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Antifilarial treatment strategies: a systematic review and network meta-analysis

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Abstract

Background The World Health Organization (WHO) prescribes mass drug administration (MDA) to eradicate lymphatic filariasis within endemic populations. The WHO endorsed using ivermectin with diethylcarbamazine and albendazole (IDA) for MDA in specific settings devoid of onchocerciasis or loiasis. Still, the utilization of IDA in sub-Saharan Africa is restricted due to the potential of diethylcarbamazine to induce severe adverse ocular events in individuals with onchocerciasis.

Aim We aim to investigate all documented combinations of antifilarial drugs available in the literature using a network meta-analysis (NWM) design, focusing specifically on the treatment of Lymphatic Filariasis (LF).

Methods A meticulous search was conducted across four electronic databases to identify pertinent studies. Subsequently, a frequentist NWM was executed. Risk ratios (RRs) served as the effect size metric for categorical outcomes, each with a 95% confidence interval (CI).

Results Our study encompassed 45 studies, including 61,369 patients. At six months, multiple doses of diethylcarbamazine plus albendazole (multiple DA) regimens demonstrated superior efficacy in reducing microfilaremia compared to a single intake of DA, diethylcarbamazine, ivermectin, and albendazole with RR and CI as follows: 0.37 [0.19; 0.72], 0.35 [0.17; 0.69], 0.30 [0.14; 0.64], and 0.28 [0.13; 0.57]. The combination of ivermectin plus albendazole (IA) also showed significant efficacy against the use of each of these drugs alone, with RR: 0.74 [0.57; 0.96] for ivermectin and 0.69 [0.53; 0.89] for albendazole, while diethylcarbamazine combined with albendazole showed substantial superiority over albendazole alone or placebo: RR = 0.09 [0.02; 0.36] and 0.08 [0.02; 0.34], respectively. By the twelfth month, diethylcarbamazine, followed by albendazole, ranked superior to IDA and DA: 0.12 [0.02; 0.89] and 0.11 [0.01; 0.79], respectively. At 24 months, no significant differences were found among the assessed drugs in reducing microfilaremia. The comparisons revealed no significant differences between the drug combinations we studied regarding safety and adverse events.

Conclusion Multiple doses of the DA regimen showed superior efficacy in reducing microfilaremia compared to combinations involving IA, diethylcarbamazine, ivermectin, and albendazole at six and twelve months. However, by the twenty-four-month, no significant differences were found. Safety profiles among interventions were generally comparable, with no specific drug showing superiority in adverse events.

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Keywords Antifilarial drugs, Drug efficacy, Microfilaremia, Network Meta-Analysis, sub-Saharan Africa

Introduction

Lymphatic Filariasis (LF) is a parasitic infection transmitted by mosquitoes, causing lymphatic issues like hydroceles and elephantiasis. The WHO's Global Programme to Eliminate LF (GPELF) has distributed over 9 billion doses of medication between 2000 and 2021 through mass drug administration (MDA). Despite progress in reducing the risk of LF transmission and the overall burden of LF, MDA is still recommended for about 885 million people in 45 countries to combat the disease [1]. Previously, GPELF recommended tailored mass drug administration: ivermectin plus albendazole (IA) where onchocerciasis exists, albendazole twice yearly in LF and Loa loa co-endemic areas, and diethylcarbamazine (DEC) plus albendazole (DA) elsewhere for combating LF [1].

Following clinical trials conducted in Papua New Guinea and Coˆte d'Ivoire, which demonstrated the superior efficacy of the combination of ivermectin plus DEC plus albendazole (IDA) compared to two-drug combinations [2–4], subsequent large-scale multinational safety trials involving over 26,000 participants revealed no escalation in treatment-emergent adverse events with IDA in contrast to DA [5]. As a result, the WHO endorsed using IDA for MDA in specific settings devoid of onchocerciasis or loiasis [6]. Nevertheless, the utilization of IDA in sub-Saharan Africa is restricted due to the potential of DEC to induce severe adverse ocular events in individuals with onchocerciasis. Hence, there persists a critical requirement for a safe and more efficacious treatment regimen applicable for MDA within LF elimination initiatives operating in onchocerciasis co-endemic regions.

In 2018, the US Food and Drug Administration authorized the utilization of moxidectin for the treatment of onchocerciasis [7]. Moxidectin, classified as a macrocyclic lactone akin to Ivermectin (IVM), exhibits increased lipophilicity, a larger volume of distribution, and an extended half-life. Studies conducted on onchocerciasis in Liberia, the Democratic Republic of Congo, and Ghana revealed moxidectin to outperform IVM in the clearance of microfilaremia among individuals with onchocerciasis while maintaining a treatment-emergent adverse events profile similar to that of ivermectin [7]. Moreover, antibiotics such as doxycycline, targeting the Wolbachia endosymbiont within the parasite, have introduced novel prospects for macrofilaricidal therapy [8, 9]. These antibiotics have also paved the way for abbreviated combined therapy approaches [10, 11]. Our study aims to investigate all documented combinations of antifilarial drugs available in the literature using a network meta-analysis (NWM) design. This approach is intended to evaluate the efficacy and safety of these combinations relative to each other.

Methods

The study's design adhered to the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions and followed the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension for network meta-analysis [12, 13]. We chose NMA because it allows for the simultaneous comparison of multiple interventions by integrating both direct and indirect evidence across a network of studies. This method offers several advantages over traditional meta-analysis, including the ability to compare multiple treatments comprehensively, yielding more precise estimates, ranking interventions to identify the most effective ones, and incorporating indirect comparisons to utilize more data.

Literature search

A detailed search was systematically conducted using multiple electronic databases, including Web of Science, MEDLINE via PubMed, Scopus, and Cochrane CENTRAL, covering the period from their inception until 29 October 2023. The search strategy involved a combination of terms related to filariasis and antifilarial drugs. The full search strategies and the number of publications retrieved from each database are provided in Supplementary Table 1.

Eligibility criteria

We included randomized controlled trials (RCTs) that compared various drug interventions such as DEC, ivermectin, albendazole, doxycycline, and moxidectin in every feasible combination and dosage documented in the literature (Table 1). These interventions were administered to individuals confirmed to have LF or to communities residing in areas where LF was known to be endemic. We included studies with any of the following endpoints: (1) measuring indicative of transmission potential (microfilariae prevalence); our primary endpoint; (2) studies assessed markers associated with adult worm infection, encompassing antigenemia prevalence; (3) studies compile data related to adverse events linked to the interventions.

We excluded non-English articles, animal studies, abstracts without full text available, and non-published data. Non-English articles were excluded due to potential translation challenges and resource limitations.

