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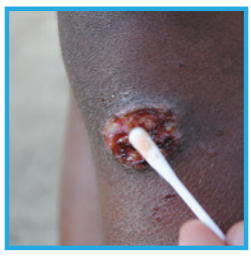


Director's note

The past decade of activity, under the umbrella of the 2012 WHO NTD Roadmap, has yielded much progress in lowering the burden of disease and infection. The Roadmap set new targets and associated milestones to enhance control, prevention, elimination and eradication of NTDs.

Soon after its publication, international health and development organisations, as well as partners from donor agencies and the pharmaceutical industry, met in London, United Kingdom, on 30 January 2012 to endorse the London Declaration in support of achieving the goals for 2015 and 2020 for 10 NTDs. Many believe these two events in combination were a 'game-changer' in focusing international attention and attracting donor support to reduce the burden of disease induced by endemic NTD infection.

Recent data published by the WHO confirmed that in 2018 more than one billion people were again treated for at least one of five NTDs targeted for control and elimination. Reports received by WHO from endemic countries show that large-scale treatment campaigns (mass drug administration) were used to distribute more than 1.7 billion treatments to populations in need.

Successful mass drug administration depends on advance planning and coordination among endemic countries, WHO, pharmaceutical and freight companies to ensure that donated medicines reach the point of delivery in the community in a timely manner. Particularly encouraging has been the progress on the recording of data on drug coverage and the impact of control measures via the Expanded Special Project for Elimination of Neglected Tropical Diseases (ESPEN).

Established in 2016, ESPEN provides direct operational and technical support to countries in Africa. In its first year, ESPEN supported 21 countries to scale up treatments targeting over 70 million people with essential medicines to prevent and treat preventive chemotherapy NTDs (PC-NTDs), and seven countries recovered 132 million tablets through ESPEN- supported supply chain analysis. ESPEN has completed the mapping of targeted PC-NTDs and launched an on-line open access data portal to give access to subnational data on NTDs in Africa, with a view to empowering Ministries of Health and other NTD partners with the information needed to make smart investments for NTD elimination and control.

The challenges for the coming decade, which will be highlighted in the new 2020-2030 WHO Roadmap, are many and varied since the 'end game' in control is much more difficult than the initial phase of bringing down the burden of infection and disease from a high starting level.

Concomitant with the challenges of mopping up the remaining hotspots of infection, and reaching those who have not been able to access treatment, will be transitioning the responsibility of procuring drugs from the current donation programme (which has been so generously supported by the pharmaceutical industry) to a situation where Ministries of Health take on the task of finding ways to support NTD control from within their own country budgets by the end of the coming decade. This will be possible for some countries but not all, and we hope that drug donations can continue for the poorest of countries and regions.

Professor Sir Roy Anderson FRS FMedSci
Director, LCNTDR

Accelerating trachoma elimination through 'Stronger-SAFE'

Dr Anna Last, London School of Hygiene & Tropical Medicine

Find out more:

What is the research?

The five year, Wellcome Trust funded 'Stronger-SAFE' research programme aims to use cutting edge molecular tools alongside detailed clinical, epidemiological, observational and entomological methods to try to better understand and define transmission of trachoma and to develop and test novel, contextually appropriate interventions to interrupt transmission, accelerating the elimination of trachoma as a public health problem, particularly in highly endemic communities in Ethiopia. The programme is a collaboration between the London School of Hygiene & Tropical Medicine, the Federal Ministry of Health in Ethiopia, the Oromia Regional Health Bureau, the Wellcome Trust Sanger Institute, Monash University (Melbourne, Australia) and The Fred Hollows Foundation. The programme aims to build technical capacity in Oromia, including the establishment of a molecular laboratory for *Chlamydia trachomatis (Ct)* diagnostic testing of conjunctival samples.

Stronger-SAFE phase one sought to improve our understanding of potential transmission routes. Our field research team collected swabs from eyes, faces, hands, clothing, bed linen, a variety of household objects and eye-seeking flies captured from the faces of young children and tested these samples for the presence of *Ct*. We found *Ct* on faces, hands and some clothing. Eye-seeking flies (*Musca Sorbens*) are thought to be a passive vector for trachoma. This was the first study to demonstrate the presence of *Ct* on *M. sorbens* flies caught from the faces of children in Oromia. Stronger-SAFE phase two involves developing approaches to interrupt these transmission routes. Following detailed observational research we are focusing on hand and face washing to remove *Ct*-carrying discharge from faces and hands, headwear repellent to *M. sorbens* and odour-baited traps to prevent *M. sorbens* breeding near households.

Why is this research necessary?

Trachoma is the world's leading infectious cause of blindness, affecting 142.2 million people globally. It is caused by repeated conjunctival infection by the bacterium *Ct* and remains a significant public health problem in Ethiopia, which accounts for 44% of the global burden, despite years of implementation of the SAFE strategy for trachoma elimination. The SAFE strategy involves **S**urgery for trichiasis, **A**ntibiotics (azithromycin) to treat *Ct* infection, **F**acial cleanliness and **E**nvironmental (F&E) improvements to suppress transmission. It is unclear which, if any, F&E measures currently applied programmatically suppress transmission. There is growing evidence that current approaches are not having the anticipated impact on infection and disease. This is a significant threat to the timely elimination of trachoma.

What is the research impact?

We have shown that discharge (and *Ct*) can be more effectively removed when faces are washed with soap than when they are washed with water only. We have just completed a clinical trial of insect repellent headwear to keep eye-seeking flies away from children's faces and are exploring the use of traps to reduce eye-seeking flies from the environment. The final F&E intervention package will be tested in a cluster randomised trial in Stronger-SAFE phase three and will include face washing promotion, prototype 'fly-repellent headwear' (caps and scarves) and a fly trap. This 'enhanced' F&E package in addition to double dose azithromycin will form the 'Stronger-SAFE' strategy, which will be compared to 'standard' SAFE implementation in the clinical trial.

