LONDON CENTRE FOR NEGLECTED TROPICAL DISEASE RESEARCH

AN INNOVATIVE RESEARCH COLLABORATION:

SELECTED RESEARCH HIGHLIGHTS 2022

@NTDResearch

Contents

Director's note

It has been a very difficult two years for health systems around the world, but especially so for resource poor settings, including those affected by neglected tropical diseases (NTDs). The COVID-19 pandemic has demonstrated the fragility of health systems and highlighted the significant dangers of inequity in health. Throughout the pandemic, global health professionals have emphasised that the measure of success for vaccine uptake cannot be restricted to high income nations in Europe and North America. Rather, success lies in our ability to coordinate a global vaccination programme that protects the most vulnerable first and leaves no one behind. The world is so highly connected today that directly transmitted respiratory viral infections will spread to every corner of the populated world very easily. As such all countries continue to be affected with the Delta variant and its newer highly transmissible offspring, Omicron, with rapid spread even in well vaccinated populations.

The COVID-19 pandemic has had a devastating impact on NTD programmes. It has considerably slowed the huge progress that had been made in the previous decade in the effective implementation of mass drug administration (MDA) programmes, WaSH programmes, surgeries and other interventions. Challenges have been further exacerbated by changing donor landscapes, including the early termination of the 'Accelerating the Sustainable Control and Elimination of Neglected Tropical Diseases' (Ascend) programme, which was formally communicated by the UK government in June 2021 following a £4 billion cut to the UK's foreign aid budget. The end of the UK's flagship health programme was a bitter blow, affecting millions of vulnerable people in East and West Africa where no alternative source of funding exists.

The impact of the COVID-19 pandemic on MDA programmes in many countries in Africa, Asia and South America has recently been assessed by the NTD Modelling Consortium, with funding from the Bill and Melinda Gates Foundation. The research simulated the possible effects of delayed rounds of MDA. Simple theory of the transmission dynamics of helminth parasites and the impact of control reveals that the key parameter influencing the time taken for helminth infections to return to pre-control levels after the cessation of MDA is the life expectancy of the adult worms in the human host, which is a key determinant of the value of the basic reproductive number of the infection R_0. Delays in MDA rounds therefore have a much greater impact on the control of the short-lived parasites, such as the trachoma bacteria and intestinal nematodes, than for the longer-lived filarial and trematode worm infections.

The research conducted by members of the London Centre for NTD Research is as relevant after recent events as it was before the pandemic in supporting countries to 'go the last mile', and achieve the ambitious targets documented in the new WHO road map for NTDs. Focus is increasingly on new diagnostics as NTD prevalences fall to low levels in many countries, the importance of wildlife reservoirs of infection and the need to identify causes of low MDA coverage levels, such as persistent non-compliance to treatment.

The 2022 research highlights booklet presents emerging research from our members, which fills critical knowledge gaps in pursuit of our shared goals of controlling, eliminating and eradicating NTDs by 2030.

We are grateful for the contributions from our members, and their ongoing commitment to research collaboration in pursuit of our shared vision of a world free from NTDs. We also welcome the contributions of our many new members, who will play a critical role in maintaining our momentum to deliver WHO road map targets.

Professor Sir Roy Anderson FRS FMedSci
Director, LCNTDR

Spillover, hybridisation, and persistence in schistosome transmission dynamics at the human–animal interface

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with Dr Nicolas Diouf, Dr Cheikh B. Fall and Dr Mariam Sene

Background

The multi-host *Schistosoma* spp. system within Africa is a key example of where spillover of animal parasites into human populations has enabled the formation of viable hybrid parasite genotypes. A recent study by this group indicated that in northern Senegal, a region where *S. haematobium* (the causative agent for urogenital schistosomiasis in people) and *S. bovis* (causative agent of intestinal schistosomiasis in livestock) are coendemic, ongoing pairing between these two species leads to creation of hybrids in human hosts. This occurs via zoonotic spillover of *S. bovis* from a livestock reservoir to people who are simultaneously infected with *S. haematobium*. The public health impact of zoonotic spillover is fundamentally determined by the force of infection from the reservoir species and the potential for onward transmission and persistence within the human population, and we aimed to unravel the transmission dynamics of this complex multi-host, multi-parasite system.

Methods

Results from diagnostic tests together with genotyped data were applied to Bayesian frameworks to estimate worm burden for each parasite genotype within each host population. These estimates were then applied to next generation matrices and a novel multi-host, multi-parasite dynamic model.

Results and discussion

The basic reproduction number for the hybrid genotype ($R0^{H,Hyb}$) within the human population was estimated to be 1.76 (95% BCI 1.59 to 1.99), greater than the critical threshold of one. This indicates that this genotype can be maintained within the human population in the absence of zoonotic spillover, and that hybrids will have the capacity to persist if introduced to new geographic localities in the presence of a suitable inter-mediate snail host. We found that the worm burden of *S. bovis* in humans corresponded to a very low percentage (0.17%; 95% BCI 0.07 to 0.34%) of the total Haematobium group worm burden in the human population being zoonotically acquired. However longitudinal simulations indicated that the relative importance of this low-level of zoonotic transmission in terms of genotype composition in the human population would increase under scenarios of near-elimination and increased MDA coverage. For example, a scenario of 90% MDA coverage predicted that the proportion of worms in the human population comprised of hybrids would reach more than 50% after 15 simulated years with current levels of zoonotic transmission. The wider public health concerns for a growing predominance of schistosome hybrids include the potential for hybrid genotypes to have an increased host range (both definitive and intermediate), increased infectivity, and altered pathology. We estimated $R0$ for *S. bovis* to be greater than one in cattle (1.43; 95% CI 1.24 to 1.85) and confirmed cattle as both maintenance and essential hosts for *S. bovis*. Understanding the pathways and drivers of zoonotic spillover, the factors that may enable zoonotic diseases to spread within human populations, and the potential consequences of interactions between multiple species and strains of pathogens is key to mitigating their impact. Our study demonstrates that such interactions could play an important role in complex disease systems, such as that represented by Haematobium group schistosomiasis, and how elimination efforts against such diseases are not only challenged by, but themselves may influence, the impact of cross-species transmission dynamics.

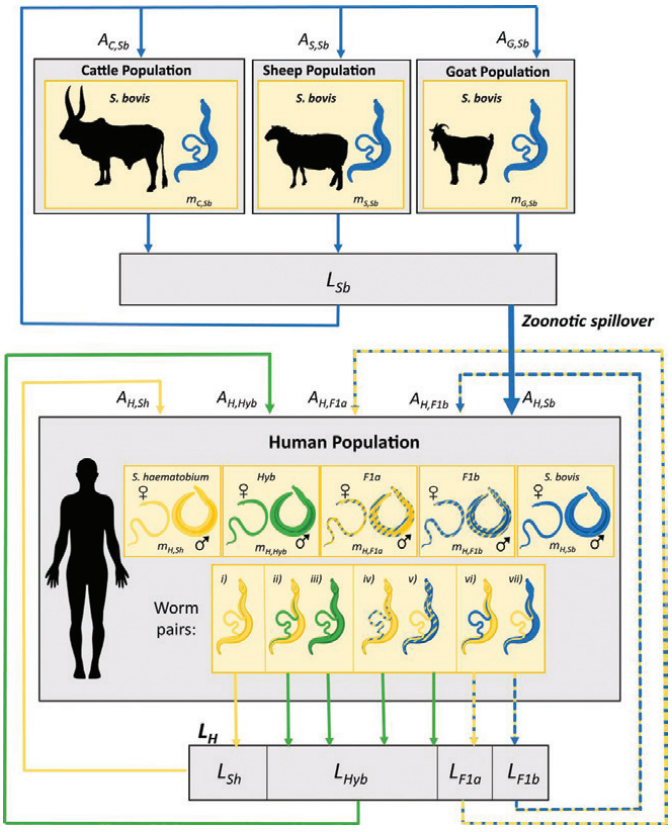

Figure 1. Schistosoma Haematobium group life cycle from a One Health perspective

Schematic of the multihost, multiparasite transmission model: S. haematobium, S. bovis, and Haematobium group hybrids in human and livestock populations.

Population impacts of hypothetical interventions on face-washing water and latrine use on the prevalence of active trachoma among children

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Emma Harding-Esch – London School of Hygiene & Tropical Medicine
With Alexander P. Keil, Matthew C. Freeman, Wilfrid E. Batcho, Amadou A. Bio Issifou, Victor Bucumi, Bella L. Assumpta, Emilienne Epee, Segni Bobo Barkesa, Fikre Seife Gebretsadik, Salimato Sanha, Khumbo M. Kalua, Michael P. Masika, Abdallahi O. Minnih, Mariamo Abdala, Marília E. Massangaie, Abdou Amza, Boubacar Kadri, Beido Nassirou, Caleb D. Mpyet, Nicholas P. Olobio, Mouctar D. Badiane, Balgesa E. Elshafie, Gilbert Baayenda, George E. Kabona, Oscar Kaitaba, Alistidia Simon, Tawfik Q. Al-Khateeb, Consity Mwale, Ana Bakhtiari, Daniel Westreich, Anthony W. Solomon, Emily W. Gower

Background

Trachoma is the leading infectious cause of blindness globally, and it disproportionately affects the world's most impoverished people. Despite the success of coordinated efforts to eliminate it as a public health problem, approximately 136 million people still live in trachoma-endemic districts across 44 countries. While environmental improvements to water, sanitation, and hygiene (WaSH) are a cornerstone of the World Health Organization's SAFE strategy (surgery, antibiotics, facial cleanliness, and environmental improvement) for trachoma elimination, current evidence regarding the role of WaSH on trachoma is inconclusive.

