tropical

LSTM
LIVERPOOL SCHOOL
OF TROPICAL MEDICINE

Technology supporting translational research

2016-2017 issue

Contents

Infrared video tracking of *Anopheles gambiae*

Researchers at LSTM have revealed the behavioural patterns of mosquitoes at the insecticide-treated bednet interface, contributing to our knowledge of how these highly effective tools function to ensure they continue to be effective against insecticide resistant mosquitoes.

Many of the malaria mosquito vectors feed indoors at night, particularly in Africa where malaria exerts the greatest toll. By exploiting this behaviour, long-lasting insecticidal bednets (LLINs) have become one of the most effective methods for reducing malaria transmission. However the future of LLINs is under threat due to emergence of mosquito populations resistant to pyrethroids, the only insecticide class that is available for use on LLINs. As a consequence there is a need for a new generation of effective LLINs, the development of which will require an understanding of how they function and of how mosquitoes behave at the net interface.

Challenges

Typically, most investigations into mosquito behaviour involve small-scale laboratory assays which are rather artificial in nature and do not always reproduce the natural behavioural patterns of mosquitoes. Such tests often use single odour attractants in place of a whole human sleeper to attract mosquitoes, or use small volumes or arenas, and allow testing of single or limited numbers of mosquitoes simultaneously. These and other technical challenges needed to be addressed in order to characterise the behaviour of mosquitoes under natural conditions.

Innovative technology

LSTM vector biologists Dr Philip McCall and Ms Josie Parker have worked with optical engineers Professor David Towers, Dr Natalia Angarita and Dr Catherine Towers from the University of Warwick's School of Engineering. To develop and construct a novel infrared video tracking system that enabled the tracking, recording and analysis of the flight paths of multiple mosquitoes in large fields of view in complete darkness. This technology, which employs optical techniques normally used in lighthouses, has enabled detailed analyses of the behaviour of the main African malaria vector, *Anopheles gambiae*, as it attempted to reach and feed on a human volunteer sleeping within an LLIN over periods of hours.

Mosquitoes are tracked using paired recording systems which capture either the upper or lower body sections, each comprising a single high power infrared LED aligned with a pair of Fresnel lenses and a monochrome camera. The room is illuminated with an infrared LED at a wavelength that is invisible to humans and to mosquitoes and does not impact on the mosquito's behaviour. Each mosquito track, from entry and exit into the field of view, is analysed independently to extract quantitative data including mosquito velocity, distance travelled, and the number and duration of contacts with the bednet. Data generated are huge: for each hour of operation, 360 000 images or 1.4 TB of data are captured, requiring purpose-designed software, written by the University of Warwick engineers.

Utilising this technology, Dr Philip McCall and Ms Josie Parker demonstrated that mosquito flight and net contact times were lower at LLINs than untreated bednets and mosquito activity at nets containing a sleeper (both untreated and LLINs) was higher than at empty bednets (Figures 1-3).

This innovative approach to studying mosquito behaviour has provided insight into how LLINs function under conditions that are as close to a natural field setting as possible, making a significant

Bednet with two pairs of Fresnel lenses visible on each side. LEDs emit light across the net and through the Fresnel lenses, focussing light at a camera.

the malaria mosquito vector,

contribution to our understanding of mosquito behaviour. The findings could potentially influence the development of new approaches to mosquito control, and

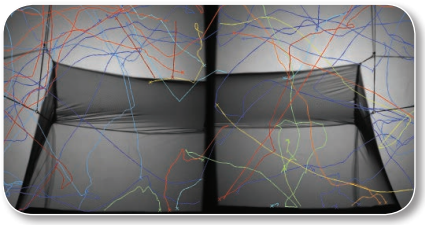


Figure 1: Flight tracks of multiple individual *An. gambiae* around an empty untreated bednet over 60 minutes.

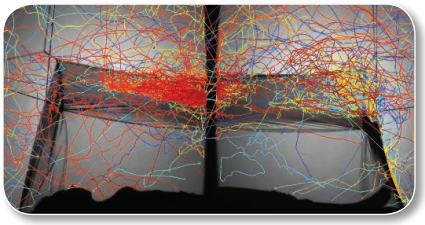


Figure 2: Flight tracks of multiple individual *An. gambiae* around an untreated bednet with a human sleeper inside over 15 minutes.

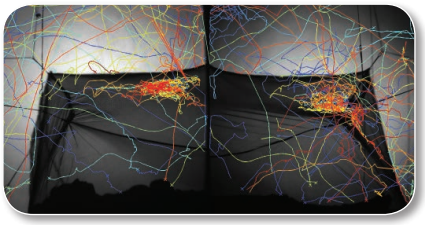


Figure 3: Flight tracks of multiple individual *An. gambiae* around an LLIN with a human sleeper inside over 15 minutes.

will be useful in the design and evaluation of the next generation of LLINs.

This work was funded as part of the € 12M EU funded AvecNet research consortium, and the team's initial results have been published in the journals ***Scientific Reports*** (Parker *et al*. 2015, **5**:13392) and ***J. Royal Society Interface*** (2016, in press).

Future developments using the technology

The tracking system has been deployed in a rural Tanzania, to study the behaviour of malaria vectors in a semi-field setting. The team was also awarded £0.9M from the Medical Research Council (MRC) for the next stage of this project, in which they will use a three-dimensional system to track mosquitoes throughout the entire domestic environment in Tanzania. These new experiments will use six cameras collecting over 4 TB of data per hour, to map mosquito behaviour from house entry to exit over periods of hours - days.

Then system will also be deployed in Burkina Faso as one element of the £2.47m Wellcome Trust Collaborative grant awarded to Prof Hilary Ranson, Dr McCall at LSTM, Prof Towers at Warwick and other collaborators for the project entitled *Improving the efficacy of malaria prevention in an insecticide resistant Africa*. In this project the behaviour of the highly resistant malaria vector populations in rural Burkina Faso will be studied with a view to identifying new approaches to the control of insecticide resistant mosquitoes.

LSTM's Vector Biology Department presented part of its work at Liverpool's famous LightNight event in May 2016. Approximately 3000 members of the public, old and young, descended on the Everyman Theatre to enjoy and explore the exciting activities on offer.

The family-friendly exhibition entitled 'The Mosquito Diaries' showed visitors the innovative life-saving research being undertaken at LSTM, in collaboration with the University of Warwick. In particular, Mosquito Diaries illustrated LSTM's research involving cameras tracking mosquito flight around insecticide treated bednets to assess how insecticide impacts mosquito behaviour, and how educational gaming can be used to explain insecticide resistance. The night also gave the volunteers an insight into what to expect when the same exhibit features at the week-long Royal Society Summer Science Exhibition in London in the summer of 2016

The team communicated three key messages to the public, with a view to inform, inspire and involve them in their research: Mosquitoes transmit malaria, insecticide treated bednets protect people from bites and, thirdly, how insecticide resistance threatens malaria control.

These messages were illustrated through a competitive buzz-wire race game, designed to mimic the flight track of a mosquito around a bednet, which encouraged the public to adopt the role of the mosquito in locating the net and navigating around a human-seeking flight

path. Computer games developed by LSTM's Engaging Tools for Communication in Health (ETCH) team allowed visitors to test virtual mosquitoes for insecticide resistance. Furthermore, live mosquito demonstrations and a mosquito mask making craft activity encouraged younger visitors to consider different aspects of mosquito anatomy and how mosquitoes use these features to feed on people.

Vector Biology's Josie Parker said "Light Night gave us a great opportunity to talk to people about how LSTM's work with mosquitoes helps in the fight against the devastating disease malaria, which disproportionally affects the world's poorest communities."

Infrared tracking continued

Engaging policy makers through gaming

Digital gaming is one of the innovative ways that LSTM uses to engage with policy makers in endemic countries to promote good insecticide resistance management practices in malaria prevention.

The Engaging Tools for Communication in Health (ETCH) unit was formed in 2014 and brings together expertise from academia, public health and the games industry to develop, evaluate and assist with the delivery of digital solutions to address key health challenges in resource-poor settings. ETCH is currently working with an indie game developer, EM Studios, in the production and evaluation of a simulation game for vector control programmes.

