to Eliminate LF (GPELF) in 2000, only part of the country's population required mass drug administration (MDA). The Ministry of Health is well aware of the 2020 target date set by the GPELF and has been taking steps to meet this goal. He expressed the hope that the deliberations and outcome of the consultation will pave the way for achieving accelerated elimination of LF.

Dr Rabindra Abeyasinghe delivered the opening remarks on behalf of Dr Shin Young-Soo, WHO Regional Director for the Western Pacific and Dr Poonam Khetrapal Singh, WHO Regional Director for South-East Asia. He referred to the goals of the GPELF to eliminate LF as a public health problem by 2020, and highlighted that the Western Pacific Region is leading LF elimination efforts. He noted that in 2016 alone, four countries of the Western Pacific Region were acknowledged for having eliminated LF as a public health problem. One of the major concerns for programmes in Malaysia and Indonesia is the reportedly persistent transmission of LF in some brugia endemic areas of Malaysia, particularly Sabah and Sarawak, and Indonesia.

Datuk Dr Lokman Hakim Bin Sulaiman was elected as the chair and Dr Kapa Ramaiah as the rapporteur of the consultation.

2.2 Updates of LF elimination challenges from the GPELF, Malaysia and Indonesia

2.2.1 GPELF updates: progress and challenges

Dr Jonathan King highlighted the two pillar strategies of the GPELF: (a) to stop transmission through MDA; and (b) to reduce suffering and improve quality of life through morbidity management and disability prevention (MMDP). The MDA programme has gradually been scaled up since its inception in 2000, and following completion of the required number of MDA rounds an increasing number of implementation units (IUs) in the South-East Asia and Western Pacific regions are implementing transmission assessment surveys (TAS). Based on the results of TAS implemented globally to date, the percentage of evaluation units (EUs) passing TAS out of those implemented in areas endemic for *W. bancrofti* was 97% (7/278) for TAS 1 and 100% (20/20, 3/3) for TAS 2 and 3 each, but in areas endemic for *B. malayi* was 72% (31/43) for TAS 1, 57% (12/21) for TAS 2 and 0% (0/1) for TAS 3. In response to this situation, WHO has developed guidance for national programmes to prevent TAS failure, investigate TAS failure and implement corrective actions in case of TAS failure.[1]

WHO also established the general framework for control, elimination and eradication of NTDs and the process for validation of elimination of LF as a public health problem.[2,3] The criteria to validate elimination of LF as a public health problem include indicators on availability of the recommended minimum package of care for patients with LF-related morbidity in all areas with known patients. The indicators include: (a) estimated number of patients per IU; (b) number of facilities providing services for IUs with known patients; and (c) quality assessment of at least 10% of designated facilities. To facilitate situation analysis and develop and implement a plan to establish MMDP activities and sustain this within health systems, the WHO MMDP Toolkit is being developed.

2.2.2 Progress and challenges to LF elimination in Malaysia

LF control programme in Malaysia started in 1960s. The control strategy at that time consisted of case detection through blood smear collection, treatment and case follow-up and surveillance every two to three years. The aim was to eliminate filariasis caused by periodic strains of the parasite and to reduce the microfilaraemia (Mf) rate to <5.0% in subperiodic strain endemic areas. The control programme focused on highly endemic areas. The programme resulted in a very drastic reduction in the Mf rate.

The national programme to eliminate LF was started in 2003. Using the GPELF guidelines, a generic pathway to achieve LF elimination was developed. Mapping was completed by the end of 2003. The subdistrict was designated as the IU. MDA was implemented, following the guidelines of the GPELF. The monitoring and evaluation included assessment of Mf in two sentinel sites and two spot check sites and also background surveillance in each IU, both in endemic and non-endemic. Six states – Kedah, Perak, Terengganu, Kelantan, Pahang and Johor – were endemic for periodic *B. malayi*, and two states – Sabah and Sarawak – were endemic for subperiodic *B. malayi*. At least seven vector species of *Mansonia* were considered to be involved in LF transmission.

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[1] WHO (2016) *Responding to failed transmission assessment surveys. Meeting of the Neglected Tropical Diseases Strategic and Technical Advisory Group's Monitoring and Evaluation Subgroup on Disease Specific Indicators. 4 December 2015, Washington DC, USA*. World Health Organization, Geneva.

[2] WHO (2015) *Generic Framework for Control, Elimination and Eradication of Neglected Tropical Diseases.* World Health Organization, Geneva. Accessible at: http://www.who.int/neglected_diseases/resources/NTD_Generic_Framework_2015.pdf

[3] WHO (2017) *Validation of elimination of lymphatic filariasis as a public health problem*. World Health Organization, Geneva.

While either Brugia Rapid™ (MBDr Selangor, Malaysia) or panLF Rapid™ (MBDr Selangor, Malaysia) was used as diagnostic in TAS 1, only panLF Rapid™ was used in TAS 2 and TAS 3. TAS sampling was determined using the Survey Sample Builder as per GPELF's recommendation.

