Invited Review

Long-Acting Antimicrobial Formulations: A Promising Frontier in Combating Neglected Tropical Diseases

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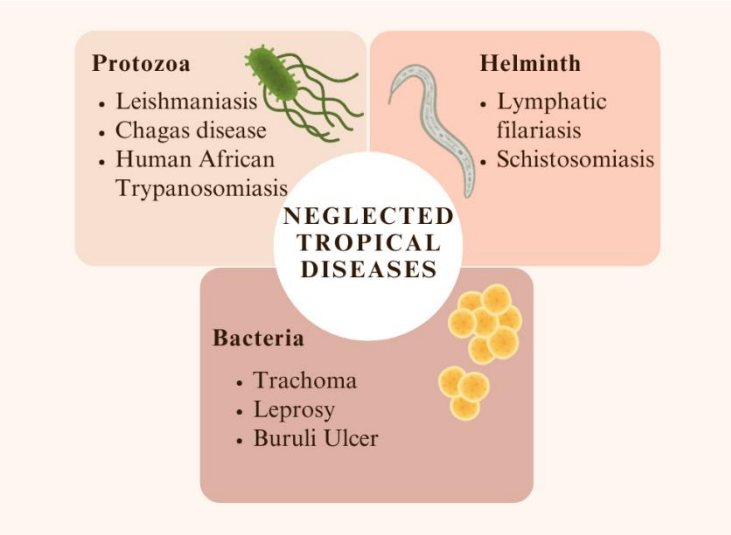

Classification of NTDs according to source of disease

Abstract

Neglected Tropical Diseases (NTDs) are a group of infectious diseases that affect over 1.5 billion people worldwide, predominantly in tropical and subtropical regions. These infections are caused by vector-borne pathogens, soil-transmitted helminths, and non-tuberculous mycobacteria. NTDs are largely concentrated in resource limited countries with inadequate sanitation, water, and healthcare. The global burden of NTDs, estimated at 56.6 million Disability-Adjusted Life Years (DALYs), is comparable to that of HIV/AIDS. Despite efforts from the World Health Organization (WHO) to control NTDs, challenges persist in treatment and control strategies, particularly due to the absence of effective vaccines and the complexity of existing frequently administered therapies. Long-acting antimicrobial formulations (LAFs) have emerged as a promising solution for improving therapeutic outcomes by providing sustained duration of drug action, enhancing patient compliance, and treatment outcomes. These formulations are being developed for several NTDs, including Leishmaniasis, Chagas disease, and Onchocerciasis. Innovations in drug delivery technologies, such as injectable depot formulations, liposomal approaches, biodegradable and non-biodegradable devices, have proven effective in other disease areas and are being applied to NTDs. Despite significant progress made, several scientific, economic, implementation and regulatory challenges exist. This review explores the potential future role of LAFs for NTD treatment and how collaborative global efforts could potentially improve access to these innovative therapies.

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Introduction

Neglected Tropical Diseases (NTDs) encompass a diverse group of infectious pathologies affecting approximately 1.5 billion individuals globally, predominantly in tropical and subtropical zones. These diseases are primarily caused by vector-borne pathogens, including protozoa (e.g., *Trypanosoma cruzi*, the etiological agent of Chagas disease), bacteria (e.g., *Chlamydia trachomatis*, responsible for trachoma), filarial nematodes (e.g., *Onchocerca volvulus*, the causative agent of river blindness), and soil-transmitted helminths (STHs) such as hookworms, *Ascaris lumbricoides*, and *Trichuris trichiura*. Additionally, non-tuberculous mycobacteria like *Mycobacterium ulcerans* (Buruli ulcer) and *Mycobacterium leprae* (leprosy) contribute to the disease burden (O'Brien, 2025). NTDs predominantly afflict individuals residing in resource limited regions with inadequate sanitation, unsafe drinking water, and limited healthcare resources. The global burden of NTDs is comparable to that of HIV/AIDS, with an estimated 56.6 million Disability Adjusted Life Years (DALYs) (World Health Organization [WHO], 2015). The WHO has identified 17 distinct NTDs within its portfolio and advocates five public health strategies aimed at mitigating the prevalence of these diseases: preventive chemotherapy, intensified case management, vector control, veterinary public health initiatives, and improvements in water, sanitation, and hygiene (Bailey et al 2017). Despite these efforts, existing control and treatment measures remain suboptimal, and infections like Leishmaniasis and Chagas disease continue to present significant therapeutic challenges due to the absence of effective vaccines and treatments. Current pharmacological interventions such as nifurtimox and benznidazole for Chagas disease exhibit limitations linked to poor bioavailability, toxicity, and contraindications during pregnancy. Similarly, the available therapeutics for STH infections exhibit low efficacy and inconsistent results when administered orally (Gyapong 2010). Long-acting antimicrobial formulations (LAAMs) represent a promising solution for overcoming these challenges through non-oral drug delivery approaches. Sustained drug release reduces dosing frequency to improve patient compliance, therapy completion rates and treatment outcomes (Moon, 2016).