Collecting conjunctival swabs to test for Chlamydia, the infectious agent of trachoma. Photo credit: Nazif Jamal

The Geshiyaro Project: identifying optimal strategies for eliminating schistosomiasis and soil-transmitted helminths in Ethiopia

Find out more:

Dr Anna Phillips, Imperial College London

What is the research

The Geshiyaro Project is a large-scale research programme, launched in January 2018, that will assess strategies to eliminate soil-transmitted helminth (STH) and schistosome (SCH) infections. It is a five-year project, funded by the Children's Investment Fund Foundation (CIFF), with ambitious goals including implementation of improved Water, Sanitation, and Hygiene (WaSH) and community-wide mass drug administration (MDA) monitored through a population census using fingerprint technology to biometrically identify study participants.

Current World Health Organization (WHO) guidelines recommend MDA targeting school-aged children living in endemic areas. Although preventive chemotherapy for STH and SCH is cost-effective and reduces infections in treated human hosts, it is limited in that it does not prevent re-infection, which is common because helminth eggs and/or larvae have the ability to survive for extended periods in the environment, which creates a source for rapid reinfection following treatment. Furthermore, members of the population who remain untreated serve as a reservoir for reinfection.

To demonstrate the feasibility of eliminating intestinal worms, CIFF is supporting partners to undertake the Geshiyaro Project. This collaboration includes the Federal Ministry of Health in Ethiopia implementing MDA, World Vision Ethiopia leading WaSH, fingerprint technology provided by Simprints and the Ethiopian Public Health Institute (EPHI) in partnership with the London Centre for Neglected Tropical Disease Research who will be responsible for interpreting, evaluating and documenting the findings.

Why is this research necessary?

Globally, over 1.5 billion people are infected by parasitic worms, with infected water sources and poor sanitation associated with their transmission. Various problems are caused by these parasites including anaemia, reduced cognitive and physical outcomes and diminished income earning potential. For several years large-scale treatment programmes providing free deworming tablets have reduced the infection burden in many countries. The global goal for intestinal worm control is to eliminate morbidity in children by 2020, attained by treating at least 75% of children in endemic areas. The Geshiyaro Project has the means to demonstrate whether intense treatment is sufficient or whether improved WaSH is necessary to achieve elimination.

What is the research impact?

To date, the Geshiyaro Project has censused over 410,000 adults and children using both study identification cards and fingerprint technology, conducted parasitological mapping in all 15 districts among 13,700 adults and children, delivered two rounds of community-wide treatment with subsequent treatment coverage surveys and completed two rounds of sentinel sites surveys. In addition, 22 shallow wells, three protected springs, two deep wells and 20% community improved sanitation has been delivered. WaSH implementation continues to scale up this year, both of hardware (latrines and provision of safe water) and software (behaviour change communication and community resource management). Field trials continue to use the census data to monitor and maintain high treatment coverage and sentinel sites to evaluate impact on parasite levels.

Biometric enrolement in the Geshiyaro Project. Photo credit: Anna Phillips

Towards planning morbidity management programmes: characterising patient needs and estimating lymphedema and hydrocele burden in Nigeria

Find out more:

Dr Obiora Eneanya, Imperial College London

What is the research?

The global programme to eliminate lymphatic filariasis (LF) aims to interrupt transmission, manage morbidity and alleviate suffering among people already infected. Interrupting transmission by treating eligible populations in endemic communities through mass drug administration (MDA), has been the emphasis of LF control programmes. However, insufficient attention has been given to morbidity management and there is currently no standard protocol for estimating patient numbers. This research contributes to the literature by providing a structure for patient reporting and characterising the psychosocial and economic impacts of LF to better prioritise requirements for morbidity management programmes.

Accurate estimates of disease burden are essential for planning morbidity management programmes. To identify LF patients, researchers used an established MDA infrastructure of community directed-distributors, health care workers, community leaders and a network of local informants to recruit LF patients in two implementation units in Nigeria. These patients were interviewed and the researchers characterised the physical and socio-economic impacts due to LF. Matching disease-free controls (matched by age, sex and residential location) were interviewed to provide a basis for comparison.

An elephantiasis patient in Anambra State, Nigeria.
Photo credit: Obiora Eneanya

Why is this research necessary?

Morbidity reduces the ability of individuals to perform basic daily activities independently, hindering employment opportunities and impeding mobility and the ability for self-care.

Health care costs are also significantly higher for LF patients, often depleting family income, which can lead to patients to being considered financial burdens by their families. The relationship between chronic LF and mental health is often neglected and insufficiently studied. This work highlights evidence of possible precursors to mental health illness, namely; abandonment, stigma, isolation, sleep problems, cognitive impairment, anxiety, and reduced concentration. It is therefore imperative to develop appropriate interventions to respond to these problems. The patient reporting system used in this work was effective in estimating disease burden within both implementation units.

What is the research impact?

The patient reporting system described in this work forms a basis for further patient identification, taking advantage of the already well established MDA programmes for LF and other neglected tropical diseases. For patients with lymphedema and hydrocele, simple hygiene measures, such as basic skin care, should be encouraged to prevent disease progression and secondary bacterial infection. Hydrocelectomy surgeries are also effective in treating hydrocele patients. For more complicated morbidity, a standard referral system, whereby patients are directed to appropriate health services, should be established. To address the mental health concerns raised, the researchers have suggested a task-shifting approach where community health workers are trained to provide mental health care within the communities, while acting as a stop-gap for inadequate mental health facilities in most of these LF endemic areas.

Schistosomiasis: assessing progress towards the 2020 and 2025 global goals

Find out more:

Dr Arminder Deol, Imperial College London

What is the research?

This study collated and analysed programmatic data from national schistosomiasis control programmes in nine countries. Researchers compared the progress these programmes had made against the World Health Organization (WHO) global targets for schistosomiasis, which estimate that national control (2020 aims) may be reached within 5-10 years and elimination as a public health problem (2025 aims) after 3-6 years. This study aimed to assess where we are at this point, how long programmes take to reach these targets and whether these targets are at all feasible, using evidence from empirical data.

