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LONDON CENTRE FOR NEGLECTED TROPICAL DISEASE RESEARCH

An Innovative Research Collaboration:

Selected Research Highlights

Imperial College London

NATURAL HISTORY MUSEUM

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

RVC Royal Veterinary College University of London

Director's Note

As we approach 2020 and review our progress towards the goals and targets laid out in the World Health Organisation's NTD Roadmap, the international research community can be proud of the vital role that its discoveries have played in incremental and major advances towards the control and elimination of NTDs.

Innovative and rigorous research supports policymakers, practitioners, donors and advocates to make evidence-based decisions, implement effective programmes and design appropriate guidelines.

The London Centre for Neglected Tropical Disease Research (LCNTDR) grew from the energy and optimism of the 2012 London Declaration on NTDs, harnessing the brightest minds in NTD research across four renowned institutions in London.

Over the six years of the LCNTDR's operation, we have collaborated to provide focused operational and research support for NTD control in more than 30 countries and made critical contributions to answer key research questions. Our work is interdisciplinary in nature and future-oriented.

New analysis techniques are examining the dynamics of NTD elimination and resurgence, demonstrating, for example, the impact of adjusting schistosomiasis treatment coverage to include adults, and testing stopping rules for onchocerciasis, lymphatic filariasis and soil transmitted helminthiasis control.

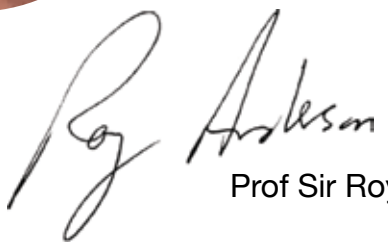
LCNTDR members are running many large-scale projects and trials, including DeWorm3 in India, Benin, and Malawi; Geshiaro in Ethiopia; TUMIKIA in Kenya; and an investigation of zoonotic schistosomiasis in West Africa.

Advances in the fields of new diagnostics and molecular genetics and genomics are pushing exciting new frontiers – giving greater precision in identifying infected people when prevalence is low – and enabling research on 'who infects whom'.

Robust interdisciplinary scientific analyses are making a very important contribution to the NTD world. The LCNTDR's depth of experience and diversity of perspectives ensures we are very well positioned in this endeavour.

We are privileged and very grateful to have financial support for our activities from a wide range of donors, and especially grateful to the pharmaceutical companies who have made drug donation programmes a cornerstone of attempts to control several important NTDs which cause much morbidity in endemic regions.

I have no doubt the LCNTDR will maintain its vigour and momentum and consolidate its progress as we move beyond 2020, and into a new era for the elimination of NTDs.



Prof Sir Roy Anderson, Director, LCNTDR

Towards the eradication of parasitic worms in Ethiopia: the Geshiaro project

Find out more:

What is the research?

A major new research programme has been launched to strengthen strategies to eradicate parasitic worms from communities in Ethiopia.

Initially focusing on the 2 million people who live in the communities of the Wolaita zone in south-east Ethiopia, the Geshiaro project aims to identify the optimal design of programmes that will break the transmission of both soil transmitted helminths (STH) and schistosomiasis infections.

The five-year project will seek to answer this question by evaluating deworming approaches that seek to ally large-scale drug treatment programmes with initiatives that improve water, hygiene and sanitation (WASH) facilities and practices. Reflecting this comprehensive approach, the project has been given a name of Geshiaro meaning "cleans inside and out" in the local Wolaytinga dialect.

The Geshiaro project is an international collaboration between the London Centre for Neglected Tropical Disease Research (LCNTDR), World Vision Ethiopia, the Ethiopian Public Health Institute (EPHI) and Ethiopia's Federal Ministry of Health, with funding from the Children's Investment Fund Foundation.

During the project, LCNTDR will provide technical support and capacity building to EPHI in the evaluation of the project. Together the evaluation team will then be responsible for interpreting and documenting the findings from Geshiaro.

The implementation of deworming during the project will be conducted by the Federal Ministry of Health, with World Vision Ethiopia leading on the WaSH infrastructure and behaviours change communication activities and the finger print technology provided by Simprints.

Why is this research necessary?

Globally, over 1.5 billion people are infected by these parasitic worms, with infected water sources and poor sanitation associated with their transmission.

The detrimental health impacts caused by these parasites have been shown to reduce the educational outcomes of children and income earning potential adults.

Taking finger prints to improve coverage and compliance of treatment. *Credit: World Vision Ethiopia.*

To help communities to free themselves from these diseases the international community has targeted their elimination through large-scale treatment programmes which provide free deworming tablets. But to achieve this, the question remains – what's the most effective way to treat people and prevent future infections?

What is the research impact?

Previous mathematical modelling by the LCNTDR has shown that the transmission of some species of parasitic worms can be broken in certain settings through provision of multiple interventions, but it has not been attempted at scale in a low-income country through the existing health system.

The innovative project is first of its kind to evaluate the impact of different treatment strategies and WaSH using biometric finger print technology to improve coverage and compliance of the interventions.

Biometric finger print technology will enable accurate identification and tracking of the estimated 200,000 individuals who will receive deworming tablets during the first year of the Geshiaro project. Creating a register of all those living in the Wolaita zone who comply with treatment is crucial for the monitoring of treatment progress over the course of the project

Dr Anna Phillips, Imperial College London

"The project is first of its kind to evaluate the impact of different treatment strategies and WaSH using biometric finger print technology to improve coverage and compliance of the interventions."

Investigating the immunological basis of scarring trachoma

Find out more:

What is the research?

Trachoma, an ancient and neglected tropical disease, remains the world's leading cause of preventable blindness. Repeated conjunctival infection by Chlamydia trachomatis during childhood can trigger a poorly understood and chronic inflammatory-scarring response in the eyelids. The eyelids eventually roll inwards (trichiasis) so that the eyelashes scratch the surface of the cornea and blinding corneal opacification develops. A team led by Prof Matthew Burton at London School of Hygiene & Tropical Medicine is seeking to identify why some people are more likely to develop chronic inflammation resulting from ocular *C. trachomatis* infection and also identify the key disease pathways that result in scarring of the eye. This will enable assessment of whether these pathological pathways can be interrupted by interventions such as treatment or vaccination.

A longitudinal cohort study was established in three trachoma-endemic villages in northern Tanzania. Over 600 children aged 6-10 years were enrolled and visited every three months for four years. Eyes were examined for clinical signs of trachoma and swabs were collected for the molecular detection of *C. trachomatis* and assessment of the expression of 46 immuno-fibrogenic genes. Dried blood spots were collected at the final timepoint for measurement of antibodies to key chlamydial antigens. Progressive scarring trachoma was determined by comparison of conjunctival photographs at baseline and the final timepoint.

A fieldworker collects dried blood spots from a study participant's finger.

Why is this research necessary?

Current trachoma control strategies focus on reducing the burden of *C. trachomatis* infection within endemic communities through the use of repeated mass antibiotic distribution and improved hygiene and sanitation. However, there are challenges with compliance to these interventions and their long-term effectiveness in halting the progression of scarring trachoma is unknown. Conjunctival inflammation often persists and new cases of scarring and trichiasis continue to develop in formerly endemic communities long after *C. trachomatis* becomes undetectable. There is currently no treatment to halt scarring progression.

In some areas, the prevalence of trachoma remains high despite many years of antibiotic distribution. A considerable amount of effort is being put into the development of an anti-chlamydial vaccine, which offers the hope that repeated mass antibiotic treatment of endemic populations would no longer be necessary. These efforts to develop a suitable vaccine are being held back by a limited understanding of how the pathological consequences of chlamydial infection develop.

What is the research impact?

