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Research **Open Access**

A Systematic Review: The Effectiveness of Triple Drug versus Dual Drug Approach Against Lymphatic Filariasis

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Abstract

Background: Lymphatic Filariasis (LF) is a neglected tropical disease caused by filarial nematode parasites (*Wuchereria bancrofti, Brugia malayi*, and *B. timori*), which is transmitted via mosquitoes in the form of microfilariae (Mf). The transmission cycle for each species is the same parasites or worms transmitted through the bite of all types of mosquitoes. The most severe clinical manifestations of LF are lymphedema and elephantiasis. The treatment of filariasis receives mass drug administration with a single dose of the triple-drug oral regimen. Therefore, the World Health Organization (WHO) reported that the triple-drug oral regimen was an LF treatment.

Methods: The research is in the form of systematic review research using the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) method, which is carried out systematically. The research was conducted in December-February with a review of articles published in the last 5 years (2018-2023). Researchers searched for literature independently through PubMed and Science Direct.

Results: Triple drug therapy or a combination of Ivermectin-Diethylcarbamazine -Albendazole (IDA) is safer and more tolerable for filariasis than dual drug (combination of Diethylcarbamazine -Albendazole/DA), according to various articles. In addition, IDA reduces microfilaria formation more than DA. Most filariasis treatment side effects are modest, such as fever and soreness.

Conclusion: In comparison to dual drug therapy, triple drug therapy exhibits a substantial advantage; however, the level of endemicity and the species of the causative agents must be considered when applying this approach.

Keywords: dual drug; lymphatic filariasis; triple drugs

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Introduction

Lymphatic Filariasis (LF) is a neglected tropical disease caused by filarial nematode parasites (*Wuchereria bancrofti*, *Brugia malayi*, and *B. timori*), which are transmitted via mosquitoes in the form of microfilariae (Abuelazm *et al*., 2022). *W.bancrofti* is the leading cause of LF worldwide, while in Indonesia, it is caused by *Brugia malayi* and *B. timori* (Supali *et al*., 2021) . The type of nematode that causes filariasis is found in lymphatic vessels and can cause lymphedema, elephantiasis, hydroceles, and disfigurement (Abuelazm *et al*., 2022; Weil *et al*., 2019).

The transmission cycle of filariasis through adult worms' nests in the lymphatic vessels disrupts the normal function of the lymphatic system (Azhar *et al*., 2023). Lymphatic filariasis is transmitted by different types of mosquitoes, for example, by the *Culex* mosquito, widespread across urban and semi-urban areas; *Anopheles*, mainly found in rural areas, and *Aedes*, mainly in endemic islands in the Pacific (World Health Organization, 2023).

The most severe clinical manifestations of LF are lymphedema and elephantiasis. Lymphatic dysfunction has been shown to predispose infected individuals to secondary bacterial and fungal infections and trigger inflammatory reactions in the

skin and subcutaneous tissue that accelerate lymphedema's progression and precipitate elephantiasis development (Kanaan Al Tameemi & Raiaan Kabakli, 2019; Kar Shantanu Kumar & Jagadish Hansa, 2018) .

Lymphatic Filariasis occurred in 81 countries, and about 68 million people were at risk of infection in 2014, including 36 million microfilaria carriers, 19 million hydrocoele cases, and 17 million lymphedema cases (Weil *et al*., 2021; Willis *et al*., 2020). In Indonesia specifically, there are 236 districts and cities, and as of the conclusion of 2021, there have been 9,354 cases of filariasis resulting in permanent disability across 34 provinces (Direktorat Jenderal Pencegahan dan Pengendalian Penyakit, 2022). The five provinces exhibit the highest prevalence of chronic filariasis cases: Papua, East Nusa Tenggara (NTT), West Papua, Western Java, and Aceh. Therefore, to stop the spread of filariasis, in 2000, the WHO launched the Global Program to Elimination (GPELF), which has now achieved very significant progress (Supali *et al*., 2021; Weil *et al*., 2021).

There are two pillars of the Global Program to Eliminate Lymphatic Filariasis is mass drug administration (MDA) with anti-filarial drugs (to reduce the risk of new infections and utilizing the following three anti-parasitic medications is essential: albendazole (ALB), diethylcarbamazine (DEC), and ivermectin (IVM) and protocols for morbidity management and disability prevention (MMDP) to help persons with lymphedema, elephantiasis and hydrocele) (Weil *et al*., 2021).

Notwithstanding the advancements, the GPELF encounters numerous obstacles, and the objective of eliminating lymphatic filariasis by 2020 was not met. Several nations with a high prevalence of lymphatic filariasis still necessitate Mass Drug Administration (MDA). Certain individuals had not yet initiated the Mass Drug Administration (MDA) (Rahim & Karim, 2022), While others had not implemented MDA in all areas affected by the disease. Furthermore, surveys done in certain countries for at least five years following the implementation of the Mass Drug Administration (MDA) revealed that the conditions required to cease MDA were not satisfied (Prada *et al*., 2020).

