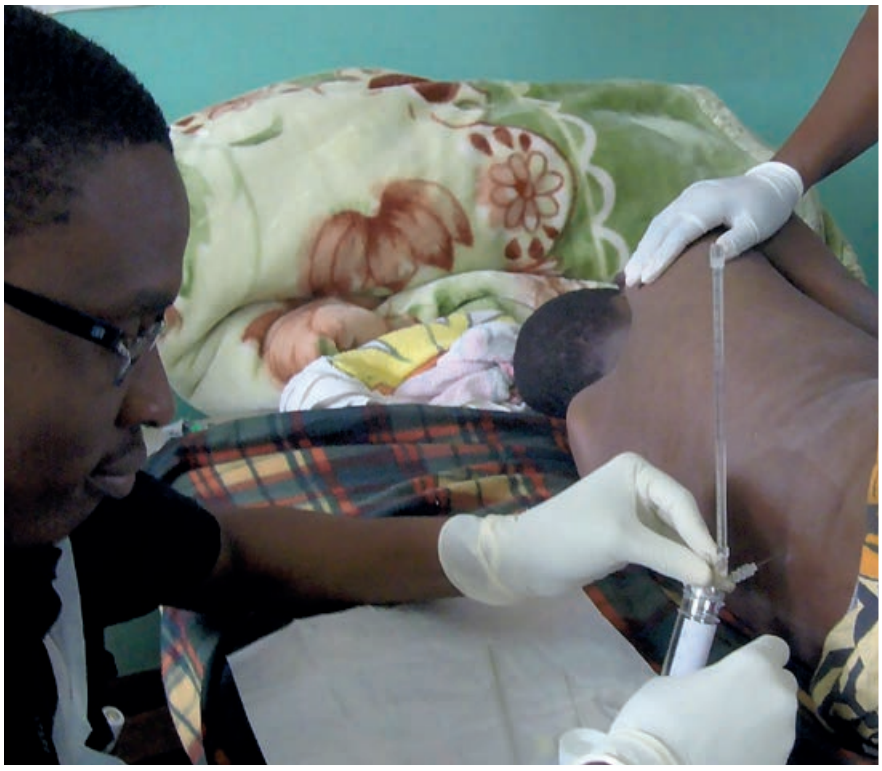
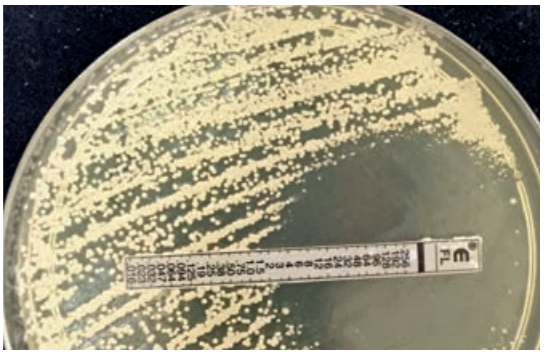
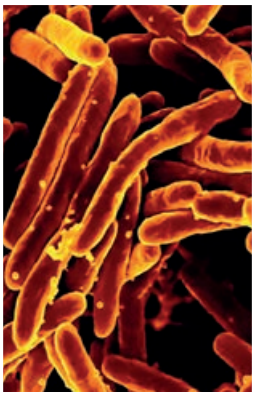
CENTRE FOR GLOBAL HEALTH

ENHANCING PREVENTION, TREATMENT AND CONTROL OF INFECTIOUS DISEASE IN LOW- AND MIDDLE-INCOME COUNTRIES







St George's University of London

INSTITUTE FOR INFECTION & IMMUNITY

CENTRE FOR GLOBAL HEALTH

The Centre for Global Health, part of the Institute for Infection and Immunity at St George's University of London (SGUL), works with national and international partners to improve the prevention, treatment and control of infectious diseases in resource-poor settings.

Our objectives are:

- **Basic understanding**: To investigate the biology of infectious organisms and host responses, to identify potential targets for drug and vaccine development
- **Intervention development**: To develop new therapies, vaccines and diagnostics, and innovative technological platforms
- **Clinical trials**: To carry out phase I, II and III trials of novel drug treatments, with national and international partners
- **Influencing policy and practice**: To work with policymakers and other stakeholders to identify knowledge gaps, to promote the implementation of proven interventions, and to advocate for greater prioritisation of our diseases of interest.

The challenges

We have particular strengths in key diseases affecting low- and middle-income countries (LMICs), including tuberculosis (TB), cryptococcal meningitis (an important opportunistic infection in people with HIV), malaria and Buruli ulcer (an ulcerative skin condition prevalent in West Africa).

We are also actively involved in projects targeting other important infections affecting LMICs, including HIV, sexually transmitted infections, dengue, Ebola, chikungunya, drug-resistant bacterial infections, paediatric bacterial infections and parasitic worm infections.

OUR GOAL IS TO DEVELOP, EVALUATE AND ENABLE THE WIDE USE OF NOVEL DRUG THERAPIES AND OTHER INTERVENTIONS FOR INFECTIOUS DISEASES AFFECTING LOW- AND MIDDLE-INCOME COUNTRIES.

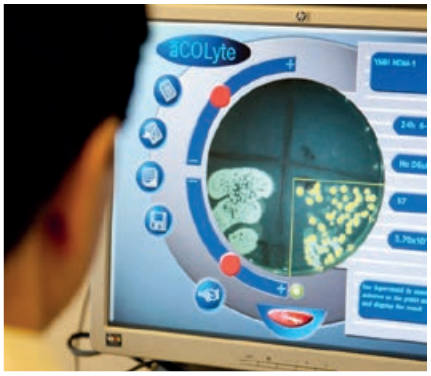
Our partners

Much of our work is carried out in the context of international collaborations. Our centre in Ecuador (see right) provides us with a long-standing presence in South America and has facilitated multiple regional collaborations. We also have extensive links with centres throughout Africa and Asia.

As well as providing a platform for research and trials, these connections enable us to make a significant contribution to training and capacity-building.

The Centre for Global Health is a coordinating centre for major international networks, including:

- The **International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis** (INTERTB), a global network of sites evaluating novel treatment regimes for TB
- The **Cryptococcal Meningitis Action Group** (CryptoMAG), a network including representatives from the WHO, US Centers for Disease Control and Prevention, and Médecins Sans Frontières, among others, advocating for greater global attention for cryptococcal meningitis.



The Centre hosts regular international meetings for INTERTB and CryptoMAG, bringing communities together for discussion and to coordinate future activities.

Alongside links to centres in LMICs, we also have extensive academic collaborations with groups in the UK and across mainland Europe, and contribute to multiple EU-funded consortia.

Track record

We have successfully run many multisite international clinical trials generating data that have influenced national and international policy and practice. Our studies on cryptococcal meningitis, malaria and Buruli ulcer have all had a significant impact on WHO treatment guidelines and on national policies, while our TB trials have been highly influential in shaping the TB research agenda.

An important and growing focus of our work is collaboration with policymakers to identify gaps in knowledge and how they might be filled, and to drive forward implementation of proven interventions – ensuring that patients ultimately benefit from advancing knowledge.