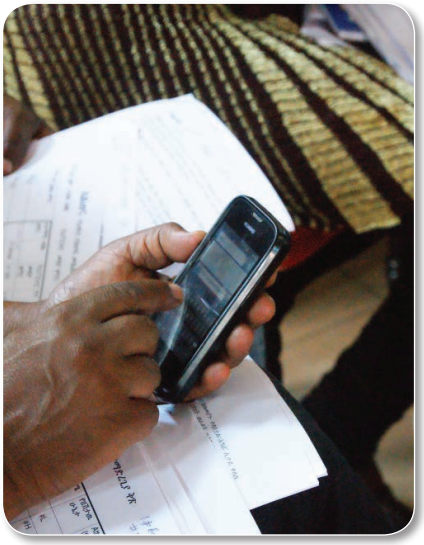
Knowing how insecticide resistance is impacting control efforts requires effective data integration; from quality assurance of interventions, to case and entomological surveillance. ETCH's new game, ResistanceSim works in a similar fashion to disease models, where users make an intervention choice and then run the program to determine the impact of their decision. However, where these models use real data and are often made up of thousands of lines of code, the mathematical model that drives the virtual mosquito population in the game is much simpler. ResistanceSim is a learning and training tool that will hopefully compliment and encourage the use of decision support systems. It allows users to explore insecticide resistance management in a 3D virtual environment. They collect data using real life insecticide testing methods. They then use the data to choose the most effective intervention, while managing their budget in the game. Principle Investigator, Dr Marlize Coleman, said: "ResistanceSim is a much needed training tool for malaria vector control programmes in Africa. It can be run on a normal PC and is simple to download. Using the very best in graphics we are able to make the user experience engaging and enjoyable."

In 2014 the pilot game was tested in Malawi and Zambia, and feedback was extremely positive. Control program officers suggested game expansion to cover other key challenges of vector control, such as financial constraints and quality assurance of interventions. This new version has now been rigorously tested internally and it will be tested by a number of vector control programme personnel in late June this year. The team will take ResistanceSim to a regional entomology training event in Zimbabwe organised by the Africa Indoor Residual Spraying project, where it will be tested by participants from 8 countries in sub-Saharan Africa. The team will then evaluate the target users' perceptions of the tool to determine the feasibility of incorporating it into existing training activities.

ResistanceSim forms part of Mosquito Diaries, an interactive exhibit which has been selected for inclusion in this summer's Royal Society Science Exhibition in London. The exhibit was first seen at the Everyman Theatre in Liverpool as part of the LightNight Festival in May 2016, where the ResistanceSim bioassay mini games were introduced, giving members of the public the opportunity to act as a lab technician testing the efficacy of insecticides in mosquito control on a purpose built tablet edition of the game.

Making hidden patients visible with a text

'*1#Salyantar,9,Majhi#3#M#49#L#2#3*' is not a coding message or a spell check gone mad but the content of a simple text message that will make a huge difference to a 49 year old male suffering from severe lymphoedema. Translated the text message means: Patient number 1 is located in Salyantar District, Ward 9 in Majhi Tole. He is reported by reporter number 3, the patient is a male, aged 49 and is with Lymphoedema. He had 2 attacks in the last 6 months and the severity is severe.



MeasureSMS is an m-Health tool which uses SMS (text) messaging to communicate the patients' details, as found by a Community Health Volunteer. The details are being texted using a simple mobile phone to a smart phone held by the NTD programme. It is one of many text messages feeding into a database, via the smart phone, and holds relevant information making visible the disease burden of people living in endemic areas of lymphoedema and/or hydrocele.

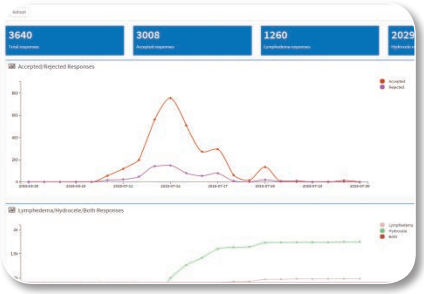
LSTM
FILARIAL PROGRAMMES SUPPORT UNIT

The mobile phone application is developed together with Tripod Software and is managed by LSTM's Filarial Programmes Support Unit (FPSU) with funding from DFID. It maps the disease burden of lymphatic filariasis on local populations in endemic areas. The results are being shared with the relevant Ministry of Health that is then able to respond and target its care more effectively where it is needed the most, i.e. by providing surgical interventions and lymphoedema care, usually with financial support provided by FPSU using DFID funds.

FPSU currently uses the tool in 6 countries: Malawi, Tanzania, Nepal, Ethiopia, Bangladesh and Liberia. As of 29 May 2016 FPSU has used the tool in 19 districts, trained 984 health workers who have reported 18,390 cases thus far (7,565 lymphoedema and 11,425 hydrocele).

'The approach makes hidden patients visible', says FPSU's Programme Officer Hayley Mableson, 'It's the pro-active approach of the community health volunteers who knock on each door collecting the data and instantly report these, with a simple text message, to the smart phone of the NTD programme. And via that smart phone to our central database.'

The results are often remarkable, such as in a city district in Dar Es Salaam, Tanzania. Where initially the assumption by district health officers was that there would be a few hundred patients in densely populated districts, FPSU's pro-active mapping in 2015 found 1,500 patients in the district and 4,000 hydrocele patients in the city in total. The data is being shared with national NTD programmes and Ministries of Health, both on national and district level. It is a major efficiency drive which allows all relevant parties to target their resources much more effectively and being able to reach patients who otherwise would have missed out on treatment.



DFID's funding for the LF Elimination Programme managed by FPSU provides technical assistance to identify and prioritise interventions that will eliminate lymphatic filariasis (LF) and reduce the burden of LF and other neglected tropical diseases. The primary role of FPSU is supporting colleagues in endemic countries with their progress towards successful elimination of filarial diseases.

This m-Health tool is part of FPSU's Morbidity Management and Disability Prevention (MMDP), also known as Disease Management Disability & Inclusion (DMDI), a key part of the DFID funded LF Elimination Programme. The aim is to relieve suffering from clinical manifestations of the disease by providing available patient care to those affected with lymphatic filariasis as efficiently as possible. FPSU supports national NTD programmes, provides technical assistance, strengthens the evidence base to inform policy makers, and identifies and prioritises interventions that will eliminate filariasis and reduce the burden of other neglected tropical diseases.

Technologies, innovation and investment in support of LSTM's translational research

LSTM has invested in a long term strategic plan to put translation at the centre of all its research activities into tropical infectious diseases. This plan has resulted in investing in the current construction of the £24.8 million Liverpool Life Sciences Accelerator Building and in the completion of the £25 million Centre of Tropical Infectious Diseases (CTID) building comprising of 22 HG3-containment laboratories (including HG3-insectaries), the highest density of such labs in UK academia. This was followed by a second phase of strategic academic appointments supporting existing strengths in Malaria, Clinical Tropical Medicine, Neglected Tropical Diseases (NTDs) and Vector Biology and establishing an international presence in Respiratory Infections such as tuberculosis – this second phase being supported by a Wellcome Trust Institutional Strategic Support Fund (ISSF) award.

Drug and diagnostic discovery and development remain one of the pillars of LSTM's activities taking place in the Research Centre for Drugs and Diagnostics (RCDD). The Centre works with industry, SMEs and larger organisations, academia and other NGOs to discover, develop and deliver novel therapies against a range of drug resistant pathogens.

LSTM
RESEARCH CENTRE FOR DRUGS & DIAGNOSTICS

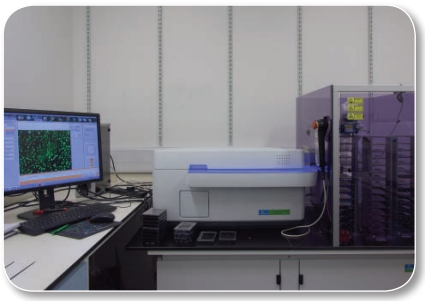
The Centre has access to state-of-the-art laboratories and equipment, including Category 3 laboratories, medicinal chemistry laboratories, analytical laboratories, robotic liquid handling and high content imaging platforms.

