LONDON CENTRE FOR NEGLECTED TROPICAL DISEASE RESEARCH

AN INNOVATIVE RESEARCH COLLABORATION:

SELECTED RESEARCH HIGHLIGHTS

@NTDResearch

Imperial College London

NATURAL HISTORY MUSEUM

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

RVC Royal Veterinary College University of London

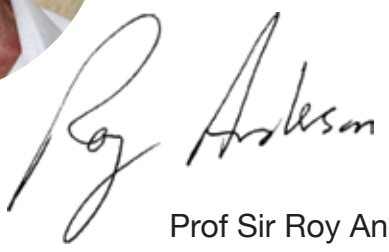
Director's Note

Since its launch in 2012, the London Centre for Neglected Tropical Disease Research (LCNTDR) has worked to coordinate, support and promote high-quality interdisciplinary research on the control and elimination of neglected tropical diseases.

Our Centre now includes four core member institutions, over 200 researchers, and numerous collaborating entities, all with the common goal of increasing the evidence base around the design, implementation, and evaluation of NTD control and elimination programmes. These scientific contributions are vital not only to ensuring that international targets (such as those set by the World Health Organization) are met, but also in order to ensure that policy makers have the most current information when the time comes to reassess and update these goals.

Over the next few years, the LCNTDR and its collaborators will look to promote interdisciplinary research, bringing new techniques to the study of infectious disease transmission and control. This will include new approaches to diagnostics, new mathematical modelling techniques to assess the potential impact of different control options and to define optimum monitoring and evaluation programmes, molecular epidemiological approaches to define who infects whom based on gene sequence analysis, and novel methods for data collection in the field. We are well placed to make rapid progress in these areas, given the depth and breadth of scientific and medical expertise in our research staff at the four core members and our associate members (such as the Wellcome Trust Sanger Institute).

The LCNTDR will continue to provide links internally and externally to the scientific community, engaging with policy makers, industry, governments, and other key stakeholders to ensure that results of our research projects are being properly communicated to those who will use them to increase the efficiency and effectiveness of NTD control programmes.



Prof Sir Roy Anderson, Director, LCNTDR

" Engaging with policy makers, industry, governments and other key stakeholders to ensure that the results of our research projects are being properly communicated."

Informing WHO schistosomiasis strategies through mathematical modelling

Find out more:

What is the research?

Schistosomiasis which impacts on the lives of over 800 million people has been targeted by school-based and community-wide mass drug administration programmes. Analysis shows that school-age children (SAC) are most likely to be infected so treatment is specifically targeted at this age group. However, young adults may also make up a large proportion of those infected.

The World Health Organization (WHO) has set goals of morbidity control and elimination as a public health problem, i.e. ≤5% and ≤1% prevalence of heavy-intensity infections in SAC, respectively. To reach these goals, the WHO has recommended the frequency of treatment that should be offered depending on the baseline SAC prevalence (SAC prevalence prior to any treatment) in a region. The higher the prevalence, the higher the recommended frequency. The WHO recommends 75% treatment coverage of SAC.

To assess the effectiveness of this strategy researchers at Imperial College London have developed a suite of mathematical models that can be used to simulate settings with different prevalence levels and carry out treatment as recommended by the WHO for 10 years. The prevalence of heavy-intensity infections is then checked to determine whether following the recommended guidelines will lead to achievement of the WHO goals.

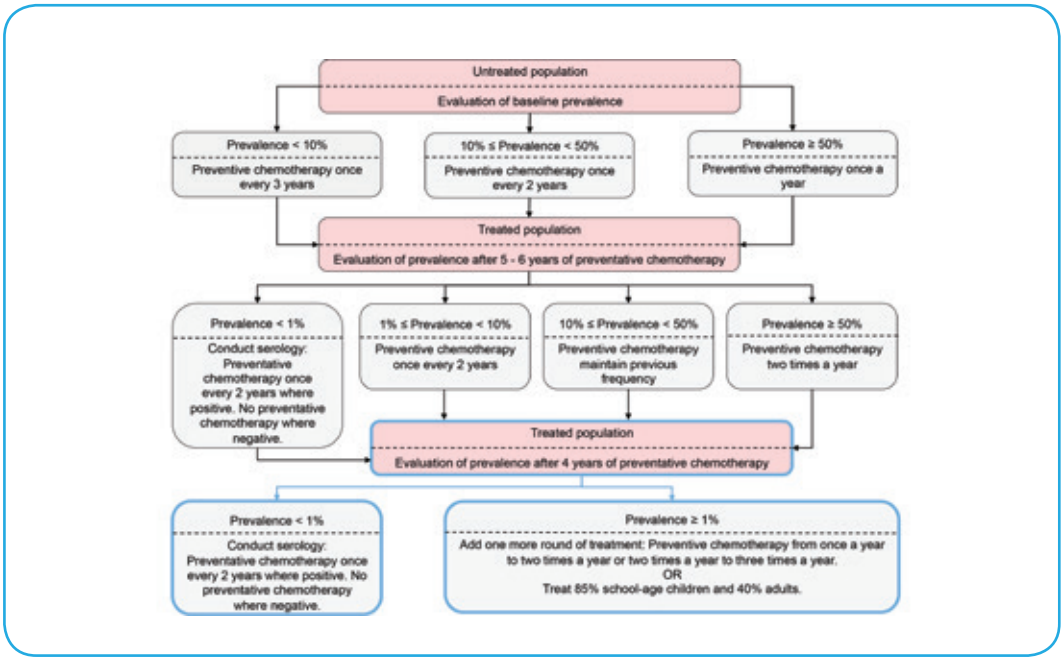
Why is this research necessary?

It is vital that the recommended WHO guidelines are investigated to determine whether they are sufficient to reach the WHO goals. The group's research focuses on the extent to which the current WHO guidelines are likely to succeed in achieving the goals and the circumstances under which they are likely to fail. In the latter case, programmatic adaptations are suggested that could be made to the guidelines to increase the likelihood of achieving the goals whilst maintaining their current structure (see diagram). As these guidelines are implemented in treatment programmes, it is important that the guidelines provided are sufficient to achieve morbidity control and elimination as a public health problem.

What is the research impact?