Over 1,300 districts (~100,000–250,000 people) have not yet met trachoma elimination targets. This suggests a need to optimise "SAFE" and its delivery. While the "A" component has a robust evidence base to guide implementation (such as recommendations for starting and stopping points for antibiotics and minimum coverage targets), similar guidance for optimising the delivery of the "E" component has not been developed, largely due to the lack of clear evidence to support specific recommendations and the general difficulty of generating the required evidence through community-randomised trials. "E" guidelines are necessarily less specific and focus primarily on working with community WaSH partners to increase the availability of these services over the "SAFE" intervention period. Previous research has been unable to determine what WaSH-related coverage is needed to optimally prevent trachoma transmission.

Methods

This research leverages data collected from the largest series of infectious disease surveys ever conducted, the Global Trachoma Mapping Project and its successor, Tropical Data. Sixteen countries contributed data from hundreds of cross-sectional surveys for this study. The objective was to explore population-level impacts on the prevalence of inflammatory trachoma among children aged 1-9 years (TF_{1-9}) when district-level WaSH coverages were increased. We used statistical models to explore how TF_{1-9} prevalence would have changed had hypothetical interventions raised district coverages from 5% to 100% for both "nearby" face-washing water (<30 minutes roundtrip collection time) and adult latrine use. A key methodological feature of this study was that we extended traditional modeling techniques with the use of g-computation to estimate *population-level* impacts, which are often closely tied to public health interventions and policy-level decision-making.

Results and discussion

We found that, among districts that had not yet met the TF_{1-9} elimination target (<5% active trachoma), increasing nearby face-washing water and latrine use coverages above 30% were generally associated with consistent decreases in prevalence. Among districts that had previously met the elimination target and were seeking to maintain prevalence below the elimination threshold, results were inconclusive.

Trachoma is targeted for elimination as a public health problem by the year 2030. Along with wider calls for increased inter-sectoral collaboration, the 2021-2030 NTD road map emphasises the need to "increase knowledge through research, and extend partnerships to increase work, specifically on facial cleanliness and environmental improvement to reduce transmission." This research promotes inter-sectoral WaSH/trachoma collaborations and provides evidence regarding potential WaSH-related coverage targets to consider for trachoma elimination which can be tested in future trials to help improve evidence-based WaSH guidance.

Understanding the role of the diagnostic 'reflex' in the elimination of human African trypanosomiasis

Jennifer Palmer, London School of Hygiene & Tropical Medicine
With Caroline Jones, Elizeous Surur, Ann Kelly

Background

To successfully eliminate human African trypanosomiasis (HAT), healthcare workers (HCWs) must maintain their diagnostic acuity to identify cases as the disease becomes rarer. HAT experts refer to this concept as a 'reflex' which incorporates the idea that *diagnostic expertise*, particularly skills involved in recognising which patients should be tested based on signs and symptoms, comes from *embodied knowledge*, which can only be accrued through practice.

Methods

We investigated diagnostic pathways in the detection of 32 symptomatic HAT patients in Nimule, South Sudan. We reflected upon what sorts of knowledge, material and social engagements facilitated the exercising of a HAT reflex in this setting to understand how such practices could be supported in other contexts in preparation for elimination.

Results and discussion

We found that this 'reflex' was not confined to HCWs. Indeed, lay people suggested patients test for HAT in more than half of cases using similar practices to HCWs, highlighting the importance of the expertise present in disease-affected communities. Three typologies of diagnostic practice characterised patients' detection: 'syndromic suspicion', which closely resembled the idea of an expert diagnostic reflex, as well as 'pragmatic testing' and 'serendipitous detection', which depended on diagnostic expertise embedded in hospital and lay social structures when HAT-specific suspicion was ambivalent or even absent. Given that expertise can be conceptualised as the marriage of theoretical knowledge with practical experience of the disease, experiences of diagnosis through the latter two typologies should be valued for the learning that happened by patients and people around them who will be better equipped to recognise syndromic cases in future. As we approach elimination, health systems should embrace both expert and non-expert forms of diagnostic practice that can lead to detection. Supporting multidimensional access to HAT tests will be vital for HCWs and lay people to practice diagnosis and develop their diagnostic expertise.

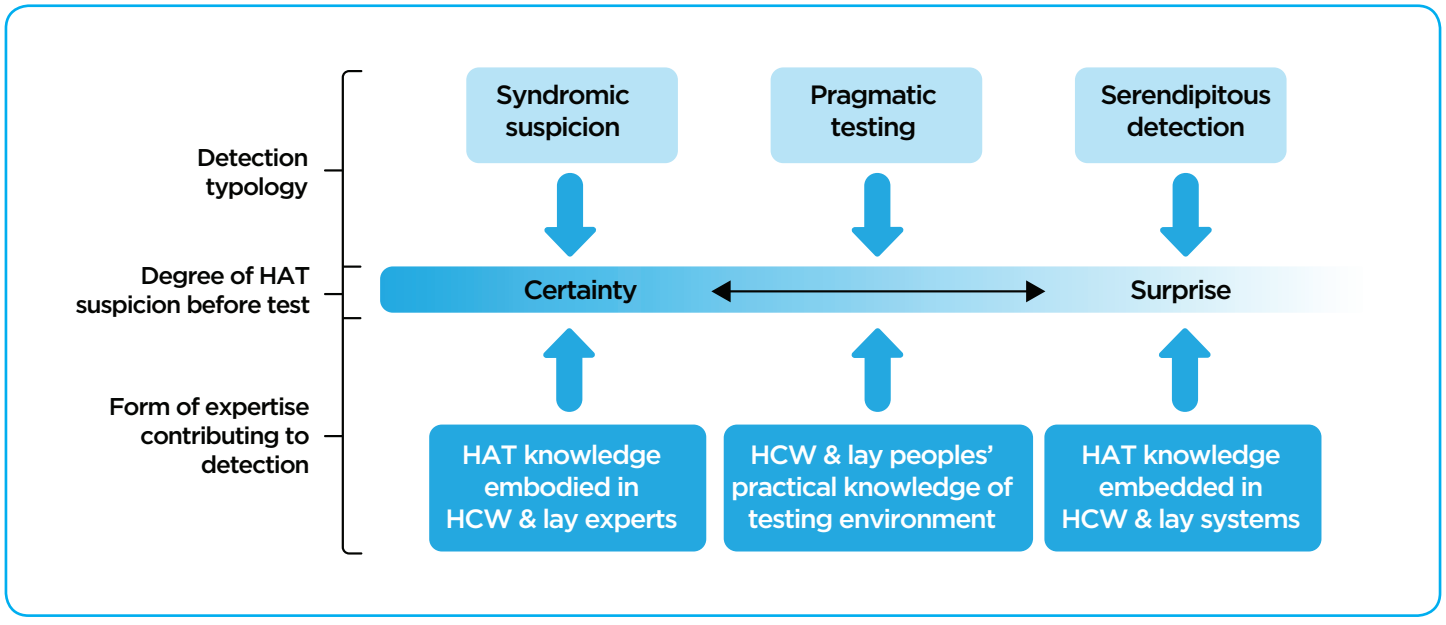


Figure 2. The gradient of certainty versus surprise along which human African trypanosomiasis (HAT) passive case detection happened, indicating the form of expertise which led to diagnosis. (HCW: healthcare worker).

Palmer JJ, Jones C, Surur EI, Kelly AH (2020). Understanding the role of the diagnostic 'reflex' in the elimination of human African trypanosomiasis. Tropical Medicine & Infectious Disease 5(2): 52.

Vaccination against *Ascaris* – How bioinformatics can help us develop reliable vaccines

Francisco Evangelista, Martha Betson, Arnoud van Vliet – University of Surrey
With Scott Lawton

Background

Ascariasis is a parasitic disease caused by the nematodes *Ascaris lumbricoides* and *A. suum.* Able to infect both humans and pigs, *Ascaris* nematodes are the most prevalent soil-transmitted helminth infection (STH) in the world, with an estimated 500 million people affected. Control of ascariasis is based on mass-drug administration (MDA) of deworming drugs (anthelmintics) and improvement of hygiene conditions in affected populations. With STHs being targeted for elimination as a public health problem in the WHO NTD road map 2021-2030, studies highlighting the potential development of anthelmintic resistance in STHs reinforce the need to search for alternative control and treatment methods to complement the ones already in use. Vaccinations for ascariasis have been under development over the past couple of decades and some degree of efficacy has been achieved in mouse and pig models, however no vaccine has undergone human clinical trials.

Methods

With the recent developments and improvements in the quality of *Ascaris* genomes and proteomes, we can use a reverse vaccinology approach to predict vaccine targets that can then be tested in vaccination assays. The reverse vaccinology approach combines genome information and bioinformatic tools to assess the potential that predicted proteins and their respective epitopes have in eliciting immunological responses in the parasite's hosts. After selecting candidate proteins, we combined them *in silico* with already known vaccination targets to form a multi-epitope vaccine. This proposed vaccine then underwent various tests using different bioinformatics tools to assess its safety and immunological characteristics and predict its usefulness before being used in vaccination assays.