An expert group meeting was held in 2010 which reviewed progress of the programme and provided guidance. In the IUs that failed TAS, additional MDAs were implemented. By 2016, LF shrank to six IUs in four districts of Sabah and Sarawak. All other IUs have passed TAS and moved to a post-MDA surveillance phase. The reported drug coverage has mostly been higher than 80%. Some IUs (Beluran, Sungai-Sungai) persistently showed >1.0% Mf rate but gradually reduced Mf prevalence, such as in Beluran and Beaufort).

In Sarawak, there were 29 endemic IUs in seven districts with a target population of 381 767 in 2003. By 2016, only three IUs in two districts were endemic. Though treatment coverage was <60% during MDA 1–4, it was improved to >70% during MDA 5–9.

Pahang State, with 28 endemic IUs in seven districts and a target population of 319 397 in 2003, achieved elimination targets by 2016, as did Perak State (with 12 IUs in four districts with a target population of 44 600) and Terengganu State (with 19 IUs in five districts with a target population of 118 480). Kelantan, Kedah and Johor States also achieved LF elimination.

Table 1. Progress summary of the LF elimination programme by state and implementation unit in Malaysia, 2016

State	IU	Situation
Sabah	Bangkalalak	MDA x 7 TAS 1 passed (2014) TAS 2 failed (2016)
Sabah	Tangkarason	MDA x 9 Pre-TAS failed x 2 Mf 0.7% (SS), 2.2% (SC)
Sarawak	Medamit Sundar Lawas	MDA x 7 TAS 1 passed (2014) TAS 2 failed (2016)
Terengganu	Hulu Chukai Kijal	Reclassified as green IU High Mf MDA x 1 (2011) Ongoing surveillance (Mf remains below 1%)
Sabah	Bekenu Debak	MDA x 7 Pre-TAS failed MDA 8 & 9 Pre-TAS, TAS 1 & 2 passed
Pahang	Bera Bebar Lepar Temai	MDA x 5 Pre-TAS failed MDA 6 & 7 Pre-TAS, TAS 1 & 2 passed
Perak	Lenggong Temengor Kenering Belukar Semang	MDA x 5 Pre-TAS, TAS 1 passed High Mf in cross-sectional survey MDA 6 & 7 Pre-reTAS 1 passed ReTAS1 passed

Terengganu	Chalok	MDA x 5 Pre-TAS, TAS 1 passed High Mf in cross-sectional survey MDA 6 & 7 TAS 2 passed (2015)

Vector control, such as indoor residual spraying (IRS) and insecticide-treated mosquito nets (ITN) has been implemented in some persistent transmission areas.

The major issues and challenges in Malaysia, specifically in Sabah and Sarawak State, include: (a) prolonged implementation of MDA; (b) resource competition with other health programmes within the government, such as the malaria elimination programme; (c) delays in drug supply; (d) suboptimal MDA due to inaccessibility of communities, poor acceptance of treatment by communities and absence of reinforcement of directly observed therapy (DOT) approach; (e) potential zoonotic transmission; and (f) use of two diagnostic kits – the Brugia Rapid™ and panLF Rapid™.

Discussion

The work done by the programme was appreciated and the teams were congratulated. It was clarified by the programme that extensive surveillance that includes night blood surveys sampling of about 30% of the population and treatment of positives has been implemented annually. Wherever TAS was failed, additional MDA was also implemented. Two different diagnostic tests were used in the programme, PanLF Rapid™ and Brugia Rapid™. The programme presented data that sensitivity and specificity of both tests were comparable. However, Brugia Rapid™ is the only test for *Brugia* spp. that is recommended for use in GPELF. The effectiveness of vector control and its impact on transmission is debatable, as *Mansonia* species predominantly rests and bites outdoors, although limited indoor transmission may occur. The budget for the programme has been fully provided by the federal government. Logistic problems are a major issue for the programme, as health workers have to travel deep into the interior and mostly are not able to stay overnight in villages due to security reasons.

2.2.3 Progress and challenges to LF elimination in Indonesia

LF is endemic in 239 of 514 districts in Indonesia – *W. bancrofti* is prevalent in 76 districts, *B. malayi* in 132 districts, both parasites in 17 districts and *W. bancrofti* and *B. timori* in 14 districts. In the 1990s, there was a control programme under which the standard DEC regimen was given to detected Mf carriers. The national LF elimination programme was started in 2002 with MDA using diethylcarbamazine citrate (DEC) and albendazole. An integrated vector control programme was also put in place. The number of districts covered by MDA increased from 31 in 2005 to 191 in 2016. The population covered by MDA increased from 6.73 million in 2005 to 67.76 million in 2016. TAS was implemented and MDA was stopped in 24 IUs by 2016, but some IUs failed TAS. The major issues and challenges to the programme in Indonesia include a very large geographical area and suspected presence of zoonotic filariasis. MDA coverage has been hampered by limited social mobilization, poor community participation, human and financial resources constraints, adverse events during MDA and difficulty in reaching many rural areas. A recent study showed that 20% of cats are infected and monkeys are also known to be reservoirs of filarial species.