The data were analysed according to schistosoma species (intestinal or urogenital), the number of treatment rounds, overall prevalence and prevalence of heavy-intensity infection. Disease control was defined as a prevalence of heavy-intensity infection of less than five per cent aggregated across sentinel sites and the elimination target was defined as a prevalence of heavy-intensity infection of less than one per cent in all sentinel sites.

Why is this research necessary?

Schistosomiasis is a parasitic neglected tropical disease (NTD) that is estimated to currently infect between 140-240 million people. Ninety percent of the disease burden is in sub-Saharan Africa, where the main species responsible for schistosomiasis in humans are water-borne parasites. These parasites belong to a group of blood flukes which are transmitted through faeces or urine, depending on the species and cause symptoms including anemia, stunting, fever, genital lesions and irreversible organ damage.

As these milestones become imminent and if programmes are to succeed, it was important to evaluate WHO's programmatic guidelines. Therefore, the group – researchers from Imperial College, the SCI Foundation (formerly known as the Schistosomiasis Control Initiative), Royal Veterinary College, RTI International and the London Centre for Neglected Tropical Disease Research, working with national control programme leaders from each participating country, analysed and evaluated data covering multi-year, cross-sectional treatment programs in sub-Saharan Africa and Yemen to assess the progress.

What is the research impact?

Results showed programmes in areas with low endemicity levels at baseline were more likely to reach both the control and elimination targets than those in areas with moderate and high endemicity levels at baseline. Intracountry variation was also evident in the relationships between overall prevalence and heavy-intensity infection, a finding that highlights the challenges of using one metric to define control or elimination across all epidemiologic settings.

The study also shows that many countries reached the control targets earlier in their programmes than estimated, highlighting that programmes may be able to reassess and/or move on to the next strategy towards elimination as a public health sooner than anticipated. This has direct implications on treatment strategies which would help control programmes reach the WHO targets for control and elimination sooner.

Children in line at a mass drug administration campaign. Photo credit: Elizabeth Hollenberg

Field-based molecular diagnostics: supporting the move towards test-and-treat scenarios in the elimination of urogenital schistosomiasis setting of Zanzibar

Find out more:

Dr Bonnie Webster, Natural History Museum

What is the research?

Molecular diagnostics can be highly sensitive and specific but most cannot be used at the point-of-care due to their high resource requirements. Recombinase polymerase amplification (RPA) is an isothermal DNA amplification technology offering several advantages in terms of its application in the endemic field setting.

This research is focused on the development of an RPA assay for *Schistosoma haematobium*, the cause of human urogential schistosomiasis, which can facilitate test-and-treat scenarios in the elimination setting of Zanzibar, Tanzania. The laboratory development of the assay proved its high sensitivity and specificity, with pilot testing on clinical samples showing a lower limit of detection of 1 egg/10ml of urine. Reactions are run at 40°C in small portable battery powered tube scanner devices and take just 10 minutes. Additionally, the development of crude sample preparations facilitate the assay's feasibility in the endemic setting. Further research is ongoing to deploy this simple, portable, sensitive and specific technology to enable the testing and treating of the few individuals acting as reservoirs of infection Zanzibar.

Why is it important?

Schistosomiasis is endemic in 74 developing countries, with over 240 million people infected and over 750 million at risk with 90% of those infected living in low or middle income countries in Africa. Efforts to control schistosomiasis are gathering momentum with ambitious goals to eliminate schistosomiasis announced by the World Health Organization and the London Declaration on NTDs.

In endemic areas, appropriate diagnostic tools are required that can be readily adapted at different stages of a control programme. Mass Drug Administration (MDA) with praziquantel, behavioural change, education and snail control are having a major impact on schistosomiasis transmission, bringing down prevalence and intensities. Sensitive and specific diagnostic tests, to prevent false negative diagnosis, are critical for the development and success of schistosomiasis control and elimination programmes. Additionally, diagnosis needs to be performed at the point-of-care/need so that infected individuals can be treated on the spot. Preventing false negative diagnosis and implementing test-and-treat methodologies will not only support the move towards elimination, but will also restrain transmission resurgence, a real risk for schistosomiasis due to the replicative biology of schistosomes within their snail hosts.

What will its impact be?

Currently the diagnosis of urogenital schistosomiasis relies on the detection of eggs in urine, a test not sensitive enough to detect low intensity infections, meaning that true prevalence is probably underestimated. Moreover, there is a critical need within elimination programmes to implement test-and-treat scenarios so that the few individuals that are maintaining transmission are treated. With the provision of highly sensitive and specific diagnostic tests that can be performed at the point-of-need/care, such as our RPA assay, we can reduce the prevalence of urogenital schistosomiasis in Zanzibar, reach and maintain elimination and prevent resurgence. This research also has implications elsewhere, providing better estimates of prevalence so that treatment strategies can be optimised. Additionally, this research is being adapted for the difficult diagnosis of related pathologies, such a Female Genital Schistosomiasis (FGS), with an aim to empower women to seek appropriate support.

Prolific water contact at a water body on Pemba Island, Zanzibar. Test and treating in this elimination setting could help find the few individuals maintaining transmission. Photo credit: Bonnie Webster

Micro-CT visualisation of the parasite-host interface in sandflies and blackflies

Find out more:

Dr Martin Hall and Brett Clark, Natural History Museum
Dr Matthew Rogers, London School of Hygiene & Tropical Medicine
With Dr Daniel Martín-Vega, Debashis Ghosh, Professor Robert Cheke, Francis Veriegh, Tony Tetteh-Kumah, Dr Mike Yaw Osei-Atweneboana

What is the research?

Leishmaniasis and onchocerciasis are neglected tropical diseases (NTDs) vectored by sandflies and blackflies, respectively. Both NTDs are associated with poverty and impose a significant health, welfare and economic burden on many tropical countries. Current methods to visualise infections within the vectors rely on invasive methods. However, using micro-computed tomography (micro-CT) techniques, without interference from tissue manipulation, this study visualised in 3-D for the first time:

- ***Leishmania mexicana* infections and their impact on laboratory reared *Lutzomia longipalpis* sandflies;**
- **an L1 larva of an Onchocerca species within the thoracic musculature of a blackfly, *Simulium damnosum*, naturally infected in Ghana.**

Why is this research necessary?