Results and discussion

Traditional development of vaccines is hindered by time and the need to use parasite samples to identify vaccine targets. The use of a reverse vaccinology approach allows us to bypass this requirement and reduces the time needed to predict vaccination targets by working with publicly available genomic and proteomic data and analyse it with bioinformatics tools. Using this methodology, we were able to identify four previously untested proteins for their potential to be used as vaccination targets. These newly identified vaccination targets were found to have epitopes that could be incorporated in a multi-epitope vaccine that could provoke a beneficial immunological response on the host. By combining these epitopes *in silico* with those identified from known vaccination targets, we designed a multi-epitope vaccine and tested for its predicted effectiveness. This proposed vaccine showed promise as it was predicted to be antigenic and elicit the desirable immune response, and to be a non-allergenic and stable compound, capable of being cloned and synthetised for further testing.

The use of bioinformatics allowed us to not only predict vaccine targets, but also develop a vaccine *in silico* that can now be tested in vaccination assays. The development of an approved vaccine will help to ensure that the emergence of resistance to anthelmintics does not hinder the elimination of ascariasis as a public health problem by 2030.

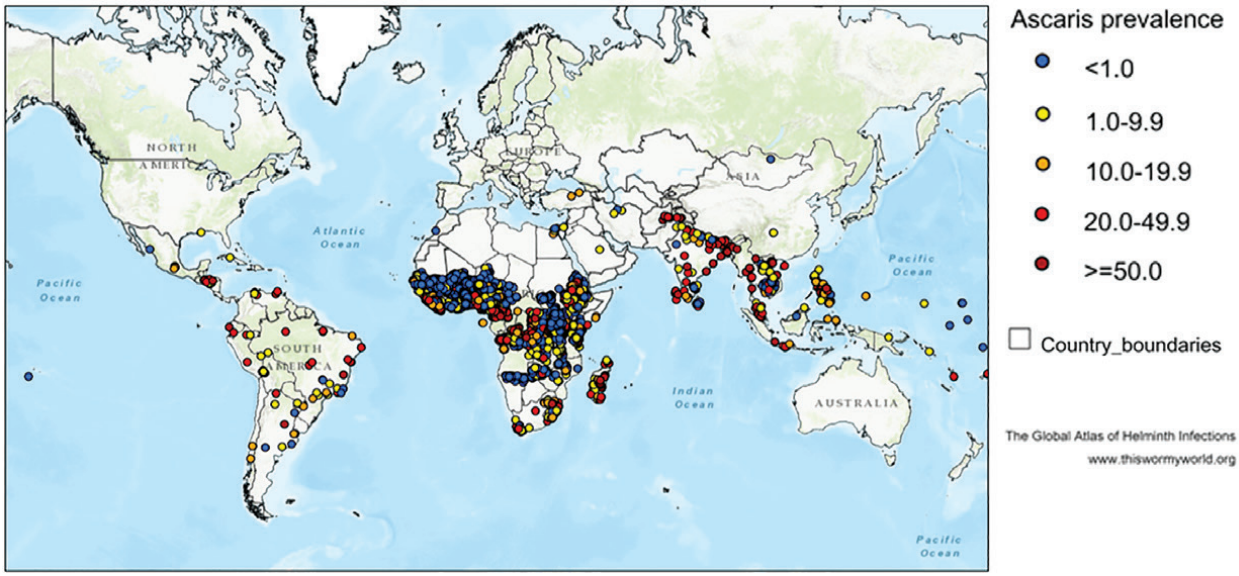


Figure 3. Worldwide *Ascaris* spp. prevalence in humans

Analysing the current cost-effectiveness estimates of preventive chemotherapy strategies for neglected tropical diseases

Hugo Turner and Jaspreet Toor – Imperial College London, on behalf of the study authors

Background

Following recommendations set by the World Health Organization (WHO), preventive chemotherapy (or mass drug administration) is widely used to control several neglected tropical diseases (NTDs). As further investment and increased domestic healthcare spending are needed to continue these programmes, it is important that the cost-effectiveness of preventive chemotherapy is assessed.

Methods

We investigated current estimates on the cost per disability-adjusted life year (DALY) averted of preventive chemotherapy strategies for lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiases (STH) and trachoma. We identified the relevant studies from previously published disease-specific systematic reviews and also carried out an updated search for more recent data published in the peer-reviewed press. We focused on cost-effectiveness estimates reporting cost per DALY averted relative to a do-nothing comparator for the predominantly used preventive chemotherapy strategies for each disease. The predominantly used strategies were assumed to be annual community-wide treatment for lymphatic filariasis, onchocerciasis and trachoma, annual school-based treatment for schistosomiasis and annual or biannual school-based treatment for STH. We also identified areas where further work is required.

Results and discussion

The cost per DALY averted estimates relating to community-wide preventive chemotherapy for lymphatic filariasis and onchocerciasis (US$3–133 per DALY averted) were particularly favourable when compared with the main cost-effectiveness thresholds used for low-income countries and when compared with other interventions conducted in low-income and middle-income countries. The estimates for school-based preventive chemotherapy for schistosomiasis and STH (US$8–1077 per DALY averted) were also generally favourable but more variable. No estimates of cost per DALY averted relating to community-wide mass antibiotic treatment for trachoma were found, highlighting the need for further research.

Although the estimates are encouraging, as the financing of NTD programmes shifts towards a greater contribution from endemic countries, it is important that policymakers consider the cost-effectiveness of these interventions relative to other diseases/priorities in their setting. In terms of this priority setting and subsequent policy decisions, it is important to consider that there are broader socioeconomic benefits of controlling these diseases. For example, a study by Redekop et al. (2017) estimated that there would be notable social-economic benefits from achieving the 2020 targets for these five diseases, both in terms of averted out-of-pocket health expenditure and averted productivity losses (totalling US$229.5 (162.3-344.8) billion in the period 2011–2030 (2015 prices)). This highlights the broader value of investment in these programmes, particularly in the context of universal health coverage, social protection and reducing inequalities, which are not captured fully by the DALYs averted metric.

We also identified several important areas that require further research to improve our understanding of the cost-effectiveness of these programmes; including how the health benefits are estimated (particularly for STH and schistosomiasis), the impact of integrating NTD control programmes, and evaluation of alternative preventative chemotherapy strategies and complementary interventions. Overall, the reported estimates showed that preventive chemotherapy is generally cost-effective, thereby supporting WHO treatment recommendations. These findings are important for informing global health policy and support the need for continuing NTD control and elimination efforts.

Photo credit: Vitor Inhane for Guinea-Bissau Ministry of Health

ZooTRIP: Zoonotic transmission of intestinal parasites: Implications for control and elimination

Martha Betson, Joaquin Prada, Arnoud van Vliet – University of Surrey
With Vachel G Paller, Vicente Belizario Jr, Vachel Paller, Billy Divina, Rico Ancog, David Lloyd, Stephen Gourley, and Jomar Rabajante

Background

Intestinal helminths (gut worms), including soil-transmitted helminths, schistosomes and food-borne trematodes, are extremely common human infections worldwide and have chronic and often insidious effects on human health and child development. Transmission of many intestinal helminths involves a faecal-oral route: worm eggs are shed into the environment by human or animal defecation and individuals become infected through egg ingestion, for example when children play in contaminated dirt. In other instances, infection occurs through ingestion of meat from infected animals. Thus, animals and environmental reservoirs play an important role in transmission, but the contribution of animals to the overall burden of human intestinal helminth infection is poorly understood.

In the Philippines intestinal helminth infections are widespread, particularly in rural communities. Backyard farming is extremely common, bringing people in close proximity to their livestock, and there are many stray dogs and cats. Therefore significant transmission of intestinal helminths from animals to people is likely. This interdisciplinary project funded by the Medical Research Council and the Department of Science and Technology-Philippine Council for Health Research and Development brings together researchers from the UK and the Philippines to assess the contribution of animals and environmental contamination to intestinal worm infection in the Philippines.

Methods

Field studies have been conducted to assess which intestinal helminths are circulating in humans, animals and the environment in eight communities on the island of Mindanao. In addition, demographic and socio-economic data and information on people's knowledge of intestinal helminths have been collected through questionnaires, interviews and focus group discussions. Molecular diagnosis and genetic characterisation of intestinal helminths in samples collected during the field studies is ongoing and whole genome sequencing of worm isolates is being undertaken. Mathematical models incorporating data from the field studies and genetic data from the helminth samples are being developed to quantify the contribution of animals and environmental contamination to transmission of helminths to humans and predict the effects of different control strategies. An evaluation of the socio-economic and health impacts of infections in the Philippines is also being carried out and policy recommendations will be developed based on model outcomes and the results of the socio-economic analysis.