The Health Organization (WHO) reported that 51 countries continued to require mass drug administration (MDA) as an LF treatment. Presently, oral administration of a combination of albendazole (ABZ) and diethylcarbamazine (DEC) is the first-line chemotherapy in MDA for LF treatment to target the filarial nematodes (Permana *et al*., 2019). However, a single dose of the triple-drug oral regimen of ivermectin (200 µg per kg of body weight) plus diethylcarbamazine (6 mg per kg of body weight) plus albendazole (400 mg) or a single dose of triple therapy (IDA or combination of IVM, DEC, and ALB) is preferable to dual therapy (IVM, and ALB or IVM, and DEC) in terms of microfilaria clearance from the blood, according to recent studies (King *et al*., 2018; Weil *et al*., 2019). IDA's effectiveness in standard dual therapy (IVM and ALB) has not been evaluated in Africa.

Computer simulation studies suggest that replacing dual therapy with triple therapy, assuming a high degree of compliance could significantly speed up the eradication of lymphatic filariasis (Irvine *et al*., 2017). The drugs employed in the triple drug regimen possess a wide safety margin; billions of doses were administered through lymphatic filariasis eradication operations. Conversely, a recent literature analysis indicates that treatment methods for lymphatic filariasis often result in minor to moderate side effects (Bjerum et al., 2023; Edi *et al*., 2019; Willis *et al*., 2020).

Our objective was to assess the effectiveness and safety of triple therapy compared to dual therapy in individuals with microfilaria infection and the community's endemic to lymphatic filariasis.

Method

On this topic, the research is in the form of systematic review research using the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) method, which is carried out systematically.

Sources for data and methods of searching

In February, we conducted a comprehensive search through the electronic databases MEDLINE (PubMed), EMBASE, and Science Direct, reviewing articles published in the last 5 years (2018-2023). Researchers searched for literature independently using keywords combined with Boolean: "Filariasis OR Lymphatic Filariasis AND Triple Drug OR Regiment Ivermectin AND Diethylcarbamazine AND Albendazole". Therefore, Articles published in English on triple-drug therapy for filariasis were mostly used by the population in this study. The inclusion criteria required to compile a systematic review include the following: 1) triple combination dose and duration of therapy; 2) effectiveness and clinical improvement of patients; 3) side effects; and 4) prognosis.

The exclusion criteria consist of 1) The article can't be fully accessed; 2) The article wasn't in the English language; 3) The article is outside the time frame; 4) The article topic is not about the treatment of LF.

The most important thing that must be done in doing a systematic review is to look at the suitability of the title and abstract in each piece of literature to see whether there is a match with the topic. This section contains the results of the research and its discussion. Adequate data must

support the results obtained from research. Research results and findings must answer the research hypothesis or research question stated previously in the introduction section.

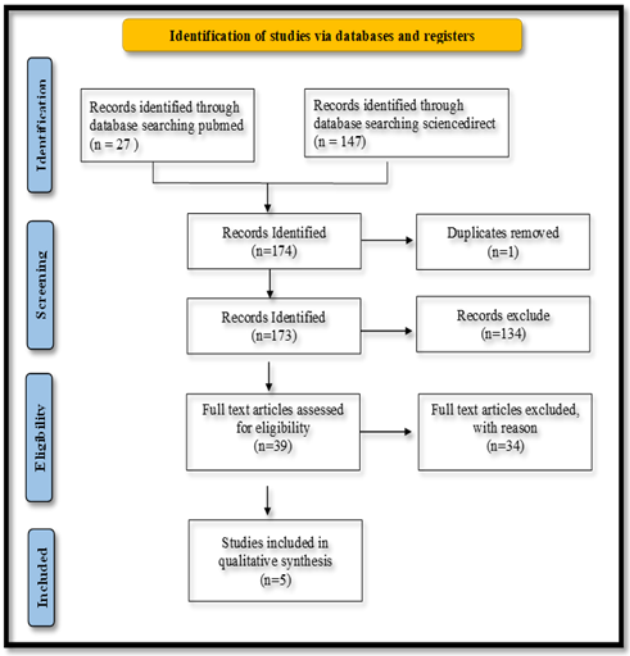

Figure 1. Prisma Flow Chart
(Agrawal et al., 2024; Akl et al., 2024)

Result

Based on database identification, several articles contain a combination of the drug albendazole (ALB), diethylcarbamazine (DEC), and ivermectin (IVM) as filariasis therapy. The article includes treatment, outcome, side effects, and prognosis. The treatment section consists of a dose that is appropriate to age. Meanwhile, the outcome is the success achieved after treatment. In addition, during treatment, side effects often occur, one of which is filariasis.