LIFE IN ECUADOR

The ECUAVIDA birth cohort – Latin America's only rural birth cohort – is generating new insight into the origins of asthma, while also providing a platform for other studies.

Launched by Professor Philip Cooper and colleagues in 2006, the ECUAVIDA birth cohort recruited some 2400 newborns in the rural district of Quinindé, Esmeraldas Province, a tropical region of coastal Ecuador. The core question being addressed is the link between worm infections and the development of atopy and allergic conditions (see page 5) – in particular, testing the hypothesis that early exposure to parasitic worms may protect against allergic conditions such as asthma.

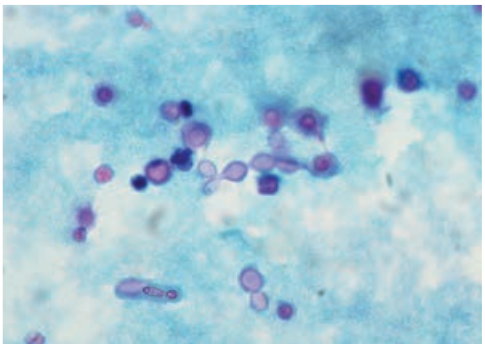
The cohort is also providing an opportunity to study related questions, such as the impact of infections on immune responses (to infections and after vaccination), on growth and development, and on markers of chronic disease.

Furthermore, the research base in Ecuador has provided a springboard for further studies, many carried out in collaboration with colleagues in Brazil. Studies have examined risk factors for asthma and the impact of social and environmental changes such as migration and urbanisation.

The site is also supporting additional SGUL studies, including work on rapid diagnostics for sexually transmitted infections (see page 11) and sexual transmission of Zika virus. In addition, Professor Cooper has established collaborations with other international groups, using the ECUAVIDA cohort to investigate the prevalence and impact of enteric viruses (such as norovirus and rotavirus) and respiratory viruses, including respiratory syncytial virus.

The presence in Ecuador and close links with Brazilian researchers also provide important opportunities for research training and capacity-building.

Cooper PJ *et al.* Cohort Profile: The Ecuador Life (ECUAVIDA) study in Esmeraldas Province, Ecuador. *Int J Epidemiol.* 2015;44(5):1517–27.



BIOLOGY AND EPIDEMIOLOGY

Researchers at the Centre for Global Health are studying a range of infectious organisms affecting LMICs, particularly *Cryptococcus neoformans*, the cause of cryptococcal meningitis, *Mycobacterium tuberculosis*, responsible for TB, *Plasmodium falciparum*, the most important species of malaria parasite, and *Mycobacterium ulcerans*, the causative agent of Buruli ulcer.

A key aim of this work on pathogen biology is to identify possible new targets for drug and vaccine development, as well as factors contributing to virulence and drug resistance.

Work on the malaria parasite, carried out by Dr Henry Staines and Professor Sanjeev Krishna, has identified new targets and generated new insights into mechanisms of drug resistance. Similarly, Dr Tihana Bicanic and colleagues' studies on *Cryptococcus* have shed light on the emergence of drug resistance. Further work on the genomics of *C. neoformans* isolates may reveal whether particular strains of this ubiquitous pathogen are causing disease, or whether susceptibility to infection is mainly a consequence of host factors.

Our work on pathogens such as TB is facilitated by state-of-the-art biosecurity level 3 laboratories – some of the most advanced such facilities in the UK.

WE AIM TO DEVELOP A DEEPER UNDERSTANDING OF INFECTIOUS ORGANISMS, HOST RESPONSES AND PATTERNS OF DISEASE, TO UNDERPIN THE DEVELOPMENT OF NEW INTERVENTIONS.

Host responses

Other Centre research focuses on the immune response to infectious organisms, particularly factors associated with susceptibility to infection or development of protective immunity. Many of these studies take advantage of samples collected during clinical trials, adding significantly to the value of trials by generating insight into the physiological mechanisms underlying drug or vaccine responses.

Genetic studies have identified factors potentially linked to susceptibility to cryptococcal infection. Dr Bicanic plans larger genetic studies in Africa to identify additional risk factors – information that could be used to screen for patients at risk of cryptococcal meningitis and to identify possible targets for host-directed therapies.

Epidemiological insight

In Ecuador, collection of epidemiological information has been an important aspect of the ECUAVIDA birth cohort. This information has enabled the team to explore multiple social, environmental and biological factors affecting the development of allergic conditions and asthma in children.

CRYPTOCOCCUS: THE PATHOGEN AND THE HOST

Dr Tihana Bicanic and colleagues have identified key pathogen and host factors affecting the outcome of cryptococcal fungal infections.

Cryptococcus is an important opportunistic infection of people living with HIV, responsible for more than 100,000 deaths a year from cryptococcal meningitis. Using samples collected during clinical trials in Africa (see page 9), Dr Bicanic identified a range of factors associated with poor outcomes[1,2]. Two projects funded by a Wellcome Trust Strategic Award in Medical Mycology and Fungal Immunology are now enabling her team to gain additional insights into *Cryptococcus* and host responses to it.

Working in Tanzania, Dr Neil Stone has analysed *Cryptococcus* isolated directly from spinal fluid samples to confirm that a mechanism of drug resistance identified in experimental animal models – transient chromosomal duplication – also occurs in human infection. Resistance to fluconazole, the drug typically used to treat *Cryptococcus* in Africa, was associated with duplication of the chromosome on which the gene encoding the target of fluconazole is located.

In terms of the host, Dr Bicanic and Dr Shichina Kannambath recently completed a case-control study to identify factors affecting susceptibility to cryptococcal meningitis. The study, which compared patients with HIV and low CD4 counts with or without cryptococcal meningitis, identified a susceptibility locus upstream of the gene coding for macrophage colony-stimulating factor (M-CSF), a cytokine implicated in macrophage activation. Follow-up laboratory studies are examining whether M-CSF boosts the capacity of white blood cells from HIV-infected individuals to kill *Cryptococcus*.

1 Sabiiti W *et al*. Efficient phagocytosis and laccase activity affect the outcome of HIV-associated cryptococcosis. *J Clin Invest*. 2014;124(5):2000–8.

2 Beale MA *et al*. Genotypic diversity is associated with clinical outcome and phenotype in cryptococcal meningitis across southern Africa. *PLoS Negl Trop Dis*. 2015;9(6):e0003847.

TRANSPORTERS AS TARGETS

The work of Dr Henry Staines and Professor Sanjeev Krishna on transporters is providing new insight into the biology of the malaria parasite, and identifying possible targets for drug development.

Transporters move metabolites across cell membranes, performing critical functions that make them attractive drug targets. For example, Dr Staines and Professor Krishna showed that inhibition of an essential sugar transporter, PfHT, disrupted growth of the malaria parasite *Plasmodium falciparum*[1], prompting several groups to launch drug discovery programmes targeting PfHT.

