

TrendsTalk

Loa loa: More Than Meets the Eye?Microfilaria of *Loa loa*. Credit: C.D. Mackenzie.

Trends in Parasitology

Filarial nematodes cause neglected tropical diseases (NTDs) such as river blindness, elephantiasis, and African eye worm. Global control and elimination efforts are well underway for the former two, and epidemiological models have played a crucial role in understanding the impact of interventions and guiding control policy. However, for the latter (caused by *Loa loa*), there are no specific transmission models, and the disease has not been included among the prioritized NTDs. María-Gloria Basáñez and her Helminth Ecology Research Group at Imperial College London work collaboratively on developing mathematical models for human and zoonotic helminthiasis and other vector-borne NTDs. In this interview, the authors shared with *Trends in Parasitology* why loiasis may be more than meets the eye and how modelling can best be leveraged to help control human filarial infections.

What does your research focus on? Is there an interesting story behind why you chose this topic?

Our research is primarily concerned with modelling the transmission dynamics of the so-called NTDs, particularly (but not exclusively) those tackled by preventive chemotherapy, including filarial diseases. Caused by parasitic worms, these diseases include onchocerciasis (river blindness) and lymphatic filariasis (elephantiasis) and they blight the lives of millions of people worldwide. The models we develop capture the population biology and epidemiological features of these parasites and are used to simulate and evaluate the impact of interventions to support policy-makers in reaching their control and elimination targets. Most of the interventions are presently based on treatment of the affected human populations with antifilarial drugs distributed through mass drug administration (i.e., without the need of an individual diagnosis of infection).

We are currently particularly interested in loiasis, a disease caused by another filarial parasite, *Loa loa*. Loiasis (African eye worm) is typically considered to be benign, and hence it has neither been included in the World Health Organization's list of prioritized NTDs nor considered in the Global Burden of Disease (GBD) studies. However, in addition to causing relatively minor ocular and systemic symptoms in a large proportion of those infected, new research has revealed a significant association between high levels of infection and increased human mortality, indicating a hitherto unrecognised public health importance. We want to understand better the population biology and epidemiology of this somewhat mysterious and forgotten disease so that we can develop new mathematical transmission models to inform the design of intervention strategies.

What is the current status of loiasis?

Loiasis is endemic across a broad region of central Africa, home to over 30 million people, with over 10 million people thought to be infected, although this value is rather uncertain and probably underestimated. No interventions currently target loiasis *per se*, although many communities co-endemic with onchocerciasis and/or lymphatic filariasis are served by annual or semi-annual mass drug administration with ivermectin (for onchocerciasis) and ivermectin plus albendazole for lymphatic filariasis. Loiasis has represented an impediment to effective implementation of mass drug administration because of rare but potentially severe adverse events following treatment with ivermectin in people with heavy *L. loa* microfilarial infections. The microfilariae are the stages transmitted to the insect vectors of these diseases, and hence, community-wide distribution of microfilaricidal drugs reduces transmission. However, in the case of loiasis, reactions to dead microfilariae can cause disabling and even fatal encephalopathy. Hence, although ivermectin is an efficacious treatment for loiasis, it is unsafe for people with heavy *L. loa* infections, and for these people treatment options are more limited.

Are there any pressing steps that, in your opinion, should be taken to control loiasis?

The latest research findings indicate that loiasis is a disease of public health importance associated with significant excess mortality of heavily infected individuals. Treatment options in these individuals are limited because of the risk of severe adverse events following administration of otherwise efficacious microfilaricidal drugs.

Moreover, because loiasis has not previously been considered a public health concern *per se*, the disease remains completely uncontrolled (and its prevalence can very high) in communities where neither onchocerciasis nor lymphatic filariasis are co-endemic. We believe that steps should be taken to control loiasis in these communities via safe delivery mechanisms, such as excluding heavily infected individuals from treatment, but also by investigating the safety and efficacy of new or existing treatments (such as albendazole) in heavily infected people. Methods for controlling the tabanid (horsefly) vectors that transmit *L. loa* should also be urgently developed to complement these chemotherapeutic strategies.

How can modelling best be leveraged to help control vector-borne diseases?

The transmission dynamics of vector-borne diseases such as loiasis are underpinned by interactions between populations of vectors, hosts, and parasites. Unlike onchocerciasis and lymphatic filariasis, for which experimental infections of the insect vector have been conducted to understand and quantify the processes determining vector competence, loiasis still presents the exciting challenge of making more translucent what has been a population biology black box. Such systems are characterised by nonlinear and sometimes unintuitive dynamics during interventions. These features limit the utility of formulating intervention strategies in an informal manner, without explicit consideration of the underlying transmission dynamics and population processes. Modelling incorporates these fundamental mechanistic processes and permits prediction of otherwise elusive epidemiological trends under different postulated intervention strategies. This provides a means to guide the design of interventions targeting these diseases in terms of their likely effectiveness and cost-effectiveness in attaining control and elimination goals.

