DISSEMINATION
Schisto_Persist

# Schistosomiasis solution is not as simple as mass drug administration: Lamberton Lab takes a holistic approach to break the cycle of infection

**Professor Poppy Lamberton**

Schistosomiasis, also known as Bilharzia, is second only to malaria in terms of its socio-economic and public-health importance. Like many neglected tropical diseases (NTDs), schistosomiasis cannot be controlled via mass drug administration (MDA) alone, and there are ongoing concerns over drug resistance.

## Schistosomiasis explained

Schistosomiasis is a parasitic disease that affects over 240 million people worldwide, over 90 per cent of whom live within sub-Saharan Africa (Steinmann *et al.*, 2006).

People infected with the disease can suffer extreme illness, e.g. enlarged liver, and it can even result in death. In children, schistosomiasis can impact physical and cognitive development, exacerbating the poverty cycle in tropical communities.

### Lifecycle

Schistosomiasis is caused by a parasitic worm that lives in freshwater in tropical and subtropical regions. Infected people pass eggs from the adult worms out of their bodies through urine and/or stool. The eggs are exposed to fresh water, then hatch and infect snails where they reproduce asexually, producing thousands of larvae that can re/infect humans by burrowing directly into the skin.

Communities exposed to schistosomiasis heavily rely on the bodies of fresh water where they are getting infected, with access to the water vital for fishing, washing clothes and bathing. Schistosomiasis is a disease of poverty, and its cycle is difficult to break due to challenging sanitary conditions. Pit latrines are common within the communities but not always accessible or acceptable, and when they are used can overflow during rainfall, washing infected material into the freshwater.

## Current treatment

As with many NTDs, MDA is the main strategy deployed to control schistosomiasis. In 2003, Uganda implemented MDA with praziquantel for schistosomiasis. MDA imposes intensive selective pressures, with 105 million people treated in 2019 (WHO, 2014). This raises serious drug-resistance concerns. In a Ugandan district that I have worked in since 2004, I have observed heavier infections in recent surveys than at baseline (Lamberton, 2014; Clark *et al.*, 2021). As there are no viable alternatives to praziquantel, goals to eliminate schistosomiasis as a public-health problem by 2030 (WHO, 2022) may be seriously jeopardised by emerging resistance.

### Challenges for policymakers

To optimise MDA programmes for schistosomiasis and other NTDs, policymakers need to know who best to target with the limited resources available. However, providing this information can be problematic. Challenges include:

- the accuracy of available diagnostic techniques essential for monitoring MDA, especially in regards to elimination and drug-resistance pharmacovigilance
- efforts to monitor drug efficacy being impeded by the inability of diagnostic methods to differentiate between surviving worms and reinfections.

**Decisions on who and when to treat with MDA** have been based on prevalence in school-aged children. When to stop treatments has been based on prevalence and intensity. This is all based on eggs found in the stool, using the **Kato-Katz thick smears**, or eggs in urine found using filtration, WHO targets (2022). But these commonly used tests for prevalence and intensity have limitations.

**Bilharzia in Bugoto, Uganda, Poppy Lamberton. https://youtu.be/t62CHi4daTY**

Image: Bugoto transmission site Feb 2017.
*Photo credit: Poppy Lamberton*

For *Schistosoma mansoni*, Kato-Katz are recommended by the WHO for diagnosis. However, there are two main issues with this, the low sensitivity of Kato-Katz in low-intensity infections and post treatment, and the 'unpopular' nature of using stool.

The urine point-of-care circulating cathodic **antigen test** (POC-CCA) offers higher sensitivity but is not 100 per cent specific. However, the test is popular as it uses urine and is a simple to use lateral flow test, making it quick and convenient.

## Schisto_Persist

**The Schisto_Persist** project, which started in 2016, set out to use interdisciplinary approaches to respond to these challenges. The project has several interlinked aims, many of which focus on diagnostic challenges, to:

- pioneer new diagnostics
- develop drug-efficacy monitoring protocols
- validate cutting-edge drug-resistance phenotypic markers
- identify factors that contribute to *S. mansoni* hotspots.

### Improving diagnostic interpretation

There is still significant room for improvement regarding the antigen test. While the test provides a limited capacity to indicate infection intensity, there have always been 'trace' readings that cannot be easily interpreted.

Dr Jess Clark uses mathematical models to investigate how effective long-term MDA programmes are in high endemic regions and how to make progress towards elimination targets set out by WHO.

Clark *et al.* (2021) analysed data from Kato-Katz and POC-CCA tests, using the manufacturers scoring guidelines and a newer 'G-scoring' method (Casacuberta-Partal *et al.*, 2019) from 210 school-aged children. Models were used to infer latent clearance and reinfection probabilities at four time points over six months.

