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Appendix
Welcome to the 2011 Annual Report of the University of Oxford–Li Ka Shing Global Health Programme. The Global Health Programme began in 2007 and has grown to now include collaborations and partners working on almost 40 research grants, in 30 institutions in more than a dozen different countries. It is a remarkable Programme. The guiding philosophy of investing in youth, in training and research, and in being flexible to respond to the great challenges of the 21st century, ensures that knowledge shapes destiny and every partner enriches the work and lives of others. We hope we have built a sustainable and powerful research community based in Asia, and one that provides a model for local action and development in the context of globalisation.

The centrepiece of this year’s activity, and the element that we have the greatest pride in, is the establishment of the Shantou-Oxford Clinical Research Unit (SOCRU) in Shantou Medical University, Shantou, China. To mark the launch of SOCRU, the Right Honourable Lord Patten of Barnes, Chancellor of the University of Oxford, visited Shantou in September 2010. Lord Patten was accompanied by Dame Jessica Rawson (Warden, Merton College, Oxford) and Diana Stent (Development Office, University of Oxford) and they toured the facilities of SOCRU, held meetings with Professor Gu, Dr Frieda Law and Professor Jeremy Farrar, and met with the students of the Medical School before Lord Patten delivered a lecture to the University on “Tackling global health challenges through education”.

In addition to the opening of the Shantou-Oxford Clinical Research Unit this year, the University of Oxford–Li Ka Shing Global Health Programme has supported Strategic Awards in areas as diverse as environmental stress, migration and health, artemisinin-resistant malaria, literacy rates in rural China, HIV, influenza, rabies and the role of bats in transmission of infections in southern China. We have Seed Awards studying pneumonia, melioidosis, infections of the brain, ethics of research in the context of epidemics, our response to climate change and disasters, and many others. Almost 500 students, clinicians and researchers are directly involved in the Programme, