TRIPLE-DRUG REGIMEN VERSUS DOUBLE-DRUG REGIMEN FOR ELIMINATION OF LYMPHATIC FILARIASIS

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Abstract

Lymphatic filariasis, commonly known as elephantiasis, is a parasitic disease caused by the transmission of thread-like nematode worms of the family Filariidae. The two main species responsible for the disease are *Wuchereria bancrofti* and *Brugia malayi*. It is primarily transmitted to humans through the bite of infected female mosquitoes, mainly from the genera Culex, Anopheles, and Aedes. Infection with filarial nematodes remains endemic in several countries worldwide and these infections are commonly associated with severe diseases. Of the estimated 120 million people affected by this disease and one-third live in India. *W. bancrofti* accounts for ~90% of the disease burden while *B. malayi* contributes the remaining ~10%. The elimination of lymphatic filariasis relies on mass drug administration (MDA) for the entire population at risk to stop disease transmission and prevent infectious morbidity. WHO recommends the use of annual medication in combination with the triple drug ivermectin therapy. The aim and objective of this article is to compare the efficacy and safety of triple drug versus double drug therapy for the eradication of onchocerciasis (LF) along with the status of lymphatic filariasis in India.

Keywords: *Lymphatic filariasis, Diethylcarbamazine, Ivermectin, Albendazole*

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Introduction

Filariasis is a parasitic illness caused by the filarial worm, which is transferred to people by mosquito bites. It is a severe public health issue in tropical and subtropical areas such as Asia and Africa, impacting millions worldwide. *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori* are the three primary forms of filarial worms that cause human illness [1]. More than 90% of the cases in Asia, Africa, and some portions of South America and the Caribbean are caused by *Wucheria* species. Whereas *Burgia malayi* is found in south Asia, and *B. timori* is only found in Timor and the Indonesian province of Flores [2].

These parasites are transmitted via different mosquito hosts, which vary geographically. Several mosquito species, especially Anopheles, Aedes, Culex, and Mansonia, with regional differences in the primary vector identity, can spread these parasites through bites. Filariasis-causing worms dwell in the lymphatic system and can produce symptoms such as fever, chills, lymphedema (limb swelling), and elephantiasis (severe swelling and thickness of the skin). Filariasis is primarily detected by blood testing; however, imaging tests such as ultrasound may be performed as per need for treatment. [1].

Filariasis is often treated with the combination of medications that kill adult worms while suppressing the body's immunological response to the infection. Surgeries are required in extreme situations to remove damaged tissues or enhance lymphatic drainage. Onchocerciasis and lymphatic filariasis (LF) are the two most significant filarial diseases in human beings. Long-term illnesses may result in elephantiasis, scrotal lymphedema (hydrocele), or significant swelling of the extremities (lymphedema). In addition, lymphatic filariasis also causes renal diseases, chyluria, acute derma to lymphangion adenitis, which may result in a consistent fever [1-2].

Protective clothing, bed nets, and mass medicine administration can be used to limit the spread of parasite infection. Much progress has been made in reducing the global burden of filariasis. Still, the disease remains a significant public health challenge in many regions, particularly in Sub-Saharan Africa and South Asia. Before the introduction of the Onchocerciasis Control Program in West Africa, blindness prevalence rates of up to 10% were seen in "first-line" villages, meanwhile skin conditions caused acute itching (pruritus), which prevented people from sleeping or working, stigmatized them, and decreased the educational prospects of children who would otherwise become caretakers for disabled adults. Due to the lack of radical curative drugs, chemotherapeutic approaches to managing and treating filarial infections have historically been a challenging problem.

Onchocerca volvulus, also known as river blindness (onchocerciasis), is the culprit behind the disease, transmitted by Simulism blackflies. The symptoms include disfiguring skin conditions, visual impairment, and permanent blindness. Such symptoms hold significant socio-economic and public health implications in severely impacted communities. Nowadays, medicines with macrofilaricidal action are used to operate control methods for both LF and onchocerciasis[3]. Many attempts to create a microfilaricide with properties suitable for use in public health have failed. To eradicate onchocerciasis as a public health issue, Merck & Co. Inc in 1987 donated Mectizan (Ivermectin) to treat and control human onchocerciasis.