The primary outcome of this project is to identify the host immune responses involved in resolution of chlamydial infection and those associated with pathological inflammation and scarring. This will have substantial importance for the development of a vaccine that can prevent chlamydial infection without provoking immunopathology. It might also enable targeted treatment to halt scarring progression.

This project has also described the key clinical factors associated with disease progression. The longitudinal data revealed that a particular type of inflammation (conjunctival papillary inflammation) was most strongly associated with scarring progression, and the pathological effect of *C. trachomatis* infection on scarring was mediated through this type of inflammation. The use of this clinical sign in surveillance programmes could provide a more accurate measure of those at risk of future blinding complications.

Dr Tamsyn Derrick, LSHTM

"... efforts to develop a suitable vaccine are being held back by a limited understanding of how the pathological consequences of chlamydial infection develop."

Arboviruses: early warning systems and optimized control strategies

Find out more:

What is the research?

By transmitting dengue, chikungunya, Yellow fever and Zika viruses, *Aedes aegypti* mosquitoes exert a huge toll on global health. This mosquito species is highly invasive, concordantly expanding arbovirus global distribution each year. As recently demonstrated by the Zika Public Health Emergency of International Concern, international travel of virus-carrying individuals into *Aedes*-endemic regions can spark huge epidemics infecting millions.

Research by Dr Laith Yakob, Associate Professor at the London School of Hygiene & Tropical Medicine, is addressing the epidemiology of these arboviral infections on multiple fronts. This work is supported by the MRC, Wellcome Trust, Bill & Melinda Gates Foundation, the European Union's Horizon 2020 programme, and Australia's National Health and Medical Research Council.

Aedes aegypti mosquito (primary vector of human arboviruses). *Credit: James Gathany, CDC.*

One research stream involves the mapping of disease and vector distributions, and using flight (and road-travel) data to inform connectivity of endemic regions. Knowledge of this connectivity, combined with both local and travel-origin meteorological data, is then used to construct i) meta-population models to determine the retrospective routes of spread, and ii) statistical models to inform early-warning systems for future arboviral outbreaks.

Another research stream involves the investigation of novel tools for controlling *Aedes* mosquitoes. This includes using mathematical models to inform optimal mosquito control utilising cutting-edge technologies such as *Wolbachia* bacteria transinfection. When infected with *Wolbachia* bacteria, arboviral replication within these mosquitoes is inhibited. Following a successful release of *Wolbachia*-infected mosquitoes in Australia, this has arguably become the most promising approach in arbovirus control, and is currently being trialled in 12 countries around the world. Computational tools are being developed to determine where this strategy can be anticipated to work best – either standalone or as part of a modernized integrated vector management strategy.

Why is this research necessary?

Despite significant investments, arboviral infections (particularly dengue virus) are maintaining a steady upward trend. Increased globalisation and international travel simultaneously expands the regions at-risk of outbreaks and facilitate the ease with which infections can spread between them. Vaccines are either absent (Chikungunya, Zika) or far from optimal in their effectiveness (Yellow fever, dengue). Treatment is generally restricted to alleviating symptoms only. Evidence for effective vector control using traditional approaches (e.g. insecticidal spray) is lacking. Novel arbovirus vector control tools are desperately needed, along with sound strategy in their implementation.

What is the research impact?

Understanding spread improves our ability to predict spread; and this forms an integral component of early warning systems to intensify targeted arbovirus surveillance and control. Reliable predictions and model-informed control strategy not only have the capacity to impact human health but also to reduce costs incurred by infectious diseases and their control. Improved cost-effectiveness of control expands its applicability to resource-poorer settings – critical for equitable global coverage. Further, capitalising upon models to inform the strategic deployment of the limited available arbovirus control options is imperative for maximising their sustainability.

Dr Laith Yakob, LSHTM

"Despite significant investments, arboviral infections (particularly dengue virus) are maintaining a steady upward trend. Increased globalisation and international travel simultaneously expand the regions at-risk of outbreaks and facilitate the ease with which infection can spread between them."

Optimising WHO's treatment strategies for schistosomiasis

Find out more:

What is the research?

Schistosomiasis is an endemic parasitic disease affecting millions of people. The World Health Organization (WHO) has recommended treatment guidelines to achieve morbidity control and elimination as a public health problem (defined by reducing prevalence of heavy-intensity infections in school-aged children to ≤5% and ≤1%, respectively). Monitoring and evaluation (M&E) activities are used to collect data which are required to inform and assess treatment strategies for schistosomiasis. Due to programmatic and financial constraints, infection data are typically collected from school-aged children (SAC) as they are relatively easy to sample and are most likely to be infected. However, adults may also form a large proportion of those infected.

To determine whether the burden of infection in adults will impact the treatment strategy required to reach the WHO goals, a group at Imperial College London have incorporated different age-intensity profiles of infection into a mathematical model .The age-intensity profiles corresponded to low, moderate and high burdens of infection in adults relative to SAC. The group then investigated whether the age distribution of infection impacts the model generated recommendations of the treatment coverage levels required to achieve the WHO goals.

Why is this research necessary?

It is important that M&E data are collected from appropriate age groups in order to inform the optimal treatment strategy for a defined region. This work is necessary because it determines whether collection of data from SAC is enough or if broader age-range data is required from M&E activities. As this data is used within mathematical models to determine the treatment coverage levels required, it is vital to ensure that the correct data is collected.

What is the research impact?

Currently, there are ongoing discussions on M&E activities for schistosomiasis, including which age groups need to be monitored. The group's analysis shows that in moderate prevalence settings, data from SAC is sufficient as treating SAC-only is likely to reach the WHO goals, regardless of the burden of infection in adults. However, in high prevalence settings, data needs to be collected from adults, as well as SAC. Here, treatment of SAC and adults is required to reach the WHO goals, with coverage levels varying with the burden of infection in adults. Hence, the optimal treatment strategy requires consideration of the burden of infection in adults as it cannot be based solely on the level of infection in SAC. This research will strengthen M&E activities allowing for more accurate determination of the treatment strategies required for achieving the WHO schistosomiasis goals.

Dr Jaspreet Toor & Prof Sir Roy M Anderson,
Imperial College London

"It is important that M&E data are collected from appropriate age groups in order to inform the optimal treatment strategy for a defined region."

Child fishing in a lake in Montepuez, Mozambique.
Credit: Dr Anna Phillips.

Schistosomiasis elimination research in Zanzibar

Find out more:

What is the research?

The Natural History Museum (NHM) acts as a WHO Collaborating Centre for schistosomiasis and is much involved in the control and elimination of this debilitating disease across Africa. The NHM was the lead partner in a 5-year operational research programme to investigate the elimination of urogenital schistosomiasis on the islands of Zanzibar (Pemba and Unguja). The Zanzibar Elimination of Schistosomiasis Transmission (ZEST) project involved the Zanzibar Ministry of Health in Unguja, Public Health Laboratory-Ivo de Carneri in Pemba, Schistosomiasis Control Initiative at Imperial College, and Swiss Tropical Public Health Institute in Basel. The main objective of the project was to implement a trans-disciplinary intervention study involving snail control and behavioral change interventions along with bi-annual mass drug administration (MDA) of praziquantel and to assess the impact of the interventions for urogenital schistosomiasis elimination in 90 study schools and communities.

Why is it important?

