Trends in Parasitology

CellPress

TrendsTalk

Uganda Schistosomiasis Symposium 2023: understanding morbidity drivers and developing controlled human infection models for vaccine research

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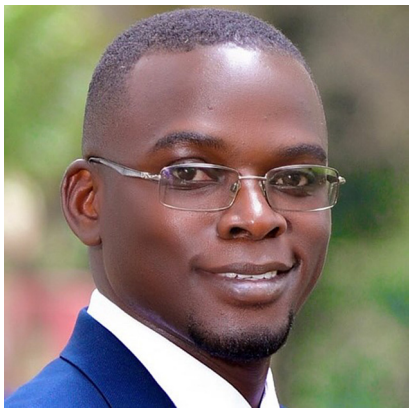
Schistosomiasis impacts African populations most strongly. Despite Uganda's leading role in the Schistosomiasis Control Initiative for mass drug administration (MDA), about half the population remains at risk and a quarter infected. Prevalence and intensity remain high, and morbidity severe, in northwest Uganda around Lake Albert and the Albert Nile. An effective vaccine could combat repeated infection following MDA, and controlled human infection (CHI) studies could enable such vaccine development. Therefore, the Uganda Schistosomiasis Multidisciplinary Research Center and CHI-in-Africa Network hosted a symposium in Uganda bringing together local and international partners to discuss research on the drivers of schistosomal morbidity and the development of CHI studies for helminth vaccine development in Africa. In this *TrendsTalk*, we invited 10 early- to mid-career researchers to summarise the symposium proceedings.

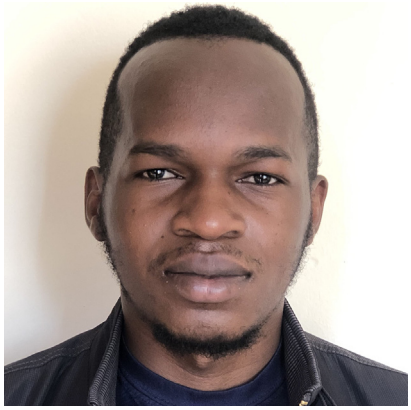


Moses Egesa

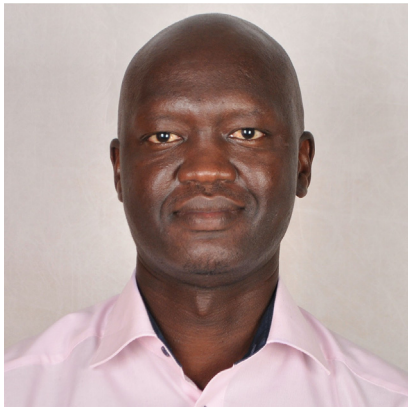
Session 1. Introductory remarks, schistosomiasis genomics, epidemiology, social science, and control

Alison Elliott [Medical Research Council (MRC)/Uganda Virus Research Institute (UVRI) and London School of Hygiene and Tropical Medicine (LSHTM) Uganda Research Unit] and Pontiano Kaleebu (Director, Uganda Virus Research Institute) welcomed 131 attendees from four continents and nine countries (Figure 1A) and affirmed that the workshop addressed a critical topic requiring solutions, considering Uganda's high schistosomiasis burden. Kicking off the scientific presentations Edridah Tukahebwa (The Carter Center, Uganda), introduced the Uganda Schistosomiasis Multidisciplinary Research Center (U-SMRC). She explained that U-SMRC aims to build Ugandan research capacity, leverage partnerships, address biological mechanisms that underpin differential schistosomal morbidity, and identify optimal intervention strategies. U-SMRC is investigating factors at each step of the parasite life cycle and how they determine differential morbidity between the Lake Albert and Lake Victoria regions of Uganda.

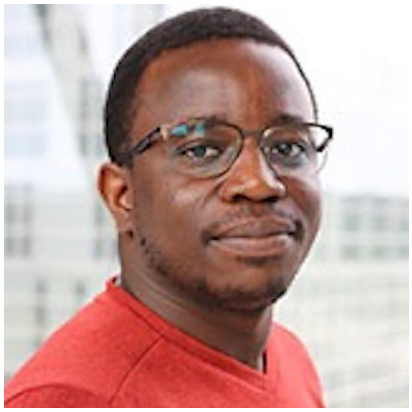
Alfred Mubangizi (Vector Borne and Neglected Tropical Diseases Control Division, Uganda Ministry of Health) gave an overview of neglected tropical diseases (NTDs) in Uganda, reporting that schistosomiasis is endemic in 93 of 146 districts. He updated the audience on progress on NTD elimination in the country; for example, transmission of onchocerciasis has been stopped in 47 of 52 endemic districts, and lymphatic filariasis has been eliminated. By contrast, schistosomiasis persists as a major public health problem. He highlighted the Ministry of Health's NTD control strategy and the challenges faced, including emerging diseases, cross-border transmission, inadequate sanitation, and funder withdrawal. Next, Goylette Chami (University of Oxford) presented work from her SchistoTrack cohort. This study seeks to identify risk factors for liver morbidity



Davis Kiberu



Richard E. Sanya



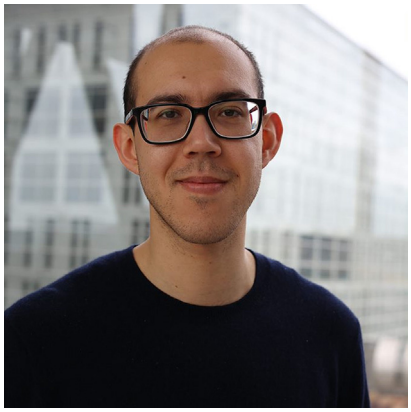
Ayodele Alabi

Figure 1. Moments of the first Uganda Schistosomiasis Symposium. (A) Group photo of symposium attendees. (B) Demonstration of the parasite life cycle by Fiona Allan and Prossy Kabuubi. (C) Group photo of best poster and short talk awardees. (D) Fiona Allan illustrates a step in the miracidia hatching process.

development and transition prospectively. The aims include assessment of individual-based transmission as opposed to community-level models, ascertaining the relevance of current infection status, and developing tools for tailored treatment and morbidity management in primary health centres in Eastern and Western Uganda.

Maxson Kenneth Anyolitho (Mbarara University of Science and Technology) presented findings from a study investigating healthcare-seeking behaviour in the absence of regular MDA in schistosomiasis-endemic communities along Lake Albert. He reported that communities are concerned about the limited praziquantel drug supplies, lack of testing before praziquantel administration, and drug side effects. Men in these communities made treatment decisions, and social-economic factors determined the utilisation of private or traditional facilities. He recommended more community engagement and increased availability of praziquantel to communities coupled with more awareness-raising regarding drug uptake. Up next was Lazaaro Mujumbusi (MRC/UVRI and LSHTM Uganda Research Unit), who presented evidence of a need for health education programmes to reduce persistent schistosomiasis in rural Ugandan fishing communities. With funding from the Royal Society of Tropical Medicine and Hygiene (RSTMH) and the National Institute for Health and Care Research (NIHR), he intends to address the lack of national health education programmes to curb misperceptions about schistosomiasis transmission, symptoms, prevention, and treatment, and messaging gaps within and between communities and village healthcare teams. Following the talk, discussion among symposium attendees emphasised the need to engage key stakeholders, such as the Ministry of Health, to ensure that such research links to policy and implementation. Andrew Edielu (MRC/UVRI and LSHTM Uganda Research Unit) presented initial results from the 'Praziquantel in Preschoolers (PIP)' trial, a Phase 2 pharmacokinetic/pharmacodynamic (PK/PD)-driven dose-finding trial for children under the age of 4 years. Approximately 36% of preschool-aged children (PSAC) in Africa have schistosomiasis. The PIP trial