Further, GlaxoSmithKline (GSK), in 1998, also provided albendazole for the treatment of LF. The extension of the Merck and Co Inc. gift of ivermectin (IVM) for LF control in nations (Africa and Yemen) where onchocerciasis and LF are co-endemic was then added to the GSK donation because of the risks associated with using diethylcarbamazine (DEC) in onchocerciasis patients [3]. Resolution (WHA -50.29) of the world health assembly calls on all state members to make lymphatic filariasis a thing of the past.

Later, to limit this spread of parasite infections in 2000, WHO launched the GPELF (Global Plan to Eliminate Lymphatic Filariasis) to eliminate LF by 2020 [4-6]. MDA (mass drug administration) of three anti-parasitic drugs: albendazole (ALB), diethylcarbamazine (DEC), and ivermectin (IVM), is the key component to stop the filarial spread. This program includes the strategy to interrupt transmission by involving the MDA of three anti-parasitic drugs (DEC + ALB + IVM) [4-5,7] and implementing morbidity management and disability prevention to prevent and alleviate the affected individual's suffering.

The precise mechanism of action by which these medications reduce transmission is not yet completely known [8]. Whether LF is co-endemic with other filarial illnesses determines the advised MDA protocol.

Recent research suggests that as opposed to years with the conventional two-medicine combination, the mixture of all three medicines (triple drug therapy - TDR) can securely remove nearly every microfilaria from the blood of infected individuals

within a few weeks. As per WHO, the transmission cycle stopped when MDA was carried out yearly for at least 4-6 years with complete coverage of the community at risk [13]. The present article aims to compare the efficacy and safety of triple-drug versus double-drug therapy for the eradication of lymphatic filariasis along with the status of lymphatic filariasis in India. Although much progress has been made in reducing the global burden of filariasis, this disease remains a significant public health challenge in many regions, particularly in Sub-Saharan Africa and South Asia.

Life cycle of Filarial Nematode

The life cycle of filarial parasites is demonstrated with *W. bancrofti*. A vector and a mammalian host play an essential role in completing the life cycle of filarial nematodes. The life cycle involves various stages (Figure 1). Initially, the infected vector transmits the infectious-stage larvae to the human host during a blood meal then these L3-stage larvae mature into adult worms. Further, this adult worm produces microfilariae (MF), which migrate to lymphatics and blood for circulation. The vector ingests the microfilariae during a blood meal on an infected host; the microfilariae then migrate through the midgut to the pectoral muscles of the vector. The microfilariae develop to the L1 stage and afterward into the L3 larvae. The L3 larvae move to the vector proboscis via the hemocoel. At last, the vector transmits the infective stage larvae into the human host during a blood meal.