The development of a disease can be predicted through prognosis, which usually depends on age, gender, and the treatment method. Providing filariasis treatment can't be done haphazardly because it should not be given just like that age < 5 years, weight less than 15 kg, pregnancy (or last menstrual period > 4 weeks ago or unknown), breastfeeding within 7 days of delivery, acute or chronic illness severe enough to interfere with activities of daily living, or any history of previous allergy to the study drugs (Supali *et al*., 2021).

Edi's study (2019) showed that all subjects experienced mild AEs; 28% and 25% of infected and uninfected participants experienced grade 2 AEs, respectively. There were no severe or profound adverse events. Only fever (16 of 32 versus 4 of 24, P<0.001) and scrotal pain/ swelling in males (6 of 20 versus 0 of 12, P = 0.025) were more frequent in infected than uninfected participants. All LF-positive participants were amicrofilaremic at 7 days post-treatment, and 27 of 31 (87%) remained amicrofilaremic 12 months after treatment (Edi *et al*., 2019).

Weil's study (2019) showed that treatment assignments in each study site were randomized by residence locality. Medical teams with active follow-up assessed adverse events (AEs) for 2 days and passive follow-up for an additional 5 days. A total of 26,836 persons were enrolled (13,535 females and 13,300 males). A total of 12,280 participants were treated with DA, and 14,556 were treated with IDA. On day 1 or 2 after treatment, 97.4% of participants were assessed for AEs. The frequency of all AEs was similar after IDA and DA treatment (12% versus 12.1%, adjusted odds ratio for IDA versus DA 1.15, 95% CI 0.87–1.52, P= 0.316); 10.9% of participants experienced mild (grade 1) AEs, 1% experienced moderate (grade 2) AEs, and 0.1% experienced severe (grade 3) AEs. Rates of serious AEs after DA and IDA treatment were 0.04% (95% CI 0.01%–0.1%) and 0.01% (95% CI 0.00%–0.04%), respectively. Severity of AEs was not significantly different after IDA or DA. Five of six serious AEs reported occurred after DA treatment. The most common AEs reported were headache, dizziness, abdominal pain, fever, nausea, and fatigue. AE frequencies varied by country and were higher in adults and

in females. AEs were more common in study participants with microfilaremia (33.4% versus 11.1%, P< 0.001) and more common in microfilaremia participants after IDA than after DA (39.4% versus 25.6%, P< 0.001) (Weil *et al*., 2019).

Hardy's study (2020) showed that 3612

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enrolled and eligible participants, 1216 were randomized to DA and 2396 to IDA. Age and sex in both groups were representative of the population. Over 99% (3598) of participants completed 7 days of follow-up. Adverse events were reported by 600 participants (16.7%), distributed equally between treatment groups, with most graded as mild (93.2%). IDA has comparable safety to DA with the same frequency of adverse events experienced following community mass drug administration. The presence of co-endemic infections didn't increase adverse events (Hardy *et al*., 2020).

Willis's study (2020) showed that In our sample of 4420 people aged ≥2 years (2.2% of the population), age-adjusted estimates indicated that 89.0% of the eligible population were offered MDA, 83.9% of the eligible population took MDA (program coverage), and 80.2% of the total population took MDA (epidemiological coverage). Overall, 83.8% (2986/3563) reported that they did not feel unwell at all after taking MDA. Mild AEs (feeling unwell but able to do normal everyday things) were reported by 13.3% (476/3563) and moderate or severe AEs (feeling unwell and being unable to do normal everyday activities such as going to work or school) by 2.9% (103/3563) of participants (Willis et al., 2020).

Supali's study (2021) showed that Fifty-five eligible participants were enrolled; 28 and 27 persons were randomized to the IDA and DA treatment arms. Only 3 of 28 participants (10.7%) were Mf positive 24 hr. after IDA treatment with a geometric mean density of 1 Mf/ml (range 1–2 Mf/ml). In contrast, 19 out of 27 participants (70.4%) were Mf positive 24 hr after DA (geometric mean Mf density 10 Mf/ml; range 1–110 Mf/ml). Only 1 of 27 participants (3.7%) in the IDA treatment group was Mf positive 12 mo after treatment (10 Mf/ml). In contrast, 10 out of 25 participants (40%) were Mf positive 12 mo after DA with Mf counts that ranged from 2 to 123 Mf/ml. Differences in percentages of participants with complete Mf clearance by treatment group were highly significant at 24 hr. and 12 months ($p < 0.001$ and $p = 0.004$, respectively). Fifteen participants in the IDA treatment group (54%) experienced 19 AEs (17 grades 1 and two grade 2). Ten participants in the DA group (37%) experienced 14 AEs, all grade 1 (Supali et al., 2021).