Friederike Sonnet



Jan Pieter R. Koopman

Joseph Baruch Baluku

aims to determine praziquantel safety and efficacy in PSAC, to provide data to support a change in indications to include young children. To achieve this, a dosage of 80 mg/kg will be compared with the standard 40 mg/kg. Nutritional parameters, gut morbidity markers, and sonographic findings were presented. Andrew's PhD project, nested within the PIP study, aims to determine the contribution of schistosomiasis to gut morbidity observed in Environmental Enteric Dysfunction (EED).

Switching gears, Matthew Berriman (University of Glasgow) concluded the session by discussing progress on the *Schistosoma mansoni* reference genome. He showed the completed sex-specific regions of the Z and W chromosomes, including details of the region where sex-determining factor(s) could have first evolved. He highlighted the use of single-cell transcriptomics to gain genome-wide functional insights, including identification of marker genes specific for the different cell types of *S. mansoni* miracidia, and discussed ongoing work with the U-SMRC to study parasite population structure and the effects of selection of the parasite genomes.

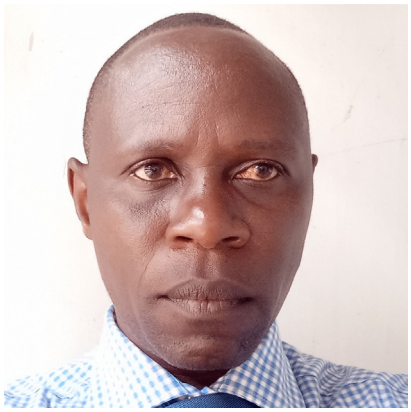
Session 2. Schistosome vaccine development, and poster sessions

In continuation of pandemic traditions, Afzal Siddiqui (Texas Tech University Health Sciences Center) gave a virtual talk on the 30-year journey of schistosome vaccine development. In a 2016 *Science* feature[i], the schistosomiasis vaccine was ranked 7th of 10 that urgently needed to be developed. According to Afzal, the preferred candidate is one that would reduce morbidity, rather than offer sterile immunity. A working vaccine in combination with MDA programmes will make it possible to control the disease. In addition to these opinions, he presented his work on an Sm-p80 antigen-based vaccine (SchistoShield®)[ii]. The Sm-p80 antigen is a protein present in the surface membrane and epithelial syncytium of the parasite. Vaccine trials in animal models (baboons and mice) have shown prophylactic, therapeutic, transmission-blocking, as well as antipathologic efficacy for both *S. mansoni* and *Schistosoma haematobium.* Afzal further reported that vaccine-specific IgG responses correlated with egg hatching (transmission blocking) and serum circulating anodic antigen (CAA) levels (health condition of the parasite). Transfer of IgG antibodies into naive mice led to a significant reduction in worm burden and eggs in the tissues. There was upregulation of cytokine expression in vaccinated animals, and network interaction mapping identified interferon (IFN)-γ as a major node of interaction. Phase 1 trials in humans are currently underway in the USA, and updates will be available in April 2023.

After the talk, a poster session was held, prior to which the presenters advertised their work in 2 min pitches. The posters covered a broad spectrum, ranging from a call to discover 'experimental snail infections with Ugandan and Puerto Rican schistosomes', to learning of 'a thousand ways to die from schistosomiasis'. Overall, the posters were well presented and led to lively discussions during and after the session.