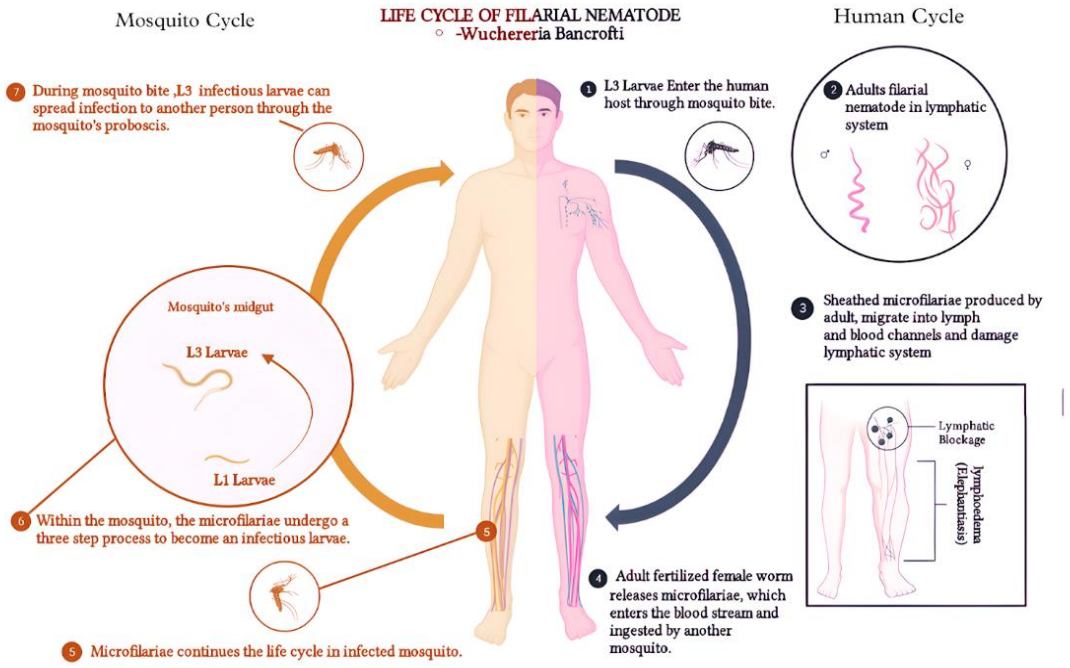

Figure 1: Life Cycle of Filarial Nematode

Pathogenesis of filariasis

In a healthy human being, lymphatic vessels transport circulating fluid and large molecules, such as proteins, from the extracellular space of almost all body tissues. The lymphatic system is vital in maintaining proper extracellular fluid volume and clearing pathogens that have crossed the skin barrier and entered the extravascular compartments. [14-15]. Antigens, pathogens, and invaders engulfed by macrophages are transported afferently to the lymph nodes, where they undergo adaptive immunity processes and are removed. After cleaning and filtering, the lymph fluid return to the vascular space. T lymphocytes are programmed to recognize, respond to, and remember foreign antigens as a part of the adaptive immune system. [16]. The presence of cell surface molecules known as CD4 or CD8 distinguishes T lymphocytes. CD4 T lymphocytes, called 'T' helper (Th) cells, are productive cytokine producers. [17]. Cytokines are hormonal messengers within the immune system responsible for cell-mediated immune and allergic reactions. They are classified as pro-inflammatory (Th1 response) or anti-inflammatory (Th2 response). In LF, lymphatic damage is caused by a reaction to the presence of

the adult worm and the products released by the worm. Compounds secreted or excreted by the live worm act on endothelial cells, causing scarring of lymphoid tissues, gradual loss of lymphatic vessel contractility, destruction of unidirectional valves, and lymphangiectasia (a pathological enlargement of the lymphatic vessels). Regardless of treatment, damage to the lymphatic system is permanent. [18]. Histology shows that live MF and adult worms rarely elicit an immune response. However, dead or dying MF worms and adult worms are highly antigenic. Although the mechanism is not fully understood, LF antigens guarantee the species' survival by modulating the host's immune system to favor an anti-inflammatory (Th2) response. [19]. This response is achieved by reducing the pro-inflammatory (Th1) response.[16] The weakening of dampening the immune system results in a significantly reduced response to opportunistic pathogens and vaccines, such as tetanus toxoid, which becomes a significant contributor to poor outcomes associated with chronic lymphedema. Children born to infected mothers are more susceptible to acquiring filarial infections. In women who received multiple treatments with anti-filariae drugs before pregnancy, the incidence of an infant developing LF decreased to less than 1% [20]. Placental transfer of antigens is suggested to modulate the infant's immune system and promote and favors TH-2 response [19]. Thus, these results support the need for pre-pregnancy reproductive education and MDA treatment in adolescent girls in endemic areas. [21].

Epidemiology

W. bancrofti occurs in sub-Saharan Africa, Southeast Asia, the Indian subcontinent, many Pacific islands, and focal areas of Latin America and the Caribbean (including Haiti). *B. malayi* occurs mainly in China, India, Malaysia, the Philippines, Indonesia, and various Pacific islands. *B. timori* occurs on the Timor Island of Indonesia. Overall, approximately two-thirds of individuals infected with lymphatic filariasis are in Asia. The epidemiology of lymphatic filariasis is changing due to implementing the global mass drug administration (MDA) program to eliminate transmission (Figure 2).

