Endgame Strategies for Filariasis Elimination 2021 in Southeast Asia: A Systematic Review

Güneydoğu Asya'da Filariasis Eliminasyonu 2021 için Oyun Sonu Stratejileri: Sistematik Bir İnceleme

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ABSTRACT

Objectives: Lymphatic filariasis is among neglected tropical diseases in Southeast Asia and Western Pacific Regions. It causes high morbidity due to a permanent disability that affects the lymphatic system drainage among those who were infected. The Global Programme to Eliminate Lymphatic Filariasis launched by the World Health Organization to eliminate lymphatic filariasis. This review aims to find out how far the implementation of end game strategies in Southeast Asia countries through comparison of the prevalence, mass drug administration regimes used, programme coverage and programme challenges.
Methods: A systematic search on articles related to lymphatic filariasis elimination programme in Southeast Asia was conducted using three databases namely Cochrane Library, PubMed and Ovid Medline. All the articles which were published within the year 2013 till 2018 assessed using the PRISMA checklist.
Results: A total of five articles included in this review based on the PRISMA checklist. All countries in the studies showed mass drug administration (MDA) programme coverage of more than 65%. Albendazole and Diethylcarbamazine Citrate during MDA have shown to be an effective combination with an obvious reduction in the lymphatic filariasis prevalence post-MDA.
Conclusions: Endgame strategies for lymphatic filariasis elimination are effective to reduce the prevalence of lymphatic filariasis. Hence, it is possible to achieve lymphatic filariasis elimination, through comprehensive programme strategies as well as extensive involvement of stakeholders that support the programme. However, it is crucial to overcome the programme challenges so that the journey towards lymphatic filariasis elimination year 2021 could be achieved smoothly.

Keywords: Disease elimination, elephantiasis, filariasis, mass drug administration

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ÖZET

Amaç: Lenfatik filaryaz, Güneydoğu Asya ve Batı Pasifik Bölgelerinde ihmal edilen tropikal hastalıklar arasında yer almaktadır. Enfekte olanlarda lenfatik sistem drenajını etkileyen kalıcı bir sakatlık nedeniyle yüksek morbiditeye neden olur. Dünya Sağlık Örgütü tarafından lenfatik filariasisin ortadan kaldırılması için başlatılan Lenfatik Filariasisin Ortadan Kaldırılmasına Yönelik Küresel Program. Bu derleme, yaygınlık, kullanılan toplu ilaç yönetim rejimleri, program kapsamı ve program zorluklarının karşılaştırılması yoluyla Güneydoğu Asya ülkelerinde oyun sonu stratejilerinin ne kadar uygulandığını bulmayı amaçlamaktadır.
Yöntemler: Cochrane Library, PubMed ve Ovid Medline olmak üzere üç veri tabanı kullanılarak Güneydoğu Asya'daki lenfatik filaryaz eliminasyon programı ile ilgili makaleler üzerinde sistematik bir araştırma yapıldı. 2013-2018 yılları arasında yayınlanan tüm makaleler PRISMA kontrol listesi kullanılarak değerlendirilmiştir.
Sonuçlar: Bu derlemeye PRISMA kontrol listesine dayalı olarak toplam beş makale dahil edilmiştir. Çalışmalardaki tüm ülkeler, %65'ten fazla kitle ilaç yönetimi (MDA) programı kapsamı gösterdi. MDA sırasında Albendazol ve Dietilkarbamazin Sitrat'ın, MDA sonrası lenfatik filaryaz prevalansında belirgin bir azalma ile etkili bir kombinasyon olduğu gösterilmiştir.
Sonuçlar: Lenfatik filaryaz eliminasyonu için oyun sonu stratejileri, lenfatik filaryaz prevalansını azaltmada etkilidir. Bu nedenle, kapsamlı program stratejilerinin yanı sıra programı destekleyen paydaşların kapsamlı katılımıyla lenfatik filaryaz eliminasyonunu sağlamak mümkündür. Bununla birlikte, 2021 lenfatik filaryaz eliminasyon yılına giden yolculuğun sorunsuz bir şekilde gerçekleştirilebilmesi için program zorluklarının üstesinden gelmek çok önemlidir.