Currently, there are ongoing discussions on whether the recommended WHO guidelines for schistosomiasis need to be improved. The group's analysis shows that in low prevalence settings, the WHO elimination targets are likely to be achieved following 10 years of treatment under the current guidelines. However, in moderate to high prevalence settings, the WHO goals are less likely to be achieved. For these settings, programmatic adaptations are required to improve the likelihood of reaching the WHO goals, such as increasing and expanding the treatment coverage to include adult treatment. By conducting this research, we hope to provide insight for the discussions on what the future WHO schistosomiasis guidelines should be.

Dr Jaspreet Toor, Dr James Truscott, Dr Marleen Werkman and Prof Sir Roy Anderson, Imperial College London.



Recommended programmatic adaptations (outlined in blue boxes) to the current WHO guidelines (in black boxes; using 75% coverage of SAC) showing the frequency of preventive chemotherapy to be carried out according to the prevalence in SAC in the region, where low prevalence < 10%, moderate prevalence between 10-50% and high prevalence ≥ 50%.

Find out more:

DeWorm3: Demonstrating the feasibility of soil-transmitted helminth elimination

An estimated 1.45 billion people are infected with at least one species of soil-transmitted helminth (STH) infection. Identifying strategies to interrupt the transmission of these diseases will have a profound effect on public health across the globe.

Current WHO STH guidelines recommend delivering preventative chemotherapy through mass drug administration (MDA) campaigns targeting children living in areas where 20% or more are infected.

With the exception of women of childbearing age and pregnant women beyond their first trimester, adults are not typically targeted by MDA campaigns. As a consequence, adults may sustain transmission by acting as reservoirs for continued reinfection of treated children. New modelling of STH transmission dynamics suggests that 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 are supporting the Natural History Museum to undertake the DeWorm3 Project. This $US27 million research project will, over the next 5 years, test the feasibility of interrupting the transmission of STH infections and to develop effective strategies for scaling-up transmission interruption programmes.

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.

Trial Design

The DeWorm3 Project is a five-year cluster randomised trial in Benin, India and Malawi. These trials are conducted in collaboration with local ministries of health.

Intervention
Twenty clusters in each site will be randomised to receive community-wide MDA twice per year. An additional twenty clusters will receive MDA targeting children only, in accordance with each country's standard of care.

Surveillance
Three years of MDA will be followed by two years of surveillance of STH infection prevalence and intensity. During surveillance, MDA will not occur in order to evaluate whether transmission was successfully interrupted.

Evaluation
An exhaustive census of each study site will be conducted to identify every household living in the site catchment area and describe population dynamics such as migration, socioeconomic characteristics, and water and sanitation access. In each site, stool samples from 20,000 randomly selected age stratified individuals will be collected at baseline and 6 months after the last MDA campaign to quantify STH prevalence and infection intensity. After two years of surveillance, 40,000 individuals will be randomly evaluated for STH infection. Each year, a longitudinal cohort of 150 individuals will be visited to monitor changes in STH infection and re-infection.

Implementation Science
Implementation science research is embedded within the clinical trials to generate evidence regarding opportunities to optimise the delivery of STH programmes with high coverage and cost-effectiveness.

A research collaboration: The DeWorm3 team convene in India.

A collaborative approach

With NHM acting as a central coordination hub the DeWorm3 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.

Natural History Museum

NHM is prominent in UK research in NTDs providing expertise, collections and biobanks to drive life-saving research into NTDs such as schistosomiasis, soil-transmitted helminths, dengue fever and food-borne trematodiases.

NHM provides a platform for the institutional oversight of investment, specialist scientific programme, and data management, as well as organising the scientific and technical advisory mechanisms that involve DeWorm3 site trials, supporting units and partners. Senior NHM staff are responsible for scientific oversight and governance as well as bridging the scientific community and the public with a goal of improving advocacy and ensuring audience understanding of the importance of disease control and transmission interruption.

Imperial College London

Imperial's NTD Epidemiology Research Group are world leaders in using statistical and mathematical models to better understand NTD transmission dynamics and predict the impact of control and treatment strategies for NTDs. The group houses the DeWorm3 Modelling and Trial Simulation Support Unit, which is contributing in three key areas:

Study Design
Different study designs for a cluster randomised trial are assessed using individual stochastic models of parasite transmission dynamics, in order to inform targeting of MDA in defined geographical locations.

Prevalence Threshold
Previously, there has been no prevalence threshold to define the breaking transmission of STH. Simulations investigate the sources of sensitivity for elimination studies and programme designs and allow the project to tailor interventions according to specific in-country conditions.

Diagnostic Tools
The need to detect break in transmission relies on the ability to detect low prevalence of STH after the suspension of MDA. The sensitivity of different diagnostic methods have been quantified to investigate the effect on the optimal prevalence threshold at which to declare the interruption of transmission.

London School of Hygiene & Tropical Medicine

The LSHTM is a world renowned centre of excellence in the design, conduct, analysis and reporting of clinical trials. The School is involved in the DeWorm3 Project in two capacities:

Trial Conduct and Coordination Support Unit
The London Applied & Spatial Epidemiology Research group (LASER) based at LSHTM have extensive field epidemiology experience with a strong focus on implementing and evaluating STH interventions. LASER have recently concluded the TUMIKIA project in Kenya to investigate the impact and cost-effectiveness of alternative treatment strategies and delivery systems in reducing the transmission of STHs. The learning and data generated from TUMIKIA is helping to inform the DeWorm3 Project. Researchers from LASER are also supporting the overall DeWorm3 trial coordination and programme implementation as well as leading on the development of data collection and management systems.

DeWorm3 Malawi
Together with the Blantyre Institute of Community Outreach, the Blantyre College of Medicine and the Malawi Ministry of Health, a LSHTM research team led by Prof Robin Bailey and Dr Rachel Pullan will be conducting the DeWorm3 Malawi trial. This builds upon long-established links between LSHTM and its Malawian partners.

Catherine Wheller, Natural History Museum

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 Mathew 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.

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.

"...seeking to identify why some people are less likely to be infected by C. trachomatis and also identify the key disease pathways."

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 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 will also describe the association between chlamydial infection frequency and progressive scarring trachoma, for which there is a significant lack of longitudinal data. In addition, the use of specific anti-chlamydial antibodies for trachoma surveillance will be evaluated. These data will be particularly relevant to trachoma control programmes in order to move towards the elimination of blinding trachoma.

Dr Tamsyn Derrick, LSHTM

A researcher performs In Vivo Confocal Microscopy on the conjunctiva of a man with trachoma. *Credit: Matthew Burton.*

Epidemiology and evolution of zoonotic schistosomiasis in a changing world

Find out more:

What is the research?

