

Reverting the neglect of loiasis:

Recognition of loiasis as WHO-listed NTD

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Executive Summary

Loiasis is a more than neglected tropical disease (NTD) that affects over 20 million residents in parts of Central and West Africa, primarily in rural communities in rain forests and adjacent savannah regions, which are often remote and economically disadvantaged.¹ Despite being associated with substantial morbidity, increased mortality, and a significant economic burden in endemic regions, loiasis is not included in the WHO's list of NTDs.^{2,3,4} The failure to recognise loiasis as a public health priority, together with a lack of profitability for the commercial R&D sector, has resulted in a lack of research efforts, and appropriate tools to diagnose, treat, and control the disease are therefore still lacking.⁵

Loiasis occurs alongside a plethora of health conditions, including malaria and NTDs such as soil-transmitted helminths, schistosomiasis and the closely related onchocerciasis and lymphatic filariasis. The control of these diseases faces similar challenges regarding limitations in access to safe and efficacious drugs, efficient healthcare systems, and population-based control programmes. Loiasis also hinders effective mass drug administration programs for onchocerciasis control in co-endemic regions.¹ Addressing loiasis alongside these diseases in a comprehensive health strategy will foster treatment and prevention efforts for these co-endemic conditions that disproportionately affect the economically disadvantaged communities of rural Central and West Africa.

To overcome the intolerable burden of loiasis, we urge all relevant stakeholders to:

- Recognise loiasis as a public health priority by supporting inclusion in the WHO's list of NTDs (this could be achieved by summarizing lymphatic filariasis, onchocerciasis, and loiasis under one category "human filariasis").
- Increase awareness of the disease among policy stakeholders in endemic regions and internationally among global health agencies (e.g. the African CDC), research organisations, and NGOs.
- Increase incentives for long-term private and public innovative research programmes on loiasis, including by designating it as a priority disease by regulators (e.g. eligibility for a priority review voucher by the US-FDA), funding agencies (e.g. GH-EDCTP-3) and other national, regional and international stakeholders to enhance understanding of loiasis and develop novel diagnostic, treatment and control tools.
- Develop and implement appropriate, setting-specific evidence-based guidelines for the diagnosis, treatment and control of loiasis.
- Strengthen health education efforts aimed at healthcare providers and residents in endemic regions.

Background on loiasis as a public health concern

Epidemiology

Loiasis is a parasite infection that is prevalent in most rural regions of Central and parts of West Africa, particularly in the habitats of its primary vectors, *Chrysops silacea* and *Chrysops dimidiata*.¹ Estimates suggest that more than 20 million residents are infected, with more than 40 million living in medium to high transmission regions, and up to 170 million in regions with ongoing transmission.¹ In high transmission regions of Cameroon, the Democratic Republic of Congo, Gabon, and Equatorial Guinea, more than 40% of adults have a history of eyeworm migration, with loiasis prevalence reaching up to 80% among adults in some rural communities.⁶ Since the classification of endemic regions into ‘high’, ‘medium’ and ‘low’ transmission zones is largely based on a history of eyeworm migration and not blood microfilaraemia, the burden of loiasis in these regions has likely been underestimated.

However, the epidemiology of loiasis varies even within endemic countries. It primarily affects rural communities in rain forests and adjacent savannah regions, which are often remote and economically disadvantaged. Residents in these areas mainly rely on farming, fishing and hunting for their livelihood, and have limited access to healthcare providers, highlighting the intricate link between loiasis and poverty.⁷ Additionally, these populations are underrepresented in national decision-making processes, leading to the neglect of loiasis from health policy considerations even in highly endemic countries. Since loiasis is most prevalent in non-English speaking countries, it has garnered comparatively little interest from the mostly English-speaking international research institutions, resulting in few peer-reviewed research articles on loiasis over the past decades, and subsequently little progress in the improvement of diagnosis, treatment and control tools. This situation facilitates a neglect of the actual burden of loiasis for affected regions due to a lack of attention to loiasis as a public health priority. **Loiasis thus fulfils the WHO’s criterion for an NTD in that it disproportionately affects economically disadvantaged populations living in tropical or subtropical regions. To interrupt the vicious cycle of neglect, we strongly recommend enhancing awareness of the disease among policy stakeholders in endemic regions, as well as within regional and international health agencies, research organisations, and NGOs, including by adding loiasis to the WHO’s list of NTDs.**