Anahtar Sözcükler: Hastalık eliminasyonu, filiyazis, filaryaz, toplu ilaç uygulaması

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INTRODUCTION

Lymphatic filariasis is one of the 15 neglected tropical diseases in the Southeast Asia Region (SEAR) and Western Pacific Region (WPR), it is the oldest and most debilitating tropical disease that affects 1.34 billion human population in the endemic region, infecting around 120 million people in 81 countries till the date of report (1). Amongst which 15 million is suffering from lymphoedema (elephantiasis), with 25 million men disturbed by urogenital swelling (1). Malaysia is a country affected by this debilitating tropical disease too, and till the year 2018, the country has not achieved elimination of filariasis. The disease manifests after lying dormant in the subject for a long time, and when seen as clinically symptomatic, can result in permanent disability especially affecting the lymphatic system drainage (2). The disfigurement from lymphatic filariasis is associated with profound stigmatization affecting the activity of daily living, social inclusion and family dynamic and further displaced the endemic population to poverty.

All three lymphatic filarial parasites: the *Wuchereria* (W) *bancrofti, Brugia malayi, and Brugia timori* – are present in the SEAR, with 95% of infections from *W. bancrofti*. *Culex quinquefasciatus* as the major vector for *W. bancrofti* (besides minority from Mansonia and Anopheles), while Aedes and Anopheles species mosquitoes are present in a few foci (3). For WPR, lymphatic filariasis is caused by *W. bancrofti* and *B. malayi*, mainly transmitted by Anopheles, Culex and Aedes mosquitoes. The World Health Organization (WHO) started to focus on the elimination of lymphatic filariasis as a public health problem in 1997 (2).

In the year 2000, WHO launched the Global Programme to Eliminate Lymphatic Filariasis (GPELF) to eliminate lymphatic filariasis as a public health problem by the year 2020, which is defined as reducing the number of infections in affected areas to below target thresholds at which transmission is assumed no longer sustainable and delivering morbidity management and disability prevention (MMDP) in all areas with known patients (4). There are two aims in this goal, which are (i) to interrupt transmission of infection through mass drug administration in affected areas and to alleviate suffering through the provision of a basic package of recommended care (such as improved hygiene and skincare, surgical drainage for men with hydrocele – global programme referred to as MMDP (2,4,5).

The Global Programme to Eliminate Lymphatic Filariasis (GPELF) controls the disease burden by practising preventive chemotherapy, vector control and morbidity management in a more comprehensive manner, integrating interventions in multi-levels packages at the global, national, and local levels (5). The programme provided an accelerating impact on the elimination of lymphatic filariasis, and the sustainability of the programme is realized upon more integration, synergy and extended coverage of the programme with other health programmes delivered to the neglected population in the regions of endemicity (6). The infectivity chain of lymphatic filariasis is disrupted by the administration of a drug regime that is targeted at reducing the density of microfilariae in the bloodstream when done in large-scale towards the affected population (called mass drug administration), will possibly stop the transmission of filariasis in the population. However, the mass drug treatment has a limited effect only on the adult parasites. Other than that, vector control is vital to prevent infestation of filaria to the mosquitoes (1). There are more than 7.1 billion treatments have been delivered worldwide in 66 countries since the introduction of the programme in 2000. Till the year 2017, there are a total of 14 countries in the Western Pacific Region validated by WHO to have achieved the status of eliminated lymphatic filariasis as a public health problem, excluding Malaysia. Otherwise, preventive chemotherapy (PC) is still considered required in 52 out of 72 endemic countries, where the total population shows a prevalence of more than 1% infection in the country (1).