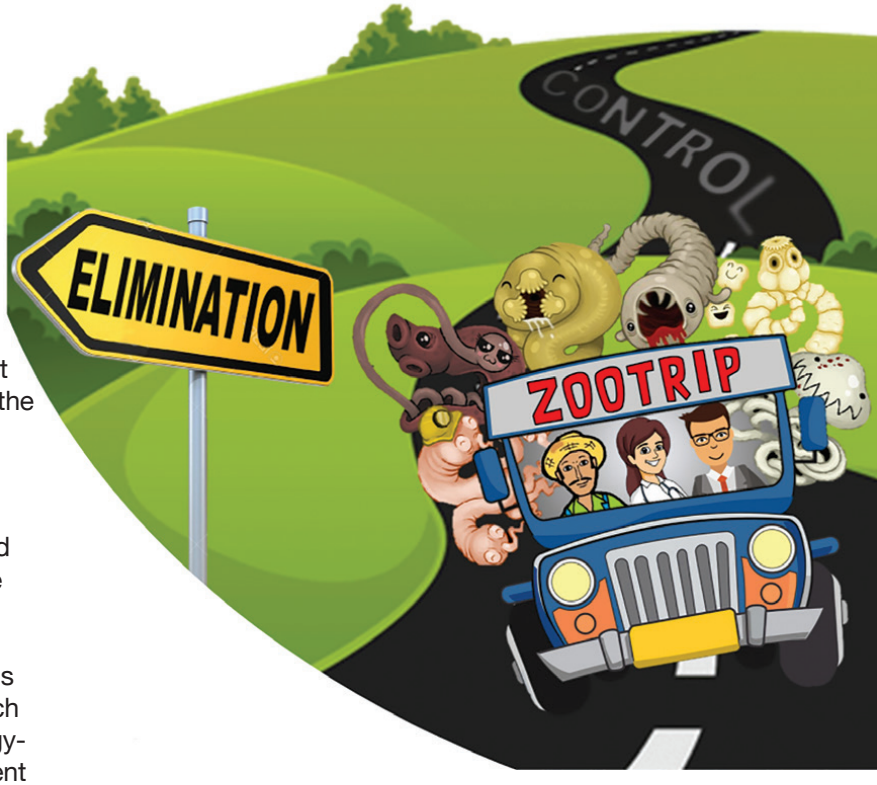


Image credit: Modesto Z. Bandal Jr.

Results and discussion

Initial results indicate a significant burden of intestinal helminth infections, including soil-transmitted helminths, schistosomes and food-borne trematodes, circulating in humans, animals and the environment on Mindanao, with potential for zoonotic transmission. This is despite ongoing school-based deworming programmes in this region.

By embracing a One Health approach this project is shedding new light on the epidemiology of intestinal helminth infections in humans and animals and quantifying the contribution of animals to human infection. It is anticipated that as control activities for intestinal helminths are scaled up in line with the WHO NTD road map, zoonotic and environmental reservoirs will become increasingly significant. It is hoped project findings will enable evaluation of existing control strategies and development of new ones, ultimately leading to increased effectiveness and sustainability of intestinal helminth control in the Philippines and worldwide and thus contributing to achievement of the 2030 NTD road map targets.

PROJECT IN FOCUS: TROPICAL DATA

What is Tropical Data?

The Global Trachoma Mapping Project (GTMP) conducted baseline surveys in all accessible suspected trachoma-endemic districts worldwide, examining over 2.6 million people across 29 countries between 2012 and 2016. Global partners recognised the need to further the work started within GTMP, and in 2016, Tropical Data was launched.

Tropical Data supports countries worldwide to collect high-quality, globally standardised prevalence data on neglected tropical diseases (NTDs), with a focus on trachoma. Health ministries are supported, free-of-charge, from the start to the end of the survey process to ensure quality assurance and quality control at every step. This process includes epidemiological support for protocol writing so that surveys are conducted using World Health Organization (WHO)-approved methodologies, support from our global network of certified trainers for survey team training, and support with data collection using the dedicated app, data storage, cleaning, and analysis.

Health ministries own the survey process and data generated. The data generated translate directly into programmatic decision-making and are used as evidence in elimination dossiers submitted to WHO. Tropical Data is a partnership between endemic countries, their partners, WHO, and a core team made up of the London School of Hygiene & Tropical Medicine, the International Trachoma Initiative, RTI International, and Sightsavers.

What has Tropical Data achieved?

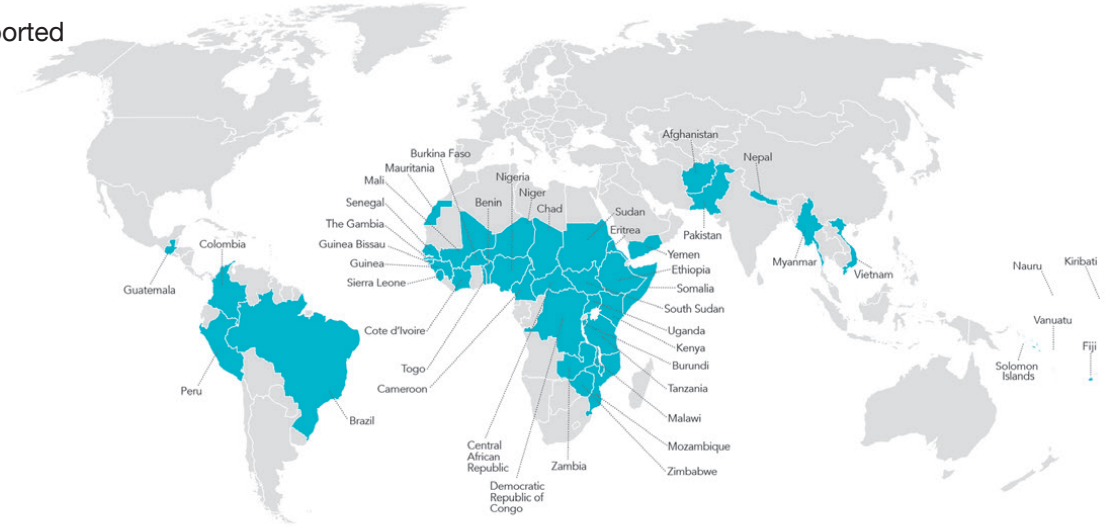
In 2021, Tropical Data celebrated its fifth birthday, having supported 45 countries to carry out baseline, impact, surveillance and trachomatous trichiasis-only surveys **in 2,200 evaluation units** (generally equivalent to a district), **examining over 6.8 million people:** a huge acceleration in progress towards trachoma elimination. Tropical Data has supported surveys in some of the most difficult-to-reach communities, ensuring no one is left behind. Since 2012, the work supported by GTMP and Tropical Data combined means that **one person is examined for trachoma every 26 seconds.**

As part of this process, Tropical Data supported eight international trainings of trainers and over **150 national level training workshops,** and **trained over 2000 trachoma graders and recorders from five continents.** Tropical Data has generated a number of online resources to support health ministries better understand and use their data, including an online publications writing workshop.

What are Tropical Data's future plans?

Tropical Data conducts and participates in operational research in order to contribute new scientific evidence, enabling the team to continually learn, review, and adapt processes to best support health ministries. Examples of existing projects include conducting integrated surveys of several NTDs, testing for ocular *Chlamydia trachomatis* infection and anti-*C. trachomatis* seroprevalence (Harding-Esch et al., 2021), and exploring the enhanced role photography could play in training survey teams and fieldwork (Naufal et al., 2021).

Figure 4. Countries supported by Tropical Data



How to find out more

For more information on Tropical Data, visit our website (www.tropicaldata.org) and resources page (https://tropicaldata.knowledgeowl.com/help) or email us at admin@tropicaldata.org.

Challenges for transmission break programmes: monitoring individual non-treatment to mass drug administration

Rosie Maddren – Imperial College London

Soil-transmitted helminths (STH) and schistosomiasis (SCH) are two of the twenty recognised neglected tropical diseases (NTDs) that affect over a billion lives in tropical and subtropical climates worldwide. These parasitic helminth infections disproportionately affect low socioeconomic communities, and are intrinsically linked to poverty, and poor sanitation. Treatment is relatively simple, through the bi- or annual mass drug distribution (MDA) of deworming preventative chemotherapy (PC). Repeated treatment is required for control since these helminth infections do not induce strong acquired immunity. Reinfection can occur rapidly if individuals are exposed to infectious larval or egg stages, especially in communities with poor access to sanitation infrastructure.

In Ethiopia, 41 million people are estimated to be infected by either SCH or STH. The Ethiopian Public Health Institute (EPHI) launched a national control programme for STH and SCH in 2015, employing school-based deworming in endemic regions. As a result of this repeated MDA in endemic communities, some regions in Ethiopia are recording low parasite prevalence levels (sub 10%), and programmatic focus will need to move from transmission control to transmission break. Wolaita, found in the Southern Nations, Nationalities, and People's Region (SNNPR) of Ethiopia is one such area with low STH and SCH parasite levels, and is the site of the Geshiyaro Project.

Over the course of 5-years, the Geshiyaro Project aims to define the most efficient intervention(s) for STH and SCH control programmes, delivered via existing government-lead infrastructure for MDA delivery. The project is investigating the impact of two interventions on the efficacy of STH and SCH control. The first is a community-wide MDA regime targeted with achieving 80-90% coverage, expanding on the current government-recommended SAC-focused protocol. Secondly, water, sanitation and hygiene (WaSH) hardware with behaviour change communication (BCC) is provided to ensure community utilisation of infrastructure, and thus reducing re-infection from the environment after MDA.