2.2.4 Outcomes of the technical working group meeting on transmission assessments surveys in Indonesia, 7–20 March 2016 in Jakarta, Indonesia

A technical working group meeting to discuss results of TAS in Indonesia was organized in Jakarta, Indonesia from 7 to 10 March 2016. The major objectives of the technical working group meeting were to review Indonesia's TAS results, determine the steps for preventing and responding to TAS failures and prioritize operational research questions and plan studies to identify factors possibly responsible for TAS failure. The national LF elimination programme has existed for 46 years with disease prevalence decreasing from 15.5% in 1980 to 4.7% in 2016. As of February 2016, 241 of 514 districts were endemic for LF and 192 districts were planning to implement MDA in 2016. Twenty-nine districts passed TAS 1, 66% of which were *B. malayi* endemic areas. TAS failure has been one of the major concerns for the programme. Prevalence of three parasite species and the involvement of multiple vectors make the epidemiological situation in Indonesia complex.

Recommendations of the group for the programme were: (a) to strictly follow the WHO recommended TAS critical cut-off levels; (b) to include use of Brugia Rapid™ in Pre-TAS data collection in sentinel sites and spot check sites in a variety of districts with and without zoophilic *Brugia* spp. in order to collect further information on antibody age-prevalence relationship and better understand how use of Brugia Rapid™ in community-based pre-TAS can predict TAS failure; (c) to investigate TAS 1 failure using the TAS failure checklist and to implement two more rounds of enhanced MDA; (d) to investigate TAS 2 and/or TAS 3 failure in consultation with WHO; (e) to prevent TAS failure by implementing effective and well supervised MDA; and (f) to ensure use of quality assured medicines.

Discussion

The complex epidemiological situation in Indonesia may require more time to achieve LF elimination in the country and enhanced funding for the Ministry of Health. The district health officers should be encouraged to implement the programme effectively. LF is a significant health problem in Papua region and the MDA programme should be extended to all areas, more so in such regions because some districts are socioeconomically very poor.

Low treatment coverage is a potential reason for persistent *B. malayi* infection in many IUs in Indonesia. An enhanced MDA and implementation of regular coverage surveys using the latest WHO tools may improve the situation in such areas.

2.3 Potential causes of persistent transmission of *Brugia filariasis* – operational research updates

2.3.1 MDA coverage and challenges in areas with persistent *brugia* transmission

Dr Khairiah Binti Ihmad presented the outcome of the recent study to follow up treatment response of positive cases in Beluran. Beluran district is the second largest district in Sabah State consisting of 505 villages with a population of 76 000. There are seven endemic IUs in the district – Beluran, Ulu Liwagu, Pamol, Jambongan, Kuala Sapi, Sungai-Sungai, and Tangkarason. Out of seven IUs classified as endemic in 2003, six IUs have already passed TAS and moved to post-MDA surveillance phase, whereas only one IU (Tangkarason, with a population of 9 274) continued to fail pre-TAS twice in 2013 and 2014 with the Mf prevalence of 2.2%, despite nine rounds of MDA. The reported drug coverage has been above 90% at each round of MDA. Many villages in Tangkarason showed above 1% Mf prevalence.

As a response to Pre-TAS failure, 4 233 night blood slides were examined in IU Tangkarason and 125 were found positive. Out of 125 positives, 19 individuals were repeated positive cases, some of which despite reportedly participating in more than four rounds of MDA, whereas 106 individuals were diagnosed as positive for the first time. Six villages recorded a relatively high number of cases. All 125 positive cases were treated with six doses of DEC and albendazole, administered daily for six days. All positive cases were followed up and examined after two months and it was found that 93 of 125 (74%) turned negative. All the cases turned negative after five months.

Dr Rohani Binti Ahmad presented the outcome of the entomological study conducted in Tangkarason village. The study included adult mosquito and larval surveys. Human landing collection was performed outdoors during 6 and 11 pm in Tangkarason village. It was not possible to continue sample collection until dawn because staffs were unable to stay in the village overnight due to security reasons. The collected mosquitoes were divided by sex and species in the laboratory. The predominant adult mosquito species was *Culex sitiens*. PCR was performed on adult mosquitoes to detect filarial infection. All mosquitoes were found to be negative for filarial larvae.

Discussion

It is a concern that Mf persisted despite nine rounds of MDA in the area. The extensive surveys carried out by the programme consisting of detection and treatment of positive cases is highly commended. High treatment coverage and compliance will make a difference to the effectiveness of the programme and thus this should be reinforced at the local level in each state. Finding no new infections in most of the IUs indicates the programme is moving in right direction. MDA should be implemented in consecutive years as interruption of MDA in between makes it less effective. The implementation units are very small in Malaysia and this may be the reason for some of the IUs failing TAS. The quality of surveillance implemented by the programme in the smaller IUs is high and the surveys are intensive, often extending to community level. The Mf surveys conducted on local and immigrant population, which are relatively less sensitive, are very extensive and often involve a huge investment in labour. Replacement of Mf surveys with immunodiagnostics using the Brugia Rapid™ is strongly recommended.