An estimate 750 million people are at risk of infection from schistosomiasis with over 90% of these living in sub Saharan Africa. Schistosomiasis also infects millions of livestock worldwide with both domestic and wild animals serving as zoonotic reservoir hosts. On-going man-made and environmental changes are exacerbating opportunities for mixing and subsequent hybridization between human and animal schistosomes. This is likely to have a substantial impact on the epidemiology, evolution and clinical outcomes of the disease. As the disease changes this presents considerable challenges to global disease control efforts. To improve our knowledge of the complex dynamics of zoonotic hybrid schistosomiasis transmission a research group led by Royal Veterinary College's Prof Joanne Webster are collecting parasite samples from humans, livestock, wildlife and snail intermediate hosts from Senegal and Niger in West Africa.

The research project which forms part of the wider Zoonoses and Emerging Livestock Systems (ZELS) programme at the RVC, is looking at the application of new molecular and diagnostic tools, as well as mathematical modeling and socio-economic surveys to elucidate the epidemiology of new zoonotic hybrid schistosomes. The research aims to provide a range of insights on how the disease impacts on its hosts, on the effectiveness of current treatment regimens and on the most effective approaches to interrupt disease transmission. By so doing, it will inform and contribute to sustainable control and development strategies for those living in areas being impacted by environmental change.

Why is this research necessary?

This research contributes to the major push to control and eliminate schistosomiasis as a public health problem as set out by in 2012 by the WHO NTD roadmap and the London Declaration. To achieve this it is essential to discover fully the extent of schistosome zoonotic infections in many regions of West Africa. In collaboration with its African partner institutions, the project is also developing, optimizing and applying methodologies for improved diagnostics and genetic analyses of zoonotic hybrid schistosomes in sub-Saharan Africa. The results produced are fed directly back into policy, including international WHO guidelines and national control programmes.

What is the research impact?

This research will improve our understanding of the evolution, ecology and transmission dynamics of this emerging disease threat. It will shed light on a wide spectrum of multi-host parasitic diseases of humans and animals, and in particular the role of evolution of host

Schistosomiasis infects both people and animals. *Credit: E. Leger.*

ranges and the transfer of genetic information within major taxonomic groups. The outcomes of this study could substantially influence the international policy on disease control and knowledge, modifying attitudes and practice of those inflicted with the threat of this disease.
A full appreciation of the interactions taking place between schistosomes of humans and animals will provide decision-makers and health services at both national and community levels with improved tools to target control interventions.

Prof Joanne Webster, Royal Veterinary College

"This research will improve our understanding of the evolution, ecology and transmission dynamics of this emerging disease threat."

How modelling is helping to identify the most effective strategies to control pork tapeworm

Find out more:

What is the research?

Taenia solium is a parasitic tapeworm that infects individuals when they consume contaminated pork (with parasite cysts) or as a result of poor hygiene (when ingesting parasite eggs). If cysts are ingested, they can develop within a person's intestines (causing taeniasis); if eggs are ingested the parasite can infect body tissue (cysticercosis) and central nervous system (neurocysticercosis). Neurocysticercosis accounts for an estimated 30% of the epilepsy cases in endemic areas where people and roaming pigs live in close proximity. Taeniasis/cysticercosis is one of the NTDs targeted for control and eventual elimination by the 2012 WHO Roadmap on NTDs.

There is a variety of context-specific control measures and strategies that can be used to tackle *T. solium* infections. There is a vital need to identify which are the most effective and cost-effective strategies to apply given the wide range of epidemiological settings in which this disease occurs.

To answer this question, the research group led by Prof Maria-Gloria Basáñez at Imperial College London is seeking to:

1) Quantify patterns of incidence and exposure to *T. solium* in the environment and in contaminated pork;

2) Develop and refine the population-based model EPICYST to simulate infection prevalence in humans and pigs;

3) Parameterise and validate modelled control interventions according to their setting;

4) Model disease burden due to neurocysticercosis and link this to economic evaluations of interventions.

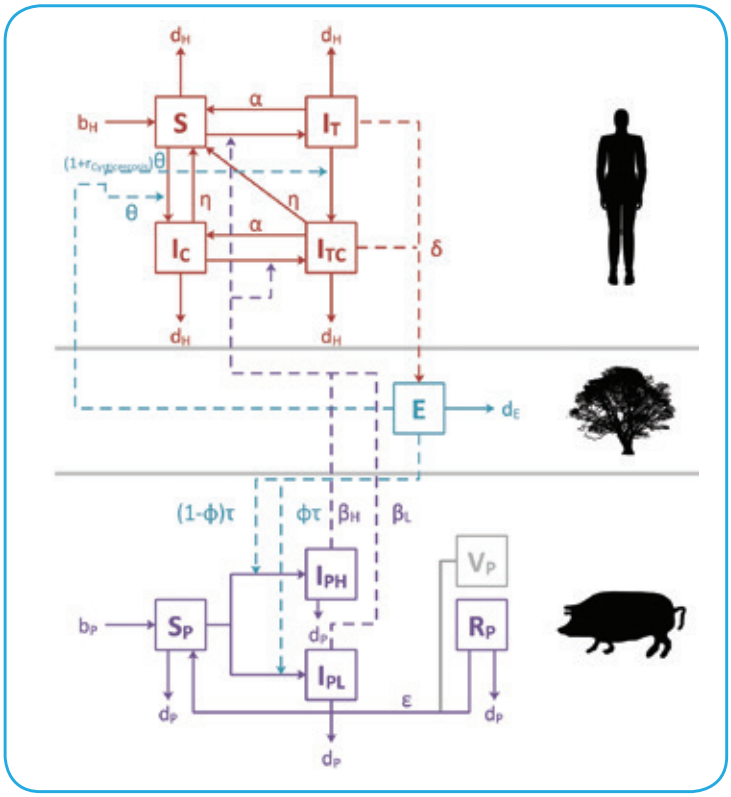
Why is this research necessary?