This program was established by WHO in 2000 known as GPELF (Global Program to Eliminate Lymphatic Filariasis). As per GPELF progress report 2021, the number of infections reduced by 74% globally since GPELF was established. According to the latest estimate (2021), 51.4 million people are still infected with LF. In GPELF, since 2000, more than 9 billion cumulative treatments have been delivered by MDA to more than 935 million people. In 2021, the total population that no longer required MDA increased to 740 million people, representing a 52% reduction in the total population that required interventions. Parasitic nematodes of LF can live in the human host for up to 6-8 years, causing lymphoedema pain and social stigmatization. Under the National Program to Eliminate LF in India first single-drug therapy with diethylcarbamazine was approved in 2004, later followed by double-drug therapy with DEC and albendazole because of better efficacy and results. Later in 2017, WHO introduced triple-drug therapy under GPELF with ivermectin, albendazole & diethylcarbamazine. Initially, GPELF's goal was to eliminate LF as a public health problem by 2020, revised to the year 2030—Union Secretary for Health and family welfare Shr. Rajesh Bhushan launched a nationwide survey Sevan or Mass Drug Administration campaign to eliminate LF, which aims to eliminate LF by 2027. This program includes door-to-door administration of anthelmintic medication by health workers in 10 filaria-affected states, mainly focusing on districts with high burdens.

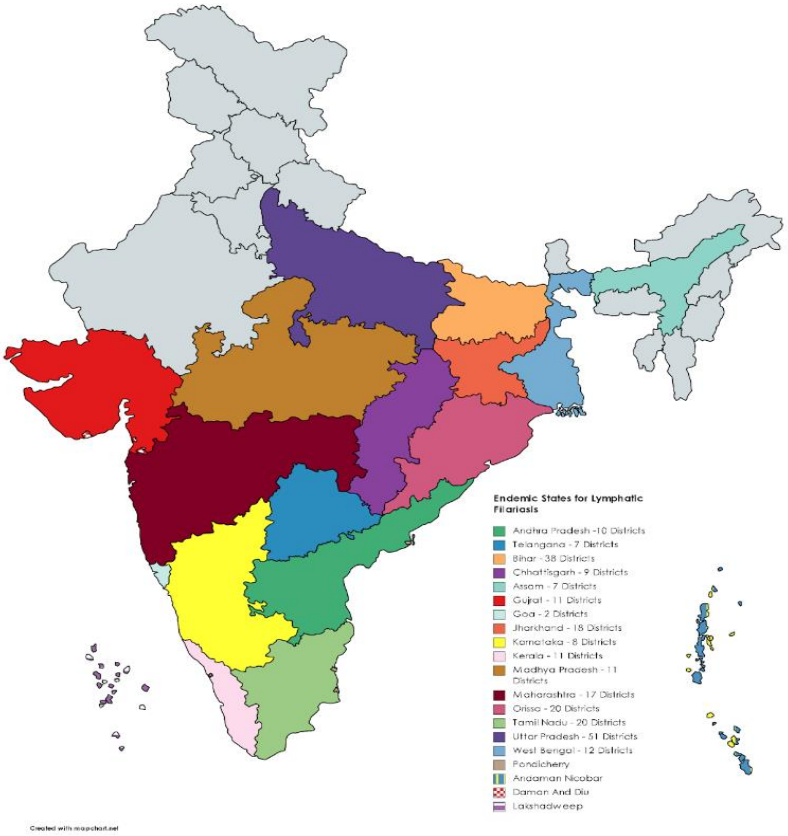

Figure 2 : Lymphatic filariasis endemic districts of India, 2023. Source: National Centre for Vector Borne Diseases Control Program, Ministry of Health and Family Welfare, Government of India (https://ncvbdc.mohfw.gov.in)

Filariasis Control Program

Programs introduced worldwide to control and eliminate filariasis (Table 1)