In research of the infection of vectors with disease agents that cause NTDs, there is tremendous scope for visualisation techniques to improve the fundamental understanding of parasite-vector interactions, the basis of vectorial competence and transmission. Precise spatio-temporal information on the progress of an infection can tell us much about the interactions required for successful colonisation and transmission. However, visualisation of these interactions within the vectors has hitherto proven difficult.

Micro-CT provides a powerful tool to follow the infection within vectors non-invasively, yielding both qualitative and quantitative data. For example, studies of sandfly infection with *Leishmania* confirmed hypotheses regarding gross distension of the fly midgut following secretion of a promastigote secretory gel (PSG) which facilitates transmission of *Leishmania*. In addition, the studies:

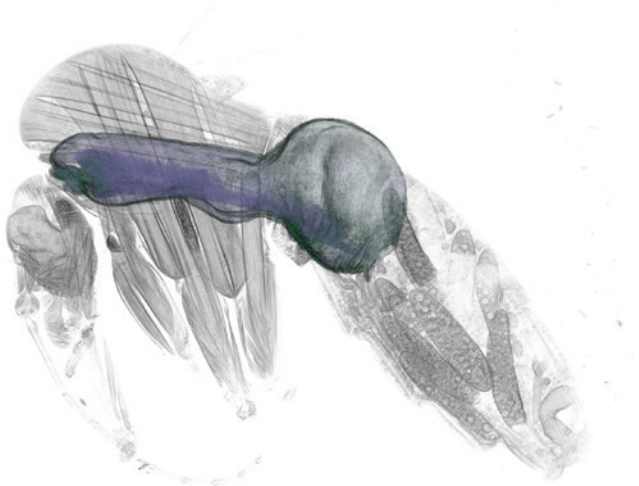
- **provided volumetric data on the midguts of infected sandflies and of the PSG within the midguts;**
- **demonstrated PSG in the pharynx of infected sandflies;**
- **confirmed the amplifying impact of a non-infectious second blood-meal on PSG in an infected sandfly.**

Similarly, in addition to visualisation of *Onchocerca* infection, questions about vector competence in blackflies can be addressed. For example, micro-CT scans of the peritrophic matrix in both 'forest' and 'savanna' blackflies preserved soon after feeding did not support the hypothesis that 'forest' blackflies have a thinner peritrophic matrix, which would allow them to develop more *Onchocerca* L3 larvae than 'savanna' blackflies.

What is the research impact?

Micro-CT studies can complement other fundamental studies of the development of NTD disease agents within their vectors, thereby helping to highlight new avenues for tackling the disease in the vector. For leishmaniasis, micro-CT has the prospect of filling in many of the missing gaps in our knowledge of the spatial arrangement of blood and PSG before, during and after transmission – and, uniquely, their precise volumes – which can all be used to begin to model the biophysics of transmission. For onchocerciasis, it will be possible to follow progress of *Onchocerca* development within a series of infected flies, shedding light on its differential development within different vector species. For arthropod disease vectors in general, fine detail of changes in internal structures may provide a more accurate way of age-grading vectors for epidemiological studies.

In addition, health education has been identified as crucial in efforts to control or eliminate NTDs. Images produced by this study and future studies could have significant value in health education by helping to illustrate and raise awareness of the role of vectors in disease transmission, at public meetings and in outreach publications.
In conclusion, although these initial studies focused on sandflies and blackflies, they demonstrate the great potential for wider use of micro-CT in the research and management of NTDs, providing novel information on many other parasite/vector systems and impactful images for public engagement.



False-coloured 3-D image of an adult female of *Lutzomia longipalpis*, nine days after ingesting a first blood-meal infected with amastigotes of *Leishmania mexicana* and five days after a second, non-infected blood meal. The cuticle is rendered transparent to enable visualisation of the distended midgut (green) part filled with promastigote secretory gel (PSG, purple) secreted by the *Leishmania parasites.*

Revisiting density dependence in human schistosomiasis using sibship reconstruction

Find out more:

Maria Inês Neves, Royal Veterinary College
Professor Joanne Webster, Royal Veterinary College
Dr Martin Walker, Royal Veterinary College

What is the research?

Schistosomiasis is a devastating neglected tropical disease caused by trematode parasites of the genus *Schistosoma*. Although earmarked for control and elimination by the World Health Organization, schistosomiasis remains a major public health concern, endemic in 54 countries and affecting approximately 240 million people worldwide. Moreover, many fundamental aspects of schistosome population biology remain unresolved, impeding the design, optimisation and evaluation of intervention strategies targeting control and elimination. A key unknown is whether and to what extent schistosome populations are regulated by density-dependent population processes. In dioecious helminth infections, density-dependent fecundity describes the reduction in egg production by female worms in high worm burden within-host environments. For human schistosomiasis, unlike some intestinal worms, investigating density-dependent fecundity is hampered by the inaccessibility of adult worms within hosts, due to the intravascular location of the parasite. Current understanding of this fundamental population process is limited to data collected from two autopsy studies conducted over 40 years ago, with subsequent analyses having reached conflicting conclusions on the operation of density-dependent egg production.