Currently, large-scale control programmes targeting *T. solium* are rare. This is in part due to a paucity of reliable mapping or data on the prevalence and burden of this disease. The identification of validated strategies according to varying epidemiological features would strengthen the economic argument for allocating resources towards national-level control efforts. Alongside debilitating health implications, *T. solium* also poses a significant economic burden both on the individual sufferers who may experience loss of earnings due to ill-health and on the wider economy in terms of its negative impacts on the agricultural sector due to the destruction of infected meat and increased pig-husbandry costs. Quantifying the societal economic burden and identifying optimal interventions that provide the most cost-effective solutions are critical in developing sustainable national control policies and achieving the WHO NTD roadmap targets.

What is the research impact?

The researchers are establishing collaborative networks with stakeholders in endemic countries to understand the epidemiological features of taeniasis/cysticercosis in different endemic areas, the type and scale of interventions being implemented, and the nature of the data being collected. Linking infection and disease outcomes will be crucial for quantifying the burden of cysticercosis/neurocysticercosis, and developing individual-based versions of the model will permit investigation of the potential of test-and-treat strategies. To-date different countries are adopting different (pig- and/or human-focused) intervention approaches that pose different challenges and opportunities. Through the work of this project it is hoped that modelling tools such as EPICYST will be able to project reliably the epidemiological and economic impact of validated control interventions against *T. solium.*

Prof Maria-Gloria Basáñez, Imperial College London



EPICYST transmission model include compartments for humans, pigs and the environment.

Identifying the best treatment regime to treat Yaws

Find out more:

What is the research?

Yaws is a bacterial infection that predominantly affects children, under the age of 15 years, living in remote communities in Africa, Asia and the Western Pacific regions. Transmission is from person to person by direct contact. Early yaws manifests as chronic skin lesions and, if left untreated, can progress to destructive lesions of the bone and soft tissues. Whilst some children with yaws have obvious disease (active yaws) many children are infected but appear asymptomatic (latent yaws).
If untreated the disease may reappear causing illness in the child and spreading to others in the community. WHO therefore recommends treating the whole community.

A team lead by investigators at LSHTM, ISGlobal, WHO, the CDC, and Ministries of Health in Ghana and Papua New Guinea conducted a randomized control trial on children with yaws to compare the efficacy of treating the disease with either a high-dose or a low-dose of the drug azithromycin. The trial, followed up children to assess both clinical healing and blood markers of infection. Overall 191 children with active yaws and 392 children with latent yaws took part. In active yaws cases, cure was achieved in 80.3% in the low-dose arm and 84·0% in the high-dose arm. In latent yaws, cure was achieved in 58·9% in the low-dose arm and 51·2% in the high-dose arm. The trial results demonstrate that low dose azithromycin is effective in treating yaws.

Why is this research necessary?

Previously, penicillin was the mainstay of yaws treatment. A single intramuscular injection of benzathine penicillin cures the disease. Two previous studies demonstrated that a single dose of azithromycin, given by mouth, was equally effective. As azithromycin is an oral treatment it is much easier to administer in remote communities. Mass treatment with azithromycin is also key to WHO's strategy for elimination of trachoma. However, the dose used in trachoma programmes is lower than the recommended dosage for yaws. This is potentially problematic, because in areas where trachoma and yaws both exist, mass treatment for trachoma might contribute to yaws eradication if the dose used is effective against yaws, but could have negative consequences if the lower dose is sub-therapeutic. Even in countries where trachoma is not found, using a lower dose of azithromycin to treat yaws might reduce both the adverse events associated with treatment and the cost of eradication. It is therefore important to establish if low dose azithromycin is an effective treatment for yaws.

Field team collecting swabs from a yaws lesion for molecular testing. *Credit: WHO.*

What is the research impact?

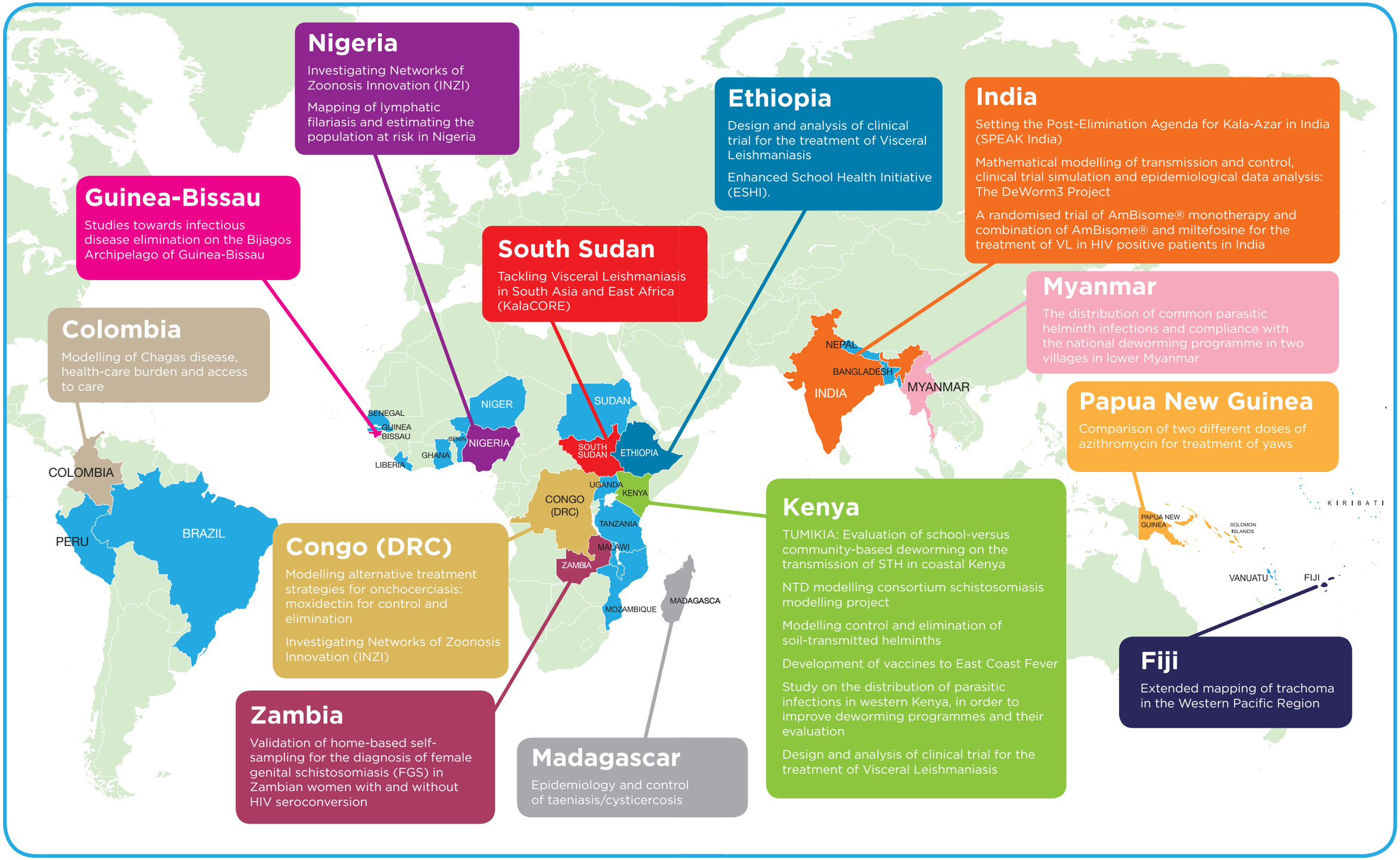
The data demonstrates that the lower dose of azithromycin is effective in treating yaws. In countries planning mass drug administration for trachoma, the current results provide reassurance that this will also have a beneficial impact on yaws. This should facilitate integration of yaws and trachoma control efforts in a number of countries worldwide.