"We have active portfolio in drugs and biologics as well as diagnostics to support the rapid identification and treatment of pathogens in a variety of endemic settings", says Professor Giancarlo Biagini, who, together with Professor Steve Ward, leads RCDD. "These activities are commonly delivered in Public Private Partnerships and take advantage of LSTM's unique cross-disciplinary expertise and global reach." This reach affords access to patient populations and pathways to drug and diagnostic evaluation and implementation in the UK, Africa, Asia and South America and further links to policy makers, completing the translational research circle.

Professor Giancarlo Biagini operating the new confocal microscope in LSTM's HG3 Imaging facility

To support this approach LSTM continues to invest in technological innovation. Work on the Liverpool Life Sciences Accelerator (LLSA) building continues with a foreseen opening in 2017. This mainly laboratory based development will enable innovative research into a range of resistance issues, including insecticide and antibiotic resistance.

The past year has seen the purchase, instalment and commissioning of the HG3 Imaging Unit funded in part by a Wellcome Trust Multi-User Equipment Grant award to Professor Biagini, and includes high content Operettas, BD FACSAria cell sorter and a Zeiss 880 Confocal Microscope. It is believed to be the first HG3-Imaging facility in a UK academic setting capable of handling HG3 pathogens including aerosol-transmittable pathogens such as *Mycobacterium tuberculosis*.



The HG3 imaging unit is involved in a variety of drug discovery programmes including TB, Malaria, Salmonella and in the search for anti-*Wolbachia* drugs as new treatments for onchocerciasis and lymphatic filariasis. The LSTM based A·WOL consortium worked alongside AstraZeneca to develop an assay to identify compounds with anti-*Wolbachia* activity. The assay screened 1.3 million compounds and this provided around 21,000 hits that are being used for further development.

A·WOL
ANTI-WOLBACHIA CONSORTIUM

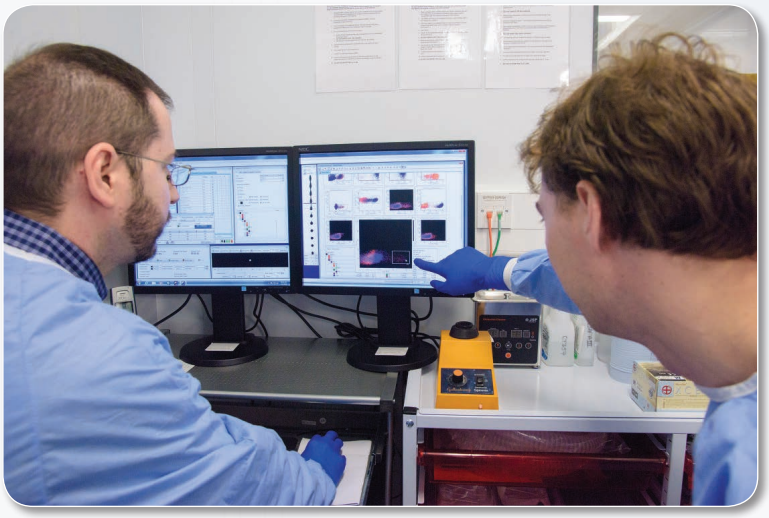
It is one example of the demand for HG3-imaging, which comes from existing and incoming appointments across LSTM, colleagues in the overseas Wellcome Trust programmes, academic collaborators, industry and the wider health community who wish to work directly with HG3 organisms e.g. *Mycobacterium tuberculosis, Plasmodium falciparum*, HIV, arboviruses et al. and not their surrogates. The HG3 laboratories and facilities at LSTM are of strategic importance to the UK's ability to work with important human pathogens and represent the first dedicated facility of its type in the Northwest region.

The Flow Cytometry Service at LSTM is open to all users from academia or SMEs (small and medium-sized enterprises) and Industry. The service also provides fluorescence activated cell sorting (FACS) by highly trained operators.

The service offers assistance in a variety of areas, including access to a BD SLRII and FACSARIA, training, experimental design, panel development and optimization, technical support and data analysis. Flow Cytometry at LSTM aims to stay at the cutting edge of cytometric technology and also introduce new fluorochromes or technologies appropriate to user's needs.

Overall it is another example of LSTM's unique translational approach to its research, where the laboratory and mathematical studies are being translated to the clinic, with LSTM and its overseas partners are involved in numerous clinical trials that aim to limit resistance or reduce transmission cycles.

Liverpool Life Sciences Accelerator Building under construction



Flow Cytometry Services provided:

- Acquisition and sorting of cells (including HG3 organisms)
- Data acquisition
- Data analysis
- Training and advice on sample preparation and acquisition
- User assistance and machine troubleshooting;
- Help with design of experiments, multiparametric panels and sourcing of reagents

We have one cytometer and one cell sorter equipped with 488 (blue), 633 (red) and 405nm (violet) lasers allowing multiparametric analysis up 18 parameters.

- BD LSR II is an analyser cytometer for screening assays, the BD LSR II offer walk-away sample handling with high throughput sampler 96 well microtiter plate. The acquisition workstation for this instrument is a PC with BD FacsDiva 6.2.1 software. The FCS 3.0 data files can be exported and analysed using other flow cytometry software applications. Post-acquisition compensation are allowed and this cytometer offer bi-exponential scales.
- BD FacsAria III Cell Sorter. This equipment is in a HG3 laboratory and can be used to sort several cell types and organisms including HG3 pathogens such as TB. Four way sorting is possible, tube holders include sizes from microtubes to 15mL tubes and collection is also possible on a 384-well plate (most of users use 96 well plate) and slides. Sample and sort collection tubes can be maintained at a cooling or heating temperature. The acquisition workstation for this instrument is a PC with BD FacsDiva 8.1 software. The FCS 3.0 data files can be exported and analysed using other flow cytometry software applications. Post-acquisition compensation are allowed and this cytometer offer bi-exponential scales.

For more information please contact Dr Jesús Reiné on +44 (0)151 705 3361 or email jesus.reine@lstmed.ac.uk

New technologies and novel adaptations in support of vaccine development

One of LSTM's themes of research is TB and Lung Health. Research is carried out across the departments, but there is a dedicated team within the Department of Clinical Sciences that looks at respiratory health and how it is affected by both infectious diseases and non-communicable conditions.

Senior Lecturer, Dr Daniela Ferreira is principal investigator for a number of studies looking at *Streptococcus pneumoniae*, the most common bacterial cause of pneumonia. Pneumonia kills more children than any other disease, and is found throughout the world. At LSTM, researchers are using cutting edge technology as well as novel adaptations of existing equipment to open new avenues in pneumococcal vaccine development.

The Experimental Human Pneumococcal Carriage (EHPC) model has been hailed as a 'milestone' by the American Journal of Respiratory and Critical Care Medicine. The model is the only one of its kind in the world and can be used for vaccine development, examining pneumococcal biology, exploring mucosal immunity and host susceptibility.

In work funded by the Bill and Melinda Gates Foundation (BMGF) and the Medical Research Council (MRC) the model involves volunteers having pneumococcal bacteria placed directly in their nasal passage and examining their immune responses and pneumococcal biology in a controlled manner.