Quality of drugs is a potential concern but the finding that all positive cases turned negative within six month of treatment seems to exclude the possibility of lower effectiveness of medicines being used in Malaysia. The remaining potential reasons for persistence of Mf in Tangkarason include: (a) implementation of MDA cycle over a long period of time due to insufficient number of staff; (b) lack of reinforcement of DOT approach; and/or (c) leaving detected Mf positive cases untreated. Enhanced MDA is warranted. In Indonesia, the programme initially used locally produced DEC. Subsequently, the country received the WHO-prequalified DEC but still often uses the drug produced locally. The quality of the drug used in Indonesia should be tested according to the guidelines of the Ministry of Health.

It was not possible to conclude if the negative result of adult mosquito survey was due to a small number of mosquito samples analysed in PCR or due to the true absence of filarial larvae at this time.

2.3.2 Sensitivity of diagnostic test (Brugia Rapid™)

Dr Rahmah Noordin shared the outcomes of various studies to indicate sensitivity and specificity of Brugia Rapid™ and panLF Rapid™, comparison of antibody and Mf positivity rate in adults and children in relation to treatment, and their cross-reactivity with other filarial parasites.

The sensitivity and specificity of Brugia Rapid™ is reported as above 95% and above 97% respectively. PanLF Rapid™ is an extension of Brugia Rapid ™ with an additional test line containing rBmSXP protein which is sensitive for detection of bancroftian filariasis for areas co-endemic with *W. bancrofti* and its sensitivity and specificity are similar to that of Brugia Rapid™. Brugia rapid™, when tested on true Mf positive and true Mf negative serum samples, produced sensitivity and specificity of 96.6% and 98.9% respectively and positive and negative predictive values of 97.1% and 98.7%[4]. The multicentre laboratory evaluation of Brugia Rapid™ conducted in 2003 found sensitivity and specificity of 93% and 100% respectively.[5] In its field validation, Brugia Rapid™ gave 9.8 to 10.4 times higher prevalence compared to Mf prevalence assessed by thick blood smear method.[6]

In the treatment follow-up study in 2001, the optical density of antibody response reached close to zero level at six months post-treatment with a six day course of DEC (6 mg/kg) and these levels were sustained up to 29 months post-treatment. [7] In another study in 2005, 20 of 22 Mf carriers turned antibody negative at 12 months post-treatment.[8] After six rounds of MDA, the antibody prevalence declined from a baseline level of 82.0% (2001) to 4.9% (2010) in a study in Eastern Indonesia.[9] In comparison of results of TAS 1 and TAS 2 in Sabah, Malaysia, reduction of antibody positive rate was from 6.3% (TAS 1) to 4.3% (TAS 2) in children and from 13.1% (TAS 1) to 7.4% (TAS 2) in adults.

Dr Peter Fischer presented the outcome of the study to compare the impact of once or twice yearly MDA on the brugian microfilariae and on the prevalence of antifilarial IgG4 in Indonesia. The study was conducted to explore alternative MDA strategies for Indonesia where only a few districts have passed TAS and stopped MDA to date. In the study, three consecutive rounds of annual MDA was implemented over three years in Paga (*B. timori* endemic) and Lewomada (*B. timori* and *W. bancrofti* endemic) and twice yearly treatment for three years in Pruda (Flores Island, *B. timori* and *W. bancrofti* endemic). Treatment compliance was above 65% in all study village groups, with slightly higher levels in Pruda. It was found that twice yearly MDA is efficient to bring down higher Mf prevalence rates in all age-groups, but if Mf densities are low, once yearly MDA is sufficient to reduce Mf rates to less than the TAS-eligibility threshold level. The *brugia* antibody levels declined from 28.9% to 3.6% and *W. bancrofti* Ag level from 22.9% to 7.0% in Pruda (twice yearly treatment). The respective values were from 31.7% to 4.1% for *brugia* antibody level and from 6.5% to 0.8% for *W. bancrofti* antigenaemia level in Lewomada (once a year MDA) and from 12.5% to 1.8% for *brugia* antibody level in Paga (once a year MDA). Within three years, the prevalence of *brugia* antibody level decreased sharply in both treatment groups and all age groups. In *W. bancrofti* co-endemic villages, the antigenaemia rate decreased in all age-groups only in the lower prevalence areas. In the higher prevalence areas, the antigenaemia prevalence rapidly decreased in young children, but stayed relatively higher in older age groups despite twice yearly MDA.

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[4] Rahmah et al. (2001) Specificity and sensitivity of a rapid dipstick test (Brugia Rapid) in the detection of *Brugia malayi* infection. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 95, 601-604.

[5] Rahmah et al. (2003) Multicentre laboratory evaluation of Brugia Rapid dipstick test for detection of brugian filariasis. *Tropical Medicine and International Health*, 8(10), 895-900.

[6] Jamail et al. (2005) Field validation of sensitivity and specificity of rapid test for detection of *Brugia malayi* infection. *Tropical Medicine and International Health*, 10(1), 99-104.

[7] Rahmah et al. (2001) A recombinant antigen-based IgG4 ELISA for the specific and sensitive detection of *Brugia malayi* infection. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 95, 280-284.

[8] Rahmah et al. (2005) Treatment follow up of *Brugia malayi* microfilaraemic and microfilaraemic individuals with serological evidence of active infection. *Malaysian Journal of Microbiology*, 1(1). 42-47.