Antigen-based models estimated higher infection prevalence across all time points compared with the Kato-Katz model, corresponding to lower clearance and higher reinfection estimates. The study concluded that treatment impact was shorter-lived than Kato-Katz–based estimates alone suggested, with lower clearance and rapid reinfection.

### Recommended papers

Reconciling egg- and antigen-based estimates of *Schistosoma mansoni* clearance and reinfection: A modeling study doi: 10.1093/cid/ciab679

Translating from egg- to antigen-based indicators for *Schistosoma mansoni* elimination targets: A Bayesian latent class analysis study doi:10.3389/fitd.2022.825721

### Interpreting trace results

Although the POC-CCA test is advocated as an improvement on the Kato-Katz method and attempts to indicate infection intensity, its use by policymakers is, in part, limited by ambiguities in interpreting trace results.

There is no way to directly see and count the number of worms (adult or juvenile) within a person. Diagnostic tests all give indirect indicators of worm presence, so there is also no way to identify how well each diagnostic works. Therefore, analysis is required.

In Clark *et al.* (2022), we established a functional relationship between Kato-Katz counts, POC-CCA scores and the score-associated probability of true infection. A model was used to quantify sensitivity and specificity measures, producing an area under the curve value that can be used to determine how well a diagnostic is working and, in turn, the optimal POC-CCA scoring system and positivity threshold. We also showed that the egg counts and POC-CCA could not really be aligned because the POC-CCA saturates at very low egg counts, so a high score on a POC-CCA does not necessarily mean you're heavily infected. Post-treatment POC-CCA sensitivity/specificity fluctuations indicated a changing relationship between egg excretion and antigen levels (living worms). However, elimination targets can be identified by the POC-CCA score distribution in a population.

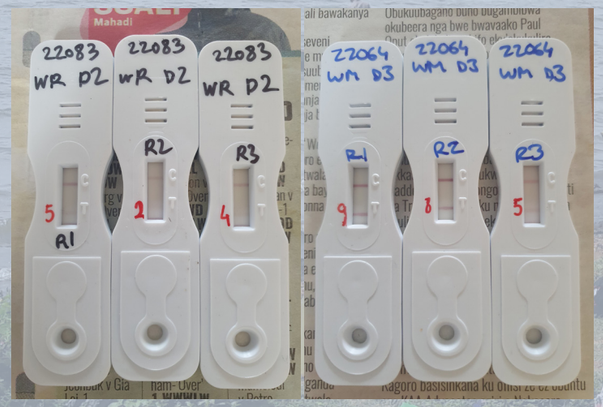


*Figure 1: POC-CCA tests conducted using the same urine sample and volume, all showing different intensity results. In some instances the different scores would result in a different infection status being recorded (postive or negative) if they were around the cut off boundary. Photo credit: Elías Kabbas-Piñango.*

## Tackling remaining issues

The WHO (2022) have published their thresholds and 2030 goals. The newly published WHO target product profile for schistosomiasis diagnostics still presents room for improvement.

## Lack of inter test (intra sample) reliability

The POC-CCA test has suffered from batch-to-batch variations (Viana *et al.*, 2019) due to manufacturing issues and a push for more sensitivity from the research community, resulting in varying specificities (Peralta and Cavalcanti, 2018; Casacuberta-Partal, 2021). Three different POC-CCA tests using the same urine sample can all give very different readings (Figure 1).

An updated version of the POC-CCA test, developed by MondialDx and Leiden University Medical Center, uses recombinant antibodies and is referred to as the recPOC-CCA. Through a recently awarded grant from USAID Task Force for Global Health, we aim to further improve the quality of recPOC-CCA tests across batches and evaluate the inclusion of one or more (lyophilised) calibrators with recPOC-CCA kits in combination with standardised visual reading. Using latent class analyses, a statistical procedure used to identify hidden values and measures in data, recPOC-CCA results from the lab and Ugandan settings will be compared to data from three days of duplicate Kato-Katz thick smears and the standard POC-CCA test. These will guide end users on the appropriate cutoff for these recPOC-CCA tests. Our study will result in improved reliability of the test, an associated higher specificity and sensitivity, and greatly enhanced accuracy and support for monitoring and evaluation of MDA programmes in endemic countries.

### Discover more

Improving POC-CCA reliability and interpretation in low and high *S. mansoni* endemicity settings using recombinant Ab-based POC-CCAs and improved quality assurance and control.

A COR NTD project and in collaboration with Uganda Ministry of Health (MOH), University of Surrey, Leiden University Medical Center (LUMC) and Mondial Diagnostics.

## Other species and new CAA lateral flow assay

So far, we have focussed only on *S. mansoni*. There are, in fact, three main species that infect humans. The work of PhD student **Elías Kabbas-Piñango**, in collaboration with **NG Biotech**, aims to develop a sensitive, specific, rapid, field-deployable lateral flow assay for active schistosomiasis–all species. After development, the test will be compared to other techniques, including DNA-based methods. The device will help detect early and low-intensity infections, and it could also be used to monitor the efficacy of future MDA programmes.

