



## Faculty of Infectious and Tropical Diseases



Students on the 2010 pilot East African DTM&H course examine water samples from Lake Albert for snails infected with schistosome miracidia.

The main focus of the research and teaching of the Faculty remains the major global viral, bacterial and parasitic diseases, with work ranging from studies on pathogens and their mechanisms of disease, through contributions to the discovery and development of drugs, vaccines and diagnostics, to interventions for disease control within clinical, vector control and water and sanitation research. There is an increasing focus on implementation and evaluation studies as well as training and capacity building. This year we have undertaken a review of the research strategy for infectious and tropical diseases which will be taken forward in the next year. Further information on the research in the Faculty follows in the contributions from each Department, and is also available at [www.lshtm.ac.uk/itd](http://www.lshtm.ac.uk/itd).

### DEPARTMENT OF CLINICAL RESEARCH

The Department works on key international health topics including malaria, HIV and tuberculosis. This report focuses on our work in sexually transmitted infections and cervical cancer; diagnostics for HIV care; and an East African innovation in our teaching programme. Our work on TB is featured in the chapter *Working on Tuberculosis* (see pages 18-20).

Cervical cancer is the most common cancer in women from low-income countries. Vaccination against human papillomavirus (HPV), a sexually transmitted virus which is the primary cause of cervical cancer, offers new opportunities for control. A Wellcome Trust-funded study in Tanzania compared uptake, acceptability and cost of two primary school-based vaccination delivery strategies: age-based versus school

class-based. Using vaccine donated through the Gardasil Access Program for GAVI-eligible countries, 5532 girls from 134 schools were offered HPV vaccination. Dose 1 coverage was 85% (86% for class-based and 82% for age-based vaccination). Lessons learnt will inform the Tanzanian Ministry of Health & Social Welfare's national Cervical Cancer Control Strategy.

In many low-income settings women have little access to cervical cancer detection, particularly important for women living with HIV who are at higher risk. Funded by the EU 7th Framework programme, the School co-ordinates the HARP (HPV in Africa Research Partnership) Consortium, providing evidence to guide cervical cancer screening programmes for women living with HIV in Africa. HARP will evaluate existing screening strategies for cost-effectiveness, including a novel point-of-care HPV test, in a cohort of 1200 HIV-seropositive women in South Africa and Burkina Faso. Research will model the impact of scaling up these strategies on cancer reduction and lives saved.

Increasing access to CD4 testing and strategic use of HIV viral load monitoring in developing country settings are key objectives in the latest Universal Access strategy advocated by WHO. There is an increasing range of technologies for determining CD4 count and HIV viral load, with wide variation in cost, performance, reliability and ease of use. The Diagnostics Group at the School, in collaboration with an HIV monitoring technologies expert working group, prepared a systematic review of the performance and reliability of all commercially available CD4 and viral load assays in a technical guidance document for WHO, which will be used to optimize the selection and specifications for use of these technologies. The School continues to work with the WHO HIV Department and UNITAID on assessments of emerging point-of-care technologies for measuring CD4 and viral load.

After 112 years in London, the Diploma in Tropical Medicine and Hygiene (DTM&H) course is expanding to Africa. The new East African DTM&H is a partnership between the School and the Hospital for Tropical Diseases, London; Kilimanjaro Christian Medical College, Tanzania; Makerere University, Uganda; and Johns Hopkins and Washington Universities, USA. Its development was supported by the 'LSHTM's Got Talent' Gates Millennium Award. In September 2011, 60 students will start this three-month course, designed for doctors intending to practise medicine in Africa, comprising 600 hours of seminars, bedside teaching and laboratory work,

delivered in Tanzania, Kenya and Uganda. It combines an evidence-based approach to tropical diseases with contemporary issues in African healthcare. Students will gain skills in the practical management of pregnant mothers and sick children and will spend three weeks in rural placements. Twenty scholarship-supported places are reserved for East African physicians, as part of the School's commitment to capacity building.

### DEPARTMENT OF DISEASE CONTROL

The Department continues to expand its research on insect vector control, environmental health and sanitation, and clinical interventions; as well as its services in insecticide and repellent testing. This report focuses on two other research areas: a fascinating but little-known aspect of hygiene - the evolution of disgust as a means of avoiding infection, and an area of malaria prevention known as 'intermittent preventive therapy' which is set to become new policy and practice.

#### Disgust research

Pathogens exert a powerful selection pressure on immune systems, but also on behaviour patterns and on the psychological processes that underpin behaviour. Those of our ancestors who felt disgusted by faeces, for example, would have been less likely to come into contact with pathogens, hence less likely to contract gastro-enteric infection. The outcome would have been enhanced health and reproductive success. The Hygiene Centre has been examining the range and nature of things that elicit a sense of disgust. In a sample of over 2000 people they found distinct categories of disgust elicitors, representing particular kinds of infection threats such as spoiled food, animals, infective people, lesions, evidence of poor hygiene, sex and objects potentially contaminated with infectious organisms.