Many African countries have been implementing MDA with the drug praziquantel in schistosomiasis endemic areas for several years. These efforts have resulted in a reduction of prevalence and intensity of infection and the associated morbidity. The question faced by successful programmes is how to transition from morbidity control to elimination of the disease. The ZEST project was designed to assess how intensified interventions could be developed and used to achieve elimination as public health problem and interruption of transmission. Central to the project was the significant increase in drug treatments to the whole community at risk, the introduction of snail control to reduce transmission using niclosamide, and the development of behavioral change tools. Lessons learnt in Zanzibar are valuable for developing elimination strategies for the much larger endemic areas of mainland Africa. Important findings included:

- The overall *S. haematobium* prevalence in children and adults decreased to below 3% on both islands. Elimination as a public health problem was achieved in most study schools and shehias. Transmission was not interrupted.
- Snail control was regularly conducted at more than 100 human water contact sites on each island. Snails returned quickly after niclosamide treatment. The number of *S. haematobium* cercariae shedding snails was very low (<1%).
- Behavior change interventions and a toolkit were developed with the local community. Laundry platforms at safe water sources to reduce water contact were well used. Children targeted by behavioral interventions reported significant changes in risk behavior.

What will its impact be?

A number of important insights were gained,which will help to guide future research and implementation of control and elimination activities in Zanzibar and elsewhere.

- Some areas were designated transmission hotspots due to rapid resurgence of infections in some years. In future, greater attention should be given to scaling up interventions in these hotspots.
- A single urine filtration is not very sensitive to identify light intensity infections. The true *S. haematobium* prevalence might be higher than the observed one. Better diagnostic tools are urgently needed.
- Treatment of a large percentage of healthy people in low-endemic areas might require a different intervention approach than MDA in the future.

Professor David Rollinson, Natural History Museum

School children in Zanzibar taking part in “Kichocho Day”. Kichocho is Swahili for Schistosomiasis. *Credit: Dr Bobbie Person.*

“Lessons learnt in Zanzibar are valuable for developing elimination strategies for the much larger endemic areas of mainland Africa.”

Supporting the response to the Democratic Republic of Congo's Ebola outbreak

Find out more:

What is the research?

Ebola virus disease is a zoonotic disease first recognised in 1976 in Central Africa. Humans can be infected from contact with infected animals or through direct contact with infected human patients or body fluids. It is a severe illness and about half of the patients diagnosed with Ebola virus disease die. There is currently no proven treatment or licensed vaccine available. A range of potential treatments are being evaluated and an experimental vaccine proved highly protective in a major trial in 2015.

The Ebola virus epidemic in West Africa in 2014-16 was the largest, most persistent outbreak and marked the first time the virus spread outside the African continent. The ongoing Ebola outbreak in North Kivu Province in the Democratic Republic of the Congo (DRC) was first reported in May 2018 and is the second largest outbreak to date.

The Imperial College Ebola Response Team, part of Imperial's MRC Centre for Global Infectious Disease Analysis, is supporting the work of the DRC Ministry of Health and the WHO to respond to this current outbreak. Imperial's Ebola Response Team's role includes real-time, ongoing analysis of data on reported cases, providing estimates of transmissibility and projections of likely future incidence and bed demand.

Why is this research necessary?

Transmission of Ebola virus disease can be reduced and controlled by early diagnosis, patient isolation and care, infection control, safe and dignified burial of people who have died from Ebola virus disease, rigorous tracing of contacts, and, more recently, the targeted use of an experimental Ebola vaccine.

Each Ebola outbreak is unique and presents different challenges. This current outbreak is located on the eastern border of DRC in an active conflict zone amidst prolonged humanitarian crises. The limited access and availability of health services and the involvement of a large urban centre which is well connected to the capital city of Kinshasa and neighbouring countries increases the risk of further spread. Combined, these factors make this outbreak the most complex and high risk ever experienced by the DRC. This presents an incredible challenge to local and international health authorities.

What is the research impact?

Real-time analysis and modelling of the outbreak can help inform situational awareness and helps the planning and allocation of resources to optimise interventions to control the outbreak. Estimates of transmissibility can help us understand the effectiveness of current control measures and whether the epidemic is coming under control. On the other hand, projections of future incidence are helpful to recognize and plan for short-term logistical needs (for example number of hospital beds) and healthcare requirements in specific areas.

Dr Anne Cori & Dr Natsuko Imai, on behalf of the Imperial College Ebola Response Team, Imperial College London

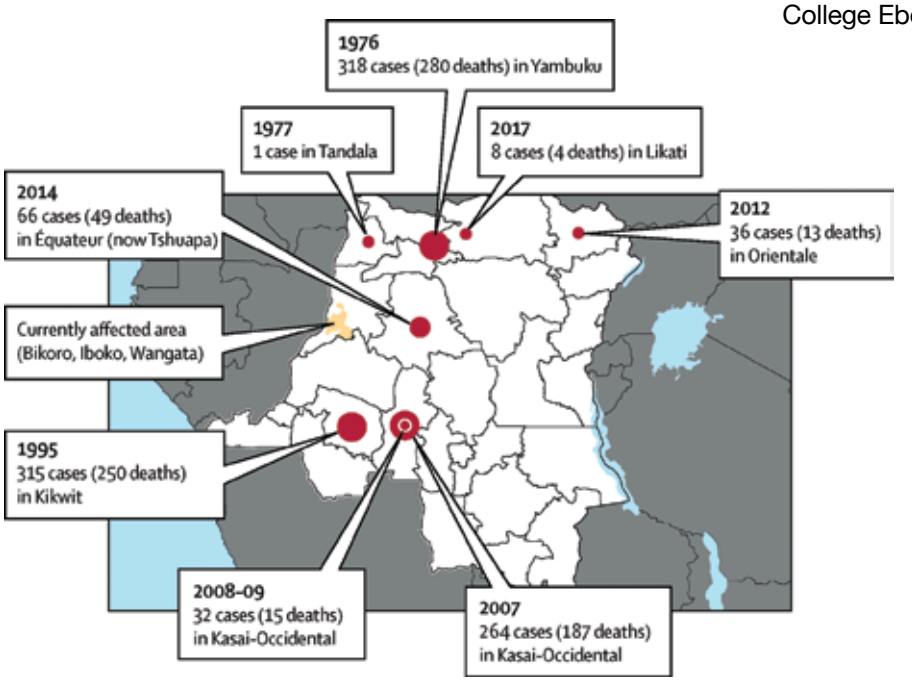


Figure 3. Past outbreaks of Ebola virus disease in the Democratic Republic of the Congo, 1976-spring 2018 *(from: The Ebola Outbreak Epidemiology Team, 2018. Outbreak of Ebola virus disease in the Democratic Republic of the Congo, April-May, 2018: an epidemiological study. Lancet 2018; 392: 213-221).*

"Real-time analysis and modelling of the outbreak can help inform situational awareness and helps the planning and allocation of resources to optimise interventions to control the outbreak."

DeWorm3: Demonstrating the feasibility of interrupting the transmission of soil-transmitted helminths

Find out more:

What is the research?

An estimated 1.45 billion people are infected with at least one species of soil-transmitted helminth (STH). Identifying strategies to interrupt the transmission of these parasites will have significant public health impacts.

Current World Health Organisation (WHO) STH guidelines recommend delivering preventative chemotherapy through mass drug administration (MDA) campaigns targeting children living in areas where 20% or more are infected. Adults are not typically targeted by MDA campaigns, and as a consequence, adults may sustain transmission by acting as reservoirs for continued reinfection of treated children.

It may be possible to interrupt the transmission of STH using chemotherapy alone – with an intensified community-wide MDA strategy that delivers deworming medicines to eligible people of all ages twice per year.

To demonstrate the feasibility of eliminating STH, the Bill & Melinda Gates Foundation is supporting the Natural History Museum (NHM) to undertake the DeWorm3 Project. With the NHM acting as a central coordination hub, the project is an innovative research collaboration that draws on the expertise of fellow LCNTDR members, London School of Hygiene & Tropical Medicine and Imperial College London, as well as other global partners.

The goals of the DeWorm3 Project are to:

- Develop epidemiological and operational definitions of STH transmission interruption.
- Demonstrate the feasibility of interrupting STH transmission through MDA in settings where lymphatic filariasis programmes have progressed to post-MDA surveillance.
- Recommend a feasible and effective approach for scaling up STH transmission interruption programmes.

"Demonstrating the feasibility of breaking STH transmission through chemotherapy alone will provide the evidence base for the WHO to extend a future global target from control to elimination."

Why is this research necessary?

STH infections of moderate to heavy intensity can cause various health problems, including abdominal pain, anaemia, malnutrition, and growth retardation. The global target for STH control is to eliminate morbidity due to STH in children by 2020, attained by regularly treating at least 75% of children in endemic areas. If DeWorm3 can demonstrate the feasibility of breaking STH transmission through chemotherapy alone, this would provide an evidence base for the WHO to extend a future global target from control to elimination.

What is the research impact?

The research has so far resulted in a clear epidemiological and operational definition of STH transmission interruption. Field trials comparing standard-of-care child targeted MDA versus community-wide MDA are underway. To date, DeWorm3 has censused and enrolled almost 370,000 child and adult participants throughout the study sites in India, Malawi and Benin, and has delivered MDA in at least two consecutive rounds in each site. Alongside proof-of-concept studies, detailed implementation and cost-effectiveness assessments are being conducted to inform the development of scalable strategies to deliver community-wide MDA.

In collaboration with country Ministries of Health and Education, the WHO and numerous other international partner organisations, DeWorm3 will generate evidence to inform future efforts to reduce or eliminate the global health impacts of STH.

Catherine Wheller, Natural History Museum

A family in Benin receives deworming medication. Treatment is given to some families twice per year, with both adults and children taking the deworming medication. In the control areas, only children will receive the medication.

A xenomonitoring system for visceral leishmaniasis in India

Find out more:

What is the research?

Setting the Post-Elimination Agenda for Kala-Azar in India (SPEAK India) is a multinational consortium of researchers, technical experts and government officials, aiming to achieve and sustain visceral leishmaniasis (VL), also known as kala azar) elimination in India. SPEAK's portfolio covers four broad areas of research: human surveillance of VL, transmission of VL, health systems strengthening, and modelling.

The primary focus of the transmission workpackage, led by researchers at the London School of Hygiene & Tropical Medicine and Rajendra Memorial Research Institute of Medical Sciences (Patna, India) is to ascertain the feasibility, scalability and cost-effectiveness of xenomonitoring as a VL surveillance method when the number of human cases is very low. Xenomonitoring involves detecting the infective forms of the causative parasite of VL, *Leishmania donovani*, in its sandfly vectors, rather than the human population. Xenomonitoring is non-invasive, thereby presenting fewer ethical issues compared with screening human populations, is possibly more sensitive than traditional passive surveillance systems and more cost effective than active case detection. It indicates when transmission has been stopped, and provides information on the transmission dynamics of VL. It therefore has the potential to significantly aid the Government of India in its goal to achieve elimination of VL as a public health problem (defined as <1 case/10,000 population at the district level), and sustain elimination in the future.

Why is this research necessary?

One factor currently hindering the utilization of xenomonitoring in VL surveillance is that standard methods of collecting *Phlebotomus argentipes* sandflies, namely Centres for Disease Control light traps, mouth aspiration and sticky traps, have not been successful in capturing large numbers of *P. argentipes* in most studies. Research into alternative methods of collecting sandflies is sparse, and does not include consideration of new standardisable suction-based techniques, such as large mechanical vacuum aspirators and improved Prokopacks.

Filling this knowledge gap provides necessary information not only for the advancement of a xenomonitoring system for VL, but also improves transmission models and surveillance of *P. argentipes* in India. Therefore, as a first step in developing an effective xenomonitoring system, researchers working on this project have conducted a field trial comparing the efficacy of CDC light traps (control) with improved Prokopack aspirators and large mechanical aspirators.

What is the research impact?

The three trapping methods under investigation were tested in four villages in Bihar state (northern India), two endemic for visceral leishmaniasis and two non-endemic, over the course of three month in 2018. The team was successful in capturing over 7,000 sandflies, which are currently being molecularly speciated and assessed for bloodmeal source and infection with *Le. donovani.* When these results are available, researchers will have a better indication of which trapping method is most appropriate for trapping large numbers of *P. argentipes,* bloodfed females, and infected female *P. argentipes*. In the future this will encourage a more nuanced and informed selection of trapping method depending on the research question being investigated. Additionally, it will facilitate further development of xenomonitoring for VL, and routine monitoring of *P. argentipesas* an indicator of VL control programme progress.

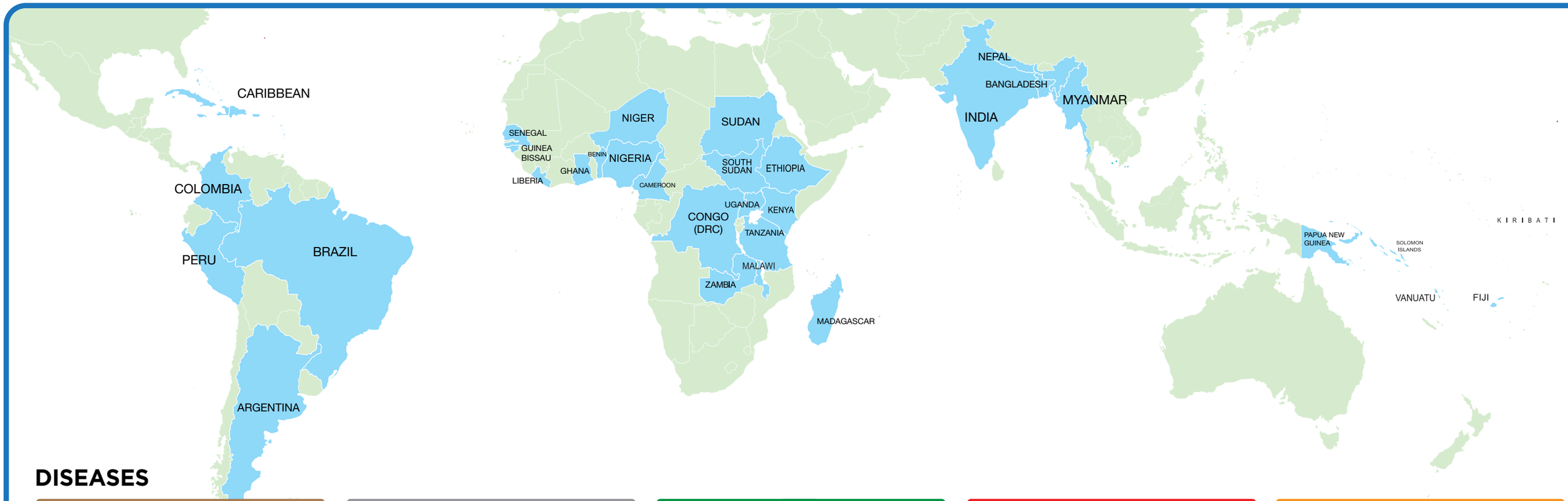
Shannon McIntyre, LSHTM

One of SPEAK's four study villages in Bihar, northern India.
Credit: Shannon McIntyre.

"Xenomonitoring involves detecting the infective forms of the causative parasite of VL, *Leishmania donovani*, in its sandfly vectors, rather than the human population."

WHERE, WHAT & HOW – LCNTDR RESEARCHERS' EXPERTISE BY NUMBERS

LONDON CENTRE FOR NEGLECTED TROPICAL DISEASE RESEARCH



DISEASES

WORMS

Food-borne trematodiases	2
Loa loa	3
Lymphatic filariasis	26
Onchocerciasis	15
Schistosomiasis	64
Soil transmitted helminths	39
Taeniasis/cysticercosis	2

VIRUSES

Chikungunya	5
Dengue	27
Ebola	7
Rabies	1
Yellow fever	4
Zika	12

BACTERIA

Buruli Ulcer	1
Leprosy	12
Trachoma	35
Yaws	3

PROTOZOA

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Human African trypanosomiasis	20
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Dicrocoeliosis	1
Scabies	5
Toxoplasmosis	1

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Explore the NTD Research Directory:

Identifying the best surgical management to treat the blinding stage of trachoma

Find out more:

What is the research?

Trachomatous trichiasis (TT), the blinding stage of trachoma, is the inward rotation of the eyelid margin and the eyelashes into the eye from progressive conjunctival scarring following recurrent inflammation triggered by *chlamydia trachomatis* infection. The eyelashes constantly scratch the cornea resulting in pain and corneal opacification, ultimately leading to irreversible blindness. About 1.2 million people are irreversibly blind, and more than 3 million people are at immediate risk of blindness from trachoma.

The World Health Organisation (WHO) recommends surgical correction of the in-turned eyelid to avert the risk of blindness by preventing corneal opacification from the trichiasis. In most trachoma-endemic settings, the surgery is mainly performed by non-ophthalmologists. Various surgical procedures have been tried before but the most commonly used are the Bilamellar Tarsal Rotation (BLTR) and the Posterior Lamellar Tarsal Rotation (PLTR).

A randomised controlled surgical trial was conducted in Ethiopia in collaboration with LSHTM, the Carter Center and the Amhara Regional Health Bureau to determine which of the two commonly used surgical procedures provide the best result under programmatic conditions. As part of this trial 1000 individuals with TT were enrolled, examined, and randomly assigned to receive either BLTR or PLTR surgery. The patients were re-examined at 6 and 12 months after surgery by assessors masked to the type of surgical management provided.

Taking ocular pictures for independent masked assessment.

Why is this research necessary?

Poor surgical outcomes have been a major challenge for surgical programmes and the global effort to eliminate trachoma by 2020. In approximately 20% of cases, trichiasis returns a year after surgery. Whilst several factors may contribute to this recurrence, the type of surgical procedure is among the major determinants of outcome. Previous trials showed that the BLTR is better than other surgical procedures, leading the WHO to recommend it as the preferred procedure to treat TT. However, the BLTR and PLTR procedures have not been adequately compared and their relative effectiveness was not known. There is a global effort to scale-up surgical output and improve treatment outcomes for millions of people with TT. And as such, which of the two commonly used surgical procedures (BLTR and PLTR) provides the best results under operational conditions has become a priority research question for the WHO.

What is the research impact?

The trial results showed that PLTR surgery was superior to BLTR surgery for the management of trachomatous trichiasis with lower trichiasis recurrence and fewer intra-operative and immediate post-operative complications. The trial results changed global policy on the surgical management of TT, leading the WHO to update its recommendations of the surgical treatment of choice to managing TT. The WHO now recommends that new trichiasis surgeons should be trained to use the PLTR, shifting away from the BLTR being the treatment of choice. Currently, trachoma control programmes worldwide are using the PLTR surgical procedure to deliver surgical services for TT cases.

Dr Esmael Habtamu Ali, LSHTM

"The trial results changed global policy on the surgical management of TT leading the WHO to updating the surgical treatment of choice to managing TT."

FibroScHot – Eliminating childhood fibrosis by optimizing treatment of schistosomiasis hotspots

Find out more:

What is the research?

Gastrointestinal schistosomiasis caused by *Schistosoma mansoni* is a devastating neglected tropical disease (NTD). Without control and disease management strategies, those infected can experience severe liver damage (and beyond) in the form of periportal fibrosis, resulting in raised blood pressure and portal hypertension. In its severest form, this can lead to sufferers vomiting blood (haematemesis) and ultimately death. Mass drug administration (MDA) of the safe and efficacious drug praziquantel (PZQ) is the cornerstone of international efforts to control schistosomiasis as a public health problem.

In lower transmission areas, MDA is targeted at school-children, combining the epidemiological knowledge that this age-group suffers the greatest burden of infection with the easier implementation that the education system provides.

FibroScHot is an new initiative which brings together research expertise from Cambridge University, Royal Veterinary College, London School of Hygiene & Tropical Medicine and the Wellcome Trust Sanger Institute, to examine the impact of increased PZQ treatment frequency within the school- structure, in addition to annual community MDA. The programme also aims to elucidate the potential causes and mechanisms involved in these ongoing cases of severe periportal fibrosis morbidity.

The programme's main approach is centred around a superior randomised intervention trial that asks the question: Does increased treatment frequency reduce the prevalence of childhood periportal fibrosis in hotspots of persistent schistosomiasis?

To answer this question FibroScHot employs a multidisciplinary range of analytical tools and measures, encompassing the clinical, immunological and anthropological approaches combined with parasite genomics and genetics, as well as statistical and mathematical analysis.

> "...despite concerted efforts and reported community treatment coverage rates of near 80%, infection intensities have remained extremely high and periportal fibrosis common, and potentially increasing."

Why is this research necessary?

Uganda was at the forefront of the treatment vanguard, first administering MDA in 2003. Amongst the communities first treated were those residing on the shores of both Lake Victoria and Lake Albert.

Childhood fibrosis caused by gastrointestinal schistosomiasis. *Credit: Prof J.R Stothard.*

Recent screenings of school-children in these fishing communities showed that despite concerted efforts and reported community treatment coverage rates of near 80%, infection intensities within the Lake Albert regions alone have remained extremely high and periportal fibrosis common, and potentially increasing, even amongst school-aged children. There is therefore a major need for alternative strategies to understand the reason for, and intervene against, these major 'hotspots' of infection and morbidity.

What is the research impact?

The ultimate aim of the FibroScHot research project is to contribute towards the Sustainable Development Goal 3 that looks to, "Ensure healthy lives and promote wellbeing for all at all ages". It seeks to make this contribution by optimising the use of PZQ to achieve elimination of severe schistosomiasis for future generations in communities where the current standard annual treatment is failing to gain control.

Results will be disseminated to national, regional and international policy makers and to a multi- disciplinary NTD research community, while communication and open access data policies will ensure a wider reach. Alongside the research findings, FibroScHot will built NTD clinical trial infrastructure capacity and provide training for young Ugandan researchers in the anthropological, genomic and immunological skills that will be essential for future clinical and observational studies on NTDs within Uganda and beyond.

Prof Joanne Webster & Dr Elsa Leger,
Royal Veterinary College

Evaluating the impact of deworming strategies for *Loa loa*

Find out more:

What is the research?

Across Central Africa, approximately 10-20 million people are infected with the filarial nematode *Loa loa*. Loiasis has been considered to be mostly a benign disease and thus has not considered among priority neglected tropical diseases by the World Health Organization. However, recent studies have highlighted that the infection can cause an array of severe symptoms (including renal failure and permanent blindness), as well as significantly increase the risk of death. These results suggest that loiasis is a serious public health problem, particularly in highly endemic areas.

Ivermectin is a highly efficacious treatment, but communities where loiasis is highly endemic typically do not receive mass treatment. This is because the few individuals who have a high infection intensity are at risk of severe adverse effects following ivermectin treatment. However, most individuals have low levels of infection and would greatly benefit from taking the drug. To explore the impact that community-based drug distributions would have on infection, transmission, and disease burden, a research collaboration between Imperial College London, Royal Veterinary College and the Université Montpellier have developed a mathematical model of loiasis transmission dynamics (EPILOA).