*Figure 2: Testing the urine point-of-care circulating cathodic antigen (POC-CCA) tests for schistosomiasis, conducted in the field (Uganda). Photo credit: Elías Kabbas-Piñango.*

## Detecting surviving worms

Even if we can accurately detect antigens and eggs, we still don't know if they are from new or surviving worms. After someone is treated with praziquantel, they may still have surviving worms in their system. If antigens are coming from worms that are only from one sex, or only single unpaired worms or juveniles, then the outcome is good, in that no eggs are being produced. However, if the antigens are from worms in breeding pairs, then egg production may have temporarily ceased, only to resume at a later date, called drug-induced embryostasis. Those worms and their offspring may be more likely to have developed some level of resistance to praziquantel.

It is, therefore, important to understand and identify adult worm treatment survival versus clearance and reinfection. We have identified reductions in worm fecundity post-treatment that suggest that egg-based measures of drug efficacy, such as Kato-Katz, may overestimate the short-term effect of praziquantel on adult-worm numbers (Lamberton, Faust and Webster, 2017). These findings have important implications for *S. mansoni* transmission control, diagnostic protocols and the potential for undetected selection toward drug resistance.

## Analysis to detect if one or both parents survived

Sibship analysis identifies sibling worms pre- and post-treatment, thus showing parental survival. If parental survival is high but associated with short-term embryostasis, then reduced susceptibility may already be being selected for but not yet detected using Kato-Katz diagnostics.

In a two-year longitudinal study, we observed that praziquantel treatments have short-term, transient impacts on parasite populations and no long-term reduction in genetic diversity events. However, parasites were observed to survive treatment. We concluded that MDA in isolation might be insufficient to reduce schistosome populations in regions with high genetic diversity and gene flow (Faust *et al.*, 2019). However, if drug resistance is being selected for, it could spread quickly with these high gene flow rates, but it could also be out-competed by high levels of parasite refugia.

## Beyond MDA

MDA alone is not the answer to combatting schistosomiasis. Practical solutions to improve sanitation are vital in breaking the transmission cycle. This may sound simple, but to be sure that efforts to improve sanitation will be implemented long term, we need to know what is sustainable, popular and affordable within the relevant communities.

The next steps for the Lamberton Lab are to build on their MRC Global Challenges Research Fund (GCRF) project entitled 'Cultural, social and economic influences on ongoing *S. mansoni* transition and the potential for change', and the new ERC Consolidator project 'WickedSchisto: Developing a robust interdisciplinary-informed WASH framework for the prevention and elimination of the wicked public-health problem of schistosomiasis'. Our aim is to provide a strong, locally-informed, behaviourally-consistent foundation for the design and feasibility of complex interventions to reduce the transmission of this debilitating disease.

You can read more about the progress of the project in our future article set for release in The Project Repository Journal in 2023.

**The Lamberton Lab**
Combatting neglected tropical diseases through interdisciplinary research.
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## References


Casacuberta-Partal, M., Beenakker, M., de Dood, C.J., Hoekstra, P.T., Kroon, L., Kornelis, D., Corstjens, P., Hokke, C.H., van Dam, G.J., Roestenberg, M. and van Lieshout, L. (2020) 'Specificity of the point-of-care urine strip test for *Schistosoma* circulating cathodic antigen (POC-CCA) tested in non-endemic pregnant women and young children', *American Journal of Tropical Medicine and Hygiene*, 104(4), pp. 1412–1417. doi: 10.4269/ajtmh.20-1168.

Casacuberta-Partal, M., Hoekstra, P.T., Kornelis, D., van Lieshout, L. and van Dam, G. (2019) An innovative and user-friendly scoring system for standardised quantitative interpretation of the urine-based point-of-care strip test (POC-CCA) for the diagnosis of intestinal schistosomiasis: a proof-of-concept study. *Acta Tropica* 199 105150. doi: 10.1016/j.actatropica.2019.105150.

Clark, J., Moses, A., Nankasi, A., Faust, C.L., Moses, A., Ajambo, D., Besigye, F., Atuhaire, A., Wamboko, A., Carruthers, L.V., Francoeur, R., Tukahebwa, E.M., Prada, J.M. and Lamberton, P.H.L. (2021) 'Reconciling egg- and antigen-based estimates of *Schistosoma mansoni* clearance and reinfection: A modeling study', *Clinical Infectious Diseases*, 74(9), pp. 1557–1563. doi: 10.1093/cid/ciab679.