Based on the literature of this study, it suggested using triple therapy rather than dual therapy. Dual therapy has several issues, such as: (1) Compared to triple therapy, dual therapy is less effective at eliminating microfilariae from the blood. For instance, studies indicate that triple therapy is associated with substantially higher clearance rates at 12 months following treatment (Abuelazm *et al*., 2022; Laman *et al*., 2022). (2) Dual therapy may necessitate multiple rounds of treatment over several years to attain the same results as a single dose of triple therapy, as it has a lower efficacy in microfilaria clearance. Consequently, a longer time is required for elimination (Laman *et al*., 2022). (3) Delayed Disease Eradication: The reduced efficacy and delayed clearance of microfilariae may restrict its effectiveness in expediting lymphatic filariasis elimination efforts, particularly in highly endemic regions (Irvine *et al*., 2017).

Triple therapy offers numerous benefits, including (1) Triple therapy (Ivermectin, Diethylcarbamazine, and Albendazole) is substantially more effective than dual therapy in removing microfilariae from the blood. In contrast to dual therapy, which has reduced clearance rates, research indicates that a single dose of triple therapy can eradicate microfilariae in up to 96% of patients within 12 months (Abuelazm *et al*., 2022) ; (2) Accelerate Elimination Objectives: The triple-drug regimen can expedite global eradication efforts by reducing the number of mass drug administration (MDA) cycles required to achieve elimination targets, particularly in regions with high baseline prevalence (Irvine *et al*., 2017; Khaemba *et al*., 2023) (3) Triple therapy is generally well-tolerated in endemic communities even though it causes more frequent moderate side effects (e.g., headache, fatigue) (Yana, 2021). (4) Single-Dose Regimen: In contrast to multiple cycles of dual therapy over several years, single-dose administration simplifies treatment logistics and enhances compliance (King *et al*., 2018; Molyneux, 2018).

Despite the numerous benefits of triple therapy, there are also a few disadvantages that must be considered, including enhanced minimal side effects (Budge *et al*., 2018; Weil *et al*., 2019); in comparison to dual therapy, triple therapy is correlated with a greater incidence of mild-to-moderate side effects, including nausea and migraines. These effects typically reach their maximum intensity within 12–48 hours of treatment but subside within a week (Gusti *et al*., 2021). Implementation Obstacles: The efficacy of triple therapy in mass drug administration programs is contingent upon high population coverage and adherence. In regions with logistical challenges, its effectiveness may be restricted by poor compliance or systematic non-adherence (Tripathi *et al*., 2022). Restricted Applicability in Specific Regions: The use of Ivermectin in triple therapy is not recommended in areas that are co-endemic with Loa Loa due to the risk of severe adverse reactions, such as encephalopathy (Boussinesq *et al*., 1998; Chesnais *et al*., 2020; Lenk *et al*., 2020).

The implementation of triple medication therapy for the eradication of lymphatic filariasis should consider several factors, which are based on the advantages and disadvantages mentioned above: High-Prevalence Areas: Countries with elevated baseline prevalence of lymphatic filariasis may contemplate transitioning to triple therapy, as it may diminish treatment cycles and expedite elimination timelines (Irvine *et al*., 2017; Njenga *et*

al., 2024; Weil *et al*., 2021). Low-Prevalence Areas: In places characterized by low prevalence or where dual therapy has already yielded

substantial advancements, the continuation of dual therapy may be adequate (Yana, 2021; Gyapong *et al*., 2018). Co-Endemic Regions: In regions co-endemic with Loa Loa or where Ivermectin administration is contraindicated, dual therapy is the safer alternative (Beng *et al., 2020;* Kamgno *et al*., 2016).

Conclusion

In summary, whereas triple therapy provides considerable advantages in high-prevalence contexts, the persistence of dual therapy in low-prevalence regions can be a sufficient and effective strategy. This technique optimizes resources while ensuring a balance between efficacy and tolerability in the last stages of LF eradication attempts. The weakness of these articles was that variations in research populations (e.g., age, gender, ethnicity), disease severity, drug administration techniques, and outcome measures that could create variability define the weakness of these studies. This could complicate the synthesis of findings and lower the validity of conclusions. The variations in control groups or comparator arms between studies could mask the actual impact of triple versus dual therapy; small sample sizes and short follow-up times in the included studies could restrict the capacity to identify long-term effects or rare outcomes, so compromising the robustness of the results.