Out of the nine endemic countries in WHO SEAR and out of the six endemic countries of lymphatic filariasis in WHO WPR, only Thailand in the SEAR and Cambodia, Vietnam and Malaysia completed five or more rounds of MDA with 100% coverage (5). Countries that have 100% coverage of mass drug administrations in SEA and WPR is the Philippine, on top of the three countries of WPR mentioned above, while India and Maldives are among the Asian countries in the SEA WHO regions which are implementing this regime (5). Among the 11 Southeast Asia (SEA) countries, only Brunei Darussalam does not require MDA (5). Mass drug regime treatment with single, once-yearly doses of albendazole in combination with either Diethylcarbamazine Citrate (DEC) or Ivermectin was most used to clear the microfilaremia to reduce the filaria load to a level below the sustainable transmission. Other than that, a combination of annual IDA, annual DA, annual IA, or biannual A has been used in different endemic regions. Albendazole (400 mg) and DEC (6 mg/kg) or Albendazole (400 mg) and Ivermectin (150–200 ug/kg) are used in areas co-endemic for onchocerciasis; or biannual albendazole (400 mg) for co-endemic areas of loiasis (2). However, the mass drug regime is ineffective against adult filaria, hence at least 5 rounds of MDA with at least 65% coverage is required to reduce the filaria load (5). Other than that, concurrent management of malaria control, helminth control, nutritional supplementation and environmental health are applied to disrupt the transmission and infection (5). There is no comparison on the reduction of the prevalence of lymphatic filariasis in countries using the different MDA regimes. Of the 81 endemic countries, only 27 (33%) have active morbidity-management programmes, including basic preventive measures for lymphedema and urogenital surgery for hydrocele.

When SEA countries are approaching the filariasis elimination, it is time to find out regarding the end game strategies implemented in SEA countries by comparing the prevalence of lymphatic filariasis, MDA regimes used, and programme coverage between these SEA countries. This review aims to find out how far the implementation of end game strategies in Southeast Asia countries through comparison of the prevalence, mass drug administration regimes used, programme coverage and programme challenges.

METHODS

Systematic search related to relevant articles from three major search engines using Boolean search strategy, search engines including Cochrane Library, PubMed and Ovid Medline retrieving all articles published from the year 2014 until 2018. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist was used as the guideline to describe the workflow of articles search for this study (6). The keywords used to search for the articles are stated as below:

Initial keyword search using PICO strategy:

P: Filaria* in Malaysia OR Brugia* in Malaysia, OR Tropical eosinophilia in Malaysia OR Wuchereriasis in Malaysia OR *Wuchereria bancrofti* in Malaysia OR lymphatic filariasis in Malaysia
I: Screen diagnose OR diagnoses OR diagnostic tool OR elimination programme, eliminate* OR mass treatment OR Filariasis Control Programme OR mass drug administration (MDA) programme OR drug treatment programme
C: SEA OR SEAR OR Southeast Asia region OR Southeast Asia countries
O: elimination OR low incidence OR low prevalence OR end game strategy

As article retrieved was almost nil, a refined PICO was used:

Filaria* OR Brugia* OR Tropical eosinophilia OR Wuchereria* OR lymphatic filariasis
AND
mass treatment OR Filariasis Control Programme* OR mass drug administration programme* OR drug treatment programme* OR transmission assessment survey OR endgame strategy *
AND
Malaysia OR Philippines or Cambodia OR Laos OR Vietnam OR Indonesia OR Brunei OR Singapore OR Timor-Leste OR Myanmar OR Thailand
AND
eliminate* OR incidence OR prevalence OR surveillance

The inclusion criteria for the article search including (i) full text, primary research articles on prevalence of filariasis (ii) comparison of MDA regimes used in the SEA countries (inclusive of WHO WPR region countries that are in SEA) reported at least one outcome of the programme (programme coverage, the prevalence of filariasis) (iii) articles published from the year 2013 – 2018. The exclusion criteria set were: (i) reviewed articles of no original research work empirical data (ii) theory of filariasis articles purely about laboratory experiments (iii) articles that include other neglected tropical diseases.