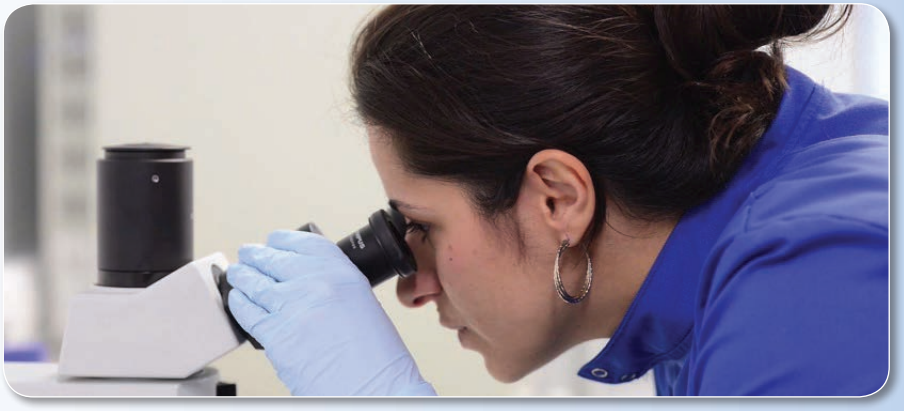
Pneumococcal bacteria is carried by much of the population, particularly children, safely in their nasal passage. As people age we know that the levels of naturally occurring pneumococcus decline, and the model demonstrates how an optimum level pneumococcal carriage can protect from the subsequent disease associated with the bacteria and explain why people are more susceptible in later life.

Volunteers are inoculated with the bacteria and then cells are taken from their nasal passage at intervals over the following days. The makeup of their cell population is examined using BD FACSAria III high speed cell sorter. The machine allows researchers to examine many samples simultaneously, adding antibodies tagged with different fluorescent markers, or fluorophores to each sample that bind with specific cells. When the sample is run through the machine the fluorophores are excited by one of the three lasers and fluoresce, allowing the machine to automatically separate the sample cell by cell. This is performed with each sample taken at different stages post-inoculation giving the research team an insight into which cells form the cornerstone of the body's natural immune response to the bacteria.

Dr Ferreira said: "We know that with healthy volunteers the levels of pneumococcus tend to decline around the seven day after we put the bacteria there, meaning that the population of the sample at this time and before are key to an effective immune response. We are now undertaking trials using different participants, those over 50 years old or those younger with asthma, groups that are more susceptible to pneumonia. This will help us to understand what is different about the cells produced by these different groups so that we can identify which would need to be boosted in order the replicate a healthy immune response and clear the bacteria safely."

The trials so far also indicate that colonisation in the nasal passage also offers a greater level of protection to the lungs as well, and potentially more than the current vaccines which are injected into the arm. The research team is hoping to build upon these findings in the next phase of the trial with some participants volunteering for a follow up research bronchoscopy (a telescope test). This research area, led by Dr Jamie Rylance, will investigate the impact of the bacteria on the lungs to examine the protection offered by vaccines and by colonisation. Immune responses in the lungs are different to those in the nose, and are key to preventing pneumonia. But human studies are relatively few, because taking samples is challenging. The research group has extensive experience of bronchoscopy (a telescope test) for sampling the immune cells in the lung lining. The team is now taking advantage of novel disposable equipment which allow the transfer of this safe procedure of novel disposable equipment which allows us to transfer this safe procedure from specialist endoscopy units and operating theatres to clinical research wards. Volunteers have commented on how this improves their comfort, and staff note the increased efficiency and improved integration of our research activities.

The EHPC itself has applications for other diseases, with the ability to take samples of the cells from the nose a much more



Dr Daniela Ferreira

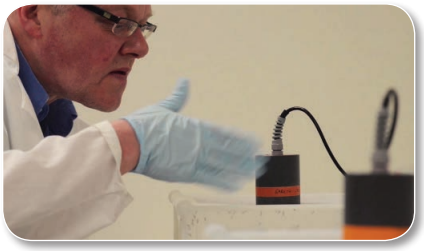
reliable indication of the immune response to certain diseases than taking blood samples, which does not give a detailed enough picture of how and when specific cells change during an immune response. Used for over 20 types of infections such as malaria, salmonellosis, dengue and cholera, which in an age of anti-microbial resistance could be key in finding new ways of fighting life-threatening diseases.

The team are also undertaking work with University College London, to produce mutants of the pneumococcus bacteria that can be developed to be placed into the nasal passage and will protect against infection there and offer increased protection within the lungs, but not invade them. Dr Ferreira continued: "When we have our first phase results from vulnerable populations using the EHPC model here in Liverpool we aim to carry out a similar trial in Malawi, so that we can understand more about what makes the population in sub-Saharan Africa susceptible. My hope is that our work identifying the natural immune response of different populations will enable us to develop a suitably safe mutant bacteria that will protect all different populations, offering a much more affordable and effective alternative to currently available vaccines."

Live bacteria inoculant being quantified after human inoculation

Applying genetically modified mosquitoes as research tools

Screening fluorescent mosquito larvae



Dr Gareth Lycett.

Within LSTM's Department of Vector Biology one team is making the most of technology to enable them to verify the genes involved in insecticide resistance by genetically modifying mosquitoes. A range of hi-tech machines enable this process to be carried out by Dr Gareth Lycett's group, the results of which are used by others within LSTM to develop effective diagnostic tools to detect resistance and enable the *in vitro* and *in vivo* testing of new insecticide compounds.

In a basic experiment, Dr Lycett modifies mosquitoes by injecting their eggs with a 'jumping gene' from another insect, along with a fluorescent marker and the gene of interest. However dealing with such tiny dimensions requires specialised technology. Using a laser heated needle puller the team extrude quartz glass capillary tubes so that the tip is only a couple of microns in diameter enabling them to inject the DNA mixture into the posterior end of the egg containing the germ cells, which is where the sperm or eggs develop. The injection process is performed under 200X magnification and utilises a joy stick controlled micro manipulator to push the needle into the egg, while a foot switch regulated hydraulic pump drives in the DNA solution when activated. Out of 100 eggs injected, an average of 40 will grow into fertile adults from which the modification process will be successful in one or two. In these few, there is still only a small proportion of their eggs (or sperm) that will carry the new genes. The offspring growing from these modified eggs however have the modified genes in every cell in their body and will glow with fluorescence when illuminated with UV light. Importantly they will pass on the modified genes to their progeny. While these seem to be small returns, so many eggs are produced that when these mosquitoes are selectively bred, thousands can be produced quickly.

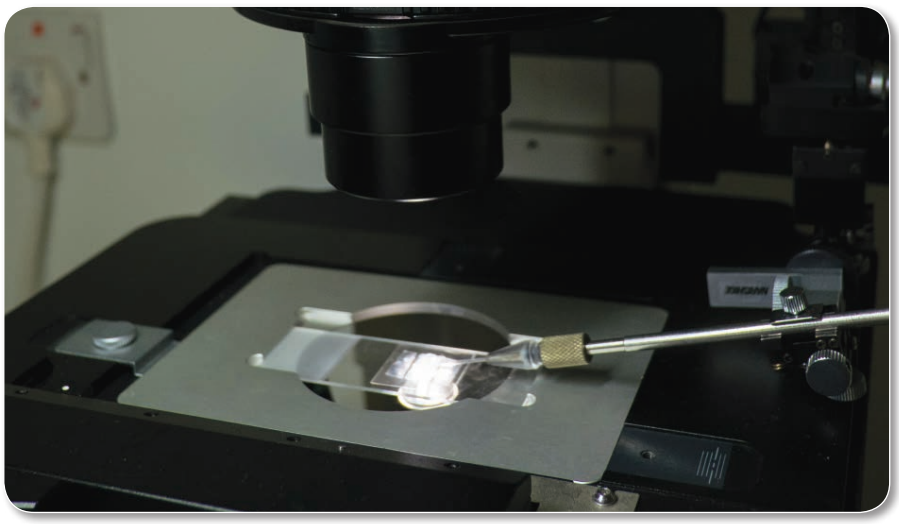
The offspring are screened on mass using a 3D fluorescent microscope with 30x magnification for the clearly identifiable fluorescent marker enabling thousands to be examined every hour. Once the modified individuals have been identified the team carryout inverse PCR, to determine at which point in the insect's chromosome the jumping gene has inserted itself. The jumping gene can insert itself almost anywhere in the chromosome, sometimes even in the middle of another gene which might knockout that gene's function. This analysis ensures that the most fit modified mosquitoes are used to produce young. The jumping gene has been manipulated to prevent it from excising and inserting itself elsewhere within the mosquito genome and, as a consequence, the linked gene of interest will be maintained through future generations at the site where it initially landed.

Being able to selectively modify *the genetic makeup of the mosquito*, enables the team to determine which genes are responsible for the development of resistance to currently used public health insecticides, and verifies that these genes will be key to the further development of resistance in mosquito populations. Fine tuning of the modification can increase or decrease expression of these genes, or even create subtle mutations, all of which is vital to understand the molecular basis of insecticide resistance and its potential impact on the control tools used in malaria prevention.

"Ultimately the work is about understanding the biology of the vector so that we can maintain the gains that vector control has made to the reduction in malaria deaths." Said Dr Lycett: "By verifying the genes that are key to the detoxification of the insecticide, we are able to identify the weapons the mosquito possesses. LSTM is developing new diagnostic tools that can identify resistance in wild populations enabling effective surveillance data to be collected which will drive change in control methods used. Our work also directly leads to the production of enzymes which predispose for resistance. Mass produced *for high throughput analysis*, these enzymes can be used to screen new chemical compounds, indicating the likely level of resistance that will be encountered so that investment can be made into those that are most likely to kill mosquitoes effectively."

The work is part of a number of research areas within the Department and LSTM, which require a clear understanding not only of the parasites and viruses which cause disease, but also the vectors that transmit them.

Dr Lycett continued: "Using technology has allowed us an insight into the biological factors which drive the development of resistance in mosquitoes. We are able to use engineering technology at a molecular level to create GM mosquitoes that express different quantities of key enzymes using machines that allow the fine manipulation of something as small as mosquito egg, as well as those that allow us to screen many thousands of specimens both quickly and effectively."



Mosquito eggs micro-injected with DNA solution

Technology to improve efficiency in a clinical setting

LSTM's Senior Clinical lecturer, Dr John Blakey, has been involved in using newer technologies in clinical and academic settings for a number of years, focussing on technology-enabled innovation to improve efficiency where resources are stretched.

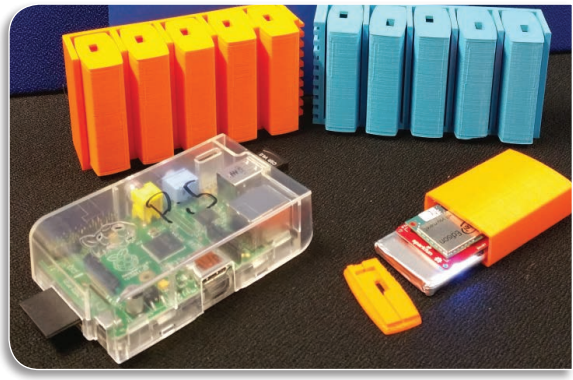
One of his current projects is Wayward, a discipline-bridging collaborative research initiative with colleagues at the University of Nottingham. Wayward aims to improve the information that hospitals have on the activity and location of staff in the out of hours period, to help realise improvements in safety and efficiency. A key Health Foundation–funded research project uses newer technologies to objectively study the work of junior doctors. This project brings together location, activity and task information and places it in the context of routine hospital data streams.

Work has been undertaken at Aintree Hospital using interviews, questionnaires, and structured observations. Current aspects gather data from accelerometry, WiFi positioning and low-energy Bluetooth to track participating junior doctors as they move around the hospital carrying out their clinical duties. This information will be combined with that from the Nottingham hospitals, and from Blackpool Victoria.

The major output from the study will be to understand the details of the actual work done by junior doctors, highlighting opportunities to improve safety and efficiency such as reducing the time to find patients and equipment in critical situations. It also illustrates that combining data from multiple systems can serve as a "Black Box", allowing detailed faster reconstruction of events that lead to an adverse incident or near miss.

"Hospitals are large and complex environments that are constantly repurposed," explained Dr Blakey. "When working out of hours in unfamiliar settings, doctors may have difficulty ordering incoming tasks in a logical geographical sequence. Ward layouts are also highly variable, potentially adding to delays. Understanding not only what people are being asked to do, but also where they are will allow us an invaluable insight into how to best improve hospital environments"

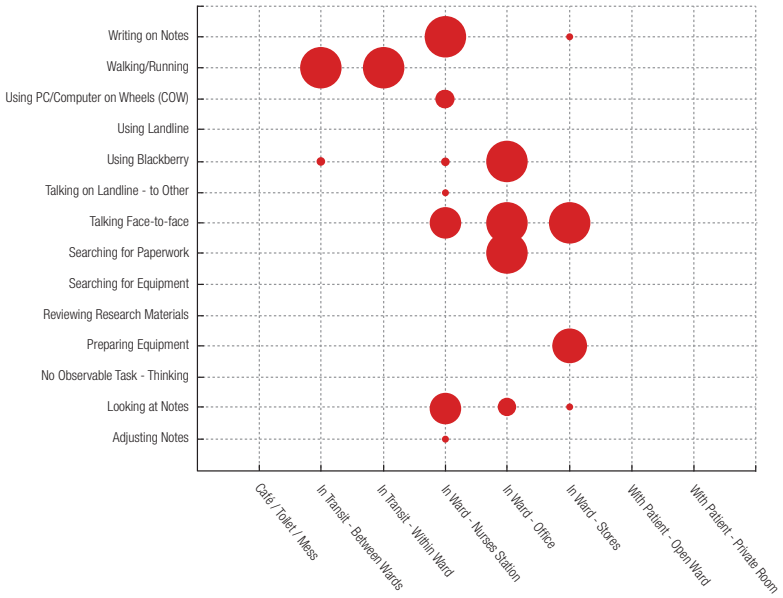
Dr Blakey has also been involved in the development of a digital task management system that allows faster and more accurate transfer of information. Already used in tandem with Wi-Fi positioning in Nottingham, related task flow systems are used in more than 40 hospitals across the UK and have been associated with significant reductions in adverse clinical incidents Out of Hours.



Data trackers; with different colours for day and night shifts

"Having this accurate record of work permits bodies like the Royal College of Physicians to make better recommendations on staffing levels, and we have shown it can be used to create simulations to improve the training offered to final year students." continued Dr Blakey. "It also provides an insight into how clinicians prioritise their work load. We've shown how new junior doctors respond to tasks differently from colleagues who have more experience in this dynamic and stressful environment."

These two areas of work complement other projects being undertaken by Dr Blakey and colleagues which have applications both in the UK and overseas.

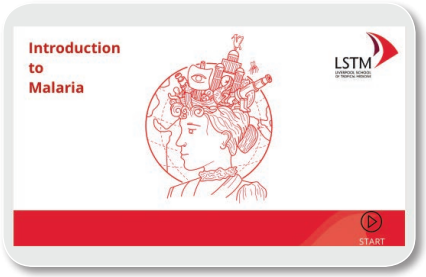


Data trackers being charged

Innovating the learning experience

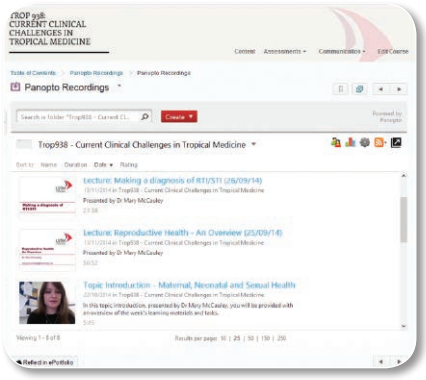
LSTM's Technology Enhanced Learning (TEL) unit has been in operation for nearly two years. It is part of the Education Department and is responsible for managing the technologies that support learning and teaching.

With students arriving for professional qualifications, masters and research degrees from over 60 countries, the unit manages a whole range of resources that place technology at the heart of the learning and teaching experience at LSTM. With a number of students carrying out much of their studies in different countries, technology can enhance the experience of students studying off campus and ensuring an equality of opportunity to students on all courses and from all backgrounds.



The Tel Unit is headed by Dan Robinson who is passionate about the positive changes that technology can bring to the sphere of education. "LSTM has been offering professional courses and research degrees for over 100 years and our current use of technology is allowing us to stay at the cutting edge of education in the field. When the team was first brought together we took our time to evaluate the needs of LSTM, and found the best technology in the market to match those needs." He continued: "Our virtual learning environment, Brightspace, incorporates a number of different support functions and allows students access to all of the tools and information that they need under a single username and password. Each student can personalise their experience through Brightspace and some of its features are particularly valuable in low resource settings, where students may be carrying out field work or additional study.

Another tool that can be used in all Brightspace enabled courses is Panopto, a video recording, management and distribution tool which can be used by staff and students for multimedia capture and secure sharing. Recordings can vary from staff delivering messages to camera, to delivering PowerPoint presentations, or demonstrating laboratory procedures. All lectures and seminars delivered within LSTM's lecture theatres can be captured using this technology. Students benefit from being able to recap and review presentations, which has proved very useful in some of LSTM's more intensive programmes and for students who do not speak English as a first language.



A number of other assessment and collaborative tools are still being embedded into the suite of technologies, but one that has already proved very useful in providing a more engaging experience for students in lectures, TurningPoint. The software allows multiple choice questions to be embedded within PowerPoint, to which students can respond via voting handsets or 'clickers', presenting an opportunity for two-way feedback. Used as a teaching tool at LSTM all of the teaching rooms are fully TurningPoint enabled and LSTM is able to offer all students a personal clicker at the start of their studies. End-of-unit feedback has been unanimously positive about their use and towards the teaching staff who employ this teaching technique. One such member is staff is Dr James LeCourse, Senior Lecturer in Parasitology and Director of Studies for the Tropical Disease Biology Masters. He said: "Turning Point personal response systems allow much more interaction in the classroom. Students can self-assess their understanding whilst I can simultaneously gauge and respond to ensure the class as a whole are meeting learning outcomes. They are fun too!"

Alongside Brightspace and TurningPoint, LSTM is also incorporating a number of other tools: Turnitin, a sector leading electronic assessment management and plagiarism detection service, which checks submitted work for text matchers against outside sources. ePortfolio is a personal area accessed via Brightspace or by downloading an app, it is a place where students can store all of their ideas, evidence, reflections and feedback. Wiggio is a collaborative leaning tool which offers a space where staff and students can enhance their collaborative experience through a group feed, document repository and virtual meeting facilities.

Dan Robinson continued: "LSTM's student body has always been diverse, from a large number of countries and with a variety of backgrounds. What technology can really do for our students is offer a level playing field. Not everyone will have unlimited access to technology but the TEL Unit is currently developing an online resource so that people can work with us remotely before arriving at LSTM, giving them the opportunity to learn how the various technologies employed work in advance and making them better equipped to fully utilise them on arrival. It is about getting the most out of their learning experience and enabling people to develop through that experience both professionally and personally."

LSTM's emergency snakebite response initiative using motorcycle ambulances coordinated by a new mobile phone application

Drs Rob Harrison and Nick Casewell from LSTM's Alistair Reid Venom Research Unit initiated a new collaboration with Drs George Omondi and Hastings Ozwara (IPR, National Museums of Kenya) termed the Kenya Snakebite Study Group in September 2015. The first output of this new collaboration was the development of a new emergency response system to serve the urgent medical needs of those suffering from snakebite in the country.

KenSERS is a new Snakebite Emergency Response System (SERS) to reduce death and disabilities of snakebite victims and is the brainchild of Drs Harrison and Omondi and funded by the Sir Halley Stewart Trust and Baringo County Health Services. *KenSERS* will be piloted by the Kenya Snakebite Study Group and their Kenyan partners in Baringo County.

The project is based on community health volunteers, equipped with a smartphone-Snakebite Emergency App who will be able to identify the snake, administer first aid if necessary and activate a special motorcycle based ambulance, carrying a paramedic with specific skills to treat snakebite during their journey to hospital. The rural remote nature of the sub-Saharan African communities at greatest risk of snakebite, and the typically poor road infrastructure, are some of the many reasons that snakebite victims often fail to access effective treatment.

Dr Harrison said: "Snakebite is a neglected medical emergency that kills 32,000 people in some of the poorest rural communities in sub-Saharan Africa, while leaving over 90,000 surviving victims with permanent physical disabilities or disfigurements. *KenSERS* is the first such snakebite intervention project of its kind in sub-Saharan Africa, and crucially is not just about getting the patient to the hospital alive and in good time, but also ensuring that when they get there the hospital or health centre has staff trained to deal with snakebite and equipped with antivenoms that are proven to be effective."

During a recent visit to Kenya, the Kenya Snakebite Study Group team conducted project-liaison meetings with the Governor, the Minister of Health and other health officials of Baringo County. Part of the reason that there is such a high mortality rate associated with snakebite in sub-Saharan Africa is that much of the antivenom imported into Africa is manufactured from Indian snake venoms and therefore can be dangerously ineffective in treating African snakebite. "Many physicians are not aware that antivenom efficacy is very snake-species specific" continued Dr Harrison. "Given the expense associated with antivenom, it is crucial that the therapies purchased will be effective. The ultimate aim of our project is policy change and we will work with local physicians to upgrade the treatment offered to snakebite victims and improve treatment outcomes. Another objective of the Kenya Snakebite Study Group is to establish an independent, preclinical antivenom-efficacy testing unit providing the Kenyan Ministry of Health with scientific data on the effectiveness of imported antivenoms, prior to human use, to neutralise the toxic effect of Kenyan snakes – an important quality control contribution to the country"

The use of the smartphone app by community volunteers will also act as a means to record the number of cases in the areas covered and the hope is, that with further funding, the project can be expanded to the whole of the region and beyond. To this end a project stream, *AfricaSERS*, has been set up with Health Action International, a Foundation NGO in the Netherlands, who will receive and process charitable donations.

In brief...

LSTM hosts the formal announcement of the Ross Fund

LSTM played host to The Chancellor of the Exchequer, The Rt Hon George Osborne MP, and the American philanthropist Bill Gates in early 2016. Both guests addressed an audience of invited guests and media to talk in detail about the recently announced Ross Fund.

The £3 billion initiative includes the Ross Fund, which is named after the UK's first Nobel Laureate and LSTM's first lecturer, Sir Ronald Ross, and will be used to support the global fight against malaria and other infectious diseases. The Fund will be supported by the Bill and Melinda Gates Foundation (BMGF) of which LSTM is a major recipient. LSTM Director, Professor Janet Hemingway CBE, welcomed all guests to LSTM, making reference to LSTM's past and its current standing at the forefront in the fight against malaria and other tropical diseases.

Professor Janet Hemingway said that 'LSTM is proud to be chosen as the venue for the more detailed announcement on the Ross Fund, given LSTM's association with Ronald Ross. It is a unique opportunity that this money is being made available to further the ongoing excellence in research, particularly in the field of resistance to infectious diseases. A huge amount of progress has been made over the past decades but we are increasingly facing new challenges especially in trying to stem the rising tide in insecticide resistance, a rapidly growing problem in vector control.'

Along with the support for malaria and other infectious diseases, the Ross Fund will also allocate £200 million to the so-called Neglected Tropical Diseases (NTDs) and over £300 million fighting AMR.

LSTM has played a key role in bringing these diseases to the attention of policy makers, most notably during last year's G7 summit in Germany, by LSTM Emeritus Professor David Molyneux. In a response he said 'NTDs are increasingly seen as true markers of poverty and LSTM utilises its breadth of scientific research, from the lab to actual implementation, for the benefit of the more than billion people who are somehow affected by these debilitating diseases.'

LSTM hosts a number of research consortia that focus on NTDs, such as the BMGF funded A·WOL consortium, which aims to develop new drugs against river blindness and elephantiasis; COUNTDOWN, funded by the Department for International Development (DFID) which aims to control and eliminate the seven most common NTDs by 2020; and the Filarial Programmes Support Unit (FPSU) which aims to eliminate lymphatic filariasis in up to 12 countries.

Sir Ronald Ross became LSTM's first lecturer in 1899, a year after LSTM was founded. He received the Nobel Prize for Medicine in 1902 for demonstrating the transmission of malaria to humans via mosquitoes. Today LSTM hosts the largest number of medical entomologists in the UK and LSTM's translational activities cover the whole so-called research trajectory: from laboratory based research through to clinical trials; implementation research and the development of tools for the monitoring and evaluation of disease transmission and resistance.

In brief...

Liverpool to host the 47th Union World Conference on Lung Health

ACC Liverpool has been chosen to host the 47th Union World Conference on Lung Health in October 2016.

The event is the premier annual international conference for researchers, health programme managers, policy experts, advocates and other leaders working to address tuberculosis, lung health and other global health issues primarily affecting people living in poverty.

The conference, taking place at the waterfront venue from October 25-29 2016, is expected to draw more than 3,000 speakers, researchers and delegates from 125 countries.

The International Union Against Tuberculosis and Lung Disease (The Union) based in Paris, draws from the best scientific evidence and expertise to advance health solutions to public health challenges affecting people living in low and middle-income countries. It has a powerful global network of 500 experts based in 13 offices and 17,000 Union members/subscribers, whose work in 156 countries has been supported by US$ 540 million in grants and donations. The World Conference is one key element of its work.

Dr Bertie Squire, past president and board member of The Union and professor at Liverpool School of Tropical Medicine (LSTM), said: "The Union's decision to host its World Conference in Liverpool is not only a recognition of our outstanding conference host city but also an acknowledgement of the leading research being conducted here in the field of TB and wider lung health."

The World Conference's five-day scientific programme will present the latest developments in the inter-related fights against tuberculosis, HIV, lung disease and non-communicable diseases.

José Luis Castro, executive director of The Union, said: "One and a half million people died from TB in 2013, yet it is a treatable and curable disease. It is a disease that affects all parts of the world, and is in fact still a public health problem even in the UK and similar countries.

"The World Conference is a critical opportunity for all those working on TB and other lung health issues to come together. I am delighted that the conference will be in Liverpool, where we have received such a warm welcome and where such great work in our field is taking place."

Mayor of Liverpool, Joe Anderson, said: "It is a huge coup for Liverpool to secure this international conference. It puts the city in the spotlight as a global leader in this field and will also provide a welcome economic boost due to the large number of delegates coming to the city."

Kerrin MacPhie, director of sales at ACC Liverpool, home to BT Convention Centre, Echo Arena and Exhibition Centre Liverpool, added: "Professor Squire, supported by the team, has driven this successful bid. This is a great example of Team Liverpool's winning formula - from the academic expertise within the city, to destination support and world-class conference facilities."

The five day conference is expected to generate around £7.8m in economic benefit for Liverpool.

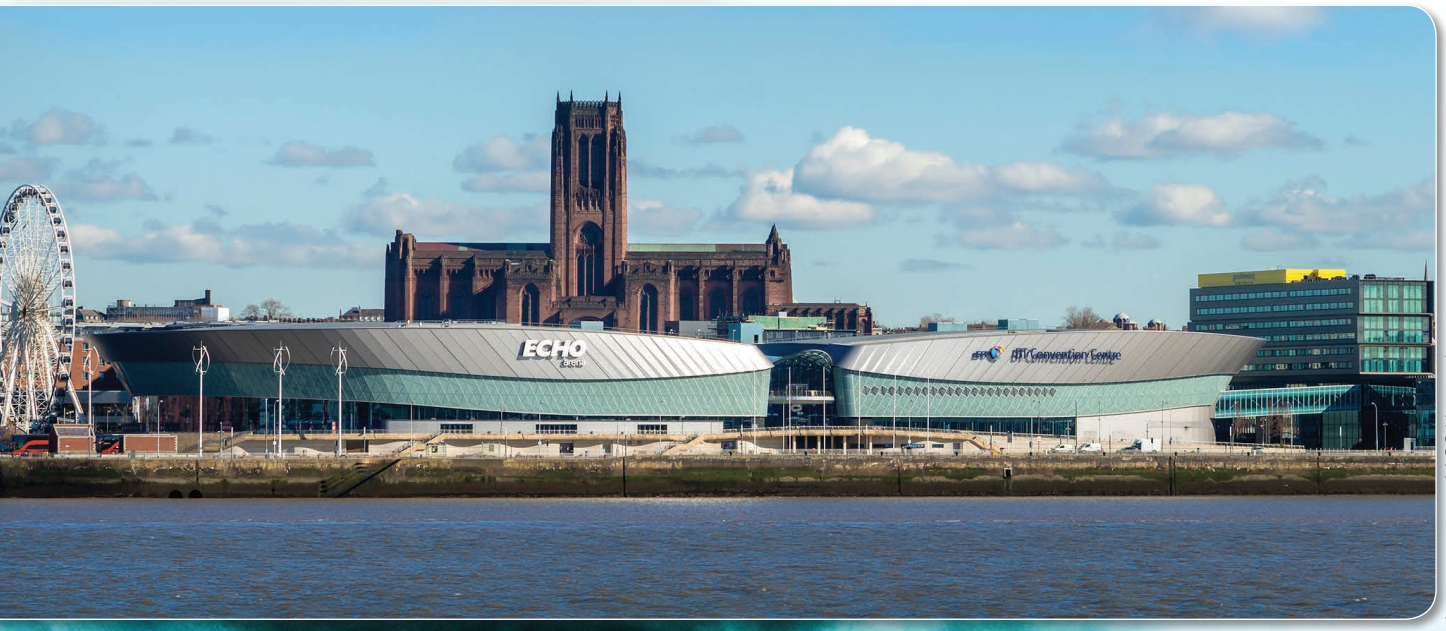


Image courtesy of ACC Liverpool

In brief...

LSTM and RCP launch the Diploma in UK Medical Practice (DipUKMP)

Liverpool School of Tropical Medicine has partnered with the Royal College of Physicians of London (RCP) to launch the Diploma in UK Medical Practice (DipUKMP). This professional diploma is open to International Medical Graduates (IMGs) working in NHS Trusts across the UK, as part of the RCP's Medical Training Initiative (MTI).

"LSTM is delighted to be partnering with the RCP on this initiative given the strong complementarity of the Vision, Mission and Values of our institutions and our joint commitment to improving the health of communities across the globe," said Michael Lurie, LSTM's Director of International Education. "The programme will allow graduates to maximise their development during clinical training. Currently MTI participants exit the scheme with a certificate of participation but this diploma represents the first formal postgraduate qualification, with potential to enhance careers and medical care."

Currently, around 125 IMGs enter the MTI annually and receive a certificate of participation on exit. They will now be able to study for a postgraduate qualification developed by two renowned institutions.

This new programme, which is led academically by LSTM's Senior Clinical Lecturer Dr Clare van Halsema, who is also an NHS consultant, aims to maximise the opportunities presented by clinical training in the NHS to develop clinical competence and understanding of UK hospital medical practice.

RCP President Professor Jane Dacre said: "The Medical Training Initiative provides an excellent opportunity for UK and overseas doctors to learn from one another. I'm very pleased that the diploma will help participants demonstrate the extent to which they have developed during their placement when they return to their home countries."

LSTM's Director, Professor Janet Hemingway CBE, said: "It is fantastic to be partnering with the RCP to formalise the skills that the MTI offers graduates each year. LSTM has a long history of collaboration with organisations throughout the world and we appreciate the importance of what can be learned by working with each other."

The diploma will be awarded by LSTM and is complementary to and based on the structure of the two years NHS training provided through the MTI, which sees the IMGs rotating though work placements in their chosen medical specialties. During these work placements they will produce a portfolio of evidence of their achievements in clinical practice and other aspects of NHS hospital work and a reflective piece of written work based on their NHS experience.

Royal College of Physicians

LSTM receives £1m donation to support Nigerian students

Liverpool School of Tropical Medicine (LSTM) has received a donation of £1m from The Bale Settlement, to provide scholarships for students from Nigeria studying on LSTM education programmes.

The Settlor of The Bale Settlement, Mr Roger Bale, who grew up in Liverpool and spent part of his career in Nigeria, was keen to give something back to the city and to Nigeria, a country which LSTM's works with to improve health. The gift of £1m will form an endowment held by LSTM, who will use the income to provide scholarships.

LSTM attracts students from all over the world. Through historic links LSTM has always been a popular choice for Nigerian students looking to expand their education, from community health to the development of new drugs and diagnostics. These education programmes are developing the postgraduate skills and knowledge of current and future health professionals. LSTM's alumni can be found in Ministries of Health, the World Health Organization and a host of leading non-governmental organisations, working on future breakthroughs to eliminate diseases that kill millions of people each year.

Mr Bale enjoyed a recent visit to LSTM to speak to staff who are part of international collaborations and who also contribute to LSTM's teaching portfolio. Mr Bale said: "I experienced the amazing work of LSTM first-hand when my son became ill while I was based in Nigeria. We took him to LSTM's travel clinic to be examined and the expert doctors successfully treated him and he made a full recovery. My relationship with both Nigeria and Liverpool made supporting LSTM in this manner a natural choice. It is rewarding to know that this gift will support future generations of Nigerian health professionals trained by LSTM."

Mr James Ross, LSTM's Chairman, was delighted to announce the donation from The Bale Settlement to trustees, members and staff during LSTM's 116th Annual General Meeting.

In brief...

LSTM led team wins bid to organise the 2018 Health Systems Global Symposium

Health Systems Global (HSG) has chosen Liverpool as the host city for its fifth global symposium on health systems research in 2018.

The winning bid was put forward by Liverpool School of Tropical Medicine (LSTM), in close cooperation with a consortium of UK institutions including the London School of Hygiene and Tropical Medicine (LSHTM) and the Institute of Development Studies (IDS) in Brighton, and ACC Liverpool.

Around 2,000 delegates are expected to attend the five day symposium on October 7, 2018, at the waterfront venue, home to BT Convention Centre, Echo Arena and Exhibition Centre Liverpool. The event will generate more than £2.5m in economic impact for the city region.

"We are delighted with this decision", said Professor Janet Hemingway CBE, Director of LSTM, "It is not only a recognition of a very strong bid that we have put in together with our partners, but also of the key research on health systems challenges that is being carried out by LSTM and our partners."

George Gotsadze, executive director of Health Systems Global, congratulated the team on behalf of the Board of Health Systems Global which is made up of key researchers and experts from across the globe. "Liverpool's winning bid was exceptionally strong and we are looking forward to working closely with LSTM and partners as we prepare this event over the coming years."

Kerrin MacPhie, director of conference and exhibition sales at ACC Liverpool, added: "Health Systems Global is a prime example of the city working together to bring a large international conference into the UK for the first time, capitalising on its expertise in this field.

"Symposia of this size coming to ACC Liverpool are so beneficial for the region, not only from an economic point of view but also proof of Liverpool's scientific credentials. We will ensure the symposium will be a great success."

Health Systems Global is an international membership organisation fully dedicated to promoting health systems research and knowledge translation. It's fourth global symposium will be held in November 2016 in Vancouver, Canada, and will focus on 'resilient and responsive health systems for a changing world.

LSTM to co-ordinate £2.5 million insecticide resistance collaboration

Researchers from LSTM and a number of prominent institutions in the UK and Africa have received £2.5 million in the form of a Wellcome Trust Collaborative Award, to look at how insecticide resistance is affecting the efficacy of bed nets in preventing malaria transmission in Africa.

The three year study is being coordinated by LSTM's Professor Hilary Ranson, head of the Department of Vector Biology and is entitled: Improving the Efficacy of Malaria Prevention in Insecticide Resistant Africa (MIRA). It will see entomologists and economists from LSTM partnering with CNRFP in Burkina Faso, infectious disease modellers at Imperial College, epidemiologists from the University of Durham, ecologists from the University of Glasgow, social scientists from the University of Oxford and engineers from the University of Warwick. The initial meeting of partners took place in Liverpool in May 2016.

During the three years the partners will collect extensive field data on bednet usage, access to treatment, malaria risk factors, mosquito ecology, behaviour and resistance. These data will be used to update malaria transmission models to represent the reality in several high burden countries where, despite national distribution of bednets, malaria remains stubbornly persistent. In parallel, economists will collect data on the cost of potential malaria control interventions. The malaria model and cost data will then be used to identify cost effective and affordable packages of interventions to control malaria in Burkina Faso and other similar settings.

LSTM's Dr Eve Worrall is one of the principal investigators on the project. She said: "I am really excited to be involved in such an extensive project which highlights the expertise that LSTM has in entomology and economics and brings together world class researchers from the UK and Burkina Faso. The issue of insecticide resistance has the potential to derail some of the excellent progress that vector control has made in the reduction of malaria deaths in Africa, which is why LSTM and our partners are determined to do all that we can to maximise the efficacy of bed nets and other interventions ensuring that malaria deaths continue to fall."

LSTM
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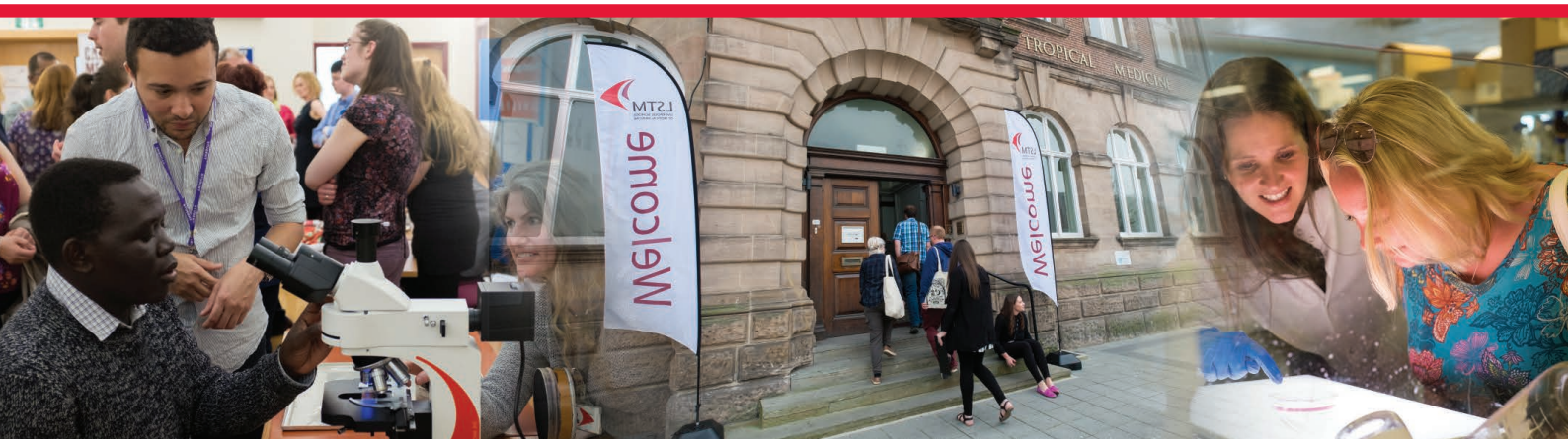
Studying at LSTM



LSTM Masters

Masters programmes attract highly motivated graduates from around the world. Our programmes cover our core strengths: International Public Health, Infectious Diseases, Child Health, Vector Biology, Parasitology and Humanitarian Assistance.

Each Masters programme runs for 1 year, from September, including taught modules and a research project, leading to the submission of a dissertation. The research project is the highlight of the Masters, taking place from May to August and often includes fieldwork overseas.

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Our suite of Professional Diplomas and Certificates are ideal for students with limited time or those wishing to study selectively. These courses offer highly intensive study and immersion into subjects whilst on study break/ annual leave from your career. They also offer huge networking potential with students coming from over 60 countries.

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Professor David Lalloo

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118 years of research and teaching excellence in tropical medicine and global health

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To save lives in resource poor countries through research, education and capacity strengthening

Mission

To reduce the burden of sickness and mortality in disease endemic countries through the delivery of effective interventions which improve human health and are relevant to the poorest communities

Values

- Making a difference to health and wellbeing
- Excellence in innovation, leadership and science
- Achieving and delivering through partnership
- An ethical ethos founded on respect, accountability and honesty
- Creating a great place to work and study

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