Reference

Abuelazm, M. T., Abdelazeem, B., Badr, H., Gamal, M., Ashraf, M., & Abd-elsalam, S. (2022). Efficacy and safety of triple therapy versus dual therapy for lymphatic filariasis: A systematic review and meta-analysis. In *Tropical Medicine and International Health* (Vol. 27, Issue 3, pp. 226–235). John Wiley and Sons Inc. https://doi.org/10.1111/tmi.13727

Agrawal, S., Oza, P., Kakkar, R., Tanwar, S., Jetani, V., Undhad, J., & Singh, A. (2024). Analysis and recommendation system-based on PRISMA checklist to write systematic review. *Assessing Writing*, *61*, 100866. https://doi.org/10.1016/j.asw.2024.100866

Akl, E. A., Khabsa, J., Iannizzi, C., Piechotta, V., Kahale, L. A., Barker, J. M., McKenzie, J. E., Page, M. J., & Skoetz, N. (2024). Extension of the PRISMA 2020 statement for living systematic reviews (PRISMA-LSR): checklist and explanation. *BMJ*, e079183. https://doi.org/10.1136/bmj-2024-079183

Azhar, S., Naeem Muhammad Abdullah, Qamar Warda, Iqbal Muhammad Jawad, Asghar Shiza, Ajaz Rahmeen, Iqbal Hrishik, Sohail MUhammad, Tahir Saleha, Assad Muhammad Ali, & Khalid Adeel. (2023). Basic Insights into Lymphatic Filariasis. *Zoonosis*, *2*, 73–88. https://doi.org/10.47278/book.zoon/2023.53

Beng, A. A., Esum, M. E., Deribe, K., Njouendou, A. J., Ndongmo, P. W. C., Abong, R. A., Fru, J., Fombad, F. F., Nchanji, G. T., Amambo, G., Gandjui, N. T. V., Biholong, B., Nko'Ayissi, G., Mbia, P., Akame, J., Enyong, P. I., Reid, S. D., Tougoue, J. J., Zhang, Y., & Wanji, S. (2020). Mapping lymphatic filariasis in Loa loa endemic health districts naïve for ivermectin mass administration and situated in the forested zone of Cameroon. *BMC Infectious Diseases*, *20*(1), 284. https://doi.org/10.1186/s12879-020-05009-3

Bjerum, C. M., Koudou, B. G., Ouattara, A. F., Lew, D., Goss, C. W., Gabo, P. T., King, C. L., Fischer, P. U., Weil, G. J., & Budge, P. J. (2023). Safety and tolerability of moxidectin and ivermectin combination treatments for lymphatic filariasis in Côte d'Ivoire: A randomized controlled superiority study. *PLoS Neglected Tropical Diseases*, *17*(9 September). https://doi.org/10.1371/journal.pntd.0011633

Boussinesq, M., Gardon, J., Gardon-Wendel, N., Kamgno, J., Ngoumou, P., & Chippaux, J. P. (1998). Three probable cases of Loa loa encephalopathy following ivermectin treatment for onchocerciasis. *The American Journal of Tropical Medicine and Hygiene*, *58*(4), 461–469. https://doi.org/10.4269/ajtmh.1998.58.461

Budge, P. J., Herbert, C., Andersen, B. J., & Weil, G. J. (2018). Adverse events following single dose treatment of lymphatic filariasis: Observations from a review of the literature. *PLOS Neglected Tropical Diseases*, *12*(5), e0006454. https://doi.org/10.1371/journal.pntd.0006454

Chesnais, C. B., Pion, S. D., Boullé, C., Gardon, J., Gardon-Wendel, N., Fokom-Domgue, J., Kamgno, J., & Boussinesq, M. (2020). Individual risk of post-ivermectin serious adverse events in subjects infected with Loa loa. *EClinicalMedicine*, *28*, 100582. https://doi.org/10.1016/j.eclinm.2020.100582

Direktorat Jenderal Pencegahan dan Pengendalian Penyakit. (2022). *G20 Indonesia 2022*.

Edi, C., Bjerum, C. M., Ouattara, A. F., Chhonker, Y. S., Penali, L. K., Méité, A., Koudou, B. G., Weil, G. J., King, C. L., & Murry, D. J. (2019). Pharmacokinetics, safety, and efficacy of a single co-administered dose of diethylcarbamazine, albendazole and ivermectin in adults with and without *Wuchereria bancrofti* infection in côte d'ivoire. *PLoS Neglected Tropical Diseases*, *13*(5). https://doi.org/10.1371/journal.pntd.0007325

Gusti, I., Ari, A., Yana, K., & Salim, M. (2021).

Comparison of triple drug therapy versus double drug therapy for lymphatic filariasis : a systematic review article. *Medical and health science journal* , 05(01).