Each author was given specific role in this review. MRH owned the whole idea and concept of the article. DSS; LS and WCM did the article search, screen, and selection.

These three authors reviewed all the search results to identify the needed articles. After all the articles were identified, each of the authors screened all the selected titles and abstracts for eligibility. Should there be any disagreement; a consensus was reached after discussion with the third author. DSS; LS; WCM and MRH wrote the first draft of the manuscript. QMG; MAAR and SSSAR did the reviewing & editing of the draft. The final draft of this manuscript reviewed by MRH; SSSAR; MSJ and QMJ. Final formatting and submission done by QMJ and FH.

The articles were first screened by titles to exclude totally irrelevant articles, then abstracts of the articles to look for PICO criteria. In total, there are a total of 27 articles retrieved based on Boolean search strategy, 13 accepted by abstract screening, leaving 10 articles, after 3 duplicated articles excluded. Finally, a total of five articles were subjected for full-text analysis after articles are filtered by using inclusion and exclusion criteria (Figure 1).

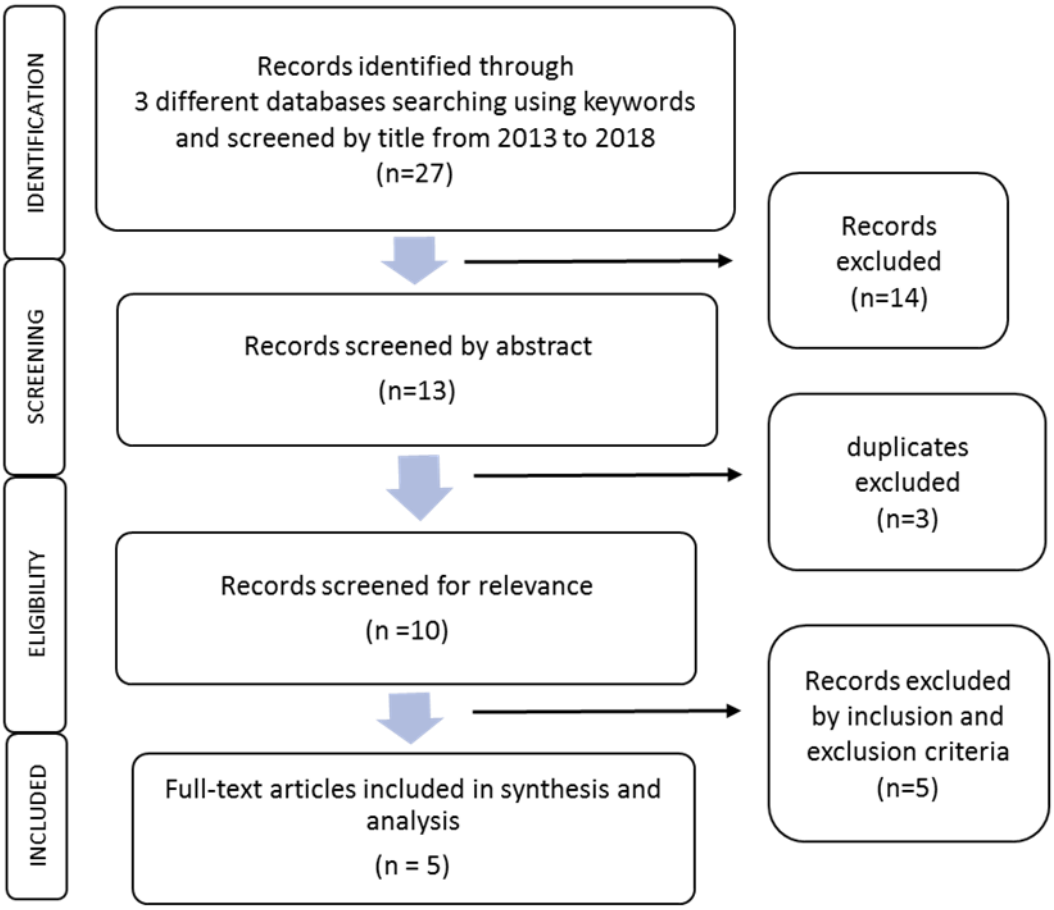


Figure 1: PRISMA checklist 2009

RESULTS

There was one quasi, 1 cohort study, 2 cross-sectional and 1 ecological study, target population sampling taken from migrant communities, 2 from districts/regions and 2 from countries in Southeast Asia (Table 1). The grading was based on the GRADE Checklist. The tool has a nine-component rating scale assessing the Risk of Bias, Inconsistency, Indirectness, Imprecision, Publication Bias, Large effect, Dose-response gradient, Plausible confounding would change the effect.

According to the checklist, interventional study designs will receive an initial 4 points grading (High) while observational studies will receive 2 points grading, subsequently, points will be added or deducted to a study according to the category of assessment. After which all papers will be grouped according to the outcome of MDA coverage – DEC bi-annually, MDA coverage – DEC+ALB annually, MDA compliance, and morbidity and disability management, and overall quality of the outcome will be given based on each outcome according to the lowest quality to avoid over-rating. The quality of each article was assessed and appraised independently by both reviewers according to the tool, any discrepancy in the rating of component is achieved by mutual consensus (Table 2).

Table 1: Results summary