Overview of Epidemiology and Socioeconomic Impact

Leishmaniasis presents a significant global health challenge, with an estimated annual incidence of 200,000 to 400,000 new cases, as shown in Figure 1. The disease burden is concentrated in high-risk nations, including India, Bangladesh, Ethiopia, and Brazil, which collectively account for nearly 90% of the cases. The disease predominantly affects individuals between the ages of 12 and 14 years, with socioeconomically disadvantaged groups experiencing a higher susceptibility (Hudu et al 2024). Lymphatic filariasis, another prevalent NTD, affects approximately 120 million individuals across 80 countries, with over 1.3 billion people at risk. Males engaged in outdoor occupations, such as hunting or fishing, who are coupled with poor sanitation, are particularly vulnerable. Schistosomiasis, affecting an estimated 252 million individuals, primarily in sub-Saharan Africa, ranks second only to malaria in terms of global incidence. The vectors responsible for Chagas disease extend throughout the Americas, affecting approximately 15 million people (Mitra, 2017). Table 1 highlights both the advancements made, such as improved access to treatment and successful mass drug administration, and the ongoing barriers, including limited healthcare access, infrastructure gaps, and disease prevalence in remote areas. Moreover, the development of long-acting formulations (LAFs) offers potential to enhance therapeutic efficacy and pharmacokinetics, facilitating improved management of these diseases. Antibiotic therapies such as amphotericin B, nifurtimox, and benznidazole are commonly used for NTDs like leishmaniasis, Chagas disease, and schistosomiasis. In particular, praziquantel has emerged as the first-line treatment for schistosomiasis, exhibiting broad-spectrum efficacy against various Schistosoma species (Siqueira, 2017).

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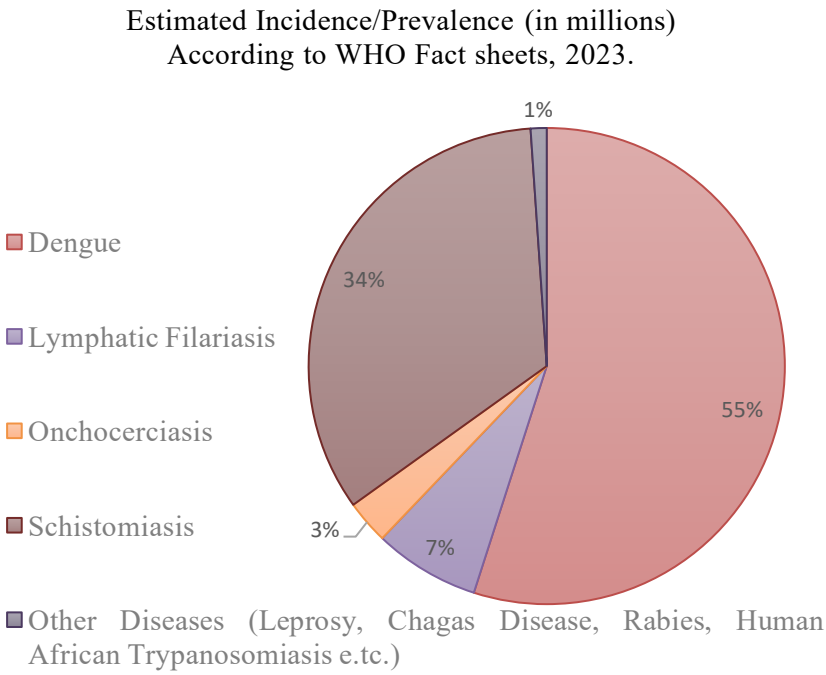