We anticipate that our data will inform global health policy on the use of azithromycin mass treatment as a strategy for yaws eradication. Building on this research there is a need for further studies to understand the optimal way to deliver treatment at the community level in order to eradicate yaws.

Dr Michael Marks, LSHTM

"...our data will inform global health policy on the use of azithromycin mass treatment as a strategy for yaws eradication."

Selected countries where LCNTDR members are working



Nigeria

Investigating Networks of Zoonosis Innovation (INZI)

Mapping of lymphatic filariasis and estimating the population at risk in Nigeria

Guinea-Bissau

Studies towards infectious disease elimination on the Bijagos Archipelago of Guinea-Bissau

Colombia

Modelling of Chagas disease, health-care burden and access to care

Ethiopia

Design and analysis of clinical trial for the treatment of Visceral Leishmaniasis

Enhanced School Health Initiative (ESHI).

South Sudan

Tackling Visceral Leishmaniasis in South Asia and East Africa (KalaCORE)

India

Setting the Post-Elimination Agenda for Kala-Azar in India (SPEAK India)

Mathematical modelling of transmission and control, clinical trial simulation and epidemiological data analysis: The DeWorm3 Project

A randomised trial of AmBisome® monotherapy and combination of AmBisome® and miltefosine for the treatment of VL in HIV positive patients in India

Myanmar

The distribution of common parasitic helminth infections and compliance with the national deworming programme in two villages in lower Myanmar

Papua New Guinea

Comparison of two different doses of azithromycin for treatment of yaws

Congo (DRC)

Modelling alternative treatment strategies for onchocerciasis: moxidectin for control and elimination

Investigating Networks of Zoonosis Innovation (INZI)

Zambia

Validation of home-based self-sampling for the diagnosis of female genital schistosomiasis (FGS) in Zambian women with and without HIV seroconversion

Madagascar

Epidemiology and control of taeniasis/cysticercosis

Kenya

TUMIKIA: Evaluation of school-versus community-based deworming on the transmission of STH in coastal Kenya

NTD modelling consortium schistosomiasis modelling project

Modelling control and elimination of soil-transmitted helminths

Development of vaccines to East Coast Fever

Study on the distribution of parasitic infections in western Kenya, in order to improve deworming programmes and their evaluation

Design and analysis of clinical trial for the treatment of Visceral Leishmaniasis

Fiji

Extended mapping of trachoma in the Western Pacific Region

The above map displays only a sample of LCNTDR members' research projects. A more complete list can be accessed at the NTD Research Database available at **www.londonNTD.org**

Reaching the 2020 elimination goals for human onchocerciasis

Find out more:

What is the research?

Onchocerciasis (river blindness) is a parasitic worm infection transmitted through the bite of infected blackflies. Symptoms include severe itching, changes in skin colour (depigmentation) and structure (atrophy) and blindness. Epilepsy and premature mortality are also associated with onchocerciasis. An estimated 25 million people are currently infected with river blindness, 99% of whom live in 31 different African countries. The World Health Organization (WHO), in its 2012 NTD roadmap set ambitious goals for the elimination of the parasite in selected endemic African countries by 2020.

A research team lead by Imperial College London's Prof Maria-Gloria Basáñez and Royal Veterinary College's Dr Martin Walker, is developing a range of mathematical models to improve the design and implementation of onchocerciasis control programmes. These models are looking to inform our understanding of:

1. The determinants of onchocerciasis elimination.
2. The optimal and cost-effective intervention strategies (human treatment, vector control) for accelerating progress towards elimination.
3. The most reliable parasitological, entomological and serological indicators that can be used for safe cessation of interventions, verification of elimination,and implementation of surveillance to safeguard the gains made.

The suite of models developed include, EPIONCHO (a deterministic version), EPIONCHO-IBM (an individual-based analogue) and a blackfly population dynamics (SIMPOP) sub-model (with which to investigate the impact of vector control).

Why is this research necessary?

Endemic countries are in pressing need of quantitative support and guidance on how to maintain well-performing onchocerciasis control programmes and strengthen under-performing ones. Mathematical modelling provides robust guidance that can be adapted by country programmes to meet their specific needs. The models developed by this project are being used to quantify the efficacy, epidemiological impact and cost-effectiveness of tried and trusted interventions (annual or 6-monthly community-wide distribution of ivermectin) as well as of novel, alternative, and complementary strategies (macrofilaricidal drugs, moxidectin, anti-wolbachial therapies, focal vector control) alone or in combination.

What is the research impact?

To support endemic countries to benefit fully from the use of these models in the design of their control interventions the project's principal researchers are members of expert elimination committees set up by the ministries of health of effected countries. This research will be refining the models to:

1. Produce model outputs aligned with the diagnostic indicators recommended for use by the WHO.
2. Help revise current guidelines for programmatic advice as to when to stop safely anti-parasitic (and anti-vectorial interventions where the latter would be feasible) and proceed to post-intervention evaluation and post-elimination surveillance.
3. Identify most suitable and cost-effective corrective actions to be undertaken if and when recrudescence is suspected/reported. Spatially-structured versions of these models are underway to investigate the dynamics of elimination and re-introduction/recrudescence in small inter-connected populations, typical of the rural settings where onchocerciasis is endemic.