Why is this research necessary?

Many uncertainties remain surrounding the epidemiology, population biology, pathology, and most importantly, control of loiasis by antiparasitic and antivectorial measures. Mathematical modelling provides a robust and analytical framework through which to explore the potential consequences of different interventions. The models developed as part of this project are being used to evaluate the effectiveness of various ivermectin-based treatment strategies.

What is the research impact?

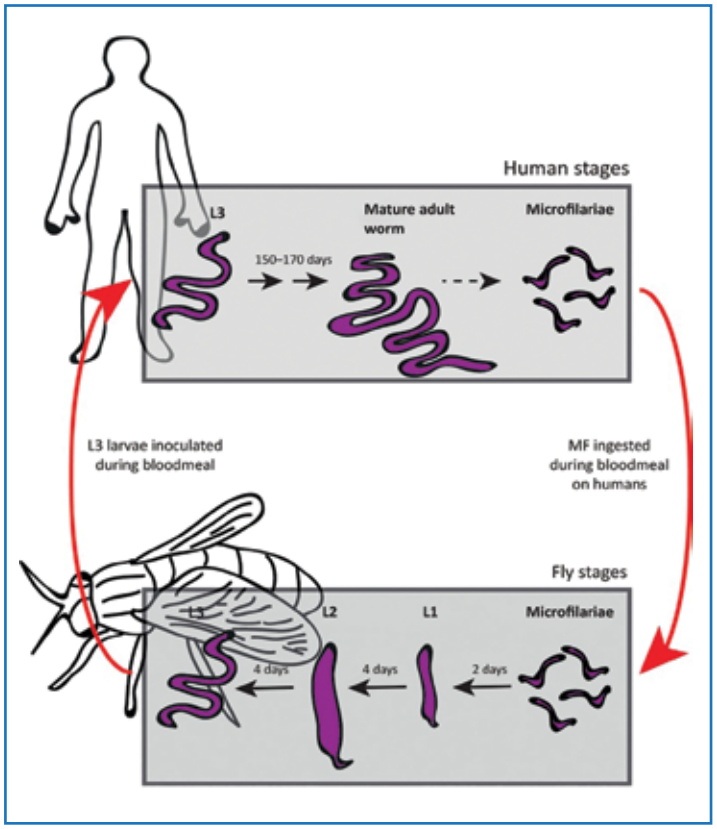
Currently, loiasis is not targeted by drug distribution programmes. Communities where the parasite is highly endemic only receive anti-parasitic drugs if they are co-endemic with onchocerciasis and/or lymphatic filariasis. The research undertaken here suggests that treating loiasis-endemic communities currently not incorporated into control programmes could substantially reduce the burden of loiasis. In conjunction with recent reports on the severe morbi-mortality associated with infection, this work suggests that treating these communities could have a substantial public health benefit.

Given this, future work will investigate the impact of other anthelmintics such moxidectin (similar to ivermectin but far more potent) and albendazole (which is less effective than ivermectin but able to be safely given to individuals with highest infection burden).

Charles Whittaker & Prof Maria-Gloria Basáñez,
Imperial College London

Dr Martin Walker, Royal Veterinary College

Dr Sébastien Pion, Dr Cédric Chesnais &
Dr Michel Boussinesq, Université Montpellier



The Life Cycle and Development of *Loa loa* Across Horsefly and Human Hosts. Credit: Whittaker et al., 2018, Trends in Parasitology 34:4.

"Many uncertainties remain surrounding the epidemiology, population biology, pathology, and most importantly, control of loiasis by antiparasitic and antivectorial measures."

Improved control of bovine brucellosis in Punjab

Find out more:

What is the research?

Brucellosis is an infection shared between animals and people. Infected animals often abort, resulting in losses to farmers. In humans, the infection may result in clinical presentations ranging from, flu-like symptoms in acute cases to long-term recurrent fevers, endocarditis and arthritis. People generally acquire brucellosis through consumption of dairy products from infected animals or direct contact with their parturition fluids or abortions. With joint funding from BBSRC and the Department of Biotechnology (DBT) in India, researchers from the UK and India have studied the frequency of brucellosis in dairy cattle, farm workers and general population in rural Punjab and factors increasing the risk of the disease. The results have been used to make recommendations for sustainable, long-term control of the infection in the livestock reservoir.

Why is this research necessary?

India is the world's leading milk producer following significant development in the dairy industry. Within India, Punjab has the highest per capita production of cattle and buffalo milk of all the States. Cattle brucellosis is known to be present at high levels in Punjab and attempts to expand cattle vaccination have so far had limited success due to limited vaccines supply and uptake from farmers. Before this research the potential impact of more strategic use of vaccines had not been formally studied. Human brucellosis has long known to occur in Punjab, but very limited surveillance in place means that the extent to which the population is exposed and the main routes of exposure remained unknown. By addressing these gaps, the research intends to inform control efforts, including vaccination strategies in livestock and public health education programmes in farm workers and general population.

"Animal and public health officials in Punjab are now using the results and protocols developed during the project."

A veterinarian checking a pregnant cow for a potential miscarriage. *Credit: Javier Guitian.*

What was the impact of this research?

The research has found that in Punjab, contact with cattle may be more important as a route of disease transmission than consumption of cattle dairy products. The general rural population is also at risk because of the commonly held ownership of a few cattle. As a pro-poor intervention, the research showed that these cattle should also be considered for vaccination. In general the age structure of dairy cows in India – where slaughter of cows does not take place – is likely to impact the effectiveness of control programmes. Computer simulation models suggest that targeted vaccination of young animals in high risk herds may be a more acceptable and highly effective strategy to reduce the burden of infection.

Animal and public health officials in Punjab are now using the results and protocols developed during the project. The findings of this work are also being shared more widely across India through the engagement of the research team with the Brucella Free village programme, a pilot control programme that will be rolled out in least ten Indian States, including Punjab.

Prof Javier Guitian, Royal Veterinary College

Spatial analysis of cysticercosis in Colombia

Find out more:

What is the research?

Cysticercosis is a parasitic neglected tropical disease caused by larvae of the pork tapeworm, *Taenia solium*. Cysticercosis is widespread among low- and middle-income countries and neurocysticercosis – resulting from *T. solium* larvae penetrating the central nervous system – is a leading cause of epilepsy and seizures. Colombia has a high burden of cysticercosis which contributes substantially to preventable neurological disease. This work analyses seroprevalence data from a national survey undertaken between 2008 and 2010 to identify spatial clusters and risk factors of cysticercosis.

Why is this research necessary?

The 2012 World Health Organization (WHO) roadmap on NTDs called for a validated strategy towards the control and elimination of cysticercosis. Spatial targeting of interventions to populations most at risk is a key component of successful and resource-optimised strategies. This work illustrates how spatial analyses of national serosurvey data can be used to identify high seroprevalence areas, spatial clusters or 'hotpots' of infection, socio-economic and individual-level risk factors. Such analyses are the precursor to targeted interventions.

What is the research impact?

Cysticercosis is distributed throughout Colombia (Figure 1) and three distinct clusters of high seropositivity were identified (Figure 2). Indicators of low socioeconomic status, low educational level, pig ownership and poor water sanitation and hygiene were identified as risk factors for seropositivity to cysticercosis. Dog ownership was also identified as an independent risk factor, raising the notion that dogs may have a role in transmission. These results will help prioritize and target public health interventions to the most vulnerable and most at-risk populations in Colombia. The approach illustrates the important role that spatial analyses have in supporting the WHO's control and elimination goals for *T. solium* cysticercosis.