Table 1 Explanation of treatment regimens and terminology

Full Name	Full Name	Description
ALB	albendazole	Albendazole administered alone.
DEC	diethylcarbamazine	Diethylcarbamazine administered alone.
IDA	Ivermectin, Diethylcarbamazine, and Albendazole	Combination of ivermectin, diethylcarbamazine, and albendazole administered together.
IA	Ivermectin plus albendazole	Combination of ivermectin and albendazole administered together.
DA	Diethylcarbamazine plus albendazole	Combination of diethylcarbamazine and albendazole administered together. (Single Dose)
Multiple DA	Multiple diethylcarbamazine plus albendazole	Combination of diethylcarbamazine and albendazole administered together. (Multiple Doses)
IVM	ivermectin	Ivermectin administered alone.
Dox	Doxycycline	Doxycycline administered alone.
MoxA	moxidectin + albendazole	Combination of moxidectin and albendazole administered together.
MoxDA	moxidectin + DEC + albendazole	Combination of moxidectin, diethylcarbamazine, and albendazole administered together.
DEC then ALB	Diethylcarbamazine followed by Albendazole	Diethylcarbamazine administered first, followed by albendazole after a certain period.
Sequential ALB doses	Multiple doses of Albendazole	Albendazole administered in multiple doses over a period.

Data extraction

For the data extraction process, we use offline data extraction sheets; we collect information regarding study characteristics and outcome data from each included study. The extracted data illustrated the following aspects: study design, geographic location, study arms, population characteristics: number and age of participants in each arm, gender distribution, treatment description, and follow-up duration; as regards outcomes of interest, it was microfilaraemia prevalence, markers of adult worm infection and safety outcomes presented in the form of adverse events.

Risk of bias assessment

Our retrieved RCTs were assessed for interventional studies using the Cochrane Risk of Bias Assessment Tool 1 (ROB1) [14]. This tool includes the following domains: selection, performance, detection, attrition, reporting, and other possible sources of bias. The authors' judgment was categorized as "high," "low," and "unclear" risk of bias. A third assessor was consulted in case of discrepancy.

Data analysis

We conducted a frequentist network meta-analysis (NWM) utilizing aggregate data to derive network estimates for the outcomes under scrutiny. In quantifying dichotomous outcomes, we employed risk ratios (RRs) as the effect size, accompanied by a 95% confidence interval (CI). A significance level of $p < 0.05$ was adopted as the threshold for statistical significance. Statistical heterogeneity was also assessed among the pooled studies using the I^2 statistic and the chi-squared test. A p-value less than 0.1 was interpreted as indicative of heterogeneity, while an I^2 value equal to or exceeding 50% indicated high heterogeneity. All statistical analyses were done using R software [15].

Results

Literature search results

Our literature search process across the distinct databases yielded a total of 1538 studies. Subsequently, after eliminating duplicate entries, 1485 records were evaluated based on titles and abstracts. Title and abstract screening yields 76 relevant articles for full-text assessment. Based on our performed inclusion criteria, only 45 studies were included in our systematic review; of them, 31 studies were eligible for NWM [2–5, 10, 11, 16–54]. Supplementary Fig. 1 represents the PRISMA flow diagram for selecting eligible studies.

Characteristics of the included studies

Our 45 RCTs were conducted mainly in India, the USA, Papua New Guinea, and 15 other countries around the world, encompassing a total of 61,369 patients. In our study, patients were subjected to ten different treatment regimens, with a total of 31,471 patients being given the IDA regimen, 5,716 were treated with IA, 989 were given albendazole, and 928 were given Placebo. Demographic characteristics of patients and a summary of the included studies are provided in Supplementary Table 2.

Risk of bias evaluation

According to the Cochrane ROB1 tool, our 45 RCTs were ranked from fair to poor quality. However, in terms of each domain, six studies represented high risk regarding selection biases, and 15 reported low risk in performance bias; only eight showed unclear detection bias, while twenty-two studies were judged as being either unclear or at high risk of attrition bias, collectively most of our included studies had a high risk regarding performance and attrition biases. However, most studies represented low risk in the domain of reporting bias. Supplementary

Fig. 2 visually depicts the risk of bias summary according to the Cochrane ROB 1 tool.

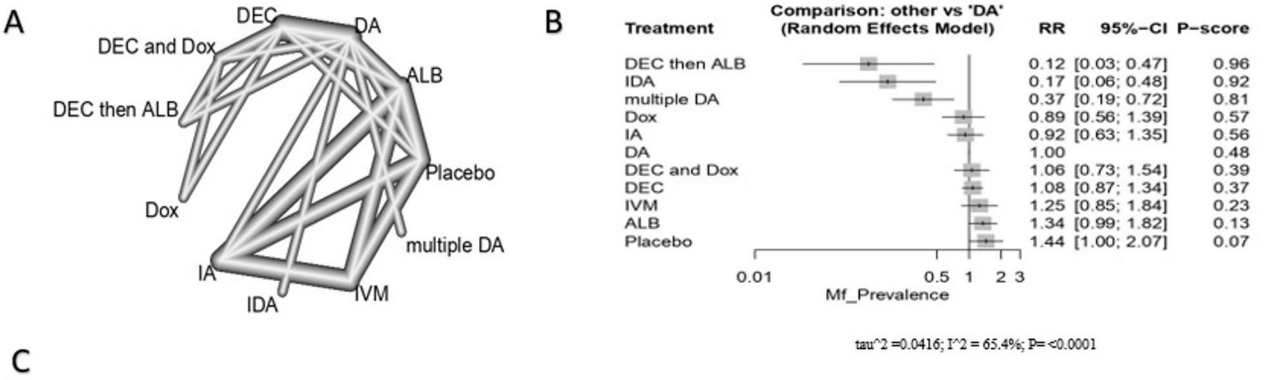
Outcomes

Primary outcomes

Measures of transmission potential Microfilaremia was assessed at six, twelve, and twenty-four months after treatment, at six months. Our pooled RR showed that multiple DA regimen was significantly superior in reducing microfilaraemia compared to the following drugs, Dox, IA, DA, DEC &Dox, DEC, IVM, ALB, and placebo with RRs as follows: 0.42, 0.40, 0.37, 0.35, 0.35, 0.30, 0.28 and 0.26 respectively. Also, IA showed significant efficacy in microfilariemia reduction compared to IVM, ALB, and placebo with 0.74, 0.69, and 0.64, respectively. However, DEC then ALB administration is significantly better than ALB alone or placebo with RRs 0.09 and 0.08 respectively; the same showed for IDA when compared to ALB or placebo with 0.13 and 0.12 respectively. Heterogeneity was significant across the pooled studies at the three-time points with chi$^2p < 0.0001$. Figure 1 illustrates this outcome's forest plot, net league, and plot.

However, at 12 months of follow-up DEC then, ALB ranked superior to IDA, DA, "ALB and Dox," DEC, IA, Placebo, IVM, Dox, and ALB with 0.12, 0.11, 0.05, 0.10, 0.03, 0.03, 0.03, 0.03 and 0.03 respectively, similarly multiple DA was significantly better than IDA, DA, DEC, IA, Placebo, IVM, Dox, and ALB. The pooled studies at 12 months showed heterogeneity with chi$^2p < 0.0006$ (Fig. 2).