[9] Supali et al. (2013) Impact of six rounds of mass drug administration on brugian filariasis and soil-transmitted helminth infections in Eastern Indonesia. *PLoS NTD*, 7(12), e2586.

The study concluded that while twice yearly MDA appears more efficient in areas with high *brugia* Mf prevalence in reducing transmission, once yearly MDA appears to be sufficient in low prevalence areas. It also emphasized that relatively slow decline of antibody prevalence compared to antigenaemia prevalence in areas of high prevalence in older age groups and that the current threshold adopted from antigen testing in bancroftian filariasis of 1% (with upper confidence limit of 2%) may be too strict in areas of *B. malayi* transmission.

Discussion

Brugia Rapid™ is considered as the most appropriate diagnostic tool in the area of *brugia* infection. Its sensitivity is 2 to 3% less than 100% and the critical threshold level in TAS is set for the maximum of 2%, thus a concern remains as to its implication for TAS outcomes, which requires antibody prevalence of less than 2% for an evaluation unit to pass. However, the same is true for antigen detection using immunochromatographic test (ICT) in the more extensive *W. bancrofti* endemic areas. The current conservative critical threshold levels to stop MDA should be retained for assurance to prevent recrudescence of transmission. It may be important to closely look at how the local community interacts with immigrants and the role of immigrants in persistent transmission. The migrant workers are mainly from Bangladesh and Indonesia. LF is not a notifiable disease, hence, has not been included in the array of tests to be carried out on immigrant workers.

2.3.3 Zoonotic transmission of *Brugia malayi*

Dr Lau Seng Fong presented the outcome of the recent study on canine and feline filariasis conducted in Tangkarasun, Beluran district, Sabah State. The canine and feline filariasis is caused by eight species of filariae. Six of them can cause disease in humans also. *Dirofilaria immitis* is of veterinary significance but its public health importance for humans is negligible. There are 400 reported human cases due to infection with *D. repens*. In the study, 45 cats and 40 dogs were tested for filarial infection. Blood smears were examined and single-step multiplex PCR was performed. Three cats (6.7%) and 22 dogs (55%) were Mf positive by blood smear, sheathed and/or unsheathed. Seven cats (15.6%) and one dog (2.5%) were positive for *B. malayi* using PCR. An oral single dose of ivermectin (400ug/kg) and DEC (6mg/kg) reduced Mf intensity from 87 to 100% at two months post-treatment and 99% at eight months post-treatment. An injection of ivermectin significantly reduced Mf intensity after four weeks post-treatment and completely cleared by nine weeks post-treatment.

Discussion

The animals living in human habitations with LF positive individuals were used in the study. No *B. pahangi* infection was found in the animals. It is not clear as to the role of animals in the perpetuation of infection at this moment. No evidence was found to suggest that zoonotic transmission is a significant threat to the programme in Malaysia.

2.4 Field visit to the area of TAS 2 failure (Beaufort district, Sabah state)

2.4.1 Overview of LF elimination programme in Beaufort district, Sabah state

Dr A. L. Liza Binti Abdul Latif presented the overview the LF elimination programme in Beaufort district, Sabah State to date. There are 11 sub-districts in Beaufort district and four districts were recorded to have LF positive cases between 1996 and 1997. No cases were recorded during 1990–

1995 as well as in 1998. More surveys were conducted between 1999 and 2002 and found Mf prevalence in six subdistricts and Mf rate ranging from 0.48% (Weston) to 7.6% (Bangkalalak) at subdistrict level. These six subdistricts included Limbawang, Kota Kilas, Lumadan, Weston, Padas Damit and Bangkalalak, and the population at the subdistrict level ranges from 2 351 to 4 964. The first round of MDA was implemented in 2003 in all six endemic subdistricts. The treatment coverage ranged from 59% to 92%. Subsequently, four more rounds of MDA were implemented between 2004 and 2007. As Mf positives were detected during 2008 (six cases) and 2009 (one case), two more rounds of MDA were implemented in 2012 and 2013. Three Mf cases were detected in 2014. A further two more rounds of MDA were implemented in 2015 and 2016. Thus, a total of nine rounds of MDA were implemented, all with above 65% coverage except for one round in Kota Klias in 2003. However, seven Mf cases were detected in 2016 again, of which five were detected in Bangkalalak alone.

TAS 1 was conducted in 2014 and TAS 2 in 2016. Four subdistricts failed TAS 1 and Bangkalalak alone failed TAS 2. In TAS 2, there were four Antibody positive cases (age 7–8 years) against the critical cut off value of two positives. In-depth surveys were undertaken in Bangkalalak subdistrict, which has 11 villages with a total population of 2 415. Mf surveys in a radius of 1 km detected seven adults with Mf and six of them participated in seven MDAs. The location of positive cases was mapped. Mf surveys were conducted in positive villages and most of the people sampled. The Mf rate ranged from 1.12% to 7.69%. All the detected positive cases were given six days of treatment. Supplementary vector control measures, such as IRS and ITN distribution, were undertaken in some villages.