A population census was conducted at the baseline, whereby all consenting participants provided their fingerprint alongside their demographic record. As a result, each subsequent interaction participants have with MDA activities can be tracked year on year. Particular attention has been paid to the analysis of individual non-treatment in the studied villages (kebeles) at each round of MDA. Such factors of compliance of particular interest to this research include; age, gender, religion and other behavioural and social variables.

There are two possible groups of non-treatment at MDA; 1) participants never reached by drug distributors, or 2) once reached, participants who refused the offered drugs. Identifying the respective demographic, if any, of each group will be crucial for control programmes. Increased efforts can be targeted to the defined populations, increasing chances of improved drug coverage. This will also treat the presumed reservoir of infective material these populations hold, currently re-infecting treated participants. Harnessing this information will enable control programmes such as the Geshiyaro Project in reaching their transmission break targets efficiently.

A novel metabarcoding deep amplicon sequencing tool for *Trypanosoma* surveillance program

Dr Umer Chaudhry and Dr Martha Betson – University of Surrey
With Professor Dr Kamran Ashraf and Professor Dr Neil D. Sargison

Background

The sensitivity and specificity of diagnostic tests for trypanosomiasis have been improved in recent years, but the reliability of infection reports vary considerably between affected areas because of the different methods used. A universal single test to detect all *Trypanosoma* species with equal reliability is needed to resolve these issues and improve surveillance systems. Advances in molecular techniques have the potential to open new areas of research and to improve surveillance of separate *Trypanosoma* species as previously demonstrated by the concept of a 'haemoprotobiome' for the quantification of the bloodborne protozoan species. The aim of the present study was to describe the species composition of *Trypanosoma* communities present in blood samples collected from animals.

Methods

The project involved designing metabarcoding Illumina Mi-Seq primers and developing an appropriate bioinformatic pathway to quantify the sequence reads generated for the different *Trypanosoma* species present. The validity of the approach was tested using test pool samples generated from known proportions of available positive control *T. brucei, T. congolense, T. vivax,* and *T.theileri* samples. The approach was then used to analyse the composition of *Trypanosoma* species in field blood samples collected from seven endemically infected regions.

Results

First, four phenotypically verified *Trypanosoma* species were used to prepare test DNA pools derived from different numbers of parasites to evaluate the method's detection threshold for each of the four species and to assess the accuracy of their proportional quantification. Having demonstrated the accurate determination of species composition in *Trypanosoma* communities, the method was applied to determine its detection threshold using blood samples collected from cattle with confirmed *Trypanosoma* infections based on a PCR assay. Each sample showed a different *Trypanosoma* species composition based on the proportion of MiSeq reads. Finally, we applied the assay to field samples to develop new insight into the species composition of *Trypanosoma* communities in cattle, camels, buffalo, horses, sheep, and goat in endemically infected regions of Pakistan. We confirmed that *T. evansi* is the major species in Pakistan and for the first time showed the presence of *T. theileri.*

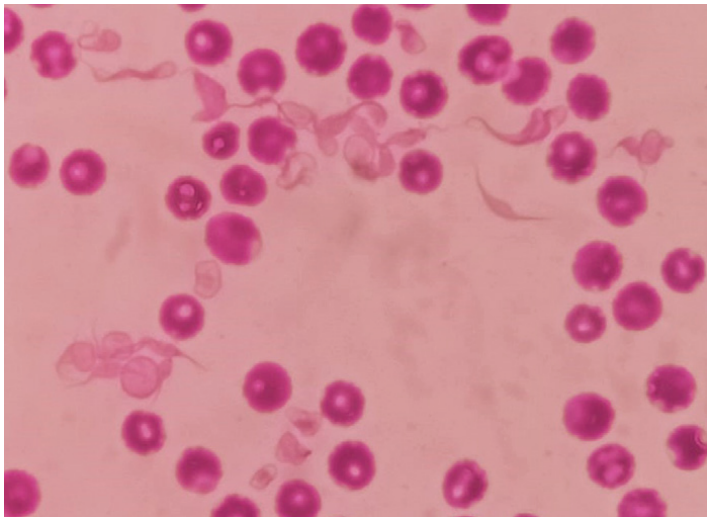


Figure 5. Trypanosoma spp. (Cattle)

Discussion

Despite distinct differences between factors that influence the rate and success of completion of the life cycles of different *Trypanosoma* species, there is considerable overlap between the vectors, biological niches and host ranges. The similarities in these characteristics between species imply that the emergence of one *Trypanosoma* species in an area could be indicative of the risk of emergence of other species within the same area. Therefore, surveillance of different *Trypanosoma* species is crucial for the successful control of trypanosomiasis, by providing insights into the host distribution, co-infection, transmission dynamics and the multiplicity of infection. Trypanosomiasis has a major impact on food and milk production losses in low and middle-income countries, where efficient agriculture is a priority according to the UN Sustainable Development Goals. The World Health Organization and the Food and Agriculture Organization have developed strategies to control trypanosomiasis in humans and livestock in endemic areas. These require a better understanding of the distribution of different *Trypanosoma* species and improved predictions of where they might appear in the future, based on accurate diagnosis and robust surveillance systems.

Understanding the incidence and timing of rabies cases in domestic animals and wildlife in south-east Tanzania in the presence of widespread domestic dog vaccination campaigns

Sarah Hayes, Imperial College London
Christl A. Donnelly, Imperial College London and University of Oxford
With Kennedy Lushasi, Maganga Sambo, Joel Changalucha, Elaine Ferguson, Lwitiko Sikana, Katie Hampson, Pierre Nouvellet

Background

'Zero by 30' is a global strategic plan to achieve zero human deaths from dog-mediated rabies by 2030. Despite the existence of safe and effective vaccines, rabies continues to kill an estimated 59,000 people each year, primarily in low- and middle-income countries. Most of these deaths are due to bites from domestic dogs. Controlling rabies in the animal populations responsible for transmitting the disease to people is an important aspect of rabies interventions. In this study, undertaken in an area of southern Tanzania with an unusually high proportion of jackal rabies cases, we seek to optimise interventions by understanding factors associated with the incidence and timing of animal rabies cases.

Methods

Data on the incidence of probable rabies cases in domestic and wild animals were collected between January 2011 and December 2018 in thirteen districts of south-east Tanzania where jackals comprise over 40% of reported rabies cases. Five mass dog rabies vaccination campaigns were undertaken in the study area between 2011 and 2016. Negative binomial generalised linear models were used to identify features associated with the annual incidence of probable rabies cases in domestic dogs and jackals whilst generalised additive models were used to investigate the presence of temporal and/or seasonal trends.

Results and discussion

The incidence of rabies cases in both dogs and jackals decreased over the study period, coincident with implementation of widespread dog vaccination. However, following cessation of vaccination campaigns in 2016, we note a slight increase in the incidence of domestic dog rabies cases at the end of the study period. Increased domestic dog vaccination was associated with a marked decrease in the incidence of rabies in both domestic dogs and jackals. A 35% increase in domestic dog vaccination coverage (the median coverage achieved during campaigns) during the three-years prior to cases occurring was associated with an 86.4% decrease (95% CI 76.0–92.5% decrease) in dog rabies incidence and a 90.6% decrease (95% CI 82.7%– 95.1% decrease) in jackal rabies incidence. A 10% increase in the land covered by savannah was associated with a 50.4% increase (95% CI 22.9% – 86.8% increase) in the incidence of jackal rabies cases.

Data regarding jackal numbers were not available for the study area but the area of land covered by savannah may be a proxy for jackal numbers reflecting increasing area of suitable jackal habitat. Thus, the level of rabies reported in jackals may be in part simply due to their presence and number in an area. A statistically significant common seasonality was identified in both species.

This study demonstrates clear evidence for the use of domestic dog vaccination to reduce animal rabies cases and provides further support for its use as an integral component of the Zero by 30 strategy. The finding of a common seasonal trend in the incidence of rabies in both dogs and jackals suggests that it may be possible to optimise the timing of vaccination strategies in this region to achieve the maximum impact, but further research is needed before recommendations can be made.

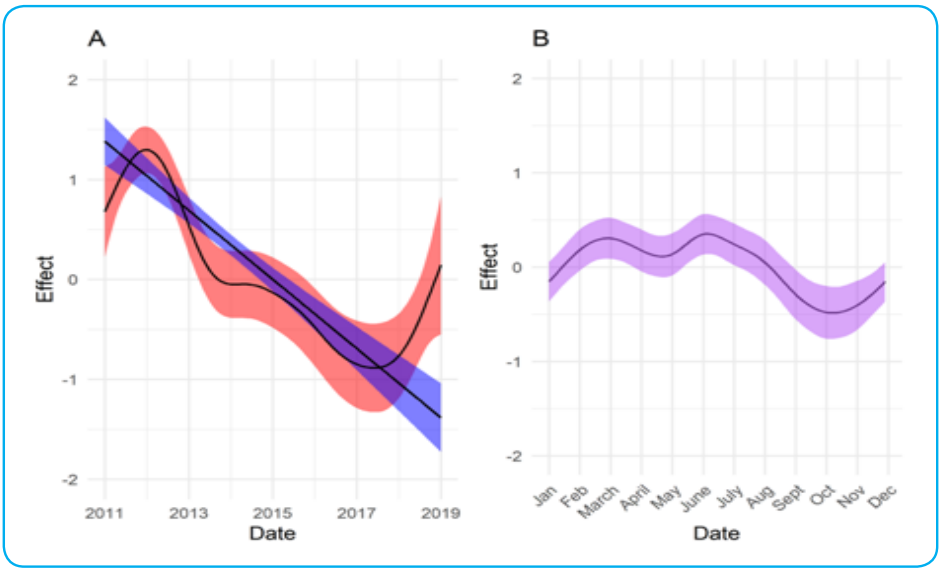


Figure 6. The overall and seasonal trend components of the best-fitting generalised additive model to rabies incidence.