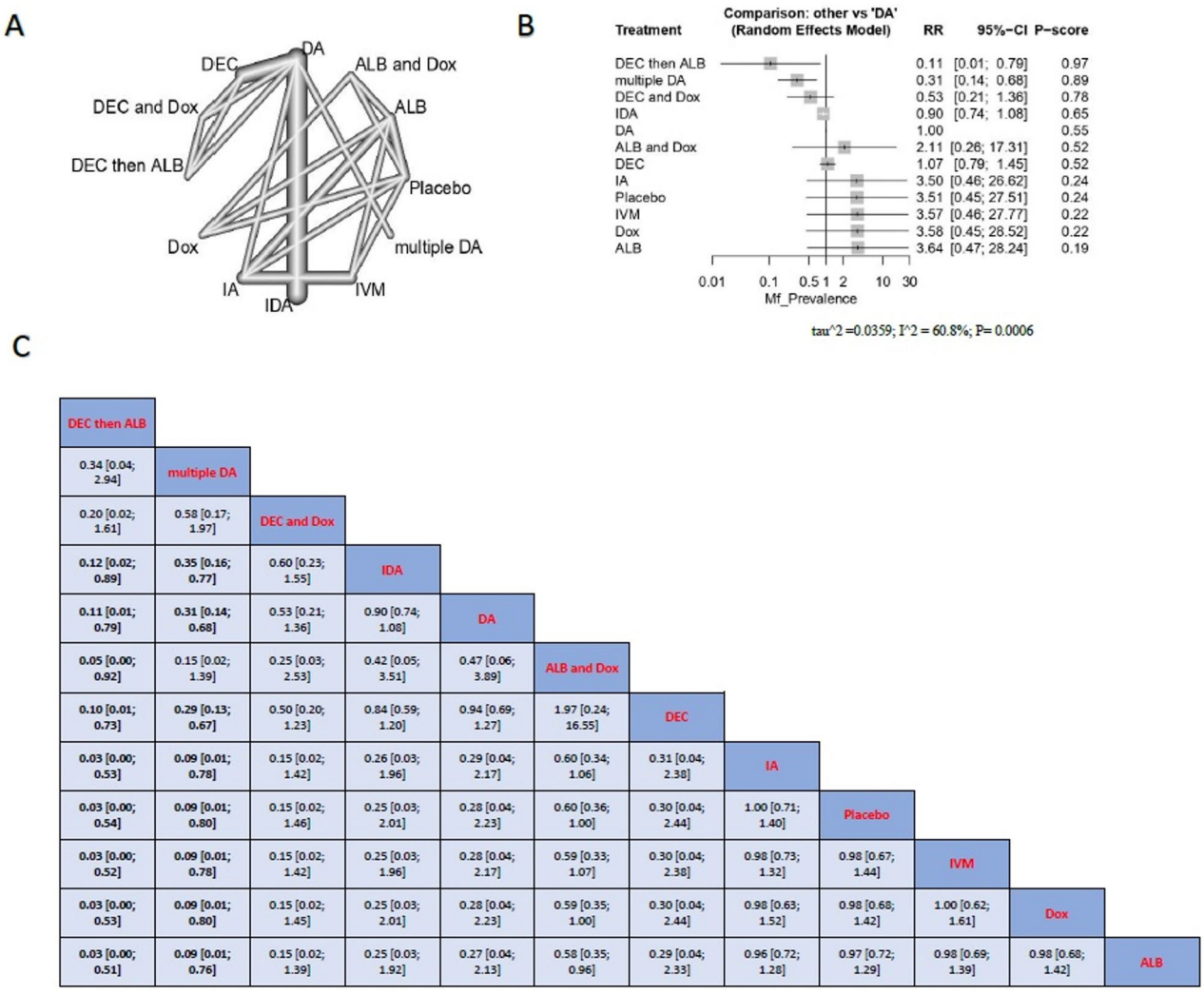
On the other hand, our NWM at 24 months revealed No significant difference between any of these drugs,



C

DEC then ALB									
0.66 [0.12; 3.80]	IDA								
0.31 [0.07; 1.46]	0.46 [0.14; 1.57]	multiple DA							
0.13 [0.03; 0.55]	**0.20 [0.06; 0.60]**	**0.42 [0.19; 0.94]**	Dox						
0.12 [0.03; 0.53]	**0.19 [0.06; 0.56]**	**0.40 [0.19; 0.86]**	0.96 [0.55; 1.66]	IA					
0.12 [0.03; 0.47]	**0.17 [0.06; 0.48]**	**0.37 [0.19; 0.72]**	0.89 [0.56; 1.39]	0.92 [0.63; 1.35]	DA				
0.11 [0.03; 0.44]	**0.16 [0.05; 0.49]**	**0.35 [0.17; 0.75]**	0.83 [0.55; 1.25]	0.87 [0.54; 1.42]	0.94 [0.65; 1.36]	DEC and Dox			
0.11 [0.03; 0.43]	**0.16 [0.06; 0.46]**	**0.35 [0.17; 0.69]**	0.82 [0.55; 1.23]	0.86 [0.59; 1.25]	0.93 [0.75; 1.15]	0.98 [0.72; 1.35]	DEC		
0.09 [0.02; 0.39]	**0.14 [0.05; 0.42]**	**0.30 [0.14; 0.64]**	0.71 [0.41; 1.23]	**0.74 [0.57; 0.96]**	0.80 [0.54; 1.18]	0.85 [0.52; 1.39]	0.86 [0.59; 1.27]	IVM	
0.09 [0.02; 0.36]	**0.13 [0.04; 0.38]**	**0.28 [0.13; 0.57]**	0.66 [0.40; 1.09]	**0.69 [0.53; 0.89]**	0.74 [0.55; 1.01]	0.79 [0.51; 1.22]	0.80 [0.59; 1.09]	0.93 [0.71; 1.21]	ALB
0.08 [0.02; 0.34]	**0.12 [0.04; 0.36]**	**0.26 [0.12; 0.55]**	0.62 [0.36; 1.05]	**0.64 [0.48; 0.86]**	0.69 [0.48; 1.00]	0.74 [0.46; 1.18]	0.75 [0.52; 1.08]	0.87 [0.66; 1.15]	0.93 [0.73; 1.20]	Placebo

Fig. 1 mf prevalence at 6 months; (**A**) Network graph showing direct evidence between the evaluated interventions. (**B**) A forest plot comparing all interventions. (**C**) The league table represents the network meta-analysis estimates for all interventions' comparisons



DEC then ALB										
0.34 [0.04; 2.94]	multiple DA									
0.20 [0.02; 1.61]	0.58 [0.17; 1.97]	DEC and Dox								
0.12 [0.02; 0.89]	0.35 [0.16; 0.77]	0.60 [0.23; 1.55]	IDA							
0.11 [0.01; 0.79]	0.31 [0.14; 0.68]	0.53 [0.21; 1.36]	0.90 [0.74; 1.08]	DA						
0.05 [0.00; 0.92]	0.15 [0.02; 1.39]	0.25 [0.03; 2.53]	0.42 [0.05; 3.51]	0.47 [0.06; 3.89]	ALB and Dox					
0.10 [0.01; 0.73]	0.29 [0.13; 0.67]	0.50 [0.20; 1.23]	0.84 [0.59; 1.20]	0.94 [0.69; 1.27]	1.97 [0.24; 16.55]	DEC				
0.03 [0.00; 0.53]	0.09 [0.01; 0.78]	0.15 [0.02; 1.42]	0.26 [0.03; 1.96]	0.29 [0.04; 2.17]	0.60 [0.34; 1.06]	0.31 [0.04; 2.38]	IA			
0.03 [0.00; 0.54]	0.09 [0.01; 0.80]	0.15 [0.02; 1.46]	0.25 [0.03; 2.01]	0.28 [0.04; 2.23]	0.60 [0.36; 1.00]	0.30 [0.04; 2.44]	1.00 [0.71; 1.40]	Placebo		
0.03 [0.00; 0.52]	0.09 [0.01; 0.78]	0.15 [0.02; 1.42]	0.25 [0.03; 1.96]	0.28 [0.04; 2.17]	0.59 [0.33; 1.07]	0.30 [0.04; 2.38]	0.98 [0.73; 1.32]	0.98 [0.67; 1.44]	IVM	
0.03 [0.00; 0.53]	0.09 [0.01; 0.80]	0.15 [0.02; 1.45]	0.25 [0.03; 2.01]	0.28 [0.04; 2.23]	0.59 [0.35; 1.00]	0.30 [0.04; 2.44]	0.98 [0.63; 1.52]	0.98 [0.68; 1.42]	1.00 [0.62; 1.61]	Dox
0.03 [0.00; 0.51]	0.09 [0.01; 0.76]	0.15 [0.02; 1.39]	0.25 [0.03; 1.92]	0.27 [0.04; 2.13]	0.58 [0.35; 0.96]	0.29 [0.04; 2.33]	0.96 [0.72; 1.28]	0.97 [0.72; 1.29]	0.98 [0.69; 1.39]	0.98 [0.68; 1.42]

Fig. 2 mf prevalence at 12 months; (**A**) Network graph showing direct evidence between the evaluated interventions. (**B**) A forest plot comparing all interventions. (**C**) The league table represents the network meta-analysis estimates for all interventions' comparisons

multiple DA, IDA, IA, ALB, DA, and DEC, regarding this outcome. (Fig. 3).

Secondary outcomes

Markers of adult worm infection In terms of adult worm infection markers, they were assessed at two-time points (six and twelve months) by measuring the prevalence of antigenemia. Based on antigenemia prevalence at six months, no statistically significant differences were shown between DA and these drugs ALB, Placebo, and DEC. Similarly, comparison between ALB, Placebo, and DEC exhibited differences; our pooled studies were homogenous with chi$^2p = 0.16$ (Fig. 4).

Regarding antigenemia assessment at 12 months, our network model did not significantly prioritize any of the following drugs over each other: "DEC then ALB", "DEC and Dox", IDA, IA, DA, IVM, ALB, DEC, and Placebo. "DEC then ALB" compared to IDA and "DEC and Dox" showed RRs 1.04 [0.75; 1.43] and 0.86 [0.65; 1.15], respectively. Homogeneity was shown among the pooled studies with chi$^2p = 0.65$ (Fig. 5).

Safety and adverse events

In terms of total adverse events, IDA showed no significant difference when compared to the following drugs "DEC then ALB", IA, "DA with Mox" and "ALB with Mox". Also, "ALB with Dox" versus "DEC and Dox", IVM, DEC, DA, IDA, "DEC then ALB", IA, "DA with Mox" and "ALB with Mox" alike all of them are insignificant. In the same manner, when we compared DA versus IDA, "DEC then ALB", IA, "DA with Mox" and "ALB with Mox" we found the following RRs respectively: 0.95 [0.80; 1.14], 0.92 [0.53; 1.60], 0.93 [0.57; 1.50], 0.84 [0.46; 1.53] and 0.77 [0.43; 1.38]. Similarly, our pooled NWM analysis illustrated no significant difference among any of these

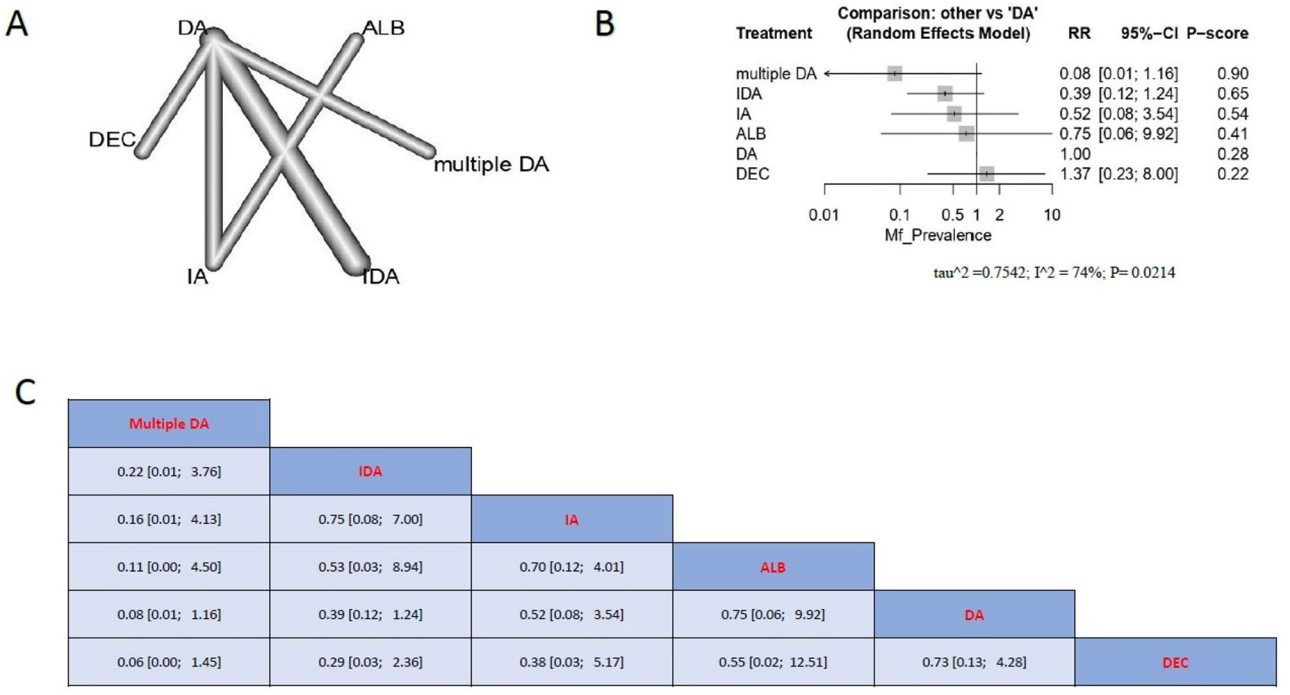


Fig. 3 mf prevalence at 24 months; (**A**) Network graph showing direct evidence between the evaluated interventions. (**B**) A forest plot comparing all interventions. (**C**) The league table represents the network meta-analysis estimates for all interventions' comparisons