2.4.2 Filariasis vector surveillance from 2014 to 2016, in Beaufort district, Sabah state

Ms. Siti Syarifah Akma bt Ibrahim, entomologist at Beaufort District Health Office, presented the outcomes of Filariasis vector surveillance from 2014 to 2016 in Beaufort. Entomological surveys were carried out in endemic IUs of Sabah. At least six species are suspected to be involved in transmission of LF. The surveys were carried out in several localities of each IU/Zone. A total of 3 171 *Mansonia* adult mosquitoes of eight species were collected between 2004 and 2016. No filarial infection was found in the dissected mosquitoes. Some samples of mosquitoes were sent to the central laboratory for PCR assay.

2.4.3 Visit to local villages where persistent transmission has been observed

All the participants visited local villages (Kampung Kukup and Kampung Sabandar), interacted with residents and enquired about the LF situation and the history of MDA implementation. Observations were made on local ecology, socioeconomic situation and presence of household animals.

In Bangkalalak, five rounds of MDA were implemented between 2004 and 2008, two more rounds between 2011 and 2013. The IU passed TAS 1 in 2014 with one positive against the critical cut off value of two but failed TAS 2 in 2016 with four positives against the critical cut off value of two positives. Three adjacent IUs passed repeated TAS 1 (re-TAS 1) in 2016. Earlier, it was only distribution of packed drugs in the community but later enhanced MDA was reinforced with better supervision of drug administration. PanLF Rapid™ was the diagnostic used in TAS. All four antibody positives found in TAS 2 were Mf negative by blood smear. One kilometre radius of all four antibody positives were investigated with night blood surveys and seven Mf positive individuals were found. In a household visited by the meeting participants, one or more family members were found positive for Mf every year, despite participating in MDA. All the detected Mf carriers were treated. In terms of

vector control, IRS, ITN and *Aedes* breeding habit manipulation have been undertaken in some households.

Discussion

Participants appreciated the extensive surveillance surveys carried out in the district. The surveys were so in-depth that they had almost described the micro-epidemiology of LF infection. It may be more cost-effective and productive to assess the infection in humans and exclude entomological assessment, as the latter requires sampling and processing of thousands of mosquitoes in low endemic situations such as Beaufort. Extensive surveys enabled the programme to identify the localities with persistent infection. The efficiency of the surveys will be dramatically increased if Brugia Rapid™ is used, replacing the Mf surveys. In such low endemic situations, particularly when attempts are aimed to completely remove the residual infection from community, it will be better to use a "test and treat" strategy. However, when using such a strategy it should be kept in mind that the tested people may again become infected from animals, if there is zoonotic filariasis. Hence, cross-sectional surveys to assess the infection prevalence and implementation of MDA in communities with above threshold level of infection are also an option. There are a lot of "green" areas adjoining the endemic areas and it may be advisable to assess the infection in green areas also, using sampling strategies such as Mini-TAS.

2.5 Recommendation on programmatic actions and priority operational research

2.5.1 Discussion on immediate and medium-term programmatic actions

Four of five LF-endemic WHO regions have at least one country that experienced a TAS failure in at least one district. TAS failures are rare in *W. bancrofti* areas whereas *B. malayi* areas have the lowest pass rate. There was an urgent need to identify why areas are failing and how to respond to failed TAS. In response, the WHO NTD STAG subgroup meeting on responding to failed TAS was convened on 4 December 2015. Dr Jonathan King presented the outcomes of the meeting. Details are available in the meeting report.[1] He also highlighted the immediate need for greater availability of positive and negative controls for diagnostic tests and research on alternative MDA regimens, impact of zoonotic *brugian* filariasis on human transmission and BmR1 antibody responses.

Dr Peter Fischer shared the updates of the randomized clinical trial of triple dose therapy using ivermectin, DEC and albendazole (IDA). The clinical trial was conducted in Papua New Guinea and Cote d'Ivoire with an aim to examine safety and drug interactions of the triple drug therapy. So far, neither significant drug interaction nor serious adverse events have been observed, while a nearly ten-fold effectiveness in reduction of Mf level was observed in triple drug therapy. Currently community-level IDA MDA studies are ongoing in five countries (India, Papua New Guinea, Indonesia, Haiti and Fiji) to assess safety in larger populations in different geographical locations.

Discussion

Mf surveys may not be cost-effective and the ratio of infection diagnosed using thick blood smear method to that diagnosed using Brugia Rapid is 1:10. This makes a strong case for using Brugia Rapid diagnostics in the programme. It is strongly recommended to switch over to use of Brugia Rapid™ in any LF surveys.

The green areas, which never required MDA but are adjacent to red areas with persistent transmission, should be reassessed. These include green subdistricts within endemic districts. Such reassessment is recommended only in Sabah and Sarawak State where persistent transmission is observed but not required in Peninsular Malaysia.

Malaysia has been doing an enormous amount of work, particularly in the area of surveillance surveys. This is done by carving out endemic areas, uniquely, into very small IUs/EUs. This, in a way, is penalizing the programme, as carving out of larger EUs may easily result in passing TAS. However, smaller IUs/EUs and extensive surveillance is a very effective strategy to eliminate residual infection completely in contrast to very large IUs in some countries. The meeting will not discourage this strategy of smaller IUs and extensive and intensive surveillance.