With colleagues in Portugal, Dr Staines and Professor Krishna have also characterised a *P. falciparum* transporter, known as PfVIT, that plays a critical role in sequestering iron in the cell vacuole[2]. PfVIT-deficient parasites showed reduced parasite loads in rodent models. Other studies have revealed how mobilisation of intracellular GLUT1 transporters to the surface of liver cells is a crucial aspect of parasite infection, increasing glucose uptake to support parasite multiplication[3].

Additional work has shone light on the function of PfCRT, which renders parasites resistant to chloroquine by ejecting the drug from the food vacuole. Abnormal variants of PfCRT caused the food vacuole to swell and also altered parasite sensitivity to chloroquine[4]. Such studies provide insight into potential physiological roles of PfCRT, and hint at the possibility of targeting PfCRT to reverse chloroquine resistance.

1 Slavic K *et al*. Use of a selective inhibitor to define the chemotherapeutic potential of the plasmodial hexose transporter in different stages of the parasite's life cycle. *Antimicrob Agents Chemother*. 2011;55(6):2824–30.

2 Slavic K *et al*. A vacuolar iron-transporter homologue acts as a detoxifier in *Plasmodium*. *Nat Commun*. 2016;7:10403.

3 Meireles P *et al*. GLUT1-mediated glucose uptake plays a crucial role during *Plasmodium* hepatic infection. *Cell Microbiol*. 2017;19(2).

4 Pulcini S *et al*. Mutations in the *Plasmodium falciparum* chloroquine resistance transporter, PfCRT, enlarge the parasite's food vacuole and alter drug sensitivities. *Sci Rep*. 2015;5:14552.

ASTHMA AND WORM INFECTIONS

Latin America's only rural birth cohort, established by Professor Philip Cooper, could reveal whether childhood parasitic worm infections confer protection against asthma.

There is some evidence, particularly from high-income countries, that a drop in the number of childhood infections has contributed to increased rates of allergies and asthma. Parasitic worms, for example, modulate the immune system, generating an anti-inflammatory state that could dampen down responses to environmental allergens.

However, there is conflicting evidence from Latin America on the possible protective influence of worm infections. The ECUAVIDA birth cohort (see page 3) was set up in a bid to provide a definitive answer to this question.

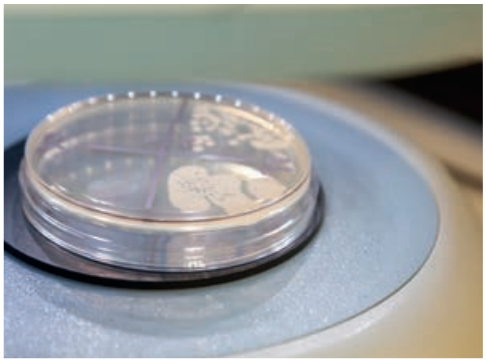
Early results suggested that worm infections were common in mothers – affecting nearly half of all pregnant women – but had no protective effect on eczema or wheezing by age 3[1]. Preliminary analyses suggest that, by age 5, childhood worm infections may be associated with a reduced risk of wheeze. A clearer picture may emerge when data collection at age 8 is completed in 2018.

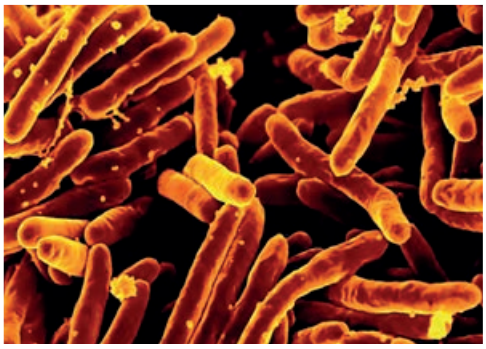
The ECUAVIDA research infrastructure has also enabled Professor Cooper and colleagues to explore the complex interplay of factors influencing the development of allergies and asthma, including urban–rural differences and migration[2], and the impact of respiratory infections and sensitisation to house dust mites[3].

1 Cooper PJ *et al*. Effects of maternal geohelminth infections on allergy in early childhood. *J Allergy Clin Immunol*. 2016;137(3):899–906.

2 Rodriguez A *et al*. Migration and allergic diseases in a rural area of a developing country. *J Allergy Clin Immunol*. 2016;138(3):901–3.

3 Ardura-Garcia C *et al*. Risk factors for acute asthma in tropical America: a case-control study in the City of Esmeraldas, Ecuador. *Pediatr Allergy Immunol*. 2015;26(5):423–30.





NOVEL INTERVENTION DEVELOPMENT

Although LMICs urgently require new interventions, infectious diseases primarily affecting such countries are not an attractive proposition for commercial organisations. New approaches and potential interventions must be mindful of obstacles that could limit the use of products in resource-poor settings, particularly in relation to affordability, accessibility and acceptability.

WE ARE USING NOVEL APPROACHES TO DEVELOP VACCINES, THERAPEUTICS AND OTHER TOOLS THAT COULD BE APPLIED TO INFECTIOUS DISEASE CONTROL IN LMICs.

Innovative products, innovative technologies

Our research is focused on the development of new preventive and treatment strategies that meet important needs in LMICs but also represent practical solutions for such countries. We have a strong emphasis on innovative new technological platforms that would be affordable and practical to implement.

For example, the use of plants to produce therapeutic antibodies or novel vaccine products, pioneered by Professor Julian Ma, could provide a technological platform readily implementable in LMICs, enabling such countries to respond rapidly to emerging outbreaks. The EU-funded **Pharma-Factory** consortium, coordinated by Professor Ma, provides an important springboard for commercialisation of these products.

The EU-funded **EMI-TB consortium**, led by Dr Rajko Reljic, is making encouraging progress testing new candidate TB vaccines based on engineered bacterial spores, nanoparticles and liposomes. Complementary studies are examining whether neutralising IgA antibodies could be used as an adjunct to TB chemotherapy, to mop up the 'persister' bacteria that are relatively insensitive to conventional TB drugs and maintain chronic infections.

Disease models

Our work extends to novel models of disease to facilitate the development of new therapeutics. Dr Yanmin Hu and colleagues' work on a new mouse model of TB, for example, was pivotal in identifying a way to shorten TB treatments.

This important contribution has been supported by a New Investigator grant from the MRC and the EU-funded **PREDICT-TB consortium**. The latter aims to identify methodological advances that ensure pre-clinical testing of TB treatments is more predictive of clinical responses, improving the disturbingly low success rate of TB drug development.

Diagnostic platforms

Innovative technological platforms are also being used to develop novel point-of-care diagnostics, to support more rapid and targeted treatment of infections and improved disease control. For example, Professor Sanjeev Krishna is leading an EU-funded consortium, **Nanomal**, developing a novel diagnostic and drug-resistance detector for malaria. Diagnostic development is an important focus of the SGUL Centre for Diagnostics and Antimalarial Resistance (CDAR) within the Institute for Infection and Immunity.

NEXT-GENERATION PHARMING

The aim of pioneering research in Professor Julian Ma's laboratory is to enable LMICs to benefit from affordable complex biopharmaceuticals made in plants.