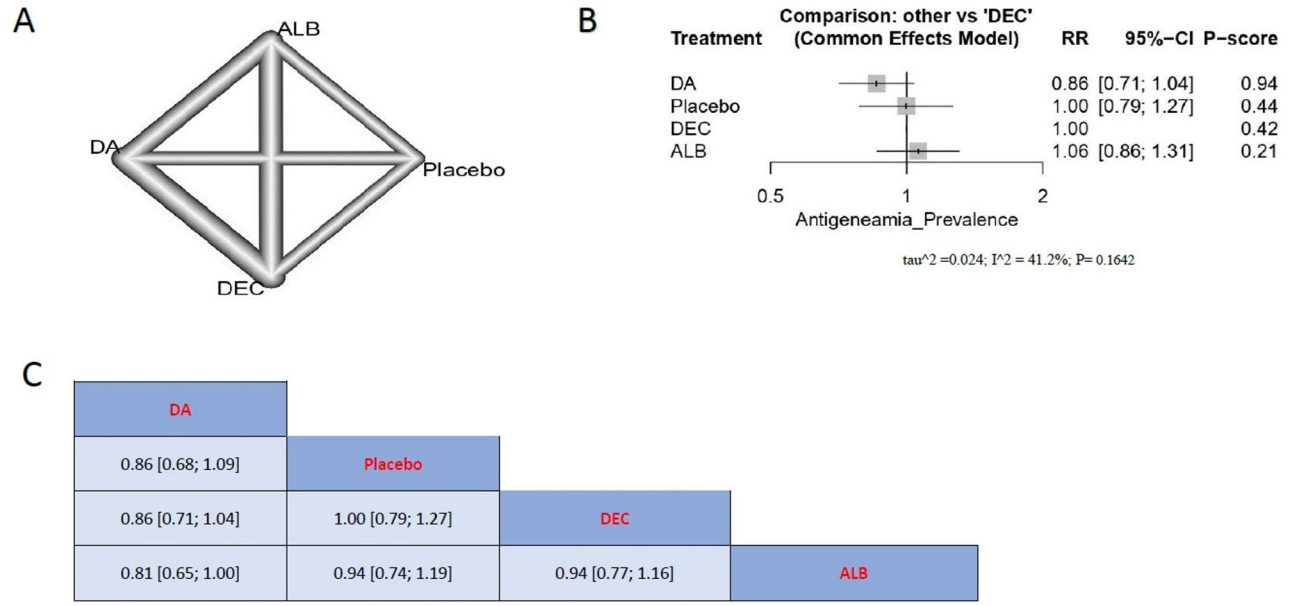
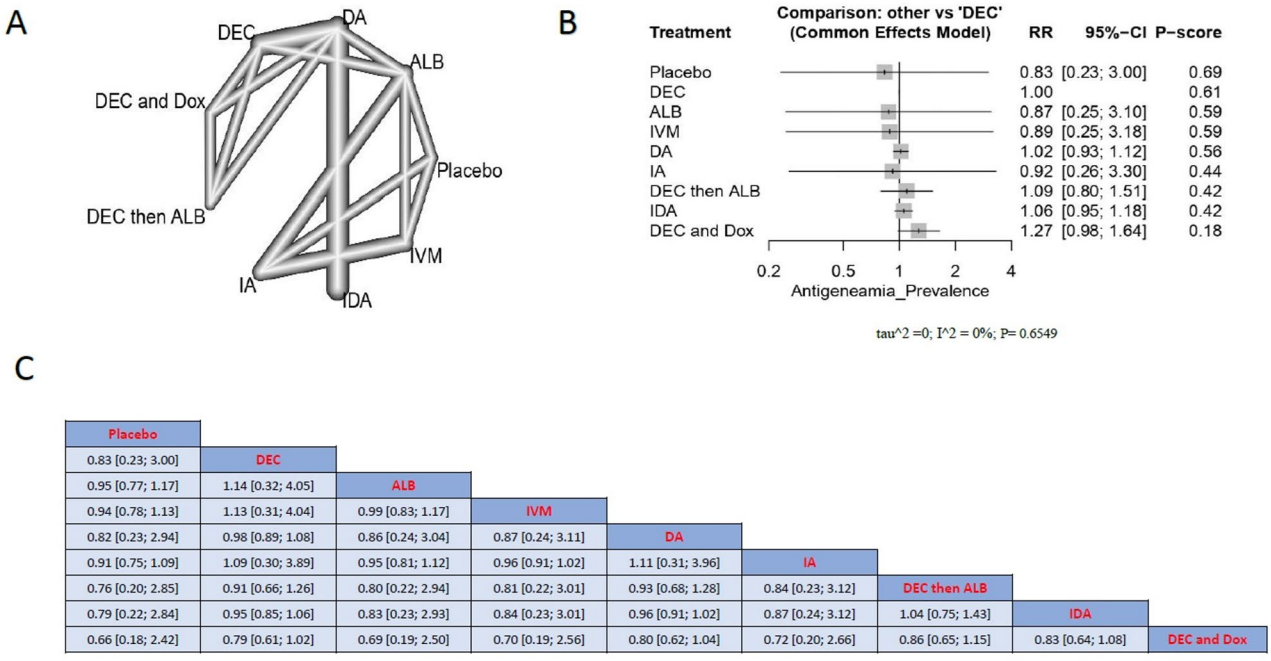


Fig. 4 Antigenemia at 6 months; (**A**) Network graph showing direct evidence between the evaluated interventions. (**B**) A forest plot comparing all interventions. (**C**) The league table represents the network meta-analysis estimates for all interventions' comparisons

treatment regimens ALB, Dox, "ALB and Dox", "DEC and Dox", IVM, DEC, DA, IDA, "DEC then ALB", IA, "DA with Mox", "ALB and Mox" and Placebo. (Fig. 6).

When comparing serious adverse events, our NWM showed no significant difference favoring any of these drugs, IDA, DEC, and DA. With pooled RRs, when IDA compared to DEC and DA, it is as follows: 0.56 and 0.53, respectively. Our pooled studies for serious adverse events exhibit homogeneity with a chi^2p value = 0.15 (Fig. 7).