A) Relative effect of overall trend in incidence in dogs (red) and jackals (blue) over the course of the study period. B) Relative effect of common seasonal trend for both species. Estimates are shown as solid lines and 95% confidence intervals as shaded regions.

Clinical development of an orally bioavailable drug for the treatment of cutaneous leishmaniasis

David Clark – St Georges University of London, on behalf of The TT4CL consortium

The Targeted Treatment for cutaneous Leishmaniasis consortium (TT4CL) is working on a clinical development programme for D121 as new, safe and affordable therapies for cutaneous leishmaniasis are urgently needed.

Background

Cutaneous leishmaniasis (CL) is a poverty-related neglected tropical disease, caused by *Leishmania* parasites. It is primarily transmitted by the bite of infected, blood feeding, sand flies. A lesion forms at the site of the bite which then develops into ulcers, often becoming super infected by bacteria. There is no effective and cheap oral treatment for CL, which can result in long-term lesions and disfigurement. The parasites and their vectors are widespread, including in: South America, the Mediterranean littoral, parts of sub-Saharan Africa and the Middle East – encompassing a very large at-risk human population. Notably canines can also be infected and act as a reservoir. The World Health Organization estimates that there are between 1-1.5 million human cases globally of CL per year causing both life changing disability to individuals and being a significant burden in endemic populations (disability-adjusted life years).

TT4CL brings together partners in Iran (where CL is endemic and a considerable disease burden), Germany, UK, Netherlands and Belgium. These groups encompass a wide range of expertise including pharmaceutical SMEs, academic fundamental research (both *in vitro* and *in vivo*), clinical trial research and front-line clinical experience. An independent advisory board with leaders in the fields of drug development, ethics and regulatory matters, business development and infectious diseases assists and guides our drug development program on matters of strategic health policy and commercialisation.

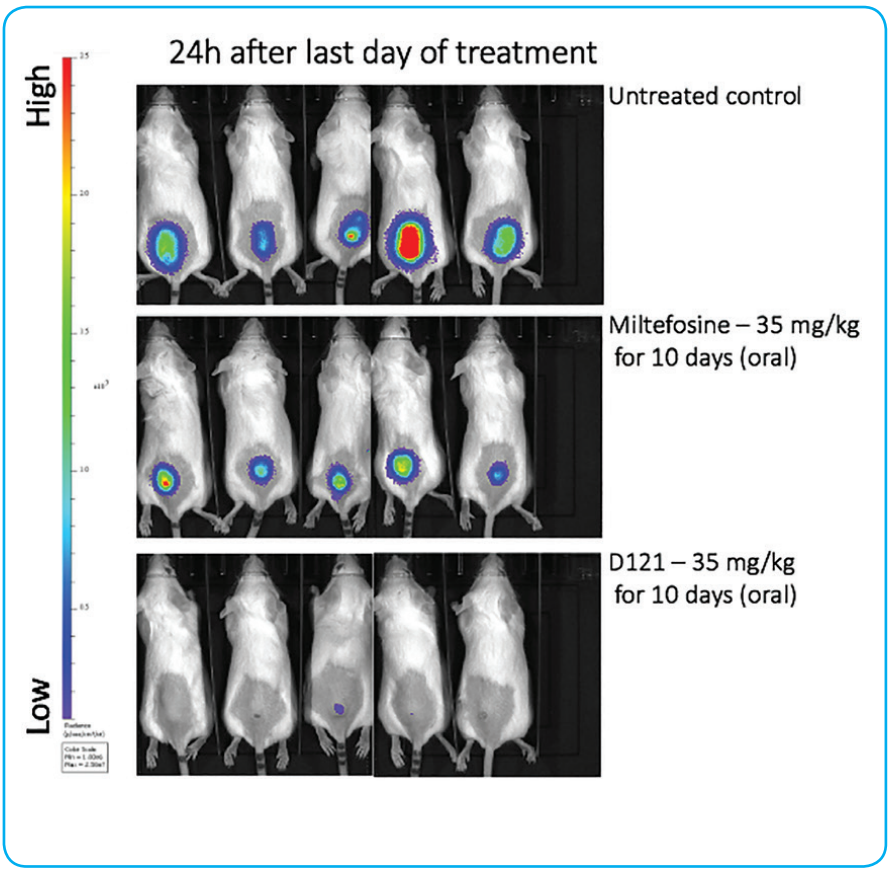
Methods

In vivo efficacy in mice and pharmacokinetic modelling, stability testing (appropriate for tropical climates) and drug formulation (as an immediate-release tablet) have been completed. A Phase I study aims to start recruitment in early 2022. New clinical isolates of *Leishmania* will also be assessed *in vitro* in Iran for susceptibility to the active pharmaceutical ingredient (API), D121, and compared with the standard in-use drugs: pentavalent antimonials, amphotericin B and miltefosine. This project received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 815622.

Results and discussion

The API is pharmacologically active *in vitro* and *in vivo* (in murine and canine models) against different CL-causing *Leishmania* species, and well tolerated in single administrations in humans. Its utility is being compared in the animal models alongside miltefosine, the only oral therapeutic for CL. In an *in vivo* Imaging System (IVIS) combined with bioluminescent *Leishmania* parasites, D121 outperforms this older drug; reducing the cutaneous parasite load in contrast to increased parasite loads in controls [see figure]. The consortium is soon to recruit healthy human participants into a Phase I trial to assess tolerability and dosing of a 21-day administration regimen, which will be used to inform subsequent clinical development.

In vitro and *in vivo* assays with different academic partners have shown that D121 potentially has further utility as an antiparasitic agent beyond Leishmaniasis, for example, as an antifungal agent. The results from our Phase 1 studies with oral formulation of D121 will accelerate the clinical research for other neglected indications.



African schistosome molecular characterisation

Bonnie Webster, Muriel Rabone, John Archer, David Rollinson, Fiona Allan, Tom Pennance,
Aidan Emery – Natural History Museum
Shannan Summers – London School of Hygiene & Tropical Medicine

Background

Thirteen *Schistosoma* species are transmitted in Africa, with definitive hosts ranging from hippopotami, bovids, nonhuman primates, rodents and humans. Routine methods for the molecular characterisation of schistosome populations collected from both intermediate (snail) and definitive (mammalian) hosts supports our understanding of African schistosomiasis. The mitochondrial *cox1* DNA region is a commonly used biomarker for species identification and also population genetic analyses. DNA barcoding of populations has revealed a striking contrast between the two major human species, *S. mansoni* (intestinal) being highly diverse and geographically structured, whereas *S. haematobium* (urogenital) has extremely low genetic diversity with two divergent groups. In our latest study we used *cox1* data to investigate the geographical and host structuring of *S. bovis*, infecting livestock and rodents, together with *S. haematobium-bovis* hybrids, commonly found in humans raising concerns of zoonoses.

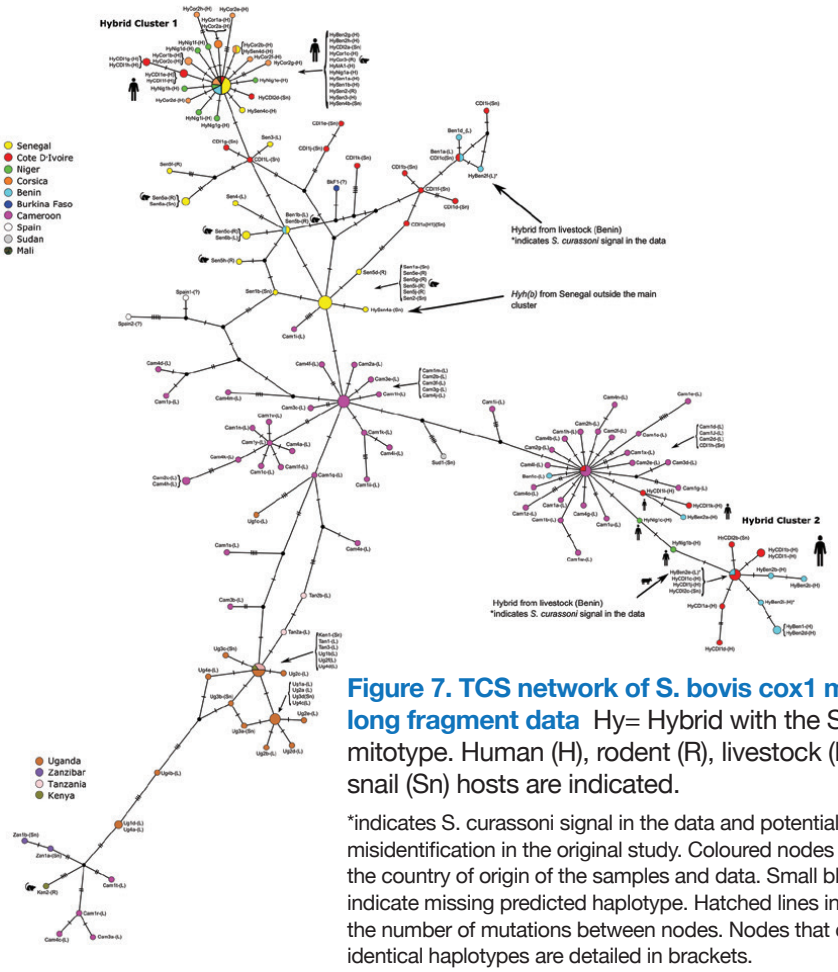


Figure 7. TCS network of S. bovis cox1 mitotype long fragment data Hy= Hybrid with the S. bovis mitotype. Human (H), rodent (R), livestock (L) and snail (Sn) hosts are indicated.