Professor Ma's group has pioneered the use of 'molecular pharming' – production of antibodies or other biologics in plants – and, with colleagues in Aachen, Germany, obtained regulatory approval for the first clinical trial of a plant-derived antibody, an antibody against HIV[1]. Having shown that topical administration is safe, the team is now working towards the first intravenous administration of a plant-derived antibody, in 'Future-Pharma' studies taking place at St George's.

As well as antibodies, Professor Ma has also been developing more complex molecular constructs, as vaccines for infections such as dengue[2]. These constructs mimic the antibody–antigen complexes formed during infection and stimulate powerful protective immune responses in animal models.

Plants offer affordability and a rapid and highly scalable manufacturing solution that is well suited to addressing emerging epidemics. As demonstrated by recent Ebola virus and Zika virus outbreaks, health systems are underprepared for such events. The long-term objective of the group's work is to develop affordable manufacturing capacity for LMIC applications, potentially even manufacturing 'in the country, for the country'. Long-standing collaborations in India, Thailand, Korea, China, South Africa and Brazil are focusing on novel solutions for emerging infections, local regulatory acceptance and developing manufacturing capability.

1 Ma JK *et al.* Regulatory approval and a first-in-human phase I clinical trial of a monoclonal antibody produced in transgenic tobacco plants. *Plant Biotechnol J.* 2015;13(8):1106-20.

2 Kim MY *et al.* Molecular engineering and plant expression of an immunoglobulin heavy chain scaffold for delivery of a dengue vaccine candidate. *Plant Biotechnol J.* 2017 [Epub ahead of print]

THE MUCOSAL ROUTE TO TB IMMUNITY

In a quest for a TB vaccine, Dr Rajko Reljic is aiming to mimic the TB-causing bacterium.

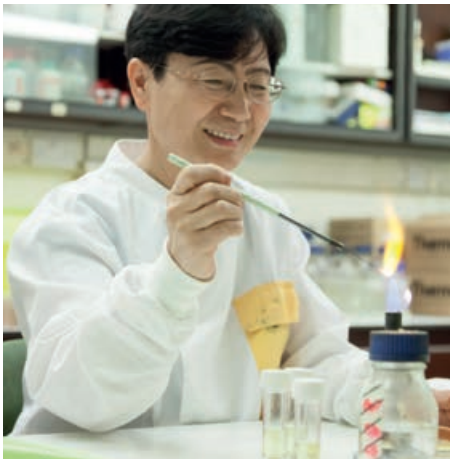
With the 100-year-old BCG vaccine only partially effective, the world urgently needs a new TB vaccine. Alongside partners in the EU-funded EMI-TB Consortium, Dr Reljic is making encouraging progress towards an inhaled vaccine that stimulates protective mucosal immunity.

As *Mycobacterium tuberculosis* is a respiratory pathogen, the lung's mucosal immune system is a critical first line of defence. Furthermore, immune responses are likely to be strongest if vaccines resemble the natural infecting agent. Hence, the Consortium has developed a range of vaccine particles that are coated with immunogenic *M. tuberculosis* antigens but also contain proteins used by *M. tuberculosis* to invade cells.

Having tested 36 vaccine formulations, the Consortium is focusing on three candidates – based on engineered nanoparticles[1], bacterial spores[2] and liposomes – that stimulate strong immune responses, and are highly protective and show a good safety profile in a mouse model of TB infection. All three could be readily manufactured in large quantities at reasonable cost and are now being taken forward for further pre-clinical assessment.

1 Stylianou E *et al.* Mucosal delivery of antigen-coated nanoparticles to lungs confers protective immunity against tuberculosis infection in mice. *Eur J Immunol.* 2014;44(2):440–9.

2 Reljic R *et al.* Mucosal vaccination against tuberculosis using inert bioparticles. *Infect Immun.* 2013;81(11):4071–80.



OVERCOMING A PERSISTENT PROBLEM

By 'reawakening' dormant TB bacteria in mice, Dr Yanmin Hu has developed a much-improved way of testing TB drugs.

TB is difficult to treat, in part because *Mycobacterium tuberculosis* can enter a dormant state, forming 'persister' cells. These cells are hard to detect, relatively insensitive to most TB drugs, and can reactivate to cause disease. Lengthy drug treatments are required to rid the body of persisters.

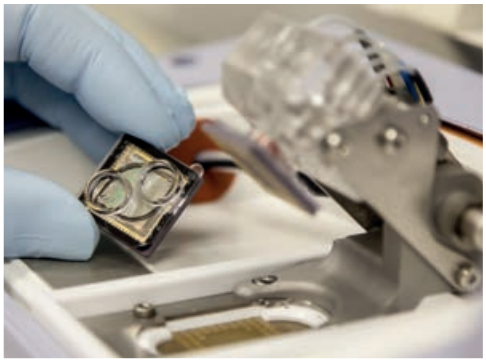
Persisters also present a challenge to drug development. Unfortunately, drug regimens that appear to work well in mice are often less successful in people. In part, this may reflect the fact it is difficult to tell whether drugs are killing persisters.

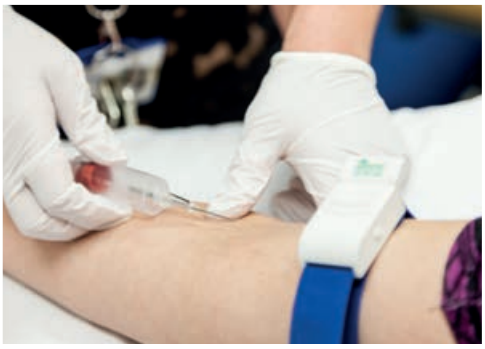
To overcome this issue, Dr Hu and colleagues made use of the finding that a cocktail of proteins known as resuscitation-promoting factors can reactivate persisters, in effect removing their invisibility cloak. It is then possible to tell what impact drug treatments are having on this class of cells.

Using this approach, Dr Hu and colleagues showed that high-dose rifampicin killed persisters[1], supporting shorter courses of treatment – a major goal of human TB therapy. This finding led to the development of a novel regimen being tested in the RIFASHORT trial (see page 9). The new model has also been used to examine interactions between drugs and their impact on persister clearance[2].

1 Hu Y *et al.* High-dose rifampicin kills persisters, shortens treatment duration, and reduces relapse rate *in vitro* and *in vivo*. *Front Microbiol.* 2015;6:641.

2 Hu Y *et al.* Investigation of elimination rate, persistent subpopulation removal, and relapse rates of *Mycobacterium tuberculosis* by using combinations of first-line drugs in a modified Cornell mouse model. *Antimicrob Agents Chemother.* 2016;60(8):4778–85.





CLINICAL TRIALS

The Centre for Global Health has developed particular expertise in the planning and organisation of phase II and phase III multicentre international trials.

Cryptococcal meningitis trials

In the mid-2000s, Professor Tom Harrison developed a method for assessing responses to antifungal drug treatments in cryptococcal meningitis patients, based on the speed of clearance of the pathogen in cerebrospinal fluid samples. This new method allowed for the design of treatment trials with much smaller numbers of patients, so new drug combinations and drug doses could be evaluated more rapidly.