Dr Erika Galipò, Dr Kim Stevens &
Dr Martin Walker, Royal Veterinary College

Matthew Dixon, Dr Zulma Cucunubá &
Prof Maria-Gloria Basáñez, Imperial Colege London

Astrid Carolina Florez, Instituto Nacional
de Salud, Bogotá, Colombia

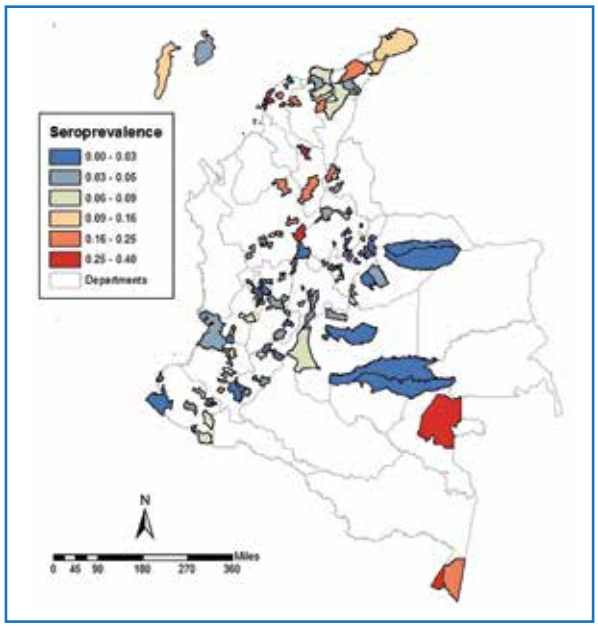


Figure 1. Seroprevalence of *T. solium cy*sticercus antibodies in 133 municipalities in Colombia. Departments are shown in pale grey lines and sampled municipalities in block colours. The serosurvey was conducted between 2008 and 2010.

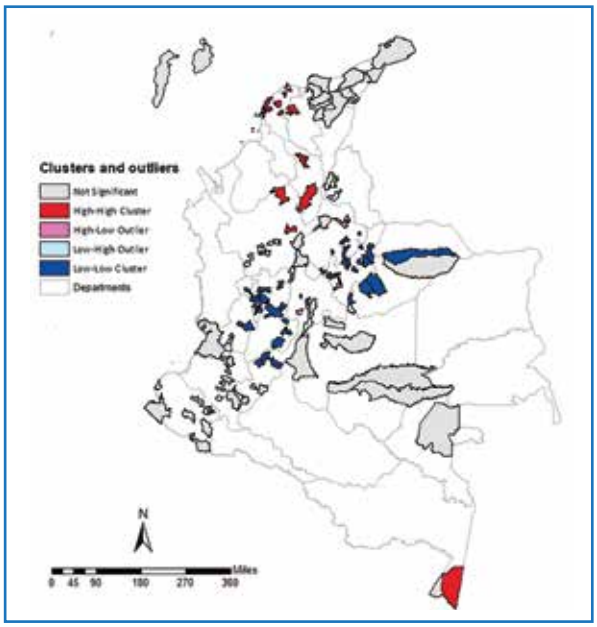


Figure 2. Local Indicators of Spatial Association map identifying 'hotspots' and 'coldspots' of seropositivity to *T. solium* cysticercus antibodies in 133 municipalities in Colombia. Departments are shown in pale grey lines and sampled municipalities in block colours.

"Spatial targeting of interventions to populations most at risk is a key component of successful and resource-optimised strategies."

Understanding how to retain, motivate and improve the performance of community drug distributors

Find out more:

What is the research?

At the heart of mass drug administration (MDA) programmes for neglected tropical diseases (NTD) are a cadre of individuals called, Community Drug Distributors or Community Directed Distributors (CDDs). These individuals are recruited by the national programme or by their communities to sensitise their fellow community members, deliver NTD treatments and report on their progress. Once recruited, there is variability in the training CDDs receive, the distances they cover, their supervision and any financial incentives available for their work.

The research team, iCHORD (Improving Community Health Outcomes through Research and Dialogue: www.ichord.org) aims to understand what motivates CDDs and to test practical and inexpensive interventions that might improve motivation, contributing to improved CDD performance and retention. Over a two year period, iCHORD has worked closely with the Ministries of Health in Cote d'Ivoire and Uganda and their national research and implementing partners.

The Improving Community Health Outcomes through Research and Dialogue (iCHORD) team. Dr Alison Krentel, front row 3rd from left.

This collaborative project is led by researchers from Canada (Bruyère Research Institute, LSHTM-affiliated researcher), Ghana (University of Health and Allied Sciences), Kenya (African Institute for Health and Development), the USA (Emory University), and WHO TDR. Funded by the Bill and Melinda Gates Foundation and the UK Department for International Development through the Task Force for Global Health, this two year implementation research project uses mixed methods design to explore CDD perspectives, communities' opinions about CDDs and frontline health workers' attitudes.

Why is this research necessary?

For many NTD programmes, CDD motivation has become a significant concern as attrition rates and poor performance amongst CDDs risk reducing the efficiency and effectiveness of elimination programmes. One of the bottlenecks to improving CDDs' motivation is the prevailing belief that if NTD programmes had money to pay CDDs (per diem, honorarium), then they would perform better and there would be better retention. Because this is often not an option, a circular discussion begins with no clear end in sight, e.g. lack of additional programme funds means no improved motivation.

What was the impact this research?

Baseline data from selected districts in Cote d'Ivoire and Uganda revealed that CDDs were motivated, and although financial incentives were important, they were not a sufficient driver of motivation. Rather, non-financial and intrinsic motivations like personal development, relationships with community members and knowledge acquisition were more essential drivers. Some of the challenges CDDs faced included no feedback about their work and community members were not always supportive during MDA, sometimes they were even aggressive. Our results showed that the more connected and supported the CDD feels to the health system and community, the more willing he or she is to continue working in the NTD programme, despite difficulties and lower financial incentive as compared to other health programmes.

To respond to these findings, a set of proposed interventions were implemented. A key consideration for these interventions was that they did not require additional funds for implementation. Interventions included: a system of feedback using text messages in Cote d'Ivoire; a digital tool that could be downloaded onto CDDs' mobile phones to use during MDA; meetings with key community leaders to generate support and accountability for the MDA outcome; and a communication tree to aid CDDs when they encounter questions. Evaluation of these interventions is ongoing, but the initial results are positive.

Dr Alison Krentel, LSHTM

'Our results showed that the more connected and supported the CDD feels to the health system and community, the more willing he or she is to continue working in the NTD programme...'

Why moving populations makes onchocerciasis elimination more difficult

Find out more:

What is the research?

Onchocerciasis (known as River Blindness), is a vector-borne neglected tropical disease caused by the parasite *Onchocerca volvulus* and transmitted via the bites of *Simulium* blackflies. The World Health Organization has proposed the elimination of onchocerciasis by 2020 where feasible, and the African Programme for Onchocerciasis Control re-defined these goals to elimination in 80% of endemic countries by 2025. Ghana started treatment programmes with ivermectin (an efficacious anti-parasitic medicine), towards the end of the 1980's. However, reports of people not responding well to treatment have been documented and the disease persists in many areas. Mathematical models can help to understand trends towards elimination, but most models consider that the parasites live in isolated populations in human communities. Human movement may transport parasites between inter-connected villages, and this may explain disease persistence or reintroduce the infection in communities responding well to regular treatment.

Why is this research necessary?