This work is being replicated in rural Bangladesh, and



Images used to assess disgust response in different people.

individual differences in disgust sensitivity and their effect on people's health and their day-to-day behaviour is being examined. Staff have looked at how and why disgust responses vary between cultures and over the life span of individuals. In a recent review they examined how simple learning rules can enable individuals to learn what's safe and what's not in a variety of situations, enabling effective pathogen avoidance without forgoing local opportunities.

Understanding how disgust operates is important to public health. It is our first line of defence against pathogens and parasites, one that can be harnessed to good effect, for example, in handwashing campaigns. The fear that one may be an object of disgust to others is an often-overlooked cost of falling ill. Conversely, the capacity to overcome one's sense of disgust is an important aspect of the job of care providers. Disgust also affects our moral judgement, a phenomenon staff are exploring in an online study with the BBC.

#### Intermittent preventive treatment for malaria control

Over the last decade, the School has developed and evaluated a set of new, drug-based preventive strategies: intermittent preventive treatments (IPT) to control and prevent malaria. These involve delivery of a treatment dose of an antimalarial drug – usually sulphadoxine-pyrimethamine (SP) – to a particular risk group at pre-specified times, regardless of the presence of malaria parasites at the time of treatment. IPT in pregnancy (IPTp) is given when women attend routine antenatal clinics. School staff showed that IPTp can reduce maternal *Plasmodium falciparum* infection by 85% and anaemia by 39% in the later stages of pregnancy.

IPT in infants (IPTi) uses routine vaccination to deliver SP during the first year of life. School staff did formative research and helped build the IPTi Consortium, a series of research collaborations designed to inform IPTi policy. A pooled analysis of six randomized controlled trials showed that IPTi reduces clinical malaria by 30%, anaemia by 21% and admission to hospital by 23%. IPTi was recommended by WHO in 2009 for malaria control in settings with year-round transmission and a heavy burden of disease among children under one.

Neither IPTp nor IPTi is very useful for controlling malaria in places where malaria transmission occurs for only a few months each year. School staff did the first trial of IPT delivered to children (IPTc) under 5 years of age during the malaria transmission season. In 2011,



a WHO Expert Group reviewed the evidence that IPTc can reduce malaria morbidity by over 80% and is recommending that the intervention, to be known as seasonal malaria chemoprevention, be incorporated into malaria control programmes.

### DEPARTMENT OF IMMUNOLOGY AND INFECTION

Research in the Department aims to improve our understanding of the molecular and cellular processes that underlie human infections, particularly those of relevance in tropical countries and economically disadvantaged communities. We study the interactions between the host and the pathogen and – for some parasitic diseases – the invertebrate vectors that transmit the pathogen from one host to another.

Inflammation is one of the earliest, most ancient and most effective responses to infection. Tissue damage caused by the pathogen (or the insect vector's bite) triggers this inflammatory response, causing an influx of immune cells to the site of infection to clear the microbes and infected host cells. However, by-products of inflammation can themselves cause tissue damage and it is essential therefore that inflammatory immune responses are carefully regulated to ensure that the infection is controlled without causing severe pathology. This balance is maintained by a complex network of immune regulatory mechanisms. Our current work focuses on the roles of host regulatory cytokines such as IL-10, IL-27 and TGF- $\beta$ , which appear to have non-redundant and distinct roles in regulating innate and adaptive immune responses during malaria infection; on immune cell inhibitory receptors, including CTLA-4 and PD-1, which attenuate immune cell function; and on induction of

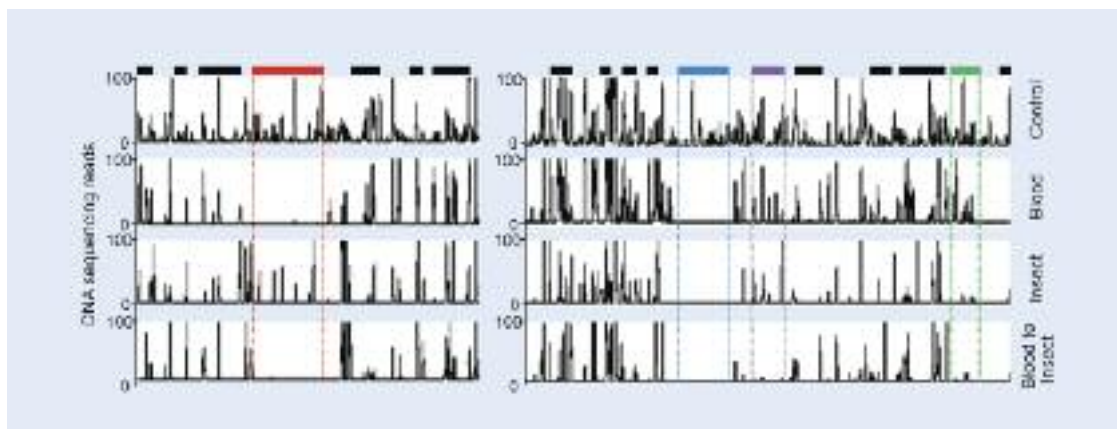
alternative (type 2) inflammatory pathways and expansion of regulatory cells during helminth infection. Despite the different natures of these infections (e.g. virulent, rapidly fatal malaria infections versus chronic, low-grade infection with very long-lived helminths) their regulatory pathways share many common features. Of particular interest, recent work has helped to define TGF- $\beta$  as a molecular switch that causes immune cells to secrete IL-9, a cytokine which is particularly important in combating helminth infections.