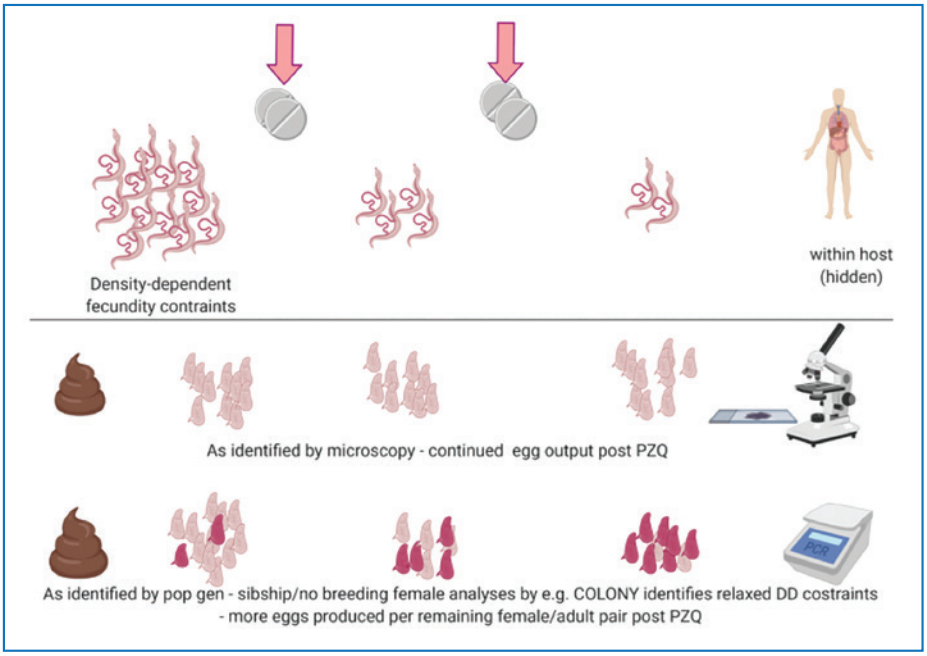
Sibship reconstruction is a branch of parentage analysis which can be used to estimate the number of parents/adult worms in individual human hosts from molecular data derived from the accessible transmission stages/offspring of schistosomes. In combination with egg count data, this provides a novel means to identify density-dependent fecundity, albeit using robust statistical methodologies to account for the bias and uncertainty of worm burden estimates which depend on the number of offspring sampled. We illustrate this approach using a recent multiplexed microsatellite dataset derived from *Schistosoma* spp. miracidia hatched from infected samples of children undergoing preventive chemotherapy in Tanzania.

Why is this research necessary?

Density dependencies enhance the resilience of parasite populations to interventions, a critical consideration when designing intervention strategies and interpreting data on the effectiveness of control. In particular, in schistosomiasis – and indeed many other helminthiases with inaccessible adult parasite stages – infection intensity is inferred from indirect measures of egg output, a proxy for the number of infecting adult female parasites. Whether egg production is regulated in a density-dependent manner is key to interpreting routine egg count data and has important ramifications for predicting or modelling the response of schistosome populations to perturbation by intervention.

What is the research impact?

We estimated a non-proportional relationship between *Schistosoma* spp. egg counts and inferred numbers of female worms, indicating that egg production is suppressed in individuals with higher worm burdens, suggesting density-dependent fecundity. Resolving this fundamental question will have multiple public health implications, including for policy decisions informed by the modelled transmission dynamics of schistosomes during intervention and for the interpretation of egg count data collected during monitoring and evaluation activities. Therefore, future work will focus on the validation of this approach by comparison between direct and indirect methods of estimating worm burdens in infected animal hosts and re-evaluating density dependence using paired molecular and parasitological data.



Relaxation of the density-dependent fecundity of *S. mansoni* parasites within a host after treatment with praziquantel. Photo credit: Joanne Webster

Spatial and temporal analysis of Zika and chikungunya epidemics in Colombia

Kelly Charniga, Imperial College London
Dr Zulma Cucunubá, Imperial College London
Dr Pierre Nouvellet, University of Sussex
Dr Christl A. Donnelly, Imperial College London & University of Oxford

What is the research?

In 2014-2017, Latin America experienced back-to-back outbreaks of chikungunya virus followed by Zika virus. Both viruses are transmitted by Aedes mosquitoes and had not been previously reported in the Americas. People with symptoms typically experience fever, rash and joint pain. Additionally, Zika virus infection during pregnancy increases the risk of severe birth defects in newborns and chikungunya fever can cause chronic joint pain that lasts weeks or months.

Colombia was one of the most affected countries during the recent outbreaks with over 100,000 Zika virus and 400,000 chikungunya virus suspected and laboratory-confirmed cases. Using surveillance data from Colombia's National Institute of Health, this study first estimated the week of invasion in each city (Figures 1-2). Next researchers fitted gravity models to study the invasion dynamics of both viruses between cities in Colombia. Gravity models describe movement from one location to another based on population size and distance.

Why is this research necessary?

There are currently no approved drugs to treat or prevent Zika virus disease or chikungunya fever and both diseases have the potential to cause further large epidemics in Latin America. Most spatiotemporal research has focused on studying these diseases separately. However, Zika virus and chikungunya virus share common vectors and were introduced into the same regions with large susceptible populations. Studying them together will improve understanding of disease spread at the subnational level, which is important for informing preparedness activities for future outbreaks.

What is the research impact?

This research found evidence that both viruses were introduced into Northern Colombia and intermediate levels of density dependence best described transmission. Although a small number of long-range transmission events were identified early in the outbreaks, invasion mainly occurred over short distances. Geographic distance fit the data better than estimated travel time to the nearest city. Both humans and vectors were likely responsible for disease spread across the country. However, the relative contribution of human versus vector movement on spatial transmission remains poorly understood. Future work on quantifying this relationship would have broad implications for surveillance and control for other vector-borne diseases such as dengue, Mayaro and yellow fever. The invasion dynamics of other epidemics could also be analysed using the approach from this study.

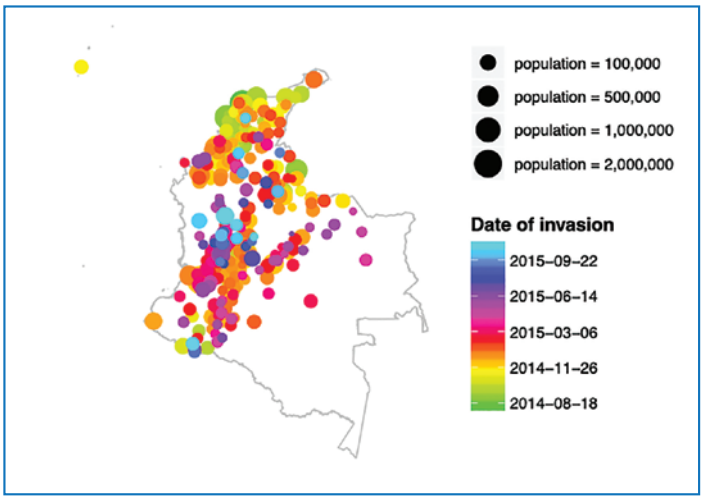


Figure 1. Date of invasion estimated from weekly times series of chikungunya virus. Each city is represented by an individual circle. Circle size is proportional to the size of the city's population and color reflects date of invasion (green areas have the earliest onsets and blue areas have the latest).