This approach has underpinned a series of phase II proof-of-concept and phase III trials of novel treatments for cryptococcal meningitis with the potential to transform treatment of the condition in Africa.

TB trials

Dr Amina Jindani has led key trials evaluating shorter treatment regimens for TB – an important goal of TB treatment and control. These studies have been carried out under the umbrella of the International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis (INTERTB), which links sites in Europe, Africa, Asia and South America.

OUR PHASE II AND III CLINICAL TRIALS ARE MAKING KEY CONTRIBUTIONS TO THE EVIDENCE BASE FOR TREATMENT OF TB, CRYPTOCOCCAL MENINGITIS AND OTHER INFECTIONS.

INTERTB aims to build the capacity of sites in LMICs to carry out high-quality clinical trials, as well as associated clinical and basic studies, for example by supporting the implementation of procedures for good clinical practice and good laboratory practice. It is thereby creating a network of sites able to carry out trials of new treatment regimens and undertake a programme of research into factors affecting response to chemotherapy and surrogate markers of relapse.

Beyond TB

Dr Mark Wansbrough-Jones has worked with colleagues in West Africa on trials of antibiotic combinations for treatment of Buruli ulcer, which have informed WHO treatment guidelines.

Professor Sanjeev Krishna has also led trials with colleagues in Tübingen, Germany, and Gabon on simplified treatment regimens for severe malaria, spanning seven sites in five African countries. He also contributed to landmark trials evaluating candidate Ebola virus vaccines in Europe and Gabon.

CRYPTOCOCCUS: BEYOND FLUCONAZOLE

Professor Tom Harrison is leading major international trials that could transform the treatment of cryptococcal meningitis.

In resource-poor settings, cryptococcal meningitis is typically treated with fluconazole which, although only weakly effective, is safe and affordable. A better option, amphotericin B, is expensive, must be given intravenously, and its toxicity requires close monitoring of patients. It is therefore rarely used in sub-Saharan Africa.

In a bid to identify more effective alternatives to fluconazole, Professor Harrison and colleagues ran a series of phase II studies which identified clinical benefits associated with higher-dose fluconazole, shorter courses of amphotericin B, and the combination of fluconazole with flucytosine (an anticancer drug with fungicidal properties).

The success of these studies led to an MRC-funded phase III Advancing Cryptococcal meningitis Treatment for Africa (ACTA) trial, which compared the high-dose fluconazole–flucytosine combination with amphotericin-B-based regimens, at sites in Malawi, Zambia, Tanzania and Cameroon. Unveiled in 2017, the results provided strong evidence of the efficacy of short-course amphotericin and the fluconazole–flucytosine combination, with mortality rates halved compared with current treatments. They are likely to lead to major changes in international guidelines.

Meanwhile, further trials are exploring a potential new generation of treatments incorporating AmBisome, a less toxic liposome-based formulation of amphotericin B. Following a successful phase II trial run in collaboration with Professor Joe Jarvis, a €10m EDCTP-funded phase III trial, AMBITION, is evaluating single high-dose AmBisome–oral combinations in Botswana, Zambia, Malawi, South Africa and Uganda.

ACTA: results presented at IAS 2017: http://programme.ias2017.org/People/PeopleDetailStandalone/4291

AMBITION: results presented at CROI 2017: http://www.croiwebcasts.org/console/player/33485?mediaType=slideVideo&

SHORTENING TB TREATMENTS

Dr Amina Jindani is leading global trials testing highly sought after shortened TB treatment regimens.

While multidrug-resistant TB attracts much international attention, most new infections are drug-susceptible but still pose a therapeutic headache. Standard treatment regimens require daily treatment for six months, leading to high levels of non-compliance, driving the development of drug resistance. Shorter and more convenient treatments are urgently needed.

With few new TB drugs available, there is a drive to make best possible use of existing chemotherapeutics. Dr Jindani, Professor Denny Mitchison and colleagues have evaluated regimens including high doses of rifampicin and its chemical relatives, in trials run under the INTERTB umbrella.

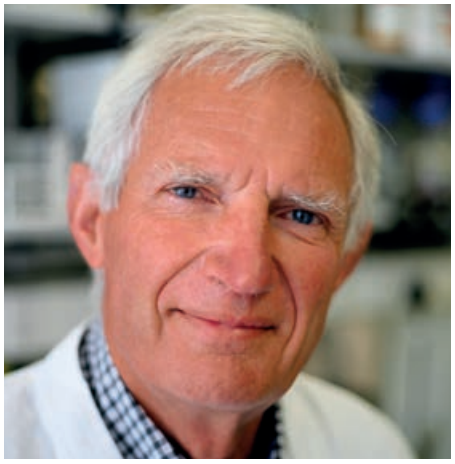
The landmark phase III RIFAQUIN trial found that shortened treatment regimens incorporating high-dose rifapentine were not as effective as standard treatments[1]. However, a weekly dose of rifapentine was as effective as daily treatment during the last four months of therapy – offering the possibility of significantly simplified treatment regimens.

The more recent phase II RIFATOX study[2] showed that higher doses of rifampicin did not increase the risk of liver damage. This finding, plus encouraging results in novel animal models (see page 7), led to the launch of the £2.2m MRC-funded phase III RIFASHORT trial[3], evaluating shorter (four-month) regimens using high-dose rifampicin in Botswana, Uganda, Peru and potentially other sites in Central America and Asia.

1 Jindani A *et al*. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med*. 2014;371(17):1599–608.

2 Jindani A *et al*. A randomised phase II trial to evaluate the toxicity of high-dose rifampicin to treat pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 2016;20(6):832–8.

3 https://clinicaltrials.gov/ct2/show/NCT02581527



ANTIBIOTIC TREATMENTS FOR BURULI ULCER

Dr Mark Wansbrough-Jones has led a series of clinical studies showing that antibiotics are highly effective treatments for Buruli ulcer.

Infections with *Mycobacterium ulcerans* cause disfiguring skin lesions, known as Buruli ulcer. The condition is common in parts of West Africa, mainly affecting children aged 5–15. Until recently, the main treatment was surgical excision, which is difficult to perform, not always successful and not accessible to people in remote locations.

Following positive studies in animal models, Dr Wansbrough-Jones with colleagues including Professor Richard Phillips (see page 12) organised a clinical study in Ghana evaluating a combination of antibiotics – rifampicin and streptomycin – given for various periods before clinical excision. Eight weeks' treatment was highly effective at killing *M. ulcerans* and preventing disease recurrence[1].

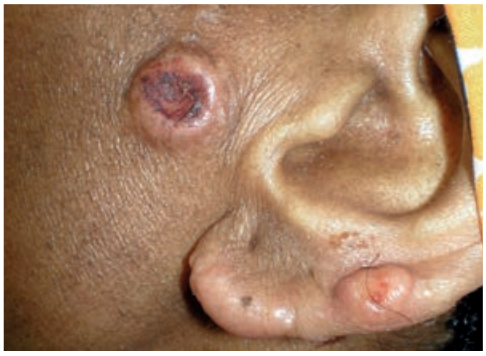
A larger follow-on study in Ghana confirmed the efficacy of antibiotic therapy even in the absence of surgery[2]. As streptomycin has to be injected into muscle, an oral drug, clarithromycin, has also been used instead of streptomycin for part or all of the eight-week treatment[3]. The latest study, in Ghana and Benin and reported to the WHO in 2017, confirmed the efficacy of an all-oral combination.