Gyapong, J. O., Owusu, I. O., da-Costa Vroom, F. B., Mensah, E. O., & Gyapong, M. (2018). Elimination of lymphatic filariasis: current perspectives on mass drug administration. *Research and Reports in Tropical Medicine*, *Volume 9*, 25–33. https://doi.org/10.2147/RRTM.S125204

Hardy, M., Samuela, J., Kama, M., Tuicakau, M., Romani, L., Whitfeld, M. J., King, C. L., Weil, G. J., Grobler, A. C., Robinson, L. J., Kaldor, J. M., & Steer, A. C. (2020a). The safety of combined triple drug therapy with ivermectin, diethylcarbamazine and albendazole in the neglected tropical diseases co-endemic setting of fiji: A cluster randomised trial. *PLoS Neglected Tropical Diseases*, *14*(3). https://doi.org/10.1371/journal.pntd.0008106

Irvine, M. A., Stolk, W. A., Smith, M. E., Subramanian, S., Singh, B. K., Weil, G. J., Michael, E., & Hollingsworth, T. D. (2017). Effectiveness of a triple-drug regimen for global elimination of lymphatic filariasis: a modelling study. *The Lancet Infectious Diseases*, *17*(4), 451–458. https://doi.org/10.1016/S1473-3099(16)30467-4

Kamgno, J., Nguipdop-Djomo, P., Gounoue, R., Téjiokem, M., & Kuesel, A. C. (2016). Effect of Two or Six Doses 800 mg of Albendazole Every Two Months on Loa loa Microfilaraemia: A Double Blind, Randomized, Placebo-Controlled Trial. *PLOS Neglected Tropical Diseases*, *10*(3), e0004492. https://doi.org/10.1371/journal.pntd.0004492

Kanaan Al Tameemi, & Raiaan Kabakli. (2019). Lymphatic filariasis: an overview. *Asian Journal of Pharmaceutical and Clinical Research*, 1–5. https://doi.org/10.22159/ajpcr.2019.v12i12.35646

Kar Shantanu Kumar, & Jagadish Hansa. (2018). New Perspective of Lymphatic Filariasis-Towards Elimination. *Annals of the National Academy of Medical Sciences*, *54*(2), 106–113.

Khaemba, C., Barry, A., Omondi, W. P., Kirui, E., Oluka, M., Parthasarathi, G., Njenga, S. M., Guantai, A., & Aklillu, E. (2023). Comparative Safety Surveillance of Triple (IDA) Versus Dual Therapy (DA) in Mass Drug Administration for Elimination of Lymphatic Filariasis in Kenya: A Cohort Event Monitoring Study. *Drug Safety*, *46*(10), 961–974. https://doi.org/10.1007/s40264-023-01338-9

King, C. L., Suamani, J., Sanuku, N., Cheng, Y.-C., Satofan, S., Mancuso, B., Goss, C. W., Robinson, L. J., Siba, P. M., Weil, G. J., & Kazura, J. W. (2018). A Trial of a Triple-Drug Treatment for Lymphatic Filariasis. *New England Journal of Medicine*, *379*(19), 1801–1810. https://doi.org/10.1056/nejmoa1706854

Laman, M., Tavul, L., Karl, S., Kotty, B., Kerry, Z., Kumai, S., Samuel, A., Lorry, L., Timinao, L., Howard, S. C., Makita, L., John, L., Bieb, S., Wangi, J., Albert, J. M., Payne, M., Weil, G. J., Tisch, D. J., Bjerum, C. M., … King, C. L. (2022). Mass drug administration of ivermectin, diethylcarbamazine, plus albendazole compared with diethylcarbamazine plus albendazole for reduction of lymphatic filariasis endemicity in Papua New Guinea: a cluster-randomised trial. *The Lancet Infectious Diseases*, *22*(8), 1200–1209. https://doi.org/10.1016/S1473-3099(22)00026-3

Lenk, E. J., Moungui, H. C., Boussinesq, M., Kamgno, J., Nana-Djeunga, H. C., Fitzpatrick, C., Peultier, A.-C. M. M., Klion, A. D., Fletcher, D. A., Nutman, T. B., Pion, S. D., Niamsi-Emalio, Y., Redekop, W. K., Severens, J. L., & Stolk, W. A. (2020). A Test-and-Not-Treat Strategy for Onchocerciasis Elimination in Loa loa–coendemic Areas: Cost Analysis of a Pilot in the Soa Health District, Cameroon. *Clinical Infectious Diseases*, *70*(8), 1628–1635. https://doi.org/10.1093/cid/ciz461

Molyneux, D. H. (2018). Advancing toward the Elimination of Lymphatic Filariasis. *New England Journal of Medicine*, *379*(19), 1871–1872. https://doi.org/10.1056/NEJMe1811455