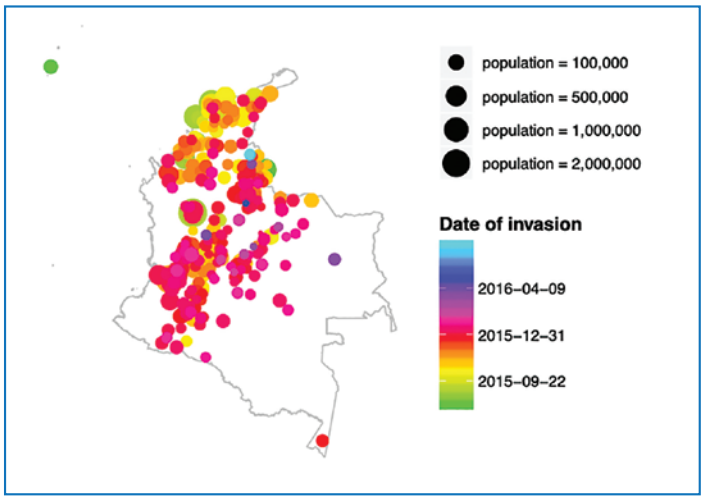


Figure 2. Date of invasion estimated from weekly times series of Zika virus. Each city is represented by an individual circle. Circle size is proportional to the size of the city's population and color reflects date of invasion (green areas have the earliest onsets and blue areas have the latest).

Clinical evaluation of a loop-mediated isothermal amplification test for *Treponema pallidum pertenue*: a diagnostic tool to support yaws eradication

Find out more:

Dr Michael Marks, London School of Hygiene & Tropical Medicine
Dr Emma Harding-Esch, London School of Hygiene & Tropical Medicine
Becca Handley, London School of Hygiene & Tropical Medicine

What is the research?

This is a European and Developing Countries Clinical Trials Partnership (EDCTP) funded project running between 2020-2022 to evaluate the potential of a new diagnostic test for yaws. The project brings together the London School of Hygiene & Tropical Medicine (UK), the Noguchi Memorial Institute for Medical Research (Ghana), the Institut Pasteur (Côte d'Ivoire), the Centre Pasteur (Cameroon), Fundació Lluita contra la Sida i les Malaties Infeccioses (Spain), University of Göttingen, University of Freiburg and Mast Diagnostica (Germany). The fieldwork for the study will be conducted in sites across West and Central Africa. Patients suspected to have yaws will be enrolled into the study and we will compare the performance of standard polymerase chain reaction (PCR) assays performed at national reference laboratories with a novel loop-mediated isothermal amplification (LAMP) assay for the diagnosis of yaws. We will also work to develop a LAMP assay which can detect the presence of azithromycin resistance in yaws.

Why is this research necessary?

Yaws affects individuals in poor rural communities in Africa, Asia and the Pacific Islands. It mostly affects children and causes disfiguring lesions of the skin. If untreated it can progress to severe and irreversible lesions of the skin, soft tissues and bones resulting in disability and stigma. Recent developments using a single dose of oral azithromycin have renewed optimism that eradication can be achieved. However, diagnostics represent a major challenge for yaws eradication. Commonly used serological tests cannot differentiate current yaws from previous infection, nor differentiate yaws from other causes of similar skin lesions. Alongside this, the emergence of resistance to azithromycin makes clear the need for monitoring of drug resistance. There is therefore a need for an accurate point-of-care molecular assay to enable early detection and effective treatment of yaws and track progress towards eradication.

What is the research impact?

The project will strengthen laboratory capacity for monitoring yaws eradication in Africa. We will develop an external quality assurance scheme to support laboratory monitoring of yaws eradication efforts worldwide. If the novel LAMP assay performs well it will enable quicker diagnosis and treatment of yaws cases and importantly improve monitoring for the emergence of antimicrobial resistance. Building lab capacity will support national programmes in rolling out azithromycin mass drug administration and achieving the ultimate goal of yaws eradication.

About yaws:

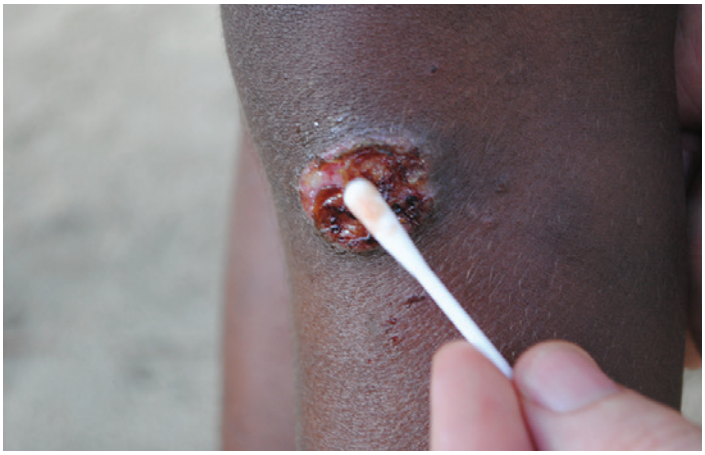
Yaws is a chronic disfiguring and debilitating childhood infectious disease caused by *Treponema pallidum* subspecies *pertenue*.

The disease affects skin, bone and cartilage. Humans are currently believed to be the only reservoir, and transmission is from person to person.

There are 15 countries currently known to be endemic for yaws. Recently, three countries that were classified as previously endemic have reported suspected yaws cases.

Yaws is cured with a single oral dose of an inexpensive antibiotic called azithromycin.