*indicates S. curassoni signal in the data and potential misidentification in the original study. Coloured nodes indicate the country of origin of the samples and data. Small black nodes indicate missing predicted haplotype. Hatched lines indicate the number of mutations between nodes. Nodes that contain identical haplotypes are detailed in brackets.

Methods

The *cox1* sequences analysed were either published or generated from samples from the Schistosomiasis Collection at the Natural History Museum (SCAN). Data was available from samples from hosts including humans, cows, goats, sheep, rodents and snails, from a broad geographical range including Europe, West, Central and East African countries. *cox1* data were aligned and a TCS haplotype network analysis performed using PopART (Population Analysis with Reticulate Trees) (Version 1.7), to investigate population structuring.

Results

The dataset included 119 published and 59 new *cox1* *S. bovis* mitotypes, from *S. bovis* or *S. haematobium-bovis* hybrids. The host range for the *S. bovis* samples encompassed rodents, livestock and *Bulinus* snails. The *S. haematobium-bovis* hybrids were almost entirely from humans and *B. truncatus* snails, indicating more stringent restricted host use although sequences were available from three rare *S. haematobium-bovis* hybrid samples from non-human mammalian hosts, a single hybrid from a rodent host in Senegal and two suggested hybrids from livestock from Benin. The *cox1* dataset formed a complexed and diverse haplotype network for S. bovis but, apart from two haplotypes, all (n=41) data from samples identified as *S. haematobium-bovis* hybrids formed two distinct genetic clusters. These clusters also showed little diversity with the majority being identical mitotypes from different hosts and countries. Additionally, the clusters did not form part of the *S. bovis* network, which showed geographical structuring into West, Central and East African *S. bovis* populations.

Discussion

The extremely low genetic diversity within the *S. haematobium-bovis* hybrids suggests genetic selection /or bottlenecking may occur during hybridisation. There was also little apparent mixing between hybrid and *S. bovis* populations, suggesting the hybrid genetic signatures we see in our human hosts may be a result of past introgression, as also highlighted within recent genomic analyses. Further studies are warranted to further elucidate the risk factors associated with these hybrid populations, especially the possibility of zoonotic transmission. *S. bovis* appears to be a diverse species with a level of geographical structuring across different geographical zones. Populations from different hosts are clearing mixing and there also appears to be cross over between adjacent regions, probably supported by livestock movement.

How important is the spatial movement of people in attempts to eliminate the transmission of human helminth infections by mass drug administration?

Ben Collyer – Imperial College London

Background

Human mobility is the principal cause of the spatial spread of many infectious diseases. Therefore understanding the role of movement in ongoing transmission is crucial for predicting the future dynamics of infection under locally delivered control interventions. The effect of mobility can be particularly important when it is uncertain whether, in a localised area, ongoing infection is self-sustainable, which may be the case when there is large spatial variation in endemicity or human host population size. Such variation is often observed in regional surveys of helminth worm infections, as seen, for example, in soil transmitted helminth infection (STH) data collected during the TUMIKIA Project (Kenya) and DeWorm3 (India, Malawi and Benin) randomised control trials. Large differences between nearby locations can exist both at baseline, and after repeated rounds of mass deworming.

Methods

We have created a modelling framework to describe the transmission of hookworm infection over a large geographical region with realistic patterns of human mobility. Space is discretized into a grid of 3km x 3km cells, and in each cell local transmission is modelled using a stochastic individual based model. Our framework incorporates people movements by including a gravity model to mathematically describe the rate of movement of people between different locations. A gravity model is a simple mathematical representation of a flow, in our case of people, where the flow rate between every pair of locations depends on the population sizes of the source and destination, and the distance between them. We have used data collected by the TUMIKIA Project, conducted in Kwale county, Kenya, between 2015-2018 to estimate the model parameters and validate the generated predictions.

Results and discussion

When our model parameters are estimated using baseline data recorded by the TUMIKIA project, our model closely reproduces the decline in prevalence observed in the survey data over four rounds of repeated mass drug administration (MDA). Perhaps more significantly, we found that including movement can have a large effect on the long-term chances of elimination. We simulated a hypothetical scenario where repeated rounds of high coverage MDA are administered to reduce hookworm infection in Kwale county to a low level of prevalence, that in the absence of human movement, leads to elimination of transmission after stopping MDA (Figure 8). When human movement is included, we find that widespread resurgence of infection is possible after MDA has stopped. This may have important implications for the design of mass chemotherapy programmes and highlights the need for surveillance for helminth diseases after successful control programmes have ended.

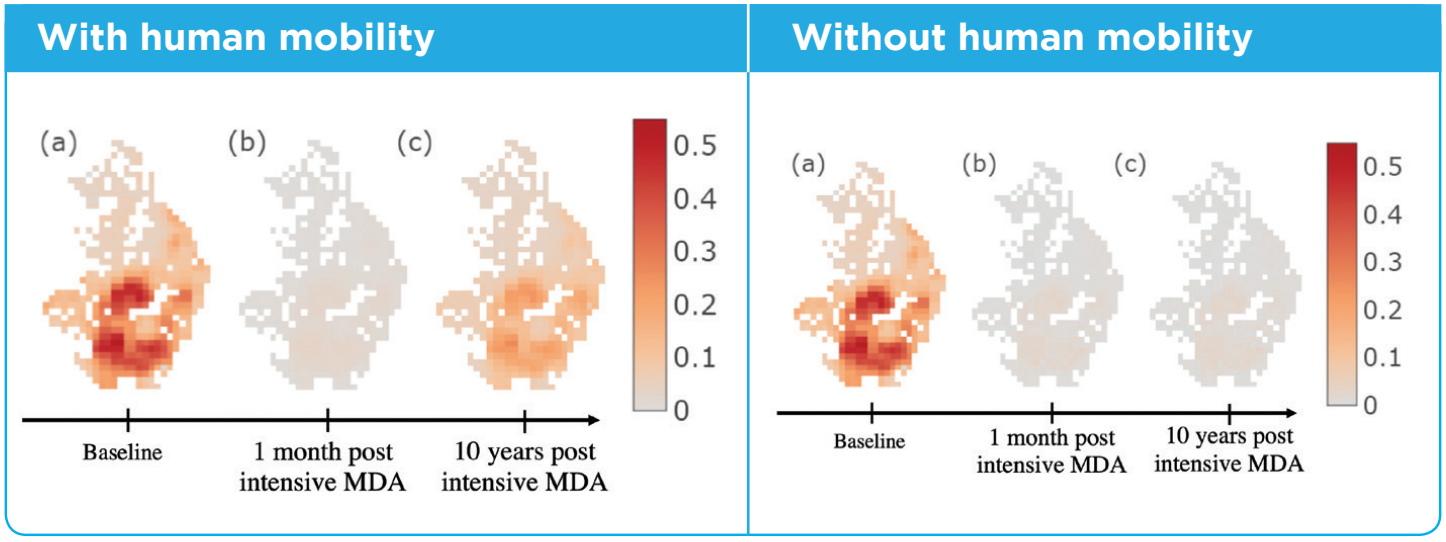


Figure 8. Model results, with and without human mobility, from a hypothetical scenario where intensive MDA is administered to treat hookworm infection. The plots show the mean prevalence of hookworm infection at (a) baseline (b) after 16 rounds of high coverage biannual MDA (c) 10 years after MDA has stopped.

Population genomic analyses of endemic *Schistosoma mansoni*

Duncan Berger, Dr Matt Berriman and Dr James A. Cotton – Wellcome Sanger Institute
Professor Joanne P. Webster – Royal Veterinary College, University of London
with Dr Tom Crellen, Dr Poppy Lamberton, Dr Fiona Allan, Dr A. Tracey, Dr J. Noonan, Dr Narcis Kabatereine, Dr Edridah Tukakebwe, Moses Adriko, and Dr Nancy Holroyd

Background

Schistosomiasis is a neglected tropical disease (NTDs) that infects over 236 million people across 78 countries, primarily in sub-Saharan Africa (SSA). The mainstay for control of schistosomiasis has been the use of anthelmintic treatment in the form of praziquantel (PZQ) monotherapy, distributed as part of mass-drug administration (MDA) programmes. The World Health Organization road map for NTDs 2021-2030 has set clear goals for the control and elimination of schistosomiasis which requires extending MDA to all endemic populations and age groups. Whilst MDA programmes have, in general, been effective at reducing infection prevalence and/or intensity, their effect on parasite transmission and evolution remains poorly understood. With the expected escalating usage of PZQ for MDA, the aim of this study was to characterize how *Schistosoma mansoni* populations, the main causative agent for urogenital schistosomiasis across SSA, South America and beyond, are changing and adapting to the long-term usage of PZQ and how this might impact the long-term success of schistosomiasis control and elimination strategies.