Table 1: Filariasis Control Program

Program	Objective of the program	Implemented strategy	Reference
Onchocerciasis Control Program in West Africa (OCP)	To eliminate human onchocerciasis, as a disease of public-health importance and an obstacle to socio-economic development, from the program area.	Priorly, vector control was the only method used. Simulium breeding locations were larvicide weekly using seven different pesticides. By the end of 2002, the OCP covered 11 West African countries, and had introduced large-scale Mectizan (ivermectin) distribution to about 10 million people, through the community directed treatment approach, with treatment coverages ranging from 51%-81%	[3,23-24]
Onchocerciasis Elimination Programme in the Americas (OEPA)	Eliminating ocular morbidity and interruption of transmission throughout the Americas by 2015 through biannual large-scale treatment with ivermectin.	Biannual large-scale treatment with ivermectin. In 2013, the Director-General of WHO issued an official letter confirming that Colombia has achieved elimination of onchocerciasis. Colombia was the first country in the world to be verified and declared free of onchocerciasis by WHO.	[23,25]
African Programme for Onchocerciasis Control (APOC)	To eliminate human onchocerciasis from the African countries in which the disease was endemic.	The co-implementation of onchocerciasis control with other health interventions that can be delivered at the community level. This approach has proved highly effective, leading to higher levels of therapeutic coverage for onchocerciasis control	[26-27]

		as well as improved delivery of other services, especially vaccination programs.	
Global Programme for Elimination of Lymphatic Filariasis (GPELF)	LF's elimination as a public health issue	Administration of drugs in large quantities for at least five years in the following ways: (i) ivermectin and albendazole to onchocerciasis co-endemic countries; and (ii) DEC and albendazole to non-onchocerciasis countries [to arrest transmission for the estimated duration of adult worm life. (iii) ivermectin (200 mcg/kg) together with diethylcarbamazine citrate (DEC) (6 mg/kg) and albendazole (400 mg) in certain settings	[3,29]

Triple-drug Regimen

The combination of ivermectin, diethylcarbamazine, and albendazole (IDA) is the latest triple-drug therapy for MDA, which is recommended by WHO and preferred as an alternative to double drug therapy against LF in some parts of the country. As per the progress report in implementing triple WHO, in 2021, IDA therapy MDA was used in 5 countries to treat 50 million people, accelerating the rapid use of this triple-drug regimen. The exact mechanism by which these medications reduce transmission has yet to be determined, but continuous studies and surveys are in progress to help us understand the precise mechanism. To study the requirement of this triple drug combination is still not determined. Planned surveys were conducted in Dominican Republic, Eritrea, Zambia and Zimbabwe to determine the need of IDA, but the results were delayed because of COVID-19-related interventions. Because of the effective outcomes of IDA mass drug administration, ten countries submitted joint application package forms to WHO, planning to implement IDA mass drug administration in 2022 for 91 international units. Under a national program to eliminate lymphatic filariasis in India first single drug therapy with diethylcarbamazine was approved, which was later allowed by double drug therapy with diethylcarbamazine and albendazole because of better efficacy and results (table 2). The MDA program was scaled up in India, covering 256 districts. International ethical committee intensified under NHM, medical colleges and the Indian Council of medical research got involved, and donations of albendazole from WHO increased. Later in 2017, WHO introduced the triple drug therapy under GPELF with ivermectin, albendazole and diethylcarbamazine. In 2018, an accelerated plan of elimination of LF (APELF) was launched in 10th GPELF meeting and IDA (triple drug regimen) was implemented in the same year in scheduled districts in phase wise manner. Union secretary for health and family welfare Sh. Rajesh Bhushan launched a nationwide survey Sevan or Mass Drug Administration campaign to eliminate LF, which aims to eliminate LF by 2027. This program includes door to door administration of anthelmintic medication by health workers in 10 filaria affected states, largely focusing on districts with high burden of LF which includes Bihar, Chhattisgarh Jharkhand, Maharashtra, UP, WB, Kara, Odisha, MP, and AP [30].