World Health Organization 2019



Swab being collected from a yaws patient. Photo credit: Michael Marks

Validation of a recombinase polymerase amplification assay for the diagnosis of female genital schistosomiasis in Zambian women using cervicovaginal lavage and vaginal self-swab samples

Find out more:

John Archer, Natural History Museum

What is the research?

Female genital schistosomiasis (FGS), caused by infection with *Schistosoma haematobium*, is associated with a range of adverse reproductive health outcomes such as destruction of the cervicovaginal mucosa, infertility, ectopic pregnancy and abortion. Further to these sequelae, FGS is now recognised as an important contributor to the transmission of sexually transmitted bacterial and viral infections (STIs). Of particular concern is the impact of FGS on HIV transmission owing to a range of characteristic genital tract pathologies known to augment HIV acquisition. Overall, FGS is believed to increase a woman's chance of contracting HIV by up to four times.

The World Health Organization estimates that approximately 56 million women currently experience from some form of FGS, though this is widely considered a vast underestimate owing to difficulties in both diagnosing infection with *S. haematobium* and in observing any genital pathology caused by infection. One diagnostic approach involves the use of polymerase chain reaction (PCR) to detect sequestered *S. haematobium* egg-derived DNA collected within cervicovaginal lavage (CVL) samples. Though promising, CVL sampling is invasive and requires specialist health personnel working within a clinical setting. In addition, PCR-based diagnostics are currently unsuited for use in endemic field settings and so typically cannot be used at the point-of-care.

Because of this, the BILHIV (Bilharzia and HIV) study, led by Dr Amaya Bustinduy at the London School of Hygiene & Tropical Medicine, was formed and aims to explore the innovative role of vaginal and cervical self-swabs for the diagnosis of FGS. Self-sampling with swabs is not only far less invasive than CVL sampling but can also be performed by the patient within the home. As part of the BILHIV study, it was recently shown that self-swab samples may be as sensitive, if not more sensitive, than CVL sampling when using qPCR to detect DNA derived from eggs sequestered throughout the genital tract.

The recently developed recombinase polymerase amplification (RPA) assay is a field-deployable DNA amplification technology and alternative to PCR. Here, we assessed the use of RPA for the detection of sequestered egg-derived DNA within CVL and vaginal self-swab samples; comparing RPA performance to that of qPCR. Our work suggests that RPA may be a viable alternative to qPCR for the diagnosis of FGS and, if used in conjunction with self-swab samples, may provide a scalable solution in resource limited areas for the diagnosis of FGS at the point-of-care.

Why is this research necessary?

Currently, there is no rapid and reliable method for detecting FGS-associated symptoms within schistosomiasis-endemic areas. Further development and assessment of the RPA assay for use with vaginal and cervical self-swab samples may provide a viable means for self-swabbing and rapid point-of-care diagnosis, empowering women, relieving stigma and enabling targeted treatment and/or intervention.

What is the research impact?

Reliable detection of FGS at the point-of-care will better our understanding of FGS prevalence and epidemiology in schistosomiasis-endemic areas, contribute to the improved health and wellbeing of those suffering from FGS-related pathologies and may even help towards the reduced transmission of sexually transmitted infections such as HIV.

Human exposure to schistosomiasis relies on freshwater contact. Photo credit: John Archer

Sensing sleeping sickness: local symptom-making in South Sudan

Find out more:

Dr Jennifer Palmer, London School of Hygiene & Tropical Medicine

What is the research?

The field of sensorial anthropology emphasises that different cultures extend the senses in different directions and use different cognitive metaphors to translate abnormal sensations into symptoms of illness. Undertaken in collaboration with Merlin and the London School of Hygiene & Tropical Medicine's RECAP project, this study investigated the local sense-making processes involved in sensing and detecting cases of human African trypanosomiasis (HAT, or sleeping sickness) in Nimule, South Sudan.

This study employed a sensorial anthropological lens which focuses on the interfaces between objective/subjective and individual/collective knowledge. It investigated how people share syndromic information in communal disease discourses and drew on them to connect partial, disparate and even nonsensical experiences of individual symptoms to diagnosis of a complete disease.

Why is this research necessary?

Syndromic case detection of NTDs like HAT is increasingly important as we approach elimination. Mass campaigns which preventatively treat or screen populations at risk is the gold standard for controlling many NTDs. However, as the burden of most NTDs falls globally, such campaigns become less cost-effective. Facility-based identification of suspected cases using health workers' assessments of symptoms they observe in patients who visit them (a strategy referred to as 'passive case detection'), is now the main way cases of HAT, visceral and cutaneous leishmaniasis, Chagas disease, leprosy and Buruli ulcer are detected to target treatment. For other NTDs, including Guinea worm, lymphatic filariasis, schistosomiasis, onchocerciasis, trachoma and yaws, syndromic surveillance is required during or after mass campaigns to help verify elimination and identify patients needing surgery and rehabilitation.

How to best involve lay people and frontline health workers in syndromic case detection of NTDs is thus a key challenge for NTD programmes. Staff need help interpreting patient accounts of disease symptoms and supplying relatable messages about the services available to people with particular symptom profiles. Compared to the legacy of robust anthropological work on local symptom sense-making for malaria, respiratory and diarrheal illnesses, however, field explorations of how hallmark symptoms inform programme engagement tend to be rare for NTDs.

What is the research impact?

This study demonstrated the ways people can combine biomedical and ethnophysiological concepts with sensations of risk from their environments to identify suspected cases of HAT.

In Nimule, the disease was sensed through four main symptoms: pain, sleepiness, confusion and, interestingly, *hunger*. The archetypal image of a HAT patient was of someone running mad, stealing neighbours' food to feed ravenous appetites, leaving chaos and violence in their wake. People who suspected HAT in themselves or others looked for subtle indications that they could be developing such a condition, such as forgetfulness or sloppy eating. Particularly when symptoms of pain and weakness were also present, this helped people decide to seek a HAT test.

While hunger and fatness have been common elements of local discourses from diverse areas of Africa for centuries, these symptoms are rarely discussed in biomedical accounts of HAT. Such difference demonstrates how "seeing" disease is a context-specific social activity which might not be visible to outsiders without the aid of culturally meaningful approaches.