Author/ year	Country	Study design	Tool	Variables (programme)	Outcome (coverage)	Challenge
Aye NN et al 2018	Myanmar	Ecological study	Transmission assessment survey (TAS) methods, measuring antigenemia (Ag) prevalence in children	Mass drug administration (MDA) regime using albendazole & DEC since 2001 involving 45 out of 65 districts (endemic districts)	– MDA Coverage: 68.7% to 98.5% – After 2-3 rounds of MDA: reduce prevalence between 0-5.9%	– Sustainability, stakeholder engagement – Interrupted DEC supply for 3 years due to delay of donation – Adverse reaction observed; no data complied
Supali et al 2013	Alor Island (East Nusa Tenggara Timor, Indonesia)	Cross sectional study	analyse anti-filarial IgG4 antibody	Annual MDA with diethylcarbamazine (DEC, 6 mg/kg body weight) combined with albendazole (alb, fixed dose of 400 mg	– Coverage rate 75% and 85% for all years of MDA – Prevalence fell from a baseline of 26% to less than 1% after round 4 MDA	– lack of post MDA 6th round surveillance data – poor follow up effort causes rebound of infection transmission
Toothong T. et al 2015	six Myanmar communities from factory and fishery areas from Samut Sakhon Province, Thailand	Cross sectional study	Interview	Mass drug administration (MDA) regime using DEC once annually, 6 migrant communities in Thai	– MDA coverage: 75% once annually – DEC access: 81.7%, by hospital (documented migrant)	– No health centre deliver bi-annual DEC to immigrants according to national guidelines – Barrier to access to DEC for undocumented migrant (illegal status); unemployed / short-term employed / short-term migrate (only given DEC upon work entry health screening); staying far (at fishery area)
Krentel A. 2016	Districts Agam and Depok city, Indonesia	Quasi (qualitative)	Micronarratives (recording success stories)	Increase compliance / uptake of LF drug / MDA program, assess first and second round of MDA	– MDA coverage: increase acceptance and compliance to LF drug by data sharing and educating district health staff, pre-MDA round technical visit to site	– Lack of fund to directly involves in the execution of MDA program
Khieu V et al 2018	Cambodia	Retrospective cohort	– Program evaluation – Transmission assessment survey (TAS) methods – Measuring antigenemia (Ag) prevalence in children – Morbidity management and disability prevention	Evaluation of National Program to Eliminate Lymphatic Filariasis	– Effectiveness of MDA: DEC + ALB annually 5 rounds, >70% coverage, – Antigenaemia reduced to 0% – Morbidity management and disability prevention in 14 provinces (for hydrocoele and lymphadema management in chronic LF)	nil