Mathematical models of onchocerciasis have highlighted the need to achieve and maintain high levels of coverage and adherence to, as well as increase the frequency of mass ivermectin treatment. These models typically assume closed populations. Connectedness between endemic foci may help to stabilise prevalence and make elimination more difficult if coverage levels and progress towards elimination differ markedly between connected foci. This study aims at understanding patterns of treatment adherence and population movement between and outside onchocerciasis-endemic communities in Ghana. The data generated will be used to inform spatial onchocerciasis models which are under development within our research group.

What is the research impact?

In Ghana, onchocerciasis persists despite long-term interventions.This study was conducted in five community clusters whose responses to ivermectin had been well characterised (parasitologically, entomologically and genetically), namely, Asunbende–Senyase, Baaya, Ohimpe, Kyingakrom and New Longoro in the Brong Ahafo region. Data from 480 individuals were obtained through interview using a purpose-designed questionnaire. 70% (of 386 eligibles) reported adherence to biannual treatment in 2017 (range: 51%, Kyingakrom–81%, Asubende–Senyase).

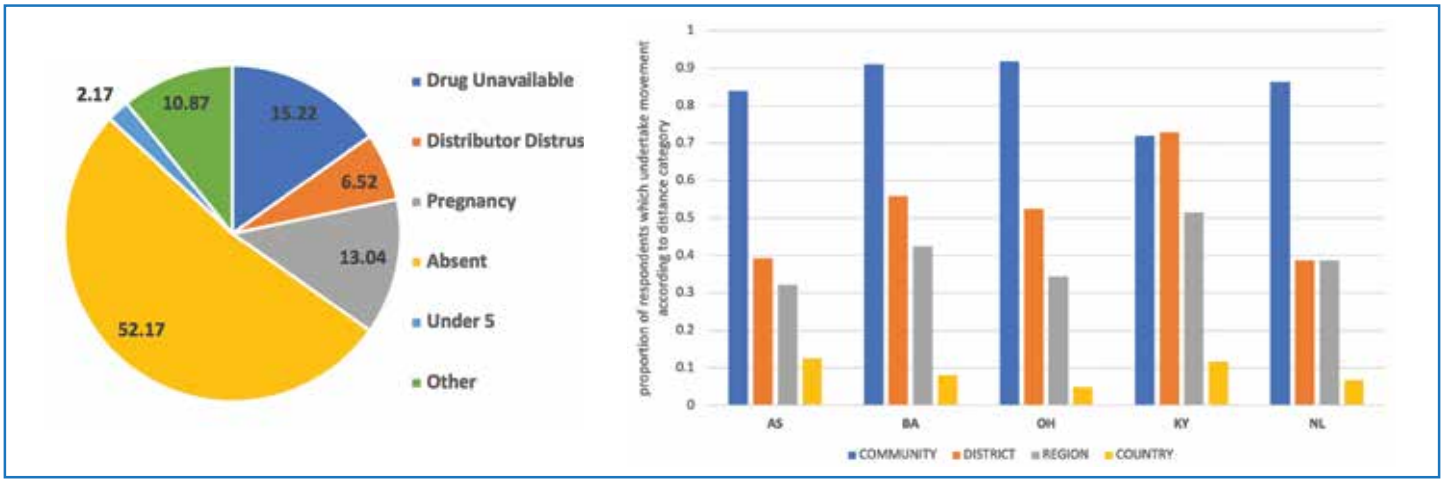
The principal factor affecting non-compliance was being absent during distribution. The proportion of the population undertaking movement decreased with increasing distance category (between communities within districts (closest), between districts within regions, between regions within Ghana and outside the country (farthest)). Kyingakrom had the lowest proportion of the population moving at community level but the highest at district and regional levels.

This is the first study investigating population movement patterns in onchocerciasis endemic communities. Greater understanding of seasonal population movement and transmission patterns would help achieve better timing of biannual ivermectin distribution to increase treatment adherence. These results will be used to motivate spatially-explicit onchocerciasis epidemiological models.

Plummer Hamilton, Dr Simon O'Hanlon, Philip Milton & Prof Maria-Gloria Basáñez, Imperial College London

Dr Martin Walker, Royal Veterinary College

Dr Mike Y. Osei-Atweneboana, Water Research Institute, Accra, Ghana



Left panel: *Reasons for non-adherence represented as a percent of respondents who did not comply with biannual ivermectin in 2017.*
Right panel: *The proportion of respondents which undertake movement according to distance category (between communities within districts (blue bars), between districts within regions (orange), between regions within Ghana (grey) and outside the country (yellow)) and community cluster (Asunbende–Senyase (AS), Baaya (BA), Ohiampe (OH), Kyingakrom(KY) and New Longoro (NL)).*

A trachoma public health team arrive unexpected at the field site to assess people for disease. *Credit: M. Gupta-Wright.*

Find out more:

Thinking critically about trachoma and its public health strategies

What is the research?

Trachoma is the commonest infectious cause of blindness in the world, disproportionately affecting the most disadvantaged populations. Like other infectious diseases, trachoma's framing within public health is dominated by biomedicine, prioritising the bacteria, *C.trachomatis*, and overlooking diverse patterns of disease, local experiences and cultural, social and political conceptualisation amongst different populations. This context-free model influences the framing of trachoma as a global public health problem and, in turn, the establishment of technocratic public health interventions.

This research uses the methods and theory of critical medical anthropology to challenge this way of thinking about trachoma. This approach looks at how broader ideas about health and misfortune, interactions with health care, social relationships, living environments, political economies and historical contexts, can illuminate unforeseen consequences of Malawi's trachoma elimination policy.

Using ethnographic methods, the researcher lived amongst a population labelled a 'hotspot' of trachoma disease in Malawi, participating in daily village life. Fieldwork included following the translation of a multi-million-pound trachoma elimination strategy nationally, regionally and locally to this particular area and population.

Learning about local daily practices, concerns, motivations and challenges, led to a greater understanding of trachoma, how it is discussed, embodied, and experienced by those suffering from symptoms, those targeted by public health campaigns, and those delivering trachoma interventions.

Why is this research necessary?

Global WHO-endorsed targets exist to eliminate trachoma disease by 2020, however 'hotspot' populations present particular challenges and are currently ill-researched.

There is an on-going tendency in global health to prioritise biomedical interventions, numerical targets, and principles of objectivity and generalisability, and to assume universal disease experience, ignoring the complexity of everyday human life in the understanding of health and disease.

Despite developments in policy rhetoric recognising the importance of the socioeconomic determinants of health, health systems, capacity building, and principles such as 'community engagement' and 'local ownership', difficulties in intervention implementation are often attributed to a poor understanding, ignorance or unwillingness of intended beneficiaries.

Infectious disease control, elimination or eradication policies remain predominantly the work of the global 'north' in the global 'south'. Donor, policymakers and, in turn, implementing organisations display a degree of strategic ignorance and misplaced assumptions leading to unforeseen consequences for the populations they set out to serve. It is rare that research has been able to show such phenomena in practice.

What is the research impact?

In addition to understanding local disease experiences, this research aims to examine the idea of elimination, and trace its repercussions at each layer of the system; to understand how being labelled a 'hotspot' could contribute to inequality and discrimination. The research examines the complexities involved in, and consequences of, delivering public health interventions such as surgical camps to correct eyelid deformities from trachoma.

The research findings will contribute to a dearth of evidence and knowledge between the disciplines of anthropology and public health for trachoma control, other infectious disease control programmes and broader public and global health policy. Opportunities to publish and present to a wide range of professional and public audiences will be sought.

Dr Maddy Gupta-Wright, LSHTM

'Learning about local daily practices, concerns, motivations and challenges, led to a greater understanding of trachoma, how it is discussed, embodied, and experienced...'

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