Methods

As part of a series of ongoing collaborative projects this study will generate whole-genome sequence (WGS) data of the major human infective species, *S. mansoni*, sampled from endemic regions. To date we have sequenced individual larval stage parasites from infected attending primary school in regions of either long-term MDA pressure (Bwondha, Bugoto, Musubi, 8–9 previous annual rounds) or short-term MDA pressure (Kocoge, 1 previous round) from two Ugandan districts ~100 km apart. Previous analyses have indicated a reduction in PZQ efficacy amongst children under long-term MDA regions, and many of the donors in this study exhibited low parasite clearance phenotypes after praziquantel treatment, indicative of PZQ-resistant parasites.

Results and discussion

Whole-genomes of 198 *S. mansoni* larvae from 34 Ugandan donors have been sequenced and included nine previously-sequenced samples. Parasites infecting donors from Lake Victoria, a transmission hotspot, formed a diverse unstructured population suggestive of a high rate of parasite movement across Lake Victoria (Fig. 1). We found no evidence of a recent population contraction, suggesting that long-term praziquantel usage has not significantly altered the dynamics or transmission of *S. mansoni* in this region. When we examined parasite populations from infected individuals we found that, while a single round of treatment was effective at reducing the intensity of infections, there was no evidence that the overall diversity of these parasite populations was reduced. These results suggest that the expected reductions in the frequency of schistosomiasis as a result of MDA could be rapidly reversible through the long-range transmission of parasites from high prevalence hotspots (and potential zoonotic reservoirs). We also found evidence of positive selection acting on multiple gene families, suggesting recent adaptation to MDA. This included some members of gene families previously implicated in PZQ mechanism(s) of action, but detected no clear evidence of resistance conferring mutations in the most known drug-resistance genes. Taken together, these findings strongly suggest that, at present, current MDA pressure with PZQ is not sufficient to cause a substantial decline in parasite populations or select for drug-resistant parasites. However, this is likely to change over the next few years and so as efforts to eliminate schistosomiasis intensify, our study provides a foundation for genomic surveillance of this major human parasite.

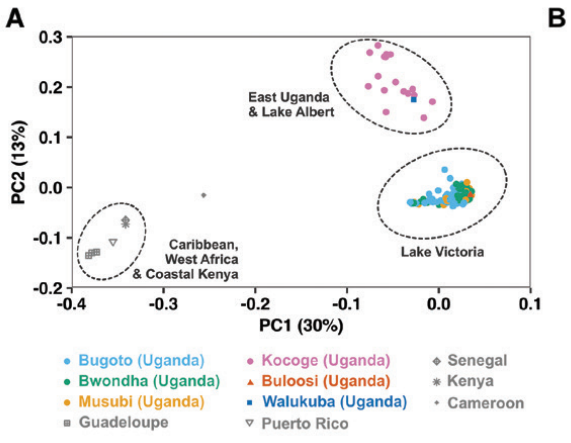


Figure legend: Population structure and diversity of S. mansoni. A). Principal component analysis (PCA) of genetic differentiation between 207 S. mansoni samples. Points represent individual samples and are coloured by location of origin: Lake Victoria (Bugoto, Bwonda, Musubi, Buloosi), East Uganda (Kocoge), Lake Albert (Walukuba), Kenya, Cameroon, Puerto Rico, Guadeloupe. B). Neighbour-joining phylogeny showing the relatedness between all 207 samples, branches are coloured based on the school or region where sample collection occurred.

The eco-epidemiology of snakebite and the benefits of redefining as a zoonosis

Dr Gerardo Martin – Imperial College London
Dr Kris Murrary – Imperial College London, London School of Hygiene & Tropical Medicine

Background

Snakebite is still one of the deadliest and neglected of the class-A neglected tropical diseases, which also makes it one of the least understood. Despite being non-infectious, venom transmission is remarkably similar to rabies' zoonotic transmission from dogs to humans, although snakebite is simpler because venom prevalence, unlike rabies, is 100% among its hosts (medically-relevant snakes). The main obstacle to better understand snakebite is the cryptic nature of most venomous snakes. To show the benefits of redefining snakebite as a zoonosis we estimated the geographic patterns of snakebite envenoming incidence using mathematical models for directly transmitted zoonotic infectious diseases.

Methods

We analysed published geostatitical estimates of snakebite incidence in Sri Lanka from a community survey, using estimates of the geographical abundance of seven venomous snakes alongside land cover maps as surrogates of occupational and socioeconomic risk factors and human population density. To estimate patterns of venomous snake abundance we used occurrence records of the seven snake taxa that occur in Sri Lanka *(Bungarus caeruleus, B. ceylonicus, Daboia russelli, Echis carinatus, Hypnale spp., Naja naja and Trimeresurus trigonocephalus).* Snake occurrence data were analysed with point process models in relation to the climatic conditions considered optimal for each species and land cover-derived variables. We combined the snake abundance estimates with human population density and land cover using a series of mathematical models representing human-snake contacts.

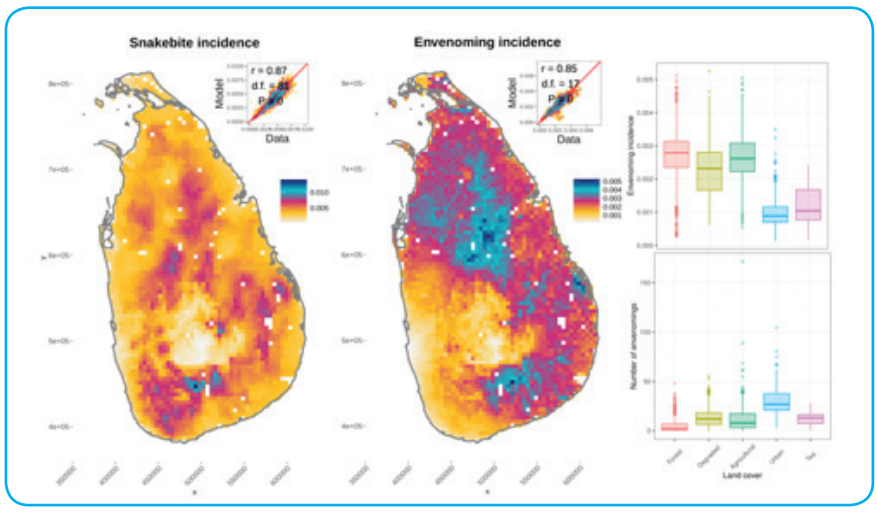
Results and discussion

Snakebite is best represented by a two-part process, 1) the bite and 2) envenoming. Bites are a function of the product of human and snake abundance, the impact of humans on snake abundance in each type of land cover, and individual snake species contact rates that summarise certain key factors. Given that snakes are more abundant in areas less impacted by humans, per capita risk of bites is higher in forest, followed by agricultural, degraded forest, urban and tea has the lowest. The probability that bites result in envenoming depends on the biting species and land cover again (indicating important occupational risk factors). Even though per capita risk was higher where populations are smaller, urban areas may have the largest number of envenoming bites in light of population size (Figure 1). Mathematically, bites follow the classic mass-action product of infectious (snakes) and susceptibles (humans) population density. The variability of contact rates between land cover likely arises because it acts as a surrogate of occupational risks. In all of the tested models, snake abundance decreased with increasing human population density, which indicates that there is ecological competition resulting in higher incidence rates in sparsely populated areas (forests).

The snake factors that were measured and influence estimated rates are aggressiveness (affecting bites), and venom toxicity (affecting envenoming). Other factors that may influence rates but were not measured are overlap of activity with farmers and frequency of venom injection after a bite, which is known to vary between snake species.

With our analyses we show some of the mechanistic underpinnings of snakebite incidence estimates: 1) climate regulates both geographic patterns of snakebite incidence and agricultural practices; 2) humans compete ecologically with snakes for space displacing them; 3) land cover represents a surrogate of human occupational risk factors. These factors make of snakebite a socioecological system whose epidemiology is susceptible to shift spatially with global change (climate, land use, socioeconomic and demographic).

Climate will affect many snake-related and food production processes, occupational risk factors and some of the effects of land use on snakebite epidemiology. Land use change could further create environmental conditions that affect or benefit the different snake species, and socioeconomic change will modify existing occupational risk factors, but also to the availability of treatment and prevention strategies. Finally, demographic change will likely keep driving land use change and competition and displacement of snakes.



Our analyses based on zoonotic spillover ecology show that there is great potential for better understanding snakebite as a dynamic system. Furthermore, we show that long-term snakebite mitigation should account for the ongoing process of global change.

Figure 9: Snakebite (left) and envenoming (centre) incidence estimates by our model. Insets in the top right corner of each map show a comparison with the estimates used to fit and select models. Blue indicates high incidence, and white indicates lower. Rightmost panels are a summary of the envenoming incidence rates (top) and total number of envenomings (bottom) per spatial unit in each of the considered land cover types (x-axis).

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