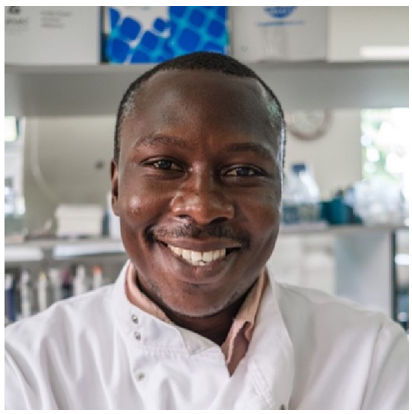
Session 3. CHI models for helminths, and *Schistosoma*-associated morbidity

The second day of the symposium focussed on CHI for helminths and schistosomiasis-associated morbidity. To inspire the next generation of scientists, we invited 15 biology students from three secondary schools in Entebbe, Uganda, to attend the day 2 presentations. Maria Yazdanbakhsh [Leiden University Medical Center (LUMC)] kicked off the day with an introduction to the current status of CHI models for helminths which, until recently, had only been established in the global north. She highlighted



David W. Oguttu

Emmanuella Driciru



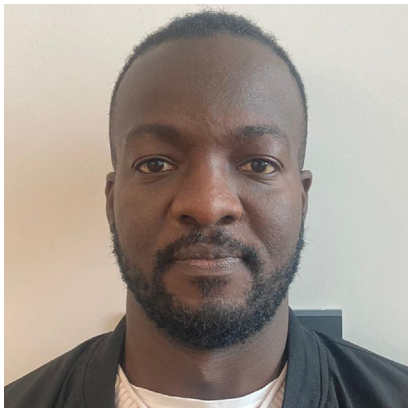
Matthew Odongo

the observed differences in vaccine-specific responses between endemic and non-endemic settings as well as between rural and urban settings in endemic countries. CHI can help us to understand these differences and shorten the time to vaccine development. Next, Selidji Todadbe Agnangji and Christine Ndong (both from Centre de Recherches Médicales de Lambaréné, Gabon) shared an update of their work on hookworm CHI in Lambaréné. The team is planning on challenging healthy men with little previous exposure to *Necator americanus* to assess the infectivity and safety of hookworm CHI. Work has been ongoing to set up and optimise good manufacturing practice (GMP)-like production of infective hookworm larvae. Closing the session on CHI, Friederike Sonnet (LUMC) presented her work on characterising immune responses after repeated immunisation with hookworm larvae and early treatment (chemo-attenuated vaccination). She reported that, upon chemo-attenuated vaccination, individuals had a reduced subsequent infection load based on stool egg output. Further, vaccinated individuals had a more activated immune profile and showed the development of a T helper type 2 (Th2) phenotype.

In the afternoon, Simon Mpooya and Alain Dessein (French Institute of Health and Medical Research) presented work on *Schistosoma* disease morbidity in the West Nile region of Uganda. In a cohort of adult fishermen and women, they reported a high burden of *Schistosoma* morbidity, characterised by severe periportal fibrosis (PPF), variceal bleeding, and ascites in severe PPF. Hepatitis B and C virus co-infection in severe PPF was prevalent and accelerated progress of liver fibrosis. Interestingly, morbidity seemed to peak between the ages of 40 and 50 years, and some individuals do not develop severe disease possibly due to genetic resistance to disease progression as has been observed in Caatinga families in Brazil. Simon's work also revealed immobilization, marital dysfunction, isolation, and inability to perform functions of daily living as consequences of *Schistosoma* morbidity.

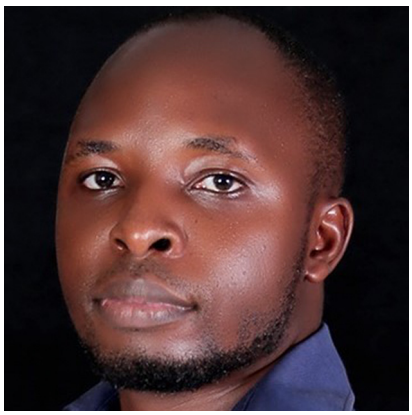
Hannah Rafferty (University College London) shared findings from Zambia where they found that cervical dysplasia (a precursor to cervical cancer), assessed with visual inspection under acetic acid, was associated with a positive PCR for *S. haematobium*. She also highlighted the feasibility of screening for *S. haematobium* in cervical cancer screening programmes. The session ended with a talk from Mario Jiz (Research Institute of Health for Tropical Medicine) who discussed work on *Schistosoma japonicum* in the Philippines. He noted an underestimation of the burden of schistosomiasis in the national surveys and discussed the role of water buffaloes in transmission. In their work, they have observed subtle morbidities: anaemia, stunting, cognitive impairment that correlated with markers of inflammation. He further reported on the safety of praziquantel in pregnancy, where, in their trial, there were no significant differences in maternal and foetal deaths, rates of abortions, and clinical profiles of children born to these women.