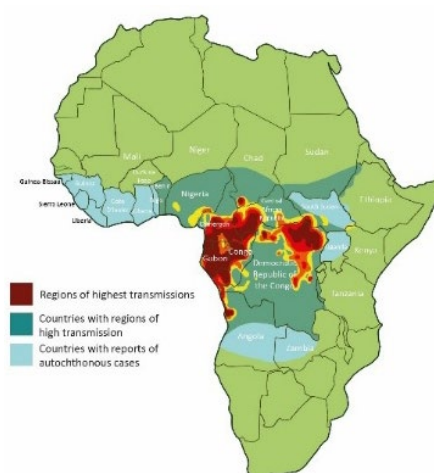


Figure 1. Loiasis prevalence. Loiasis is highly prevalent in rural regions in Central and West Africa, especially the Democratic Republic of the Congo, Cameroon, Gabon, and Equatorial Guinea. From Ramharter et al., 2024. Rights to this figure are owned by medical-artist.com and the Bernhard Nocht Institute for Tropical Medicine. Permission was granted to use these graphics for publication.

Parasitology and entomology of loiasis

Loiasis is transmitted by the blood-sucking *Chrysops silacea* and *Chrysops dimidiata* flies, which live in the canopy of tropical rainforests and trees in the nearby savannah.¹ These flies breed in stagnant, muddy waters, which are not easily accessible to vector control measures. They are attracted by movement, colours, and woodfire, but not effectively to currently available insect traps, posing a considerable challenge for vector control. **As there are currently no practicable vector control tools to support individual protection or population-based control-programs, further research is urgently needed to manage transmission in highly endemic regions in the future.**

Infectious larvae transmitted by *Chrysops* actively enter the human host and develop into adult worms in subcutaneous tissue. They can live up to 20 years, grow up to 7 cm, and migrate under the skin, causing loiasis' typical symptoms – Calabar swelling and eyeworm migration. Female worms produce large numbers of larvae called microfilariae, which can be detected in the peripheral blood, following a diurnal pattern. Microfilaraemia varies significantly between patients, is usually first detectable about a year after infection, and remains remarkably constant over time. However, a large proportion of patients exhibits an occult form of the disease, with no microfilariae present in peripheral blood, rendering diagnosis difficult.⁸

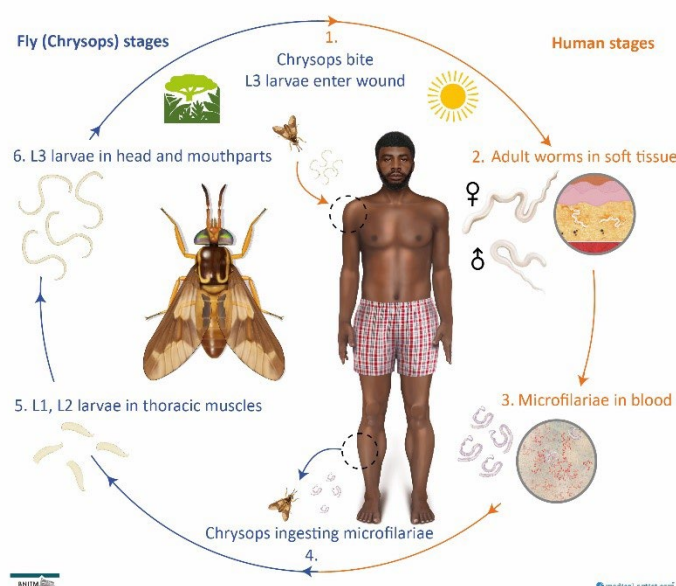


Figure 2. *Chrysops* life cycle. Infectious larvae enter the human host's subcutaneous tissue, where they develop into adult worms. Adult females produce large number of microfilariae, which circulate in the peripheral blood following a diurnal pattern. Microfilariae are taken up by *Chrysops* during a blood meal. From Ramharter et al., 2024. Rights to this figure are owned by medical-artist.com and the Bernhard Nocht Institute for Tropical Medicine. Permission was granted to use these graphics for this publication.

Medical aspects of loiasis

Signs and symptoms

Loiasis is a complex disease with highly variable clinical penetrance. Some individuals remain asymptomatic, while others exhibit classical symptoms such as eyeworm migration and Calabar swellings.⁷ Additionally, patients may experience non-specific symptoms including fatigue, severe headaches, myalgia, arthralgia and tooth pain, as well as rash. These chronic symptoms can significantly impact the affected individual's quality of life. A subset of patients may develop severe, life-threatening organ complications, including spontaneous encephalitis, cardiomyopathy, renal failure, and pulmonary involvement.¹ **The pathophysiology of these diverse clinical manifestations is only incompletely understood, and there is a lack of markers to identify those at risk of severe complications**