Test and treat appears to be the best strategy, as already extensive surveillance surveys are in place. However, this strategy needs to be viewed in the back drop of suspected zoonotic transmission. Zoonotic transmission, if any, may cause reinfection of those treated. Such situation may favour implementation of MDA as an intervention possibly coupled with treatment of animals.

Test and treating the immigrants is a laborious process. Alternative strategies to treat the infection among immigrants, such as pre-arrival screening may be explored.

Vector control is resource intensive. An integrated vector control approach is the best suited strategy. Mosquito transmission of LF is known to be inefficient. The vector control efforts of the programme are commendable. Vector control is expected to contribute to sustain the elimination status once interruption of transmission has been achieved in Sabah and Sarawak State. IVM strategy should be developed in accordance with local vector bionomics.

The situation in Sabah and Sarawak has a parallel with Sri Lanka, where residual infection also persists in focal areas. Sri Lanka recently received acknowledgement of elimination of LF, but continuing with surveillance activities. Most probably, in Sabah and Sarawak also, LF ceases to be a public health problem, which is the goal of GPELF.

It is recommended that the programme will take next steps as per the outcomes of this consultation and also based on further consultations and recommendations from WHO.

2.5.2 Discussion on operational research

Dr Patrick Lammie reminded the age-specific comparison of Mf, antigenaemia and antibody level and highlighted the remaining questions to be studied.

1. Are thresholds for antigen suitable for antibody?
2. How rapidly does seroreversion occur?
3. Can Brugia Rapid^{TM} be used consistently and accurately in the field?
4. Does the presence of zoophilic *Brugia malayi* lead to persistent infection in humans?
5. Do animal filarial species induce immune responses in children that cross-react with BmR1?

He suggested the followings as operational research options that can be immediately implemented in Indonesia and Malaysia:

a. collection of both Brugia Rapid and Mf data in pre-TAS in *Brugia* spp. areas, ideally including some zoophilic and anthropophilic areas and also in areas which failed TAS 2 but have not started MDA from all ages, to assess antibody age prevalence curves; and
b. collection of both Brugia Rapid™ and Mf data from all ages in zoophilic *Brugia* spp. areas with a high number of positives detected during TAS and with and without human interaction with potential animal reservoirs to assess potential contribution of zoonotic transmission to humans.

Discussion

It was recommended that a case-control study be developed and implemented in Malaysia to understand the role of zoonotic transmission in persistent human transmission of Brugian filariasis where resources permit. The current status of LF in Alor, Indonesia, will need to be examined.

3. CONCLUSIONS AND RECOMMENDATIONS

3.1 Conclusions

- Malaysia was congratulated for progress in achieving elimination threshold in the majority of IUs, the quality and extent of monitoring impact, and proactive response in the few areas of remaining infection.

- Indonesia was congratulated for rapid scale-up of MDA to all endemic districts through the National Lymphatic Filariasis Elimination Campaign (BELKAGA), progress with TAS implementation, and commitment to investigation and response in districts failing TAS.

- More information is needed to understand possible contribution of zoonotic transmission to human infection. Case control study is considered as a first step to compare animal infection in households with and without infected persons.

- More guidance is needed for programmatic use of xenomonitoring, particularly in areas where Mansonia spp are the primary vectors of LF.

3.2 Recommendations

Malaysia

(1) Use of Brugia Rapid™ in all LF transmission assessment surveys (TAS) is strongly recommended for cost-effectiveness.

(2) In areas with repeated pre-TAS failure or TAS failure, either enhanced MDA or test and treat strategy using Brugia Rapid™ is recommended, subject to availability of resources and logistic convenience.

(3) In a district with suspected persistent transmission, originally green IUs adjacent to red IUs should also be re-assessed using mini-TAS protocol with Brugia Rapid™ to identify any evidence of transmission.

(4) Quality assurance of diagnosis in terms of sample collection and reading of slides/tests should be reinforced.

(5) Development of validation dossier with compilation of historical data and updating of morbidity data should be initiated.

Indonesia

(1) MDA supervision checklists should be modified and implemented in all districts by the 2017 National Lymphatic Filariasis Elimination Campaign (BELKAGA).

(2) During the 2017 BELKAGA, coverage supervision tool should be implemented in districts achieving below 65% coverage in the 2016 BELKAGA.

(3) The results of TAS conducted in 2016 should be reported to WHO using the WHO Epidemiological Data Reporting Form.

(4) TAS should be repeated in Tanjung B. Barat.

(5) Repeated TAS 3 should be implemented in two evaluation units in Alor.

ANNEX 1

Consultation to accelerate elimination of *Brugia malayi* transmission in Indonesia and Malaysia
13-15 December 2016; Kota Kinabalu, Malaysia

Objectives of the consultation:

1. To discuss potential causes of persistent transmission of *Brugia malayi* in the area of Indonesia and Malaysia and results of the relevant studies to date; and

2. To determine the immediate and medium-term programmatic actions and operational research priorities to address this issue.