Placebo								
0.83 [0.23; 3.00]	DEC							
0.95 [0.77; 1.17]	1.14 [0.32; 4.05]	ALB						
0.94 [0.78; 1.13]	1.13 [0.31; 4.04]	0.99 [0.83; 1.17]	IVM					
0.82 [0.23; 2.94]	0.98 [0.89; 1.08]	0.86 [0.24; 3.04]	0.87 [0.24; 3.11]	DA				
0.91 [0.75; 1.09]	1.09 [0.30; 3.89]	0.95 [0.81; 1.12]	0.96 [0.91; 1.02]	1.11 [0.31; 3.96]	IA			
0.76 [0.20; 2.85]	0.91 [0.66; 1.26]	0.80 [0.22; 2.94]	0.81 [0.22; 3.01]	0.93 [0.68; 1.28]	0.84 [0.23; 3.12]	DEC then ALB		
0.79 [0.22; 2.84]	0.95 [0.85; 1.06]	0.83 [0.23; 2.93]	0.84 [0.23; 3.01]	0.96 [0.91; 1.02]	0.87 [0.24; 3.12]	1.04 [0.75; 1.43]	IDA	
0.66 [0.18; 2.42]	0.79 [0.61; 1.02]	0.69 [0.19; 2.50]	0.70 [0.19; 2.56]	0.80 [0.62; 1.04]	0.72 [0.20; 2.66]	0.86 [0.65; 1.15]	0.83 [0.64; 1.08]	DEC and Dox

Fig. 5 Antigenemia outcome at 12 months; (**A**) Network graph showing direct evidence between the evaluated interventions. (**B**) A forest plot comparing all interventions. (**C**) The league table represents the network meta-analysis estimates for all interventions' comparisons

Discussion

Our study assessed microfilaremia reduction over six, twelve, and twenty-four months following various drug regimens. At six months, multiple doses of the DA regimen demonstrated superior efficacy in reducing microfilaremia compared to Dox, IA, DA, DEC & Dox, DEC, IVM, ALB, and placebo. IA also showed significant efficacy against IVM, ALB, and placebo, while DEC combined with ALB showcased substantial superiority over ALB alone or placebo. By the twelfth month, DEC, followed by ALB, ranked superior to several regimens, including IDA, DA, and various combinations involving ALB and Dox. Still, multiple doses of DA remained notably better than several drug combinations. At the twenty-four-month mark, no significant differences were found among the assessed drugs in reducing microfilaremia. In terms of adult worm infection markers, there were no significant differences between most studied interventions. Regarding safety and adverse events, the comparisons revealed no significant differences between several drug combinations, including IDA against DEC, then ALB, IA, and various combinations involving DA and ALB or Mox. Similarly, no significant differences were found between DA, IDA, DEC, and other combinations. The analysis of serious adverse events did not favor any specific drug over others, with no significant differences observed between IDA, DEC, and DA.

The primary approach employed by the GPELF involves implementing community-wide MDA across populations deemed at risk. The objective is to halt the transmission of the disease and mitigate morbidity resulting from infection. Prophylactic medication is deemed essential in regions, such as provinces, districts, or smaller units within a country, where the prevalence of infection within the total population reaches 1% or higher. Preventive chemotherapy aims to disrupt disease transmission by consistently diminishing community microfilariae levels to a critical threshold or entirely eradicating the microfilariae [55, 56]. GPELF advocates for annual administration of a single-dose regimen comprising two drugs (albendazole combined with either DEC or ivermectin [56]. This regimen is recommended for a minimum duration of five years, aligning with the reproductive lifespan of the adult worm. The goal is to attain a coverage rate of at least 65% among the at-risk population to prevent disease transmission effectively [17]. The WHO has advocated for the utilization of an annual triple-drug therapy involving ivermectin, DEC, and albendazole (known as IDA) in specific settings instead of the previously recommended two-drug therapy consisting of albendazole and DEC [6]. In the absence of treatment, it is believed that the overall prevalence rates of microfilariae remain relatively constant over time within endemic communities due to the cycle of reinfection and the continuous production of microfilariae by new adult worms [57].

DEC has been a longstanding treatment for filariasis for over 50 years. Initially, the recommended regimen for DEC was 6 mg/kg daily for 12 days [56]. Subsequently, clinical and community trials determined that