The Department hosts researchers studying the important but neglected parasitic disease, leishmaniasis. In addition to an established programme of antileishmanial drug discovery, our activities in leishmanial immunology and vector biology have expanded this year. This includes identification of a pathway which prevents healing of cutaneous leishmania lesions. We showed that non-healing disease is characterized by high levels of the enzyme arginase, breaking down the amino acid L-arginine, which is essential for effective immune responses and therefore prevents effective clearance of the parasite. Highly analogous findings have now also been made in Ethiopian patients with visceral leishmaniasis, a frequently fatal disease. This is an excellent example of a pathogen subverting one of the host's usual pathways of immune regulation for its own ends. Remarkably, other work in the Department has revealed that the leishmania parasite manipulates this immunomodulatory arginase pathway right from the very earliest stage of infection: parasites inside the insect vector (the sand fly) secrete a carbohydrate gel into the sand fly gut which is deposited into the skin when the fly bites and immediately induces macrophages to produce arginase.

Leishmania transmission.  
(Left): Female *Lutzomyia longipalpis* sand fly taking blood.  
(Right): Scanning electron micrograph of Leishmania promastigote embedded in parasite gel inside sand fly gut.



Figure 1. RIT-seq identifies *T. brucei* genes that are essential for growth generally (blue), for growth specifically in the bloodstream (red) or insect (green) or for life cycle transitions (purple).



## DEPARTMENT OF PATHOGEN MOLECULAR BIOLOGY

The Department focuses on the genetics, biochemistry and molecular biology of bacterial, viral and parasitic pathogens and their hosts, in the context of improving the understanding and control of infectious diseases. Our researchers aim to gain a greater understanding of the complex and dynamic interactions that modulate virulence and host/pathogen interactions. These approaches, in combination with epidemiological and field-based studies, provide a framework for the rational design of long-term intervention strategies.

### Pathogen genomics and high throughput functional screening

Biomedical science this century has been characterized by major progress in our ability to generate and handle extremely large datasets. Pathogen research is now being driven by advances in DNA sequencing technology and high-throughput functional analysis of genes, coupled with the rapid development of appropriate computer software. Second-generation sequencing technologies such as Illumina and HiSeq2000 can yield full sequence information simultaneously on many pathogen isolates (e.g. >300 *Mycobacterium tuberculosis* genomes in a single run). This technology is highly amenable to addressing important biomedical and epidemiological questions, exploring genome diversity and undertaking whole genome association studies. Outputs from these approaches will be central to the design of new antimicrobial agents and vaccines, as well as improving genetic bar-coding for disease monitoring and surveillance.

The Department is involved in more than 15 ongoing sequencing projects with the Wellcome Trust Sanger Institute (WTSI), focused on a wide range of infectious

diseases. This access to high-throughput sequencing, at low cost, enables the Department to exploit its large, well-characterized pathogen sample collections and allows our experimental groups to rapidly translate important genomic findings. We have a growing informatic and statistical capacity to take advantage of the wealth of new data. Collaborative projects with the WTSI include diversity studies of *Clostridium difficile* and enteric pathogens, drug-resistant *M. tuberculosis*, *Plasmodium falciparum* and functional mapping of the African trypanosome genome. Further projects are planned for other pathogens (e.g. *Leishmania*), in other -omics (e.g. proteomics), and in piloting new forms of technology. Enhanced collaboration with the WTSI also plays an important part in developing our teaching and research degree training.

Researchers in the Department have developed tools that facilitate high-throughput functional analysis of the African trypanosome genome. The challenge was to identify genes that are functionally important, have a role as 'virulence factors', potential as drug targets, or are central to drug-resistance mechanisms. The group developed a screening method using RNA interference (RNAi) libraries in *Trypanosoma brucei*, and then, in collaboration with the WTSI, used high-throughput RNAi target sequencing (RIT-seq) (see Figure 1). With this approach, they generated data for all 7500 genes, genetically validated more than 1000 potential drug targets and identified more than 50 genes that impact on drug resistance. The results are facilitating drug target triage and have substantially improved prospects for the rational design of more efficacious and durable therapies, and for monitoring resistance. The functional screening technology is versatile and is currently being used to address a range of other problems including the identification of genes that control antigenic variation and genes specifically required for growth *in vivo*.