What is the key message our readers should retain from your review?

Despite the long-standing perception as a benign disease, and the paucity of recent research, loiasis is a significant public health concern for millions of people living in impoverished rural communities of central Africa and warrants more attention and recognition by the global health community. Prerequisite to better control of loiasis is better understanding of the population and transmission processes that shape the epidemiology of this most neglected tropical disease. Ultimately, a better understanding of these underlying processes will permit the design and implementation of effective intervention strategies that will improve the health and wellbeing of millions of affected people in the central regions of Africa.

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Spotlight

Praziquantel Interaction with Mammalian Targets in the Spotlight

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Chan *et al.* recently demonstrated that the antischistosomal drug praziquantel has a potent and specific interaction with human 5-HT_{2B} receptors, and that the drug also elicits contraction of mouse mesenteric vasculature apparently mediated by the same receptor subtype. We consider what this might mean about the drug's molecular therapeutic targets in both the worm and the host.

Schistosomiasis continues to infect between 230 and 440 million people throughout the world [1]. Individual treatment of the afflicted, programs to control morbidity, and campaigns for geographical eradication all depend heavily on chemotherapy in the persistent absence of effective vaccines. Praziquantel (PZQ) was introduced in 1978 and has since remained the cornerstone of our antischistosomal chemotherapeutic toolkit. Despite the heavy reliance on PZQ to treat this devastating disease, 40 years later, the drug's mechanism of action remains enigmatic.

PZQ has immediate, dramatic, and debilitating effects directly on schistosomes at low concentrations (>1 μ M). The most obvious and immediate include a spastic paralytic contraction of the somatic

musculature and a dramatic disruption of the tegument, the worm's complex outer surface. Widespread calcium dysregulation is tightly linked to these hallmark effects. The only molecular target in the worm that has a demonstrated potent and specific interaction with PZQ remains an atypical schistosome β subunit of voltage-operated calcium channels (VOCCs) [2]. PZQ (100 nM) enhances calcium currents through heterologously expressed VOCCs containing these atypical subunits. However, evidence of this interaction actually occurring in worms continues to escape detection, and there is compelling evidence that these most obvious responses are not sufficient to explain PZQ's therapeutic efficacy.

Chan *et al.* recently demonstrated that PZQ binds to and acts as a partial agonist at human 5-HT_{2B} receptors at concentrations (10 μ M) well within those achieved in plasma through therapy [3]. This stereoselective effect was limited to the (*R*) enantiomer, to which most of the therapeutic efficacy is credited. In heterologous expression assays, both receptor binding and Ca²⁺ liberation occurred below 10 μ M. PZQ did not interact with any other human 5-HT receptor subtypes in similar concentration ranges.

The investigators also showed that (*R*)-PZQ phenocopies serotonin-induced contraction of the mesenteric vasculature of mice; this effect on the mammalian host requires concentrations significantly higher than those needed to elicit responses in worms, but still within those achieved in the mesenteric blood flow with therapeutic treatment (50 μ M).

Further, the (*R*)-PZQ-induced constriction of the murine mesenteric arteries was blocked by the specific 5-HT_{2B} receptor antagonist SB204741, which also blocks (*R*)-PZQ-induced Ca²⁺ liberation in cells expressing human 5-HT_{2B} receptors.

Does this mean that PZQ could be interacting with a schistosome G-protein-coupled receptor (GPCR) that is like a mammalian 5-HT_{2B} receptor?

In the broadest sense, the work of Chan *et al.* shows that PZQ interacts very specifically and stereoselectively with a GPCR. At a minimum, these results substantively endorse the possibility that PZQ could interact with a worm GPCR as part of its therapeutic action.

It is worth noting that serotonin and PZQ are both myoexcitatory on worms, but their overall responses are significantly different; there is not a serotonergic response that mimics the overall PZQ response. Further, schistosome receptors readily recognizable as similar to mammalian 5-HT_{2B} receptors have not yet been identified. That observation, however, is only tenuously germane. Most flatworm GPCRs remain classified only by algorithmic forecast, and those are quite unreliable at subtype level classification, especially when they are forced to extrapolate backwards across vast evolutionary distances. The lion's share of schistosome GPCRs remain completely uncharacterized biologically. It certainly remains possible that one of the large number of uncharacterized schistosome GPCRs could interact with PZQ.