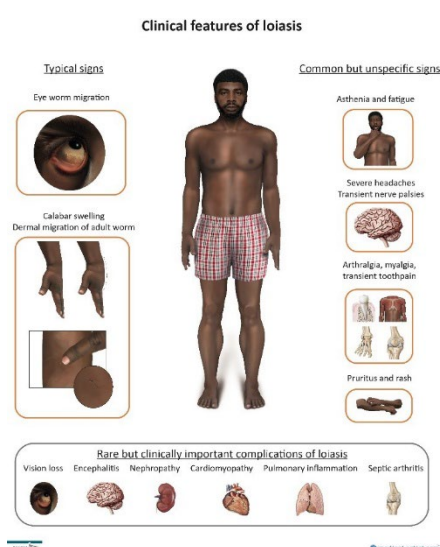


Figure 3. Clinical features. The clinical features of loiasis include the classical symptoms – eyeworm migration and Calabar swellings, as well as chronic unspecific symptoms such as fatigue, severe headaches, myalgia, and pruritis. In rare cases, patients may develop severe, life-threatening symptoms such as encephalitis, cardiomyopathy or pulmonary inflammation. From Ramharter et al., 2024. Rights to this figure are owned by medical-artists.com and the Bernhard Nocht Institute for Tropical Medicine. Permission was granted to use these graphics for this publication.

Diagnosis

Although diagnosis often relies on a patient history of eyeworm migration, the parasitological gold standard for diagnosis is the detection of microfilariae by microscopy of stained daytime blood samples. The relative complexity and time intensity of this diagnostic assay limit its use in remote settings. An automated mobile phone-based microscopic assessment (LoaScope™, NTDScope™) has been developed to quickly assess loiasis microfilaraemia in the field.⁹ It has primarily been used to detect hyper-microfilaraemia in individuals prior to ivermectin administration in onchocerciasis mass drug administration (MDA) programmes. However, the usefulness of these tools for individual case management of loiasis remains unclear. Molecular detection of microfilariae has good sensitivity and high specificity but requires sophisticated equipment and trained personnel, making it impractical in remote settings where loiasis is most common. Antibody-based rapid diagnostic tests showed some promise for epidemiological assessments

but their usefulness for individual case management remains limited due to low specificity in endemic regions. In summary, there is a lack of reliable, easily deployable diagnostic tools for population-based control programs and for individual patient management. **We therefore advocate for increased research efforts to develop next-generation diagnostic tools and setting-specific diagnostic guidelines. This will prove essential to facilitate individual case management and rapid screening for MDA programmes to control human filariasis.**

Treatment and control

Only few drugs are available for the treatment of loiasis, and there are currently no safe and efficient drug-based control programmes established in endemic regions.¹ Diethylcarbamazine (DEC) is the current gold standard for loiasis treatment in non-endemic regions, as it is effective against adult worms and larval stages. Due to its rapid onset of action, however, DEC can cause severe, life-threatening adverse reactions, particularly in hyper-microfilaraemic individuals. In addition, DEC is contraindicated in patients with active onchocerciasis, a human filariasis often co-endemic with loiasis. DEC is therefore rarely accessible and infrequently used in endemic regions and DEC is unsuitable for MDA due to safety concerns.

Ivermectin is one of the most commonly used antiparasitic drugs, and rapidly reduces loiasis microfilaraemia after the administration of a single dose. It is unclear whether ivermectin also exerts some adulticidal activity. Mass drug administration programmes with ivermectin to address onchocerciasis have been shown to reduce the rate of loiasis transmission, indicating that broad control and elimination programmes for loiasis are conceivable. However, similarly to DEC, ivermectin may induce life-threatening encephalopathy in patients with high microfilarial load, and is therefore not suitable for MDA programmes in which hyper-microfilaraemia is not routinely assessed.¹⁰ The risk for severe side effects in loiasis hyper-microfilaraemic patients has furthermore severely impaired ivermectin MDA for the control of onchocerciasis, and onchocerciasis control programmes had to be suspended in most meso- and highly co-endemic regions.

Albendazole is a broad-spectrum anthelmintic drug that gradually reduces loiasis microfilaraemia when administered over a period of 3-6 weeks. There is also limited evidence that longer treatment regimens or combination treatment with ivermectin may kill adult worms.¹¹ Despite a lack of systematic evaluation, albendazole is therefore often used for curative treatment of microfilaraemic patients in endemic regions. However, as albendazole requires prolonged treatment regimens and regular biochemical and haematological assessments to rule out potential liver toxicity, it is unsuitable for widespread loiasis control. **Overall, it is apparent that loiasis has been neglected by research, and that the disease would be amenable to broad control, elimination and eradication programmes. A better understanding of the pathophysiology of loiasis, the development of accurate rapid diagnostic tests suitable for use in remote settings, and new, safe and efficacious treatment regimens for individual and population-based treatment are crucial for reducing loiasis-related morbidity and mortality in affected communities. We therefore strongly advocate for increased efforts by funders and the research community to invest into the development of appropriate tools to achieve these objectives**

Burden of loiasis

Although historically seen as a rather benign condition, loiasis is now known to represent a significant health burden. In parts of Cameroon and the Republic of Congo, microfilaraemic loiasis has been shown to increase mortality by up to 15%.^{3, 12} In addition, loiasis leads to significant morbidity due to chronic unspecific symptoms such as severe headaches, myalgia, arthralgia and pruritus.² These often debilitating symptoms heavily impact affected individuals, and some research indicates that loiasis is one of the most common reasons for healthcare seeking in some endemic regions. Disability-adjusted life years (DALYs) for loiasis as marker of disease burden reaches levels comparable to those of other neglected tropical diseases (up to 400 per 100,000 in certain endemic regions in Gabon), suggesting that **loiasis is a significant health problem**.

Furthermore, **loiasis-associated morbidity and mortality exert a significant economic burden on the affected communities**. Qualitative surveys indicate that acute symptoms of the disease are frequent causes for absenteeism from formal and informal work, highlighting the indirect costs associated with the disease. A recent, comprehensive cost-of-treatment study conducted in a highly endemic region in Gabon suggests that the average annual costs attributable to loiasis amounted to around 40 USD per individual, compared to an average monthly income of 70 USD. These costs included both indirect and direct costs, such as costs for diagnosis and treatment, as well as costs for transport to healthcare providers.¹³

Loiasis therefore represents a major health and economic burden in the highly affected rural communities, fulfilling WHO's criterion that any disease considered for inclusion as NTD causes significant burden that warrants a global response. To mitigate this burden, we advocate for increased research efforts aimed at establishing efficient treatment and control measures for endemic regions.

Qualitative research results

Loiasis is well known in communities in endemic regions, as shown by a recent survey in a high-transmission region in Gabon.¹⁴ Residents recognise the disease's signs and symptoms, but, strikingly, few are aware of its mode of transmission. This knowledge gap importantly hinders prevention and control efforts and limits the capacity of residents of affected regions to protect themselves from infection. **We therefore recommend enhancing health education initiatives for healthcare providers and residents in endemic regions, as this will ultimately support the effectiveness of loiasis prevention and control programs.**

Loiasis in the broader context of human health in endemic regions

It is important to consider loiasis not only as an isolated disease but rather within the broader context of human health in endemic regions. Loiasis occurs alongside a broad range of locally endemic infectious diseases, including amongst others malaria, soil transmitted helminths, and schistosomiasis. Co-endemicity with other filarial diseases such as onchocerciasis and lymphatic filariasis represent a particular challenge. Control programmes targeting these diseases rely on ivermectin MDA to the entire at-risk population. Loiasis constitutes a barrier to the implementation of ivermectin-based control programmes as patients with high levels of loiasis microfilaraemia are at risk of developing potentially lethal treatment-associated encephalopathy.¹⁰ However, the overlap of onchocerciasis and loiasis is estimated to be as high as 70%, and the vast majority of people living in these co-endemic areas are likely to benefit from MDA. Ivermectin administration in these areas would require cost-intensive screening strategies aimed at excluding hyper-microfilaraemic individuals, as effective treatment alternatives that are safe for patients with co-infections are still lacking. Additional investments in research and drug development for the combined treatment of loiasis and other filarial diseases therefore constitutes an important public health priority.

It is equally important to consider that (co-) infections with loiasis and other endemic infectious diseases can severely impact an individual's overall physical and mental health. For instance, helminths and malaria co-infections increase the risk of anaemia and severe inflammation, and may compromise immune function, leading to greater susceptibility to further infections, poor nutritional status, and higher mortality.¹⁵ In children, the burden of these co-infections can impair physical and cognitive development, affecting school performance and attendance, while in adults, it may cause work absenteeism, posing an economic burden. Chronic symptoms and disabilities from co-infections can also lead to depression and anxiety, and may result in societal marginalisation and stigmatisation. Limited access to healthcare services and inadequate diagnostic and therapeutic tools for these conditions further exacerbate negative outcomes.⁶

Overall, current evidence thus shows that co-endemic, poverty-associated diseases interact in complex ways to negatively impact human health, and face similar challenges regarding appropriate diagnosis, treatment and control in the affected regions.