To create awareness, some practices and work plan was adopted by the states [30]. In Uttar Pradesh, direct-to-consumer programs have used social media to contact 80 lakh households with LF messages about the value of MDA drugs. Through initiatives in camps, schools, and universities and the creation of community-level micro plans like polio programs, Odisha hopes to reach 1.36 crore recipients.

West Bengal conducted the sessions in seven districts, reaching nearly 60 lakh people. Additionally, mobile health teams are prepared to prevent any untoward events.

Health workers from Andhra Pradesh have been assigned to one area and will visit homes to ensure the patients consume these medications. Maharashtra has intensified efforts to guarantee drug intake in the company of medical personnel by utilizing the Jagruk Balak Program (JBP), which will encompass four districts and 16 blocks. Madhya Pradesh will perform rounds in eight districts with a specific emphasis on IEC and activation through intersectoral cooperation. The MDA and Vikas Yatra 2023 activities are combined to increase drug intake at stations. To address the state's migrant community, mobile teams are formed. Karnataka will focus on the endemic district and two blocks, ensuring officers check and provide the broadest possible coverage.

Bihar has increased its efforts to implement an effective MDA by urging the community and recipients to show up and actively engage in the rounds. For the MDA promotion, Khan's father and Manoj Bajpai, two celebrities with sizable followings on social media, have been enlisted.

Table 2: Clinical Trials for Triple-drug Regimen for Lymphatic Filariasis

Study	Method	Conclusion	Reference
A trial of a triple-drug treatment for lymphatic filariasis	Three-drug regimen - 60 participants Single dose of the two-drug regimen - 61 participants Two-drug regimen – 61 participants A single dose of the above drug regimens is given once a year for 3 years to the participants. Clearance of microfilariae from the blood was measured at 12, 24, and 36 months after trial initiation.	At 12 months, 52 of 54 subjects (96%) were free of microfilaremia, followed by 55 of 57 participants (96%) at 24 months, and 55 of 57 participants (96%) at 36 months. In 20 of 59 subjects (34%) at 12 months, 42 of 56 participants (75%) at 24 months, and 51 of 52 participants (98%) at 36 months, the two-drug regimen given once a year for three years cured microfilaremia.	[11]
Efficacy, Safety, and Pharmacokinetics of co-administered Diethylcarbamazine, Albendazole, and Ivermectin for Treatment of Bancroftian Filariasis	Adults were randomized into 2 treatment arms, DEC 6 mg/kg + ALB 400 mg (N = 12) or DEC 6 mg/kg + ALB 400 mg + IVM 200 μg/kg (N = 12), and monitored for microfilaria, parasite antigenemia, adverse events (AEs), and serum drug levels.	In comparison to a 1-log decrease with two medications, triple-drug therapy caused >2-log reductions in microfilaria levels at 36 and 168 hours after treatment. One year after therapy, none of the 12 patients who got three drugs had microfilaria, whereas 11 of the 12 patients who received two drugs had microfilaria. For Bancroftian filariasis, triple-drug treatment is safer, more efficient, and may hasten lymphatic filariasis eradication than DEC + ALB.	[9]
A triple-drug treatment regimen to accelerate elimination of lymphatic filariasis: From conception to delivery	Regulatory affairs case studies report	Clinical studies showed that IDA is well tolerated and more efficient than earlier LF therapies at resolving microfilaremia. The fact that all IDA's components were already legally available medicines aided in the quick creation and adoption of the combination therapy. In nations where onchocerciasis and loiasis are not coendemic, IDA has the potential to hasten the eradication of LF.	[31]
Evaluation of effectiveness of diethylcarbamazine/albendazole combination in reduction of Wuchereria bancrofti infection using multiple infection parameters	A total of 170 participants were randomly assigned to albendazole (n = 62), DEC (n = 54), and DEC plus albendazole (DEC/ALB) combination (n = 54)	Albendazole increased DEC's effectiveness, and bulk administration of the two medications would therefore better the stopping of W. bancrofti spread in endemic regions.	[32]
Efficacy and Safety of a Single Dose of Ivermectin, Diethylcarbamazine, and Albendazole for Treatment of Lymphatic Filariasis in Côte d'Ivoire: An Open-label Randomized Controlled Trial	Single dose of IDA (n = 43) or 3 annual doses of IA (n = 52) in an open-label, single-blinded trial.	To reduce the total MF burden by 24 months, a single dosage of IDA performed better than two doses of IA.	[33]
An open label, block randomized, community study of the safety and efficacy of co-administered ivermectin, diethylcarbamazine, albendazole versus diethylcarbamazine and albendazole for lymphatic filariasis in India.	Diethylcarbamazine dosing was age-based with a dose of 100 mg for persons aged 2–5 years, 200 mg for persons aged 6–14 years, and a maximum dose of 300 mg for persons above age 14. Ivermectin dosing was weight-based (200 μg/Kg body weight). Albendazole was provided with a uniform dose of 400 mg for all participants.	IDA was more successful than DA at removing MF (84% vs. 61.8%)	[34]