After the talks, symposium attendees had the opportunity to visit different laboratories at the UVRI. Emmanuella Driciru (MRC/UVRI and LSHTM Uganda Research Unit) gave a tour of the snail laboratory which was set up in preparation of the controlled human *Schistosoma* infection study in Uganda. Fiona Allan (University of St Andrews) and Prossy Kabuubi (MRC/UVRI and LSHTM Uganda Research Unit) gave a wonderful demonstration of the different aspects of the schistosome life cycle to the biology students and other interested symposium attendees (Figure 1B).



Bridgious Walusimbi

Alison M. Elliott



Gyaviira Nkurununngi

The day ended with a sumptuous dinner, highlighted by an inspirational speech from Narcis Kabatereine[iii] about his exceptional contribution to schistosomiasis research, training, and control over many years with the Uganda Ministry of Health and international organisations. He narrated his journey from a young schistosomiasis researcher – navigating the vagaries of transport by train and bicycle in the 1980s, the challenges of the civil war and pandemics in northern Uganda, his contribution to the implementation of MDA, the tireless work in hard-to-reach settings – to a consultant with the World Health Organisation, contributing to global health policy on NTDs.

Session 4. Snails in schistosomiasis transmission, and CHI studies for schistosomiasis

Russell Stothard (Liverpool School of Tropical Medicine) presented on the importance of understanding medical malacology in schistosomiasis research and its control. He gave a historical background of early malacology works and interested the audience in diverse experiences of snail studies in Zanzibar, Malawi, and Uganda. He described recent invasion of Lake Malawi by *Biomphalaria pfeifferi* and the introduction of *S. mansoni* as a notable recent experience in the changing epidemiology of schistosomiasis in Africa. He touched on controversies in snail identification by classical morphology and advanced molecular techniques. He highlighted key biological factors such as genetic diversity and environmental aspects that must be studied carefully to understand how snail distribution and human population movements can determine schistosomiasis distribution. He ended by explaining what the malacology studies in the U-SMRC will entail and the expected contribution to knowledge in schistosomiasis control in Uganda, for example, by clarifying the dynamics of snail–schistosome interactions and its microepidemiology.

The next talk was given by Julius Tumusiime (Mbarara University of Science and Technology), who detailed efforts to use a citizen science approach involving schistosomiasis-endemic communities in surveillance of snails. From a study conducted in Lake Albert shoreline communities, he concluded that literate residents of schistosomiasis-endemic areas can voluntarily carry out snail collection, identify snails to genus level, and report to health units as a cheap way to monitor schistosomiasis and other snail-borne disease transmission if their capacity is built and key equipment provided. This is an innovative approach which enables great opportunity for large-scale monitoring of snail population dynamics, essential for a better understanding of seasonal transmission of various snail-borne diseases.