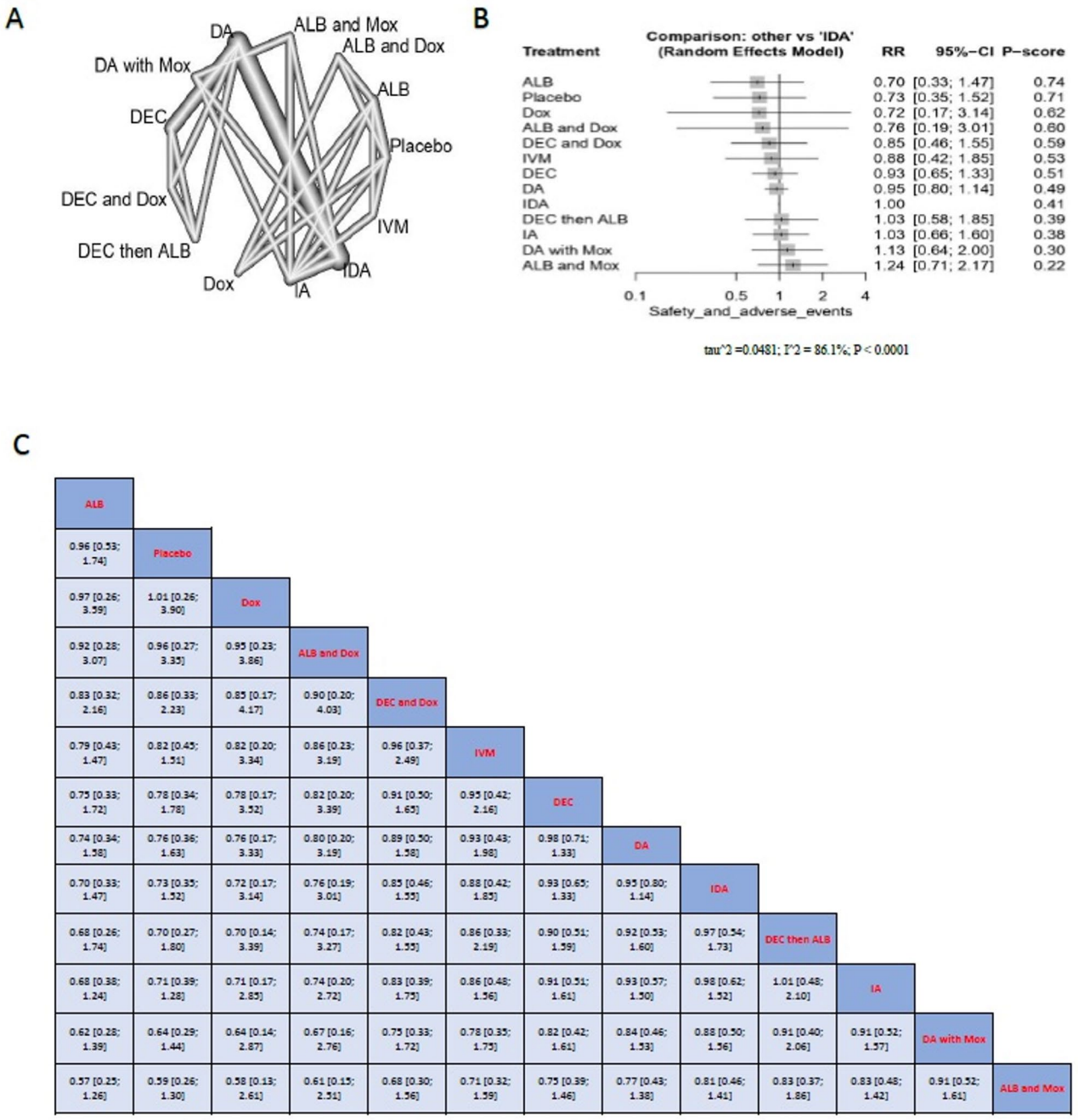


Fig. 6 Adverse events; (**A**) Network graph showing direct evidence between the evaluated interventions. (**B**) A forest plot comparing all interventions. (**C**) The league table represents the network meta-analysis estimates for all interventions' comparisons

single doses administered at varying intervals—weekly, monthly, semi-annually, and annually—proved to be equally effective [16, 58]. Substantial evidence from ultrasound and clinical observations indicates that DEC can eliminate certain adult worms following single doses [56, 59].

Ivermectin is a treatment for onchocerciasis caused by the filarial worm Onchocerca volvulus. It has also demonstrated effectiveness in community control programs targeting LF [60, 61]. In regions where both onchocerciasis and LF coexist, ivermectin is preferred over DEC due to the risk of ocular damage associated with DEC administration in individuals with onchocerciasis. However, ivermectin is not recognized for its macrofilaricidal activity. Ultrasound studies have indicated that even at high doses over six months, ivermectin does not eliminate adult worms [17].

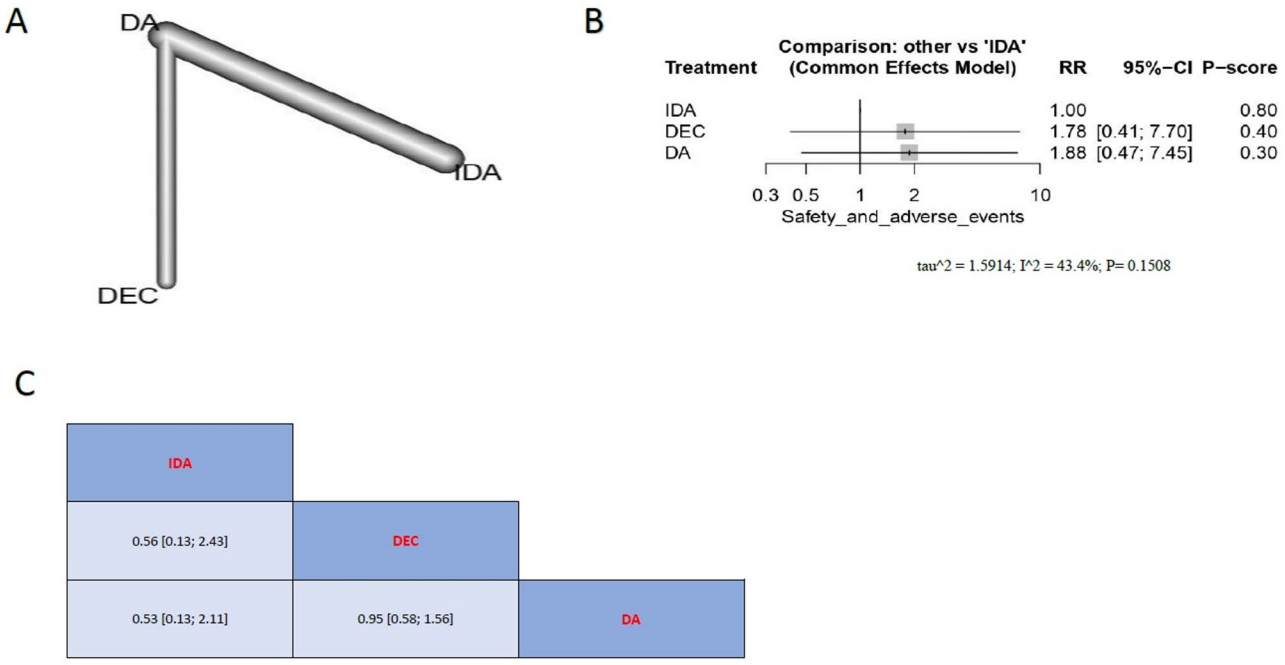


Fig. 7 Serious adverse events; (**A**) Network graph showing direct evidence between the evaluated interventions. (**B**) A forest plot comparing all interventions. (**C**) The league table represents the network meta-analysis estimates for all interventions' comparisons

In regions of Central and West Africa where both LF and Loa loa, the eye worm causing loiasis, coexist, treatment with ivermectin or DEC can lead to serious adverse events when Loa loa microfilariae densities are high, surpassing 30,000 mf/mL [62, 63]. In these areas, the recommendation is to administer albendazole alone twice a year, combined with vector control, if ivermectin has not been previously distributed for either onchocerciasis or LF [6, 64]. However, in cases where individuals with onchocerciasis have high Loa loa densities, ivermectin treatment can also lead to SAEs. Despite this risk, treatment with ivermectin is still recommended for meso- and high-endemic areas of onchocerciasis, employing one of three strategies to manage complications should they arise [65].

Albendazole, widely used since the late 1980s against intestinal parasites, shows promise in LF control [66]. Addiss et al. suggested high doses might sterilize or eliminate Wuchereria bancrofti adult worms, yet uncertainty lingers over its impact when combined with DEC or ivermectin [67]. Its role in MDA programs extends beyond filariasis control, aiding in managing other helminth infections [68]. However, it's cautioned that albendazole alone isn't recommended for filariasis treatment [69].

Macfarlane et al. metanalysis included 13 trials involving 8,713 participants [56]. Results for microfilariae prevalence showed no significant difference when albendazole was used alone or combined with another drug. Ultrasound detection of adult worm prevalence at 12 months indicated minimal difference when albendazole was combined with another drug. Adverse events reported by participants did not significantly differ with albendazole use. Overall, evidence suggested limited or negligible effects of albendazole on various filariasis indicators, with uncertainties in some outcomes due to low-certainty evidence [56].

A previous trial involving a seven-day coadministration of DEC and Albendazole was inconclusive regarding the swift clearance of microfilariae within a 90-day timeframe [19]. Turner et al. noted that a three-week course of doxycycline treatment, combined with standard anti-filarial therapy, proves more efficacious in eliciting prolonged amicrofilaremia than standard treatment administered alone [24]. Nevertheless, De Britto et al. reported a significant decrease in microfilaria count 30 days after treatment, regardless of whether a single dose or combination therapy was administered [10]. Field trials have demonstrated that a four-week course of doxycycline completely eradicates adult worm nests from scrotal lymphatics in 100% of infected individuals during an 18-month follow-up period [70]. Additionally, a three-week doxycycline therapy combined with a single dose of DEC at four months post-treatment achieved complete clearance of microfilariae, adult worm nests, and a reversal of lymphatic pathology at 12 months post-treatment [71].

While the Multiple DA regimen demonstrated superior efficacy in reducing microfilaremia, it is important to consider the logistical implications of administering multiple doses of diethylcarbamazine. This approach requires

careful planning and coordination to ensure adherence and effective implementation, which may pose challenges in large-scale mass drug administration (MDA) programs. In contrast, the current approach of administering the drug for LF elimination at the same time is more straightforward and may be easier to implement in endemic regions.

Supali et al. study revealed that the IDA regimen exhibited a faster clearance of microfilariae from the bloodstream than the DA regimen. Specifically, 25 out of 28 and 8 out of 27 subjects achieved complete microfilariae clearance within 24 h after treatment with IDA and DA, respectively [23]. These superior results in microfilariae clearance observed with IDA align closely with findings from similar clinical trials conducted in Papua New Guinea to treat W. bancrofti infection [2, 22]. Contrarily, a separate clinical trial for W. bancrofti infection in Cote d'Ivoire reported an 89% clearance of microfilariae six months after IDA treatment, reducing to 71% clearance after one year [4]. Consequently, the outcomes of B. timori infection in Indonesia closely resemble the results observed in the W. bancrofti trials in Papua New Guinea rather than those from trials conducted in Cote d'Ivoir.

Adverse effects stemming from antifilarial drugs can be significant, although fatalities are rare, often hindering individuals from initiating or completing treatment. The most severe adverse reactions seem to arise from a host immunologic response triggered by the rapid elimination of microfilariae, associated with the release of inflammatory Wolbachia lipoproteins [72]. Such adverse effects encompass fever, headache, malaise, muscle pain, and the presence of blood in urine. Additionally, localized effects may manifest as localized pain, tender nodules, lymphadenitis, and lymphangitis [56]. The safety profile of IDA has been established through small randomized trials [22, 73] and, more recently, in a comprehensive multi-site community safety trial, including Fiji [5].

Previous investigation revealed a substantial positive correlation between markers indicating filarial infection and the frequency of adverse events (AEs) [74]. This association was particularly pronounced among participants exhibiting microfilaremia identified by the 60 µl smear. Notably, a similar pattern was observed in participants who tested positive for circulating filarial antigen without detectable microfilaremia. Given that most adverse events are linked to the death of microfilariae [74], it is plausible that these participants might have harbored low-density microfilaremia undetectable by smear or had microfilariae not actively circulating at the time of testing. The uncertainty regarding the presence of microfilariae could have been mitigated if we had utilized the more sensitive membrane filtration method with 1 ml venous blood. However, this approach was not feasible for a study involving a large number of participants [75].

Our study represents the introductory NWM encompassing a comprehensive array of interventions and regimens for diverse filariasis treatments. Our systematic review incorporated a total of 45 studies, encompassing 61,369 patients evaluated at three distinct time points. The extensive inclusion of these studies renders our evidence robust, potentially serving as a cornerstone for guiding future clinical practices and formulating guidelines concerning filariasis treatment.

However, our study was not free of limitations. First, most of our studies had unclear or even high risk of bias. Second, although we included many comparison arms, many arms were less representative than others. Third, the effectiveness of a single dose of the triple-drug regimen in clearing microfilariae a year after treatment has shown varying results across different regions. In Papua New Guinea and Haiti, it achieved clearance rates between 94% and 97%. However, the clearance rate in India was 84%, 78% in Côte d'Ivoire, and 63% in Fiji [4, 18, 20–22]. These differences could stem from factors such as the varying susceptibility of adult worms to the drugs, differences in how the drugs are absorbed and metabolized in individuals, as well as variables like compliance with taking the drugs as prescribed and the possibility of reinfection. These factors collectively contribute to the observed variability in the measured effectiveness of the treatment. Fourth, in Papua New Guinea, LF is transmitted by anopheline mosquitoes, considered less efficient vectors than culicine or Aedes mosquitoes. Due to this difference in vector efficiency, areas where transmission is through Culex or Aedes mosquitoes might require more rounds of mass drug administration with the triple-drug regimen to eliminate LF [76]. This need for additional treatment rounds is based on the understanding that more competent vectors can sustain transmission more effectively, potentially requiring increased intervention efforts to interrupt the disease's spread and achieve elimination in those regions. The observed variations mentioned earlier warrant further investigations to stratify these variables and assess their potential impact on treatment regimens. Additional studies could provide insights into how these factors influence the effectiveness and outcomes of different treatment protocols.

Our study contributes to the World Health Organization's global LF control efforts by providing evidence on the most effective drug regimens for reducing microfilaremia. This is directly aligned with WHO's goal of eliminating LF as a public health problem by ensuring safe and effective treatment regimens for mass drug administration programs.

Conclusion

Multiple doses of DA regimen exhibited heightened efficacy in diminishing microfilaremia in contrast to combinations involving IA, diethylcarbamazine, ivermectin, and albendazole at six and twelve months. Nevertheless, as the study progressed to the twenty-four-month mark, no significant differences were observed. Safety evaluations across interventions generally revealed comparable profiles, with no specific drug displaying superiority in inducing adverse events. However, the earlier discussed limitations underscore the necessity for further investigations to stratify these variables and evaluate their potential impact on treatment protocols. Subsequent studies could provide valuable insights into how these factors influence the effectiveness and outcomes of distinct treatment regimens.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-11105-z.

Supplementary Material 1: Supplementary fig.1: PRISMA flow diagram for the selection process of eligible studies in our systematic review and NWA

Supplementary Material 2: Supplementar fig.2: Visually depicted the risk of bias summary according to the Cochrane ROB 1 tool

Supplementary Material 3: Supplementary table 1: Detailed search strategy for the retrieved databases

Supplementary Material 4: Supplementary table 2: Summary and baseline characteristics of the included studies

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Author contributions
The conceptualization was performed by MA and ES. Data curation was performed by MA, ES, SS, MA, HE, and ME. Formal analysis was conducted by MA, SS, MA, and ES. Quality assessment and risk of bias evaluation were performed by SS, MA, ES, and AM. Methodological guidance was provided by HE and HE. Project administration was managed by MA. Resources were acquired by MA. Software management was handled by SS. Validation of analytical methods was carried out by HE, HE, SS, MA, and ES. Data visualization and interpretation were led by MA. Writing of the original draft was done by MA, ES, and MA. Writing– review and editing was contributed by MA, ES, SS, MA, HE, and ME. Funding acquisition was handled by HE. All authors reviewed the manuscript.

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Data availability
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
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