Efficacy of single dose combinations of albendazole, ivermectin and diethylcarbamazine for the treatment of bancroftian filariasis	Single dose of albendazole 600 mg alone or in combination with ivermectin (iver) 400 μg/kg or diethylcarbamazine citrate (DEC) 6 mg/kg was compared with a single dose of the combination DEC 6 mg/kg and ivermectin 400 μg/kg over a period of 15 months after treatment.	The most efficient treatment for removing MF from night blood was alb/iver: 15 months after treatment, 9 of 13 subjects (69%) were found to be amicrofilaremic by membrane filtration, as opposed to 1 of 12 (8%), 3 of 11 (27%), and 3 of 10 (30%) in the groups treated with alb, alb/DEC, and DEC/iver, respectively.	[35]
Comparison of the efficacy of single doses of albendazole, ivermectin, and diethylcarbamazine alone or in combinations against Ascaris and Trichuris spp.	Infected children were randomly assigned to treatment with albendazole + placebo, ivermectin + placebo, diethylcarbamazine + placebo, albendazole + ivermectin, or albendazole + diethylcarbamazine.	In comparison to diethylcarbamazine, albendazole, ivermectin, and drug combos greatly improved cure and egg reduction rates for ascariasis. The infection rates were reduced 180 and 360 days after treatment, and albendazole + ivermectin considerably outperformed the other therapies for trichiniasis in terms of cure and egg reduction rates.	[36]
Safety of mass drug coadministration with ivermectin, diethylcarbamazine, albendazole, and azithromycin for the integrated treatment of neglected tropical diseases: a cluster randomized community trial.	7,281 (46.3%) received the combined regimen and 8,375 (53.3%) received standard treatment with IDA for lymphatic filariasis	There were 21 (0.3%) grade 2 adverse events (AEs) in the mixed treatment group, 33 (0.4%) IDA individually and 18 (0.2%) AZI separately. Nobody in the group needed medical attention for any Injury. Deaths, severe adverse events, or AEs of particular concern were not seen.	[37]

Conclusion

On comparing the clinical trial results of triple versus double drug therapy for lymphatic filariasis, it can be concluded that triple drug therapy is relatively more efficacious in eliminating filarial parasites from blood and has lesser side effects. In several trials, side effects were reported for triple drug combinations. Still, they were non-serious and generally disappeared in 2-3 days, making them a better candidate for its use in other settings. As per National Centre for Vector-Borne Diseases Control Program, in 2023, India still has 21 endemic states. Hence, a mass drug administration campaign to eliminate LF was initiated by the government to eliminate LF by 2027, which includes door-to-door administration of anthelmintic medication by health workers in 10 filaria-affected states, which is a great initiative itself. Still, triple drug therapy in such areas can accelerate the number of non-infected people in such states. Early detection and treatment of the disease, along with community education and engagement, play a vital role in controlling and eventually eliminating lymphatic filariasis. Whereas continued commitment to sustained treatment efforts and public health interventions will be essential to achieve the ultimate goal of eradicating lymphatic filariasis globally.

Conflict of Interest

No conflicts of interest exist, according to the authors, with the publishing of this work.

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