These findings have shaped WHO guidelines on treatment of Buruli ulcer, which are likely to be updated in light of the latest findings.

1 Etuaful S *et al*. Efficacy of the combination rifampin-streptomycin in preventing growth of *Mycobacterium ulcerans* in early lesions of Buruli ulcer in humans. *Antimicrob Agents Chemother*. 2005;49(8):3182–6.

2 Sarfo FS *et al*. Clinical efficacy of combination of rifampin and streptomycin for treatment of *Mycobacterium ulcerans* disease. *Antimicrob Agents Chemother*. 2010;54(9):3678–85.

3 Phillips RO *et al*. Clinical and bacteriological efficacy of rifampin-streptomycin combination for two weeks followed by rifampin and clarithromycin for six weeks for treatment of *Mycobacterium ulcerans* disease. *Antimicrob Agents Chemother*. 2014;58(2):1161–6.



INFLUENCING POLICY AND PRACTICE

To complement our research activities, we seek to influence policy and practice, and galvanise international activity through a range of advocacy activities.

Professor Mike Sharland and Professor Paul Heath are making major contributions to global initiatives mapping the burden of paediatric infectious disease, antibiotic prescribing practices and the impact of antibiotic resistance – raising policymakers' awareness of threats to infant health and informing future research priorities. Professor Sharland leads a global neonatal sepsis initiative, and participates in the Global Antimicrobial Resistance, Prescribing, and Efficacy Among Neonates and Children (GARPEC) global surveillance network.

Professor Heath contributes to studies on the global burden of infectious disease in neonates, particularly of group B streptococci (GBS). Through the international GAIA (Global Alignment of Immunisation Safety Assessment in Pregnancy) consortium, he is helping to lay the foundations of a global programme of research in maternal vaccination, building on GBS and pertussis vaccine trials run at St George's Vaccine Institute.

Professor Sharland is also an adviser to the WHO's Essential Medicines List Committee, and helped to shape the recommendations for antibiotic use in the 2017 revision of the WHO's Essential Medicines List. Other SGUL staff also have connections with the WHO, including Dr Mark Wansbrough-Jones, who chairs the WHO's Technical Advisory Group on Buruli Ulcer.

Implementation research

We are also becoming more involved in implementation research, to identify the most effective ways to integrate new interventions or ways of working into routine care. Dr Angela Loyse, for example, is leading an innovative study exploring implementation of rapid diagnostic tests and optimised treatments for HIV-related meningo-encephalitis in Africa.

OUR WORK IS STRONGLY ROOTED IN THE NEED TO INFORM NATIONAL AND INTERNATIONAL POLICY AND PRACTICE.

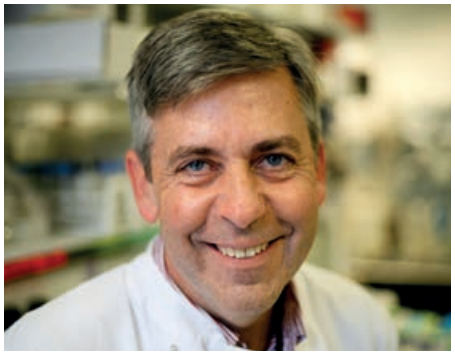
Our presence in Ecuador also provides opportunities for implementation studies. Ongoing and planned studies include Dr Tariq Sadiq's work on rapid diagnostics for STIs and new models of community asthma management.

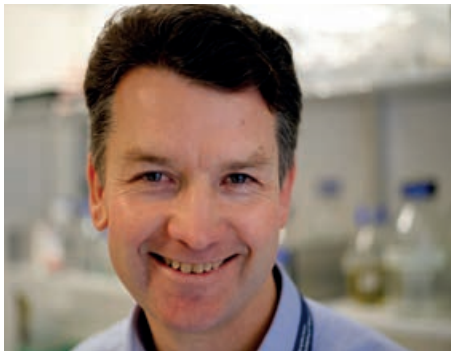
Advocacy

For cryptococcal meningitis, we have argued strongly for more international attention for the disease and for enhanced access to diagnostic tests and antifungal drugs.

This work is carried out under the umbrella of the **Cryptococcal Meningitis Advocacy Group (CryptoMAG)** chaired by Dr Loyse, which includes representatives from the US Centers for Disease Control and Prevention (CDC), Médecins Sans Frontières Access Campaign, Clinton Health Access Initiative and other bodies.

CryptoMAG is undertaking a range of measures to improve global access to antifungal drugs and diagnostics, and to persuade governments, global funders and policymakers to make cryptococcal meningitis a higher priority. It has argued that cryptococcal meningitis should be formally designated a neglected tropical disease, and has successfully called for amphotericin B and flucytosine to be added to the WHO's Essential Medicines List.





NEW TREATMENTS FOR NEONATAL SEPSIS

Professor Mike Sharland and Professor Paul Heath are leading global efforts to identify an improved treatment for neonatal sepsis.

Neonatal sepsis is responsible for around a million deaths a year, mainly in LMICs. Growing levels of antibiotic resistance are adding a further challenge, undermining the effectiveness of the WHO's recommended treatment – ampicillin and gentamycin.

In partnership with the WHO and as part of its Global Antibiotic Research and Development Partnership (GARDP), the Drugs for Neglected Diseases Initiative (DNDi) recently launched a neonatal sepsis programme, being led by Professors Sharland and Heath. Its key aim is to identify more effective treatment regimens for serious bacterial infections in neonates.

The eight-year programme, launched in 2017, is aiming to generate a comprehensive evidence base on neonatal infections globally and the antibiotics available to treat them. The SGUL team is establishing a global network of around 20 neonatal care units, to identify the current burden of disease, patterns of antibiotic resistance, and approaches to treatment.

Complementary studies will examine possible alternative antibiotic treatments for neonatal infections, based on currently available drugs. Ultimately, the most promising combination will be evaluated against current WHO recommendations in a global multicentre trial.

https://www.gardp.org/programmes/neonatal-sepsis/

DREAMMS OF IMPLEMENTATION

An innovative implementation project being run by Dr Angela Loyse is aiming to integrate diagnostic testing for HIV-associated meningo-encephalitis into routine hospital care.

The cryptococcal antigen (CrAg) dipstick assay is a highly accurate diagnostic for cryptococcal meningitis, the commonest cause of HIV-related meningo-encephalitis in LMICs in Africa, supporting early initiation of antifungal therapy. SGUL researchers have helped to generate compelling evidence of the cost-effectiveness of the CrAg diagnostic. However, only a small number of countries have adopted CrAg testing in routine care.

In the €1.88m DREAMM project, funded by the EDCTP and supported by the Institut Pasteur and the CDC, Dr Loyse is working with hospital teams in Malawi, Tanzania and Cameroon to develop new patient and laboratory pathways and implement clinical algorithms that integrate timely diagnosis and treatment of HIV-related meningo-encephalitis.