Clark, J., Arinaitwe, M., Nankasi, A., Faust, C.L., Adriko, M., Ajambo, D., Besigye, F., Atuhaire, A., Wamboko, A., Carruthers, L.V., Francoeur, R., Tukahebwe, E.M. Lamberton, P.H.L. and Prada, J.M. (2022) 'Translating from egg- to antigen-based indicators for *Schistosoma mansoni* elimination targets: A Bayesian latent class analysis study', *Frontiers in Tropical Medicine*, 3, 825721. doi: 10.3389/fitd.2022.825721.

Faust, C.L., Crotti, M., Moses, A., Oguttu, D., Wamboko, A., Adriko, M., Adekanle, E.K., Kabatereine, N., Tukahebwa, E. M., Norton, A. J., Gower, C. M., Webster, J. P. and Lamberton, P.H.L. (2019) 'Two-year longitudinal survey reveals high genetic diversity of *Schistosoma mansoni* with adult worms surviving praziquantel treatment at the start of mass drug administration in Uganda', *Parasites and Vectors*, 12(1), p. 607. doi: https://doi.org/10.1186/s13071-019-3860-6.

Lamberton, P.H.L., Kabatereine, N.B., Oguttu, D.W., Fenwick, A. and Webster, J.P. (2014) 'Sensitivity and specificity of multiple kato-katz thick smears and a circulating cathodic antigen test for *Schistosoma mansoni* diagnosis pre- and post-repeated-praziquantel treatment', *PLoS Neglected Tropical Diseases*, 8(9), e3139. doi : 10.1371/journal.pntd.0003139.

Lamberton, P.H.L., Faust, C.L. and Webster, J.P. (2017) 'Praziquantel decreases fecundity in *Schistosoma mansoni* adult worms that survive treatment: evidence from a laboratory life-history trade-offs selection study', *Infectious Diseases of Poverty*, 6(110). doi: 10.1186/s40249-017-0324-0.

Peralta, J.M. and Cavalcanti, M.G. (2018) 'Is POC-CCA a truly reliable test for schistosomiasis diagnosis in low endemic areas? The trace results controversy', *PLoS Neglected Tropical Diseases*, 12(11), e0006813. doi: 10.1371/journal.pntd.0006813.

Steinmann, P., Keiser, J., Bos, R., Tanner, M. and Utzinger, J. (2006) 'Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk', *The Lancet. Infectious Diseases*, 6(7), pp. 411–425. doi: 10.1016/S1473-3099(06)70521-7.

Viana, A.G., Gazzinelli-Guimarães, P.H., Castro, V.N., Santos, Y., Ruas, A., Bezerra, F., Bueno, L.L., Dolabella, S.S., Geiger, S.M., Phillips, A.E. and Fujiwara, R.T. (2019) 'Discrepancy between batches and impact on the sensitivity of point-of-care circulating cathodic antigen tests for *Schistosoma mansoni* infection', *Acta Tropica*, 197, 105049. doi: 10.1016/j.actatropica.2019.105049.

WHO (2021) *Schistosomiasis and soil-transmitted helminthiases: treating millions of people, despite the pandemic*. Available at: https://www.who.int/news/item/08-12-2021-schistosomiasis-and-soil-transmitted-helminthiases-treating-millions-of-people-despite-the-pandemic.

WHO (2022) *WHO guideline on control and elimination of human schistosomiasis*. Available at: https://www.who.int/publications/i/item/9789240041608.




**PROJECT NAME**
Schisto_Persist

**PROJECT SUMMARY**


Schisto_Persist aims to understand why schistosomiasis is not reducing in some areas despite nearly 20 years of mass drug administration. Overarching questions: What is the best way to monitor schistosome infections and drug efficacy? Has praziquantel resistance been selected for and what is its potential for spread? What other factors drive maintained transmission? What other factors affect parasite clearance? All require improved diagnostics and interpretation to be answered. Here we discuss the advances the Lamberton Lab are making for *Schistosoma* diagnostics.


**PROJECT LEAD PROFILE**

Poppy Lamberton graduated from the University of Oxford, undertook a PhD, Postdoc and Fellowship at Imperial College London, before moving to the University of Glasgow in 2015, where she is now a Professor in Global Health. She leads an interdisciplinary team aiming to reduce community level transmission of NTDs, mainly schistosomiasis and onchocerciasis. She is funded by the ERC, UKRI, Royal Society, Royal Society of Edinburgh and Drugs for Neglected Diseases *initiative*.

**MAIN PROJECT PARTNERS**

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**Leiden University Medical Centre, Netherlands** (Dr Govert van Dam, Dr Paul Corstjens)
**NG Biotech, France** (Maxime Laroche, Dr Arnaud Chalin, Dr Lucie Baujard-Lamotte)

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# Cracking the quantum gravity conundrum

## Higher spin symmetry in quantum gravity, condensed matter and mathematics


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