Figure 1: Estimated Incidence and prevalence of Neglected Tropical Diseases according to WHO fact sheets, 2023

The Significance of Long-Acting Antimicrobials

Several long-acting drug delivery approaches are being explored to improve therapeutic outcomes for NTDs. For instance, a long-acting formulation of ivermectin is being developed to provide extended prophylaxis against onchocerciasis, reducing the need for frequent doses. Similarly, albendazole and moxidectin are being explored as potential long-acting formulations to improve treatment outcomes for lymphatic filariasis. For visceral leishmaniasis, a liposomal formulation of amphotericin B (AmBisome) has demonstrated improved efficacy by reducing the need for prolonged hospitalization and enhancing patient adherence. As extensively discussed elsewhere, a long-acting version of benznidazole for Chagas disease could potentially improve adherence to treatment and minimize the duration of medication (Brindha et al., 2021). For these emerging formulations to create an impact in resource limited settings, production costs and cold chain storage requirements for some of the formulations will need to be addressed.

Innovative Approaches to Long-Acting Formulations

Recent preclinical advancements in the development of long-acting formulations for NTDs include injectable depot formulations such as nanosuspensions, *in situ* forming implants and microparticles. Injectable depot formulations, which are capable of sustained drug release, provide the advantage of reduced dosing frequency, thereby improving therapeutic compliance. Nanotechnology has shown significant promise in the field of drug delivery, enabling enhanced transport of medications to infection sites to restrict replication of pathogens such as parasites, viruses, and protozoa (Pandian et al., 2021). Liposomal formulations could potentially be utilized to mitigate side effects associated with some of the synthetic drug delivery polymers. The liposomal formulation of amphotericin B, for example, has shown greater efficacy and reduced toxicity compared to its conventional counterpart

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(Kumari et al., 2021). Continued development of patient centered long-acting formulations could further improve clinical outcomes.

Table 1: Data Summary of Neglected Tropical Diseases

Disease	Elimination goal year	Burden (cases)	Key interventions	Challenges	Progress
Leishmaniasis	2030 (Elimination as a public health problem in priority areas)	Over 7,00,000 cases annually	Vector control, improved diagnostics, treatment	Poor access to health care, conflicts in endemic areas	Improved access to treatment in endemic areas
Schistosomiasis	2030 (Control as a public health problem)	Over 200 million infected globally	Mass Drug Administration, Improved sanitation	Limited sanitation infrastructure, reinfection risk	Significant reduction in morbidity in some regions
Chagas disease	2030 (Interruption of vectorial and transfusion transmission	6-7 million people infected globally	Vector control, screening of blood transfusion, treatment	High prevalence in rural / isolated areas, asymptomatic cases	Progress in blood screening, vector control in Latin America
Lymphatic filariasis	2030 (Elimination as a public health problem)	50 million people globally infected	Mass Drug Administration, Vector control	Coverage gaps in remote areas, drug resistance concerns	Elimination achieved in several countries

Case Studies

Liposomal Amphotericin B vs. Conventional Amphotericin B Deoxycholate

A clinical trial comparing liposomal amphotericin B to conventional amphotericin B deoxycholate demonstrated superior therapeutic outcomes for the liposomal formulation. In this trial, patients receiving a single dose of liposomal amphotericin B (10 mg/kg) exhibited a 100% cure rate, whereas the conventional amphotericin B deoxycholate group showed a 98% cure rate after 15 infusions of 1 mg/kg. These findings underscore the efficacy of liposomal amphotericin B in enhancing patient outcomes and reducing hospital stays, with improved patient compliance and fewer side effects (Sundar et al., 2010).

Subcutaneous Injectable Long-Acting Ivermectin (LAFI) for Onchocerciasis

A study evaluating a long-acting injectable formulation of ivermectin (LAFI) for the treatment of onchocerciasis demonstrated improved efficacy in a preclinical model of human onchocerciasis. The study, conducted on zebu cattle, revealed that while LAFI was not macrofilaricidal, it demonstrated substantial embryostatic effects, providing a potential adjunctive approach for onchocerciasis control in humans. This highlights the promise of LAFI's in minimizing disease transmission (Boussinesq et al., 2020).