The diagnostic/clinical algorithm will include an upgraded version of the CrAg test (developed in collaboration with the Institut Pasteur) that provides quantitative information on fungal load, identifying the need for more intensive treatment. It will be deployed at the bedside (alongside additional rapid diagnostic tests) rather than in centralised hospital laboratories.

As well as hospital authorities, results will also be fed back to local ministries of health. A set of guidelines on the management of HIV-associated meningo-encephalitis in African LMICs will also be developed to encourage wider uptake.

REALISING THE POTENTIAL OF RAPID DIAGNOSTICS

Dr Tariq Sadiq and colleagues are beginning pilot studies in Ecuador to explore how new rapid diagnostics could benefit vulnerable groups such as sex workers.

In the UK, Dr Sadiq is leading pioneering studies developing new diagnostic tests for sexually transmitted infections (STIs) and exploring novels ways of integrating such tests into patient care pathways. Rapid point-of-care tests are providing opportunities to design radically new pathways that fit better with people's daily lives.

Taking advantage of SGUL's research base in Ecuador (see page 3), Dr Sadiq has begun to explore how new tests could be implemented in this setting. His initial focus is on vulnerable groups such as female sex workers, who experience notably high levels of STIs.

Preparatory work includes a mapping of the prevalence of key STIs – *Chlamydia*, gonorrhea, *Trichomonas* and *Mycoplasma genitalium* – in female sex workers in Quito. In addition, social scientist Dr Sebastian Fuller is exploring the perspectives of key stakeholders, including sex workers, to shape the design of new services.

Planned field studies will assess the take up of diagnostic services and the impact on STI prevalence in sex workers, while health economic analyses will provide policymakers with important information on the cost-effectiveness of new models of service delivery.

EDUCATION, TRAINING AND CAPACITY-BUILDING

Researchers in the Centre for Global Health have worked with colleagues in SGUL's Institute of Medical and Biomedical Education to develop **undergraduate and postgraduate courses in global health**.

The one-year undergraduate global health course is offered to intercalated medical students and third-year biomedical sciences students at SGUL. Launched in 2015, it provides a highly popular introduction to key issues in global health, from global health diseases to conflict and catastrophe medicine.

Six postgraduate courses – an **MSc in Global Health**, with a range of specialist pathways – were launched in 2017, attracting applicants from the UK and LMICs, including a mix of clinicians and healthcare professionals, non-clinical scientists, and those with a background in policy, the social sciences and the humanities. The course offers a broad range of modules, with a particular emphasis on research training, enabling students to undertake a research project overseas.

Research training and capacity-building

The Centre also offers a supportive and stimulating environment for early-career researchers, hosting multiple PhD students and trainee clinical fellows. SGUL is a partner in the **Wellcome Trust–Bloomsbury Centre for Global Health Research**, which helps clinical and non-clinical scientists develop their early careers in global health research. The Wellcome Trust is funding a Clinical PhD Programme in Global Health Research at the Bloomsbury Centre, which will train 20 fellows over five years.

Our researchers also have strong collaborations with multiple groups based in LMICs, providing an additional route through which researchers can undertake a period of research at SGUL. Our presence in Ecuador and links to South American groups has enabled us to support the development of researchers from Latin America. In addition, strong links with Ghana, supported by the MRC, have provided an opportunity for capacity-building in West Africa (see right).

WE ARE TRAINING THE NEXT GENERATION OF GLOBAL HEALTH SPECIALISTS.

BUILDING WEST AFRICAN RESEARCH CAPACITY

Justice Boakye-Appiah (above left) is the latest in a long line of clinicians able to develop their research skills at SGUL thanks to its close links with Dr Richard Phillips in Ghana.

After completing his medical training in Ghana, Dr Phillips (right, centre) studied for a PhD under Dr Mark Wansbrough-Jones, working on *Mycobacterium ulcerans* infections and the ulcerating skin disease Buruli ulcer.

Following his PhD, in 2005 Dr Phillips returned to Kwame Nkrumah University of Science and Technology (KNUST) in Ghana to establish his own research group, and has continued a highly productive collaboration with Dr Wansbrough-Jones, including influential clinical studies of antibiotic therapy for Buruli ulcer (see page 9).

In 2012, Dr Phillips was awarded major funding through the MRC's African Research Leader scheme, which provided an opportunity to strengthen links with SGUL. As well as supporting research into Buruli ulcer – particularly on why recovery times vary so dramatically between patients, and the immunological mechanisms underlying the occasional flare-up of ulcers following antibiotic treatment – the award enables staff from Ghana to spend time at SGUL.

These links have provided important training opportunities for technicians, master's students and medical trainees to develop their technical and research skills. The latest of these is Justice Boakye-Appiah, who recently completed his foundation years in Ghana. He is now undertaking a PhD with Dr Rajko Reljic, exploring the possibility of developing a vaccine for Buruli ulcer by modifying the main toxin produced by *M. ulcerans*, mycolactone, to enhance its immunogenicity.

IN-HOUSE SUPPORT

AN OUTSTANDING CLINICAL TRIALS TEAM IS CRITICAL TO OUR MULTICENTRE INTERNATIONAL TRIALS.

The Centre for Global Health has successfully led multiple large-scale clinical trials, and is currently running trials and other studies with large numbers of international collaborators in locations across Africa, South America and Asia (as well as multicentre trials in Europe).

Each trial is a major logistical exercise, calling for efficient communication between academic collaborators, trial sites, funders and multiple other stakeholders, such as local health officials and ethics and regulatory bodies. Trial protocols have to be applied consistently and to a high standard, potentially at sites that have had little prior exposure to clinical research and are operating in a highly resource-constrained environment. Ethical and regulatory approvals in multiple countries can be complex and time-consuming to negotiate.

The smooth running of our trials owes much to an experienced and dedicated inhouse trials team led by Dr Sile Molloy and Claire Robb, our Senior International Trial Managers. A member of the project management team is assigned to each trial and takes the lead in coordinating activities across the project, training all site teams on trial protocols, site specific procedures and good clinical practice, managing all trial-related paperwork (including submissions to ethics committees and reporting to funders and trial oversight bodies), and in quality-assuring activities at trial sites, including laboratory testing and clinical data collection – making regular trips to all participating sites. They also coordinate data collection and storage, and contribute to statistical analysis of trial data.