CHI models have important potential to accelerate vaccine testing. Moses Egesa (MRC/UVRI and LSHTM Uganda Research Unit) provided updates on efforts to establish a CHI model for schistosomiasis in Uganda, with the aim of assessing safety, tolerability, infectivity, kinetics, and immunological and microbiome profiles in a setting of intense-prior exposure (fishing community) and minimal-prior exposure (university community). Moses reported that a 'roadmap' to establish this model, drawn during a stakeholders' meeting, has guided these efforts. To develop local infrastructure, a snail laboratory with local Ugandan snails has been approved by the national regulator, and snail infections with Ugandan and Puerto-Rican schistosomes have been performed. In the same vein, Jan Pieter Koopman (LUMC) presented an overview of CHI models for schistosomiasis in the Netherlands. A prior model involved infecting volunteers with male cercariae only. A female-only model has been developed with the rationale that vaccines may need to be tested with female infections as well. In a slow dose escalation trial

(10–20 cercariae), tolerability and safety have been proven; however, female worms on their own seem less susceptible to praziquantel compared with male worms.

In keeping with the multidisciplinary nature of the meeting, the next speaker asked the question: 'is the effect of helminths and urbanisation on cardiovascular risk mediated through the gut microbiome?'. Bridgious Walusimbi (MRC/UVRI and LSHTM Uganda Research Unit) introduced his talk by describing previous studies linking schistosomiasis infection to reduced low-density lipoprotein (LDL)-cholesterol, and rural living with reduced blood pressure. Nested in the same studies, his work has shown that rural living is associated with higher bacterial diversity and richness compared to urban living, with distinct microbiome signatures associated with reduced cardiovascular risk. In addition, schistosomiasis infection significantly influenced the gut microbiome and metabolomic profiles in urban settings, and subsequently enriched pathways that are associated with cholesterol metabolism.

Following the talks, the symposium organising committee conducted a ceremony to award prizes to the best poster and short-talk presenters (Figure 1C). The best poster award went to Emmanuella Driciru for her work on CHI models for schistosomiasis, while Bridgious Walusimbi won the best short-talk award. Victor Ilemobayo (Kampala International University) was awarded second place, with Francis Ssenkuba (Mbarara University of Science and Technology) and Matthew Odongo (MRC/UVRI and LSHTM Uganda Research Unit) jointly in third for the poster awards. Hannah Rafferty received second place, and Julius Tumusiime third place, in the short-talk category.

The day concluded with a field visit to Kigungu village in Entebbe Municipality. The visit aimed to demonstrate to symposium attendees how human stool collection and testing to identify high *S. mansoni* egg count samples (to be used in hatching miracidia, day 4) is performed. Ten community volunteers converged at Kigungu Health Center III, gave informed consent, and donated urine and stool samples.

Session 5. Workshop on preparing miracidia from stool samples for parasite genetics

After all the scientific talks highlighted earlier, especially about the integral role that parasite genetics might play in explaining the disproportionate morbidities and prevalence of schistosomiasis in different regions, the attendees were afforded the opportunity to appreciate the processes involved in preparing samples for parasite gene sequencing. The symposium was therefore capped off by an interactive practical session (Figure 1D) entailing preparation of miracidia from stool samples of participants from Kigungu fishing village (Entebbe, Uganda), from whom consent had been obtained during the aforementioned field visit (day 3). This session was led by Fiona Allan, Prossy Kabuubi, and Gloria Oduru (MRC/UVRI and LSHTM Uganda Research Unit). Each attendee had a hands-on experience with the Kato Katz technique and was able to identify parasite eggs in the stool of Circulating Cathodic Antigen-positive participants. Samples containing *S. mansoni* eggs were then selected for hatching of miracidia. Following this process, each miracidium was carefully transferred to an FTA card. The latter preserves the DNA of miracidia used for molecular identification and characterisation of the parasite. Every successful catch of a swift-swimming miracidium by an attendee drew cheerful chants from the rest of the group waiting for their turn.

The closing remarks were made by Moses Egesa, co-chair of the organising committee. While thanking the organising team and participants, he emphasised our collective responsibility to ensure an end to the neglect of this very important tropical disease.

Acknowledgments

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Resources

[i]https://doi.org/10.1126/science.351.6268.16

[ii]www.pailifesciences.com/schistoshield

[iii]https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0000546

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