AGENDA

Day 1: Tuesday, 13 December 2016		
08:30 – 09:00	Registration	
Opening Session		
09:00 – 09:30	Welcome address	Datuk Dr Lokman Hakim Sulaiman, Deputy Director-General of Public Health, Ministry of Health, Malaysia WHO SEARO WHO WPRO
	Meeting objectives	Dr Rabindra Abeyasinghe Coordinator, WPRO/MVP
	Self-introduction of participants and observers	
	Nomination of the Chair and rapporteur	
	Administrative announcements	Dr Aya Yajima, NTD focal point, WPRO/MVP
09:30 – 10:00	*Group photograph followed by coffee/tea break*	
Session 1:	***Updates on LF elimination challenges from GPELF, Malaysia and Indonesia***	
10:00 – 10:20	Global GPELF updates: progress and challenges	Dr Jonathan King, LF Focal Point, WHO HQ
10:20 – 11:30	Progress and challenges to LF elimination in Malaysia	Dr Jenarun Jelip, Sabah State Health Department, Malaysia
	Discussion	All
11:30 – 12:30	Progress and challenges to LF elimination in Indonesia	Ministry of Health, Indonesia
	Outcomes of the expert consultation on transmission assessment survey in Indonesia, 2016	Dr Patrick Lammie, US CDC
	Discussion	All
12:30 – 13:30	*Lunch break*	
Session 2:	***Potential causes of persistent transmission of Brugia filariasis – Operational research updates***	
13:30 – 14:30	MDA coverage and challenges in areas with persistent Brugia transmission – Follow up of positive cases after treatment in Malaysia – Entomological study in Study in Kg Tangkarason, Beluran, Sabah, Malaysia	Dr Khairiah Binti Ibrahim, Ministry of Health Dr Rohani Binti Ahmad, Institute for Medical Research, Malaysia
	Discussion	All

14:30 – 15:30	Sensitivity of diagnostic tool (Brugia Rapid) – Antibody and Mf relationship – Cross-reaction with animal filariasis	Dr Patrick Lammie and Dr Peter Fischer, Washington University, USA Dr Rahmah Binti Noordin, Universiti Sains Malaysia
	Discussion	All
15:30 – 16:00	*Coffee/tea break*	
16:00 –16:30	Zoonotic transmission of *Brugia malayi* – Canine and feline filariasis in Beluran, Sabah – Zoonotic transmission survey in Thailand	Dr Lau Seng Fong, University Putra Malaysia Dr Aya Yajima
16:30 – 16:50	Discussion	All
16:50 – 17:00	Summary of potential causes of persistent transmission	The Chair
19:00 – 21:30	*Dinner meeting hosted by Deputy Director General of Public Health, Ministry of Health.*	

Day 2: Wednesday, 14 December 2016		
Session 3:	***Field visit to the area of TAS 2 failure***	
07:00 – 09:30	Travel from Kota Kinabalu to Beaufort Health Office, Sabah	All
09:30 – 09:45	Welcome speech	Datuk Dr Christina Rundi, Director, Sabah State Health Office
09:45 – 10:15	Overview of Lymphatic Filariasis Elimination Program (LFEP) in Beaufort District	Dr A.L. Liza Binti Abdul Latip, Beaufort District Health Office
10:15 – 10:45	Transmission Assessment Survey (TAS 2) IU Bangkalalak and positive case	Dr A.L. Liza Binti Abdul Latip
10:45 – 11:15	Questions and answers session	All
11:15 – 12:00	*Lunch break*	
12:00 – 15:00	Field visit to Kampung Kukup and Kampung Sabandar, Bangkalalak	All
15:00 – 17:00	Travel back to Kota Kinabalu, Sabah	All

Day 3: Thursday, 15 December 2016		
Session 4:	***Recommendation on programmatic actions and priority operational research***	
08:30 – 09:00	Findings from the field visit	Dr Aya Yajima
	Discussion	All
09:00 – 10:00	Potential programmatic actions – Checklists and Enhanced MDA supervision – Triple drug therapy (DEC + ALB + IVM) – Vector control	Dr Jonathan King Dr Peter Fischer Dr K. Krishnamoorthy, Vector Control Research Center, India
10:00 – 10:30	*Coffee/tea break*	
10:30 – 11:00	Discussion on immediate and medium-term programmatic actions	All
11:00 – 12:00	Potential operational research on surveillance – Antifilarial antibody – Xenomonitoring – Animal study	Dr Patrick Lammie Dr K. Krishnamoorthy Prof Dato Dr C.P. Ramachandran, Malaysia
12:00 – 12:30	Discussion	

12:30 – 13:30	*Lunch break*	
13:30 – 15:00	Discussion on operational researches – Research topics – Study outline – Implementers and partners	All
15:00 – 15:30	*Coffee /tea break*	
15:30 – 16:30	Discussion on operational researches (cont.)	All
16:30 – 16:50	Conclusions and recommendations	Dr Rabi Abeyasinghe
16:50 – 17:00	Closing	Datuk Dr Lokman Hakim Sulaiman
17:00 – 19:00	*Cocktail reception*	

ANNEX 2

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