Nil: information not available

Table 2: Overall articles quality rating by outcome/ domain based on GRADE criteria

Quality criteria	Relative Importance	Quality of the evidence (circle one per outcome)	Recommendation
Outcome #1: MDA coverage – DEC bi-annually (Article 3)			
	Important	⊕⊕⊕◯ Moderate	Suggests considering this public health measure in policy
Outcome #2: MDA coverage – DEC + ALB annually (Article 1, 2, 5)			
	Not important	⊕⊕◯◯ Low	Suggests considering this public health measure in policy only if feasible
Outcome #3: MDA compliance (Article 1, 2, 3, 4, 5)			
	Important	⊕⊕⊕◯ Moderate	Suggests considering this public health measure in policy
Outcome #4: Morbidity and disability management (Article 5)			
	Not important	⊕⊕◯◯ Low	Suggests considering this public health measure in policy only if feasible

Overall, there are two outcomes with moderate quality, two with low quality. The outcome of biannual DEC as mass drug regime and drug compliance received moderate quality, hence it is suggested to consider this public health measure in policy, while Morbidity and disability management and MDA coverage – DEC+ALB annually received low quality, therefore suggested only to consider this public health measure in policy if feasible. However, policy implementation must be balanced against cost-effectiveness (Table 2). There may be systematic errors inherent in study designs used which result in a poor outcome, different checklists adopted for assessment may also produce different outcomes, although the GRADE checklist is the most adopted assessment tool for epidemiological issues.

Most of the studies were on the mass drug administration regime for lymphatic filariasis for 5 rounds using DEC and albendazole, except for Khieu et al who evaluated the aspect of morbidity management and disability prevention in the National Program to Eliminate Lymphatic Filariasis (7). Transmission assessment survey (TAS) methods, measuring antigenemia (Ag) prevalence in children, and morbidity management and disability prevention are recommended tools for the evaluation of prevalence reduction of lymphatic filariasis reduction following the national elimination program for Lymphatic Filariasis, 2 articles are describing the evaluation using these tools, Supali et al described analysing the microfilaremia load using anti-filarial IgG4 antibody, while the other 2 studies utilize communication and data sharing/experience sharing to raise awareness among the target population, Toothong et al achieved through interviewing health staffs who served as front liners and administrator of the program to improve surveillance and MDA, while Krentel et al described testimonial sharing to the community to improve compliance and acceptability to the Lymphatic Filariasis drug regime (8-10). Some studies showed demonstrated MDA delivered using biannual DEC, while some studies reported MDA DEC+ Albendazole annually (7-9,11). Overall, all five studies reported success in achieving >65% coverage of MDA, reduction of microfilaremia load, hence LF prevalence after the mass drug administration with DEC & Albendazole. Only one article mentioned post-MDA program surveillance and reported failure to follow up. Various challenges reported as obstacles to the success of the National Program to Eliminate Lymphatic Filariasis, most commonly faced challenges is lack of health staff commitment in the follow-up of a 5 year long community-based program, lack of documentation or surveillance data and the issue of funding to the program.

DISCUSSION

Programme Effectiveness

Overall, all studies showed the effectiveness of the filariasis elimination programme via MDA coverage achieving the GPELF goal, which is to interrupt the transmission through at least five annual rounds of MDA with 65% coverage of the total population (2). However, it is shown that MDA coverage among migrants lower compared to local people, due to treatment accessibility issues (9). A study done among disadvantaged groups of migrants showed that they had problems in terms of medications compliance especially among adults in rural areas and could be handled with collaboration from influential leaders (12).

The prevalence of lymphatic filariasis reduced significantly from baseline in all countries in the studies, because of MDA implementation (8,9,11) Study in Kenya showed a significant reduction in lymphatic filariasis prevalence in malaria-endemic areas not only because of MDA but could also be attributable to the application of insecticide-treated bed nets which may lead to a reduction of human exposure towards filariasis vectors (13).