Njenga, S. M., Kanyi, H., Okoyo, C., Githinji, E., Mwatele, C., Matendechero, H. S., Omondi, W. P., Gitahi, P. N., Owaga, C., Onsongo, J. K., & Gass, K. (2024). Triple-drug therapy with ivermectin, diethylcarbamazine and albendazole for the acceleration of lymphatic filariasis elimination in Kenya: Programmatic implementation and results of the first impact surveillance. *BMJ Yale*. https://doi.org/10.1101/2024.01.30.24301765

Permana, A. D., Tekko, I. A., McCrudden, M. T. C., Anjani, Q. K., Ramadon, D., McCarthy, H. O., & Donnelly, R. F. (2019). Solid lipid nanoparticle-based dissolving microneedles: A promising intradermal lymph targeting drug delivery system with potential for enhanced treatment of lymphatic filariasis. *Journal of Controlled Release*, *316*, 34–52. https://doi.org/10.1016/j.jconrel.2019.10.004

Prada, J. M., Davis, E. L., Touloupou, P., Stolk, W. A., Kontoroupis, P., Smith, M. E., Sharma, S., Michael, E., De Vlas, S. J., & Hollingsworth, T. D. (2020). Elimination or Resurgence: Modelling Lymphatic Filariasis after Reaching the 1% Microfilaremia Prevalence Threshold. *Journal of Infectious Diseases*, *221*, S503–S509. https://doi.org/10.1093/infdis/jiz647

Rahim, S., & Karim, M. M. (2022). Lymphatic

Filariasis: A systematic review on its morbidity and road to elimination. In *African Journal of Biological Sciences (South Africa)* (Vol. 4, Issue 4, pp. 116–126). African Science Publications. https://doi.org/10.33472/AFJBS.4.4.2022.116-126

Supali, T., Djuardi, Y., Christian, M., Iskandar, E., Alfian, R., Maylasari, R., Destani, Y., Lomiga, A., Minggu, D., Lew, D., Bogus, J., Weil, G. J., & Fischer, P. U. (2021). An open label, randomized clinical trial to compare the tolerability and efficacy of ivermectin plus diethylcarbamazine and albendazole vs. Diethylcarbamazine plus albendazole for treatment of brugian filariasis in Indonesia. *PLoS Neglected Tropical Diseases*, *15*(3). https://doi.org/10.1371/journal.pntd.0009294

Tripathi, B., Roy, N., & Dhingra, N. (2022). Introduction of Triple-Drug Therapy for Accelerating Lymphatic Filariasis Elimination in India: Lessons Learned. *The American Journal of Tropical Medicine and Hygiene*. https://doi.org/10.4269/ajtmh.21-0964

Weil, G. J., Bogus, J., Christian, M., Dubray, C., Djuardi, Y., Fischer, P. U., Goss, C. W., Hardy, M., Jambulingam, P., King, C. L., Kuttiat, V. S., Krishnamoorthy, K., Laman, M., Lemoine, J. F., O'brian, K. K., Robinson, L. J., Samuela, J., Schechtman, K. B., Sircar, A., … Subramanian, S. (2019). The safety of double-and triple-drug community mass drug administration for lymphatic filariasis: A multicenter, open-label, cluster-randomized study. *PLoS Medicine*, *16*(6). https://doi.org/10.1371/journal.pmed.1002839

Weil, G. J., Jacobson, J. A., & King, J. D. (2021). A triple-drug treatment regimen to accelerate elimination of lymphatic filariasis: From conception to delivery. *International Health*, *13*, S60–S64. https://doi.org/10.1093/inthealth/ihaa046

Willis, G. A., Mayfield, H. J., Kearns, T., Naseri, T., Thomsen, R., Gass, K., Sheridan, S., Graves, P. M., & Lau, C. L. (2020). A community survey of coverage and adverse events following country-wide triple-drug mass drug administration for lymphatic filariasis elimination, samoa 2018. *PLoS Neglected Tropical Diseases*, *14*(11), 1–18. https://doi.org/10.1371/journal.pntd.0008854

World Health Organization. (2023). *Lymphatic Filariasis*. World Health Organization.

Yana, I. G. A. A. K. (2021). Systematic Review: Comparison of triple drug therapy versus double drug therapy for Lymphatic Filariasis. *Medical and Health Science Journal*, *5*(1), 34–45. https://doi.org/10.33086/mhsj.v5i1.1878