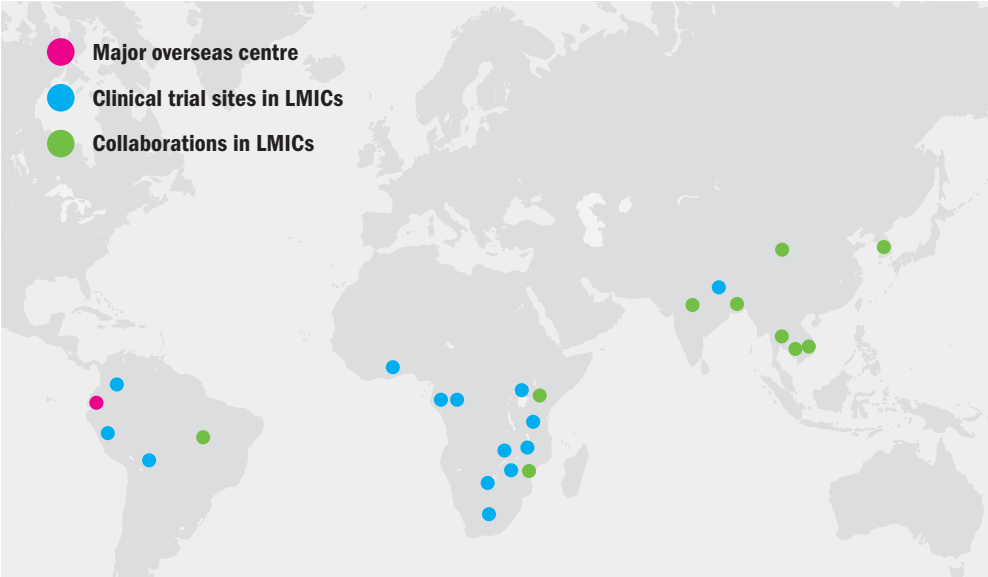
SOCIAL SCIENCE SUPPORT

Dr Sebastian Fuller provides valuable social science input into the Centre's projects.

With 15 years' experience in community engagement and applied social science in sub-Saharan Africa and elsewhere, Dr Fuller brings a unique combination of skills to our global health research projects.

After working in community engagement and HIV prevention in his native USA, Dr Fuller spent two years in Ghana developing local capacity in community engagement. For his PhD research, he explored novel methods for encouraging young men to participate in research in rural South Africa. In 2014, he was appointed a technical adviser to the WHO on point-of-care diagnostics for STIs.

His core interest has been on how fostering a sense of ownership can promote engagement and encourage participation. At SGUL, his work has focused on engagement with a range of public and professional groups, to promote participation and inform the design of clinical pathways and novel technologies. He is contributing to several global health projects, including work on STI diagnostics in Ecuador (see page 11), re-engineering of patient pathways to accommodate cryptoccocal diagnostics in sub-Saharan Africa (see page 11) and developing public engagement for the use of plant biotechnologies for molecular pharming (see page 7).



GLOBAL CONNECTIONS

We are committed to working with collaborators in academic and clinical centres in LMICs. We have a major and long-standing presence in Ecuador, as well as multiple well-established collaborations, particularly in sub-Saharan Africa but also in South-East Asia and South America. We also work in partnership with a wide range of clinical trial sites globally.

We are also a coordinating centre for major international networks, including the International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis (INTERTB), a global network of sites evaluating novel treatment regimes for TB, and the Cryptococcal Meningitis Action Group (CryptoMAG), a network advocating for greater global attention for cryptococcal meningitis.

We welcome the opportunity to establish new partnerships – if you would like to get involved in our work, please get in touch with the Director of the Centre for Global Health, Professor Tom Harrison (tharriso@sgul.ac.uk).

Major overseas centre

Ecuador

Clinical trial sites in LMICs

Gabon
Ghana
Malawi
South Africa
Tanzania
Zambia
Cameroon
Botswana
Uganda
Zimbabwe
Peru
Colombia
Nepal
Bolivia

Collaborations in LMICs

Brazil
Vietnam
Mozambique
Kenya
India
Bangladesh
Cambodia
Thailand
China
Korea

CROWDFUNDING FOR CANCER

Professor Sanjeev Krishna has led a successful crowdfunding campaign to raise funds for a trial of artesunate treatment for colorectal cancer.

Colorectal cancer accounts for around 10% of cancer cases globally. New treatments are urgently needed, particularly for patients in LMICS who have limited access to current surgical and chemotherapeutic treatments.

One option could be the relatively affordable antimalarial drug artesunate, known to have anticancer properties. Following a promising pilot trial at St George's Hospital[1], Professor Krishna (right), Professor Devinder Kumar and Dr Yolanda Augustin have secured funds – through an innovative online crowdfunding project – to support a larger multicentre phase II trial on 200 patients to prevent disease recurrence after surgery[2]. In an attempt to widen access to the treatment, an extension of the trial is also being run in Vietnam.

1 Krishna S *et al.* A randomised, double blind, placebo-controlled pilot study of oral artesunate therapy for colorectal cancer. *EBioMedicine*. 2014;2(1):82–90.

2 http://neoarttrial.org

CGH PEOPLE

The Centre for Global Health is founded on the expertise of researchers in the SGUL Institute for Infection and Immunity with interests in understanding and treating infectious disease in LMICs.

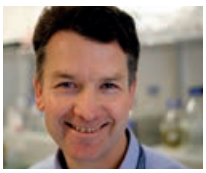
Centre Lead
Tom Harrison

Tom Harrison
Cryptococcus pathophysiology, management and prevention, and TB chemotherapy.

Tihana Bicanic
Fungal pathogens and invasive fungal infections, in particular *Cryptococcus neoformans* and cryptococcal meningitis.

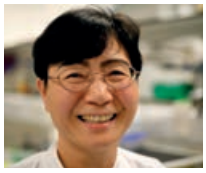
Phil Cooper
Allergy epidemiology and helminth parasites – diagnosis, host response and treatment.

Sebastian Fuller
Community engagement and applied social science.



Paul Heath
The epidemiology of paediatric vaccine-preventable diseases, clinical vaccine trials, and perinatal infections.

Carwyn Hooper
Postgraduate education, medical ethics and law.

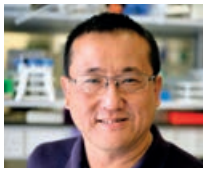


Yanmin Hu
Molecular pathogenesis of tuberculosis and novel anti-tuberculous drug discovery.

Amina Jindani
Clinical trials of TB treatment regimes.

Sanjeev Krishna
Treatment and diagnostics of malaria and other neglected diseases.

Angela Loyse
Cryptococcus and cryptococcal meningitis.



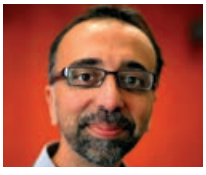
Julian Ma
Engineering plants to produce recombinant protein anti-infective biopharmaceuticals.

Síle Molloy
Epidemiologist and Senior International Trials Manager.

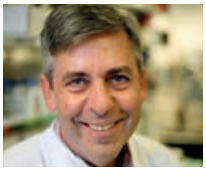
Matthew Paul
Project manager.

Claire Robb
Senior International Trials Manager.

Rajko Reljic
TB immunotherapy and vaccine development.

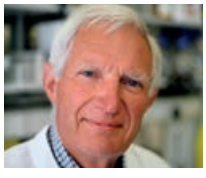


Tariq Sadiq
STI pathogenesis, diagnostics for point-of-care antimicrobial profiling, e-health and personalised medicine.



Mike Sharland
Antimicrobial use and resistance in children.

Henry Staines
Drug development, resistance mechanisms and diagnostics for malaria and other neglected pathogens.



Mark Wansbrough-Jones
Mycobacterium ulcerans infection and Buruli ulcer disease.

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