Long-Acting Albendazole Formulation for Lymphatic Filariasis

A study focusing on long-acting albendazole formulations for the treatment of lymphatic filariasis found that a single dose of the long-acting formulation resulted in prolonged therapeutic efficacy compared to standard albendazole treatments. This formulation not only enhanced the

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pharmacokinetics of the drug but also improved treatment adherence, reduced the burden of repeated dosing, and contributed to reduced transmission in endemic areas. The promising results advocate for further clinical trials to assess its potential for broader implementation in filariasis management (Addiss et al., 1997).

Moxidectin Long-Acting Formulation for Filariasis

A clinical investigation into long-acting moxidectin formulations for the treatment of filarial diseases demonstrated that the extended-release profile of moxidectin significantly reduced the frequency of administration required for effective parasite control. This formulation showed notable efficacy in treating *Wuchereria bancrofti* and *Onchocerca volvulus*, making it a viable candidate for use in mass drug administration programs aimed at controlling lymphatic filariasis and onchocerciasis. Its potential to improve patient compliance and treatment outcomes makes it a promising therapeutic for long-term management of filarial infections (Moon et al., 2016).

Mechanisms of Long-Acting Formulations in Enhancing Therapeutic Efficacy

The enhanced pharmacokinetic properties and sustained delivery of therapeutic drug levels at sites of infection contribute to the observed superior efficacy of LAFs compared to daily formulations. To combat the emergence of drug resistance, strategies such as combination therapy, drug cycling, dose optimization, and improved diagnostics are critical. Single-dose administration of amphotericin B has been shown to yield superior survival rates and bacterial clearance compared to divided doses administered over several days (Garcia etal., 2000). For infections that require combination therapies, incorporation of multiple drugs into a fixed dose long-acting formulation may further improve adherence and treatment outcomes.

Challenges in Developing Long-Acting Formulations for NTDs

While the development of long-acting formulations offers considerable promise, significant scientific, economic, regulatory, and social challenges remain. Achieving sustained and controlled drug release is particularly challenging for pathogens residing at restricted sites of infection such as the central nervous system. Advanced delivery technologies, such as drug conjugates and nanotechnologies, are being explored to address these challenges, although their application remains limited (Pfarr et al., 2023). Moreover, the cost of manufacturing LAFs, which requires specialized technology, poses a significant barrier to accessibility in resource-constrained regions [17]. Other hurdles related to safety, efficacy, PK variability and compatibility with diverse populations further complicate the development and implementation of LAFs (Li et al., 2022).

Implications for Global Health and Policy

LAFs hold significant promise for integration into global health frameworks. They align with the WHO's roadmaps for NTD control through access to innovative and effective treatment strategies. Public-private partnerships and collaborative initiatives, such as the Drugs for Neglected Diseases Initiative (DNDi), are key to facilitating scale up production and equitable access to LAFs. By improving treatment adherence and disease control, LAFs could potentially contribute to long-term economic and social benefits, alleviating poverty cycles perpetuated by NTDs (DNDi Annual Report, 2023).

Future Directions

To fully exploit the potential of LAFs in NTD management, continued research and technological innovation are necessary. Prioritizing research on optimal drug delivery formulations, ensuring stability in tropical climates, and targeting intracellular pathogens will be essential. Emerging technologies, such as 3D-printed drug delivery systems, microarray patches and application of artificial intelligence in the design of novel compounds and formulations, show promise for improving

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drug precision and prolonging therapeutic effects (Bardosh et al., 2018). Combination therapies incorporating multiple drugs could address issues of resistance and enhance therapeutic efficacy. Additionally, tailoring LAFs for pediatric and pregnant populations remains a critical priority for achieving equitable access.

Conclusions

Long-acting antimicrobial formulations represent a potential transformative solution to the challenges posed by neglected tropical diseases. By reducing dosing frequency, improving patient adherence, and enhancing treatment outcomes, LAFs offer a promising strategy for mitigating the global burden of these diseases. Overcoming the scientific, economic, and regulatory barriers to LAF development will require collaborative global efforts, but with continued investment in research, infrastructure, and equitable access, LAFs have the potential to revolutionize NTD treatment and significantly reduce the global health burden.

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