Appendix

Table 1. Articles list detail

Data Author	Title	Methods	Treatment	Outcome	Side Effect	Prognosis
Edi et al., 2019 *(Edi et al., 2019)*	Pharmacokinetics, safety, and efficacy of a single co-administered dose of diethylcarbamazine, albendazole, and ivermectin in adults with and without *Wuchereria bancrofti* infection in Co^te d'Ivoire	Cohort Study and randomized	A fixed dose of 400 mg ALB was used for all participants. IVM and DEC doses were 200 µg/kg and 6 mg/ kg, respectively	A single co-administered dose of ivermectin (IVM) plus diethylcarbamazine (DEC) plus albendazole (ALB), or triple-drug therapy, was recently found to be more effective for clearing microfilariae (Mf) than standard DEC plus ALB currently used for mass drug administration programs for lymphatic filariasis (LF)	Fever, Hemodynamic changes, hematuria, headache, abdominal pain, diarrhea, fatigue, muscle/ joint ache, lightheadedness, scrotal pain/swelling, itching, cough, swelling, back pain, rash, and nausea/vomiting	Triple-drug therapy was well tolerated in both LF-infected and uninfected individuals. It was adequate for clearing Mf of *W. bancrofti* in Ivorian participants for up to 1 year after treatment.
Weil et al., 2019 (Weil *et al*., 2019)	The safety of double and triple-drug community mass drug administration for lymphatic filariasis	Cluster randomized study	Participants were treated with a single oral dose of IDA (IVM 200 µ g/kg + DEC 6 mg/kg + ALB (a fixed dose of 400 mg)) or with DA alone.	A more effective treatment, such as IDA, might be expected to be associated with a higher rate of AEs. Indeed, mild to moderate AEs were more common after IDA treatment than after IA or DA in clinical trials	Fever, headache, and myalgia are believed to be triggered by the death of Mf, and the risk of systemic AEs following treatment is related to blood Mf counts.	The triple-drug IDA regimen was well tolerated in a variety of LF-endemic settings and generally as safe as the reference two-drug DA regimen
Hardy et al., 2020 (Hardy *et al*., 2020b)	The safety of combined triple drug therapy with ivermectin, diethylcarbamazine, and albendazole in the neglected tropical diseases co-endemic setting of Fiji: A cluster randomized trial	Cluster randomized study	ALB was provided as a fixed oral dose of 400mg. DEC and IVM were dosed according to weight and whole tablet ranges, aiming for 6mg/ kg and 200µg/kg, respectively.	Three anti-parasitic drugs, albendazole, diethylcarbamazine, and ivermectin, have therapeutic efficacy against lymphatic filariasis and so have been included by WHO in MDA recommendations, with the specific choice of agents dependent on the presence of other endemic pathogens	Fatigue, headache, dizziness, myalgia, diarrhea, rash, dyspnea, and chills. One participant who received a dual drug regimen had dizziness and hypertension, requiring overnight hospitalization. One participant with pre-existing lower limb lymphoedema developed cellulitis of the limb five days after triple-drug treatment	MDA using triple drug therapy as an elimination strategy for lymphatic filariasis in Fiji is as safe as the current dual drug combination implemented and accepted by communities since 2002. Our results provide confidence in the safety of IDA within other Pacific populations where lymphatic filariasis remains endemic, along with scabies and soil-transmitted helminths
Willis et al., 2020 (Willis *et al*., 2020)	A community survey of coverage and adverse events following country-wide triple-drug mass drug administration for lymphatic filariasis elimination, Samoa 2018	A cross-sectional cluster	The number of tablets was calculated based on body weight IVM 150 – 200 µg/kg, DEC 6mg/kg, and ALB 400mg	WHO recommends the use of two annual rounds of a triple-drug combination (ivermectin, diethylcarbamazine, albendazole [IDA]), a regime shown to be potentially more effective for achieving sustained clearance of microfilariae	Mild AEs: Fever, headache, dizziness, malaise, myalgia, fatigue, and GI. Localized AEs : Subcutaneous/scrotal nodules, spermatic cord swelling, lymphadenitis, or new onset hydrocoele or lymphoedema occur less frequently	For community acceptance of MDA, medications must be well-tolerated, and side effects must occur at an acceptably low level.
Supali et al., 2021(Supali *et al*., 2021)	An open label, randomized clinical trial to compare the tolerability and efficacy of ivermectin plus diethylcarbamazine and albendazole vs. diethylcarbamazine plus albendazole for treatment of Brugian filariasis in Indonesia	Randomized	Participants treated with a single oral dose of IVM 200 µg/ kg body weight DEC 6 mg/kg and ALB (a fixed dose of 400 mg)	IDA was highly effective for clearing Mf for at least one year, and it was as well tolerated as DA. The present study also showed that IDA cleared Mf from the blood more quickly than DA	Fever, muscle pain, lower back pain, joint pain, abdominal pain, headache, drowsiness, cough, and chronic surgical site infection	IDA was well-tolerated for treatment of *B. timori* infections and that it cleared *B. timori* Mf more efficiently than DA. If these results are confirmed in larger community trials, IDA has the potential to accelerate LF elimination in Indonesia and in other areas that are endemic for Brugian filariasis

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