Using the example of HAT, this study provides a novel lens through which to research local sense-making of NTD symptoms and value the life-saving contributions of local syndromic knowledge which help make disease control programmes work.

Illustration from nineteenth century West Africa depicting HAT patients as fat and greedy. Artist unknown, image held by the Wellcome Trust Library

Drivers of the variability in albendazole pharmacokinetics and their consequences for anti-helminthic treatment: a systematic review and meta-analysis

Charles Whittaker and Professor Maria-Gloria Basáñez, Imperial College London
Dr Martin Walker, Royal Veterinary College
With Annette C. Kuesel, Cédric B. Chesnais, Sébastien D.S. Pion, Joseph Kamgno, Michel Boussinesq

What is the research?

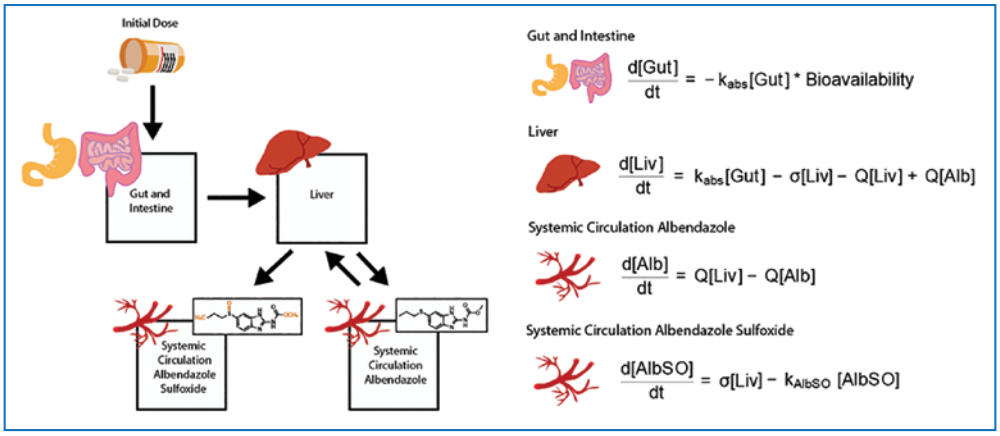
Albendazole (a benzimidazole) is an anti-parasitic medication used in a wide array of both clinical and programmatic contexts to treat (neuro-)cysticercosis, echinococcosis, infection with soil-transmitted helminths, lymphatic filariasis and loiasis, amongst others. The drug is characterised by extensive pharmacokinetic variability, with this variation likely to have important consequences for treatment success both at the individual and population level. In order to better characterise the determinants of this variation, we carried out a systematic review to identify references containing information on the pharmacokinetics (PK) of albendazole following a single oral dose of the drug. These results were then integrated into a mathematical modelling framework in order to infer key PK parameters, including the maximum concentration reached (C_{Max}), the area under the curve (AUC, reflecting total drug exposure), the bioavailability of albendazole and the half-life of its pharmacologically-active metabolite, albendazole sulfoxide. Using a regression-based approach, we related the values of these parameters to characteristics of the populations receiving treatment. Specifically, we assessed, on albendazole PK parameters, the effect of age, weight, sex, dosage, infection and co-infection status, whether patients had received a fatty meal prior to treatment and co-administration of other drugs.

Why is this research necessary?

The therapeutic efficacy of albendazole has been investigated against a wide array of helminth parasites, but its PK features are characterised by extensive variation. This variation has implications for treatment and is thought to contribute to the failure of cure in some treated patients. For example, whereas some patients typically require only one course of treatment, others require a multiple treatment regimen and in a number of instances, complete treatment failure has been observed in clinical settings. Similar results have been recorded in field studies, where for example, cure rates (the proportion of those treated who achieve parasitological clearance) for hookworm infection have been observed to vary from 53% to 95% across different communities in Ghana. Similar variability in albendazole's efficacy has also been observed for programmes treating lymphatic filariasis in the Democratic Republic of the Congo. Transmission dynamics models tend to assume fixed efficacy values when making projections of the impact of treatment in populations or population groups, but variation in efficacy among these groups is seldom considered. Although some studies have explored the drivers of this variation in the literature, our understanding of the phenomenon remains for the most part, incomplete. Frequently, these studies have focussed on a single factor and so a systematic understanding of the precise determinants and drivers of albendazole's extensive PK variation, their comparative impact and whether they interact with one-another, remains outstanding.

What is the research impact?

This research provides insight into the mechanisms underlying the variation in albendazole's PK suggesting potential avenues for clinical and programmatic optimisation of drug delivery, the outcome of which, it is hoped, will be more consistent pharmaceutical efficacy of the drug when deployed to treat parasitic infections. Additionally, the research highlighted key biases relating to which populations and individuals have previously been studied during research into albendazole, a finding which should motivate further research into key groups (such as children and women) currently underrepresented within the literature. Ultimately, we advocate for a better collection, collation, curation and understanding of individual patient data regarding the efficacy, pharmacodynamics and pharmacokinetics of albendazole for the treatment of human helminthiases.



Schematic of the pharmacokinetic model of Albendazole and Albendazole Sulfoxide: A compartmental model consisting of a series of linked ordinary differential equations (ODEs) was developed to simulate the pharmacokinetics of Albendazole and its pharmacodynamically active metabolite, Albendazole Sulfoxide, in the blood following a single oral dose of the drug

LONDON CENTRE FOR NEGLECTED TROPICAL DISEASE RESEARCH

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- **Providing evidence-based technical and training support to countries investing in national NTD programmes;**
- **Supporting harmonisation of multi-sectoral partnerships and collaborations;**
- **Acting as an NTD knowledge base for disseminating innovative and evidence-based information for policy and programme formulation;**
- **Providing a neutral coordinating platform for partner collaboration on NTD control and prevention efforts;**
- **Carrying out research on new approaches to the study of the geography, transmission dynamics and control of NTDs, with a particular focus on integrated diagnosis and mapping and integrated control of more than one NTD.**

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