There are a few determinants of programme success. First, if the country had low transmission baseline levels at baseline with most microfilariae (Mf) rates of less than 15%, the higher chances for the programme to be successful (11,13). Other than that, the MDA regime which consisted of albendazole, and DEC is considered a highly effective combination against the parasite (15). Directly observed therapy (DOTS) may assist in programme success. Despite that, good health system infrastructure, administration and training also may lead towards programme success (2).

Challenges

Achieving the WHO 2020 roadmap to control or eliminate the neglected tropical diseases via the Global Programme to Eliminate Lymphatic Filariasis seems not too far-fetched as most countries are showing good progress in achieving the goal of elimination (11). Some of the issues that can hinder the progress are concerning the challenges faced to implement the MDA in these endemic countries. Some of the pertinent challenges faced can be categorized into the health system or the endemic communities themselves (16).

Some of the issues of the healthcare system are the sustainability of MDA where most of these endemic countries are developing countries that are not able to sustain the provision of the drug by the government. Most of them rely on the drug supply by the donors, which are often being interrupted (12). Lack of drug supply coupled with poor resources such as health education material and basic training of health staff further interrupts their sustainability (9,11). The second healthcare system challenge is a lack of funding (8-11). This not only affects the drug availability but so for the developing countries, funding is needed for providing incentives to the community health volunteers (CHV). Since most of the endemic countries are vast with inadequate healthcare workers to carry out MDA, these CHV are needed to run the programme. In Madagascar, due to the limited capacity of health care workers to supervise the community distribution of MDA, their administration is inadequate and requires further assistance (17). Without the provision of many incentives, these CHVs are not inclined to join the programme as that would be their only source of income (16). Contrary to that, Mali has recognized this problem and ensures that funds for the CHVs are set aside and only used for them (18).

Subsequently post programme, the challenge arises from lack of follow up and post MDA data collection (8,17). As mentioned in a study in the UK, monitoring and evaluation procedures are done to establish the interruption of transmission is important for the endgame as we approach the 2020 target (19). Gyapong et al also mentioned data reporting and collection can be either under or overestimated (16). This is due to most healthcare systems not including filariasis elimination as part of their health indicator. Apart from that, in countries like Ghana and most developed countries the programme is funded by donors and managed vertically, therefore data collection is more for the donor needs than health system needs.

Another neglected group is the migrant workers in the endemic countries especially undocumented immigrant workers and the highly mobile population (9). Universal treatment coverage needs to be made available so that the programme can reach all targeted populations in the endemic countries.

Community participation is also one of the major challenges that need to be overcome on the road to success. Evidently, there is a lack of awareness and knowledge among the community regarding the disease, the treatment, and the impact on the country (9,10,20). Due to the poor understanding, there is a lack of participation from the community. Some may understand the existence of the disease but are not aware of the MDA programme in their area (20). Most of them would fear the side effects of the drug and hence lead to poor compliance. Some of the side effects experienced are intolerable dizziness, muscle ache, tiredness, nausea, and vomiting (related to microfilariae density in the blood) (11).

Aiming to achieve the endgame of filariasis would still be within reach if we address all the challenges. The first step would be to empower the community. Once they are empowered, they will be more receptive to the challenges the healthcare system faces and aid in ensuring better coverage of the MDA. Subsequently, filariasis should be given importance and its burden being acknowledged to ensure more attention and funding can be channelled to their elimination programmes and ensure its sustainability.

CONCLUSION

The end game strategies for lymphatic filariasis elimination are shown to be effective to reduce the prevalence of lymphatic filariasis. Programme challenges can be handled by maintaining the support from various stakeholders, focusing on the marginalized populations such as migrants or those who live far from healthcare access, empower, and educate the community as well as maintaining the surveillance. Systematic, structured strategies may lead to achieving the target to eliminate lymphatic filariasis in Southeast Asia.

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Conflict of interest
No conflict of interest was declared by the authors.

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