Gap analysis

As outlined above, there are important gaps that need to be met to appropriately address the significant burden that loiasis exerts on affected communities. These include re-assessment of the prevalence and economic burden of the disease, improvement of vector control tools, gaining a better understanding of its pathophysiology, developing new accurate and easily deployable diagnostic tools as well as the conception of effective prevention and treatment programmes. Based on dedicated health education efforts in affected populations to empower the most affected communities, all these efforts must be conceived in a comprehensive, setting-specific approach to be implemented in the national and regional health care and public health systems, and

- **Re-assessment of loiasis burden:** The assessment of loiasis prevalence is based on partially outdated data that relied mostly on patient histories of eyeworm migration. We recommend that these data be updated in a systematic approach combining clinical and parasitological surveys. These data should be supplemented with estimates of the health and economic burden of loiasis in endemic regions, as well as evaluation of co-endemic diseases, to assess where interventions are most urgently needed.
- **Vector control:** Currently, no vector control instruments exist, since *Chrysops* breeding sites are difficult to access, the adult fly is only poorly attracted to insect traps, and no individual protective tools are available. New research is therefore vital to develop new and effective vector control tools for endemic regions.
- **Diagnosis:** Accurate loiasis diagnosis in remote settings is hampered by the need for sophisticated equipment and trained personnel. The development of accurate and easily deployable rapid diagnostic tests constitutes a vital step towards improved management of loiasis and will also facilitate the re-introduction of MDA programmes controlling other filarial diseases in co-endemic areas. The development of diagnostic tests for occult loiasis constitutes another research priority.
- **Treatment and prevention:** Therapeutic options for the treatment and prevention of loiasis in endemic settings are limited especially due to the risk of severe side effects in patients with hyper-microfilaraemia. It is vital to develop new safe and efficacious regimens for the treatment and prevention of loiasis in the setting of the frequently occurring co-infections with other poverty-related infectious diseases.
- **Comprehensive approach:** Loiasis is co-endemic with several other infectious diseases and disproportionally affects economically disadvantaged communities with poor access to healthcare systems. To be effective, loiasis prevention and treatment programmes need to be embedded into these complex settings and should ideally also aim at improving overall healthcare infrastructure in the affected communities to improve access to medical care.
- **Health education:** Even though residents in affected communities generally know about loiasis and its associated symptoms, the mode of transmission and possibilities for prevention and treatment of the disease are often poorly understood. Health education programmes should be established in endemic regions, both for the benefit of healthcare personnel and affected individuals.

Action steps

To address these gaps, action steps are pertinent to improve the intolerable situation of loiasis. These gaps require action by national legislators in endemic regions as well as by international stakeholders.

- To legitimize loiasis as public health concern and to promote research and development through increased funding from national, regional and international agencies, **it is of highest importance that loiasis be promptly included on the WHO's list of NTDs** and the NTD R&D roadmap. This inclusion will encourage political stakeholders, funding agencies, and researchers to take steps to combat the disease. It is suggested that loiasis could be included as part of a disease group 'human filariasis' in the WHO's list of NTDs, rather than listing onchocerciasis, lymphatic filariasis and loiasis as separate disease entities. As outlined above, inclusion in the NTD list is warranted, as loiasis fulfils the WHO's criteria: loiasis is a disease that disproportionately affects economically disadvantaged populations living in remote, tropical regions of Central and West Africa, and is associated with significant morbidity and mortality that warrants a global response. Although loiasis is theoretically amenable to broad control and eradication programmes, rare but life-threatening side effects in a subset of patients with high microfilaraemia have led to the suspension of ivermectin mass drug administration programmes. Since loiasis has been relatively neglected by research, safe alternative treatment and control options are still lacking.
- It is vital to **provide financial incentives for researchers and institutions to develop long-term, innovative research programmes** in the field of loiasis. Including loiasis as NTD and priority disease on the lists of regulatory authorities (e.g. US-FDA), funding agencies (e.g. GH-EDCTP3), and other national, regional and international stakeholders and funding bodies is considered an important step towards creating such financial incentives.
- National stakeholders in endemic regions **require increased awareness** of the health burden caused by loiasis in the rural communities to better adjust the health care system to cater for the needs of the affected populations and to conceive control programs.
- Health policy stakeholders, community leaders, faith-based health organisation and not-for-profit organisations in endemic regions need to **increase efforts to promote health education** about loiasis targeted to healthcare providers and affected communities alike.
- Health care professionals should **develop evidence-based guidelines** for the management and control of loiasis in the respective healthcare settings. This will prove pivotal for the long-term establishment of necessary infrastructures and capacities to provide access to prevention and treatment programmes in affected communities.

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