Prof Maria-Gloria Basáñez, Imperial College London and
Dr Martin Walker, Royal Veterinary College

Measuring height to determine the correct dose.
Credit: Suzanne Porter, Sightsavers.

Understanding the impact of lymphatic filariasis in Nigeria

Find out more:

What is the research?

The Global Programme for Elimination of Lymphatic Filariasis (GPELF) goals are to prevent new infections and interrupt transmission of lymphatic filariasis (LF) by 2020 and to manage morbidity and alleviate suffering among people already infected. An Imperial College London team led by Prof Christl Donnelly and Dr Tini Garske, is building the evidence-base to inform effective morbidity management programmes through the development of a robust surveillance system for use in endemic communities.

To do this the team characterised the social, physical and economic impacts of the debilitating swellings and fevers symptomatic of LF on sufferers in rural Nigeria. In partnership with health care workers, community directed-distributors and community leaders, researchers recruited and interviewed 52 LF patients from hard-to-reach communities. Using the findings from these interviews researchers were able to characterise the physical and socio-economic impacts of the disease. Disease-free individuals (matched by age, sex and residential location) were interviewed to provide a basis for comparison.

Why is this research necessary?

Lymphatic filariasis is the second biggest cause of long-term disability in the world. Disability reduces the ability of individuals to perform basic daily activities independently, also leading to reduced time spent on income-generating activities and subsequently low income. Treatment costs are high in LF patients, often depleting family income and patients are sometimes considered to be financial burdens by their families, potentially leading to abandonment, stigma, isolation, and anxiety; all of which are known precursors to mental health illness and depression.

What is the research impact?

The research team hopes that the patient reporting system described in this work forms a basis for further patient identification, taking advantage of the already well established LF and NTD control and treatment programmes. The research has already highlighted the health and socio-economic impacts due to LF. Simple hygiene measures, such as basic skin care, should be encouraged to prevent disease progression. For more advanced 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, acting as a stop-gap for inadequate psychiatric facilities in most of the LF endemic areas. The researchers are currently constructing spatial and ecological niche models of pre-control LF prevalence in Nigeria. This modelling will help identify as yet unmapped areas of historically high disease burden and better inform LF control programmes and subsequent transmission assessment surveys.

Obiora Eneanya, Imperial College London

Obiora Eneanya with a LF patient in Nigeria.
Credit: Imperial College London.

"...building the evidence-base to inform effective morbidity management programmes."

Developing a new vaccine to protect against Trachoma: TRACVAC

Find out more:

What is the research?

TRACVAC is a multi-centre, international collaboration between LCNTDR members from LSHTM and Imperial College London together with partners from IDMIT-CEA Paris and SSI Copenhagen to develop a vaccine to protect against trachoma, the leading infectious cause of blindness worldwide.

Trachoma is caused by conjunctional infection by the *C. trachomatis* bacteria. TRACVAC are working on a new vaccine that uses proteins taken from *C. trachomatis* to enable a person to produce antibodies that will neutralise an infection before it takes hold. The proteins are selected by taking samples from individuals in The Gambia and Tanzania who do develop immunity to the infection and precisely identifying the areas of the proteins that are recognised.

The vaccine strategy employs immuno-repeat technology delivered with an adjuvant that increases both the quality and quantity of protective neutralizing responses. An immunisation regimen for the eye will be developed and optimised, leading to clinical evaluation.

Why is this research necessary?

In line with a global target to eliminate trachoma infections by 2020 WHO-endorsed control efforts have increased dramatically in the last decade. In 2016, over 85 million doses of Pfizer-donated Zithromax were distributed globally through community-based mass drug administration (MDA). Despite this, only three countries have officially declared elimination, while 51 countries remain endemic for trachoma, leading to an estimated 2.2 million people with some form of trachoma visual impairment or blindness. There are significant barriers to current trachoma control programmes. Trachoma is common in politically unstable regions, owing to its association with low income, poor hygiene and sanitation, which makes accessing affected communities difficult. MDA also increases the potential for introduction of antibiotic resistance and it may also interrupt the natural acquisition of clinical immunity to ocular *C. trachomatis* infection, without completely eliminating the infection from targeted communities. A vaccine for trachoma has the potential to be an extremely cost effective method of completely controlling trachoma, whilst at the same time having the additional benefit of reducing urogenital *C. trachomatis* infection.

What is the research impact?

The primary objective of TRACVAC is to evaluate a new trachoma vaccine and regimen in a phase I safety and immunogenicity trial. The studies undertaken in development of this vaccine will also improve our understanding of immune responses induced by *C. trachomatis* infection, particularly those associated with protection from infection and disease sequelae. The long-term goal of TRACVAC is delivery of a protective and cost-effective vaccine, which can supersede the programmatically challenging distribution and repetitive administration of antibiotics to entire communities. A vaccine and immunisation regimen, aims to reduce the need for repeated rounds of MDA, expediting and improving the likelihood of elimination of trachoma as a public health problem.

Prof Martin Holland and Harry Pickering, LSHTM

"A trachoma vaccine has the potential to be an extremely cost effective method of completely controlling trachoma."

Trachoma clinical examination, sample collection and data collection in The Gambia.

WHO Collaborating Centre for the identification of schistosomes and their snail hosts

Find out more:

What is the research?

The Natural History Museum (NHM) works in collaboration with WHO to promote the use of modern approaches in the fields of molecular biology, genetics, ecology and parasitology, for the identification and characterisation of schistosome species/strains and their snail intermediate hosts. The WHO Collaborating Centre, led by Prof David Rollinson, has developed and optimised a number of rapid and cost effective methods to capture and store trematode larval stages from endemic areas in Africa. These new approaches have revolutionised the molecular techniques that researchers can now employ to analyse these parasites. The Centre's research on improving sampling and storage tools has enhanced, utilised and made more accessible the NHM's extensive schistosomiasis collection. In partnership with WHO and the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE), the Centre undertakes operational studies on the control and elimination of schistosomiasis using interventions to target human behaviour and snail control in addition to preventative chemotherapy. An example of this approach is in the control and elimination of urogenital schistosomiasis on the islands of Zanzibar (Unguja and Pemba). At the request of WHO the Centre provides technical assistance to monitor and evaluate schistosomiasis control programmes and transmission verification surveys. The Centre also trains and builds the capacity of local stakeholders to control snail populations.

Why is this research necessary?

The schistosome-snail interaction is complex and differs across endemic areas of disease, the genetic analysis of schistosomes and snails can provide important information to guide control programmes in terms of when and where to treat. Increased drug pressure together with the movement of people and their livestock impacts on the genetic diversity of schistosomes and this needs to be monitored. Likewise, climatic and environmental changes can influence the availability of freshwater, which is intimately linked with snail distribution and disease transmission. As countries move from morbidity control to elimination, there is a greater need to identify and map transmission hotspots.

What is the research impact?

The research conducted by the WHO Collaborating Centre is helping partners to define the schistosome parasites and snail vectors in their region. Improving knowledge of the transmission of this debilitating parasitic disease across Africa and adjacent regions helps to focus control interventions. By providing tools for population sampling and analysis, developing new diagnostics for case detection in low transmission areas and by storing genetic samples for future research, the Centre is supporting stakeholders in the global battle to reducing the burden of schistosomiasis.

Prof David Rollinson, Natural History Museum

Prof David Rollinson teaching participants of the WHO Malacology and Snail Control Meeting held in Pemba about snail collection and parasite isolation.

"...new approaches have revolutionised the molecular techniques that researchers can now employ to analyse these parasites."

Slides or dipsticks? Identifying the best diagnosis tools for schistosomiasis

Find out more:

What is the research project?

Schistosomiasis, or Bilharzia, is a parasitic infection that affects over 200 million people worldwide, predominantly in Africa as well as parts of Asia and South America. Symptoms associated with infection include childhood stunting, anaemia and higher risks of bladder cancer, infertility and HIV/AIDS.

Currently, the mainstream diagnostic method for intestinal schistosomiasis is the detection of eggs in stool samples by the Kato-Katz technique. This method, however, is costly, time-consuming and may be particularly unreliable where there is low levels of infection, as would be expected after several rounds of treatment. In order to overcome some of the pitfalls of this diagnostic method, there are a range of alternative tests which are potentially easier to use and offer increased sensitivity of diagnosis. Antigen detection in urine (using a dipstick called "POC-CCA") has been documented to be a sensitive and specific alternative to Kato-Katz in settings where there is a high risk of schistosomiasis.

Data comparing the performance of stool microscopy (Kato-Katz) and a urine dipstick (CCA) in low Schistosomiasis prevalence settings, however, is currently lacking. In this context, a research team from Imperial College London's Schistosomiasis Control Initiative (SCI) are filling this evidence gap by comparing the performance of Kato-Katz with more novel diagnostic methods such as POC-CCA, another antigen test that detects schistosomes in the urine (CAA). The research is being conducted in Brazil in the low endemic area of Minas Gerais State and in a moderate endemic area of Sergipe State.

Why is this research necessary?

For the design of effective control programmes, it is important to determine an accurate estimate of infection prevalence in the targeted area. In recent years, there have been efforts to map intestinal schistosomiasis in Brazil, however, these studies are based on reading only one Kato-Katz slide from one faecal sample. Analysis has shown that in such cases the infection prevalence obtained by one slide from one faecal sample can be up to 4.5 times lower than after examining two slides from three separate faecal samples (six slides in total). This research aims to identify diagnostic techniques which can be used quickly and cost-effectively to support the accurate mapping and targeting of schistosomiasis infections.

What is the research impact?

In addition to increased sensitivity of the test, the advantages of POC-CCA and CAA over Kato-Katz for diagnosing intestinal schistosomiasis are the use of a non-invasive urine sample rather than stool, substantial savings in time for specimen collection and processing, with results available within 20 minutes, and that the test does not require trained microscopists. These findings may change the way that national control programmes are able to quickly and effectively assess the health impact and epidemiological situation of intestinal schistosomiasis, and subsequently permit rapid and accurate treatment decisions.

Dr Anna Phillips, Schistosomiasis Control Initiative, Imperial College London

Diagnosis of prevalence of schistosomiasis in school children in Minas Gerais and Sergipe State in Brazil. Credit: Anna Phillips.

"Filling the evidence gap by comparing the performance of Kato-Katz with more novel diagnostic methods."

Spraying fences in Sudan to reduce visceral leishmaniasis transmission

Find out more:

What is the research?

Visceral leishmaniasis (VL), also known as *kala azar*, is caused by a protozoan parasite that is transmitted by the bite of infected female sand flies. The disease causes chronic fever, weight loss and organ damage, and if left untreated is usually fatal in symptomatic patients.

To support the control and elimination of VL the KalaCORE partnership with funding from UK Aid was created to work in six of the most endemic countries globally, namely India, Nepal and Bangladesh in South Asia and Ethiopia, Sudan and South Sudan in East Africa.

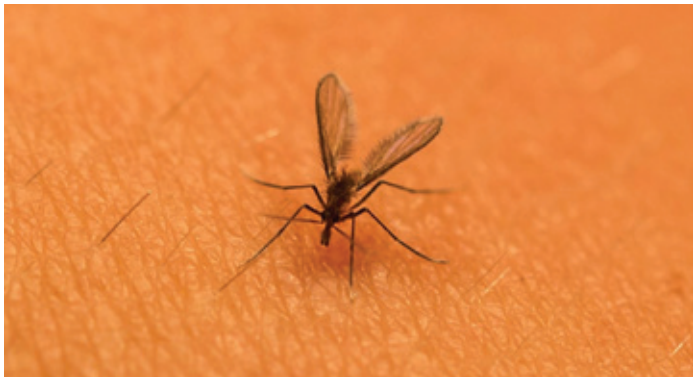
KalaCORE brings together four key organisations – Drugs for Neglected Diseases Initiative; Mott MacDonald; the London School of Hygiene & Tropical Medicine (LSHTM) and Médecins Sans Frontières – that each supply distinct and complementary skills for combatting VL.

A key focus of the partnership is on reducing the health and economic impact of VL, by supporting progress towards elimination in South Asia and by building stronger capacity for an effective VL response in East Africa.

An example of this approach is in Sudan where researchers are conducting randomised trials to assess the effectiveness of controlling sand flies through the spraying of insecticide on boundary fences and the outside walls of dwellings. The findings of this research can be used to inform government control efforts designed to reduce VL transmission.

Why is this research necessary?

Previous integrated vector management programmes in Sudan have not been successful due to the exophilic nature of sand flies, i.e. they bite predominantly in outdoor settings which are not conducive for indoor residual spraying of insecticide. Evidence gathered also shows that sand flies are active between March and June before rapidly disappearing at the onset of the rainy season in July. This is out-of-sync with the current national Ministry of Health spraying programme.



The visceral leishmaniasis vector in Sudan is the sand fly *Phlebotomus orientalis.*

The entomological research carried out by the KalaCORE team is looking at how the privacy barriers that are routinely constructed around dwellings and compounds affect sand fly density. It has previously been observed that significantly higher sand fly numbers were observed immediately outside these barriers than within. It was hypothesised that if these boundary fences and the outside walls of dwellings were sprayed with insecticide this could reduce sand fly numbers both within the compound and outside.

Compound walls in Sudan. Credit Vanessa Yardley.

What is the research impact?

Initial proof of concept studies were carried out in 2016 and 2017 and 2018 will see a community-based randomised trial to see if this can be scaled up successfully to reduce transmission of VL.

The study intends to provide evidence that community-wide spraying of boundary fences and the outside walls of dwellings will have a significant impact on the densities of sandflies and that this will in turn reduce the transmission of VL. If this targeting spraying can be incorporated into the national IVM programme it could have a significant impact on VL transmission.

On behalf of KalaCORE – Dr Vanessa Yardley, LSHTM

WEAR: WEarable Aedes Repellent Technologies

Find out more:

What is the research?

Clothes, jewellery and flip-flops impregnated with mosquito repellent are some of the innovative new approaches being developed by researchers at London School of Hygiene & Tropical Medicine (LSHTM) to reduce the transmission of diseases including zika, dengue, yellow fever and chikungunya. As part of the Zika Preparedness Latin American Network (ZikaPLAN) a team led by LSHTM's Prof James Logan have been funded by European Union's Horizon 2020 programme to develop the next generation of wearable technologies to protect people from Aedes-mosquito bites.

To ensure that the products developed meet the needs of the target communities, extensive focus group discussions were held in Colombia and Brazil. The ZikaPLAN researchers will use this information to guide the development of technologies ranging from wash-in repellent detergents for clothing, to long lasting plastic formulations to create bracelets, necklaces, and flip flops that can be easily adopted by communities and offer continuous protection. Before moving on to large-scale field trials, the products are undergoing rigorous laboratory testing and mathematical modelling to determine their anticipated efficacy in the reduction of disease transmission.

Aedes-mosquito. Credit: Laurence Sanders.

Why is this research necessary?

Mosquitoes are a significant global public health problem because they transmit pathogens that are responsible for the death of over one million people every year. For malaria control, the first line of defence is long lasting insecticide-treated bed nets and indoor residual spraying of insecticides, but these are becoming less effective due to insecticide resistance and there is evidence that mosquito behaviour is changing, leading them to bite more frequently outdoors. Insecticide treated bed nets and indoor residual spraying are also not appropriate for day biting Aedes mosquitoes that transmit dengue, Zika, yellow fever and chikungunya. Whilst topically applied repellents are known to be effective, they are relatively short-lived and people often do not like to use them. Researchers at LSHTM, as part of ZikaPAN, are addressing these problems by creating new, safe, long-lasting wearable repellent technologies, utilising novel, wash-in detergents and an innovative long-lasting plastic formulation.

What is the research impact?

Researchers at LSHTM will develop the next generation of repellent technologies with novel encapsulation methods that will revolutionise personal protection, providing continuous effective spatial repellency with unprecedented longevity. The target products will allow for flexibility in form which means they can be used to create almost any wearable item, which allows targeting of any demographic, catering to different consumer needs. These innovations will require little behavioural change for the users, and will offer significant health improvement to millions, contributing to reducing the global crisis of mosquito-borne diseases.

Prof James Logan and Dr Thomas Ant, LSHTM

"...the next generation of repellent technologies with novel encapsulation methods that will revolutionise personal protection, providing continuous effective spatial repellency with unprecedented longevity."

BALZAC: Behavioural Adaptations and Zoonose Control in Bangladesh

Find out more:

What is the research?

The BALZAC project studies the behaviour of people working in the Bangladeshi poultry farming and trading system. It aims to identify the socioeconomic, cultural, and epidemiological factors that shape the structure of live bird trade networks in Bangladesh, and the types of changes in the network structure which could facilitate the emergence of zoonotic pathogens and influence their maintenance and dissemination.

Employing an inter-disciplinary perspective, the project involves a combination of traditional ethnographic techniques, such as observations and semi-structured interviews, innovative techniques using methods developed in experimental economics, biological sampling from both humans and poultry, and the development of joint epidemiological and socioeconomic models. Avian influenza viruses, and in particular H5N1, is used as a model to study the traders' and farmers' responses to disease risk.

BALZAC is a collaboration between the Royal Veterinary College and LSHTM in the UK, the Chittagong Veterinary and Animal Science University, the Bangladesh Livestock Research Institute, the Department of Livestock Services, the Food and Agriculture Organization of the United Nations and the Institute of Epidemiology, Disease Control and Research in Bangladesh, and the University of Queensland in Australia.

Why is this research necessary?

The rapid growth of the Bangladeshi poultry sector has triggered a drastic increase in the volume of traded live poultry, as most poultry transit in live bird markets. These trading activities, while providing smallholders with an important source of income, play a major role in the transmission of zoonotic pathogens, such as avian influenza viruses. The structure of the network shaped by traders' movements influences the potential of a pathogen to invade poultry populations and the level of human exposure. In the face of poultry disease outbreaks, farmers and traders may change their practices in order to reduce economic loss, altering the structure of the trading networks. These changes may modify the way disease spreads, and even prolong and strengthen the epidemic.

What is the research impact?

BALZAC seeks to develop control and surveillance strategies tailored to the evolving characteristics of live bird trade networks. These interventions would target behaviours that may spread the infection, and achieve both a significant reduction in disease spread through live bird trade networks and protection of smallholders' health and livelihoods.

In addition to enhancing our understanding of the factors shaping trade networks, the inter-disciplinary approach adopted developed in BALZAC will introduce a new methodological departure which should be of interest to academic epidemiologists in fields beyond the concerns of the present research, including NTDs.

Prof Dirk Pfeiffer and Dr Guillaume Fournié,
Royal Veterinary College

A Bangladeshi poultry market.

"The structure of the network shaped by traders' movements influences the potential of a pathogen to invade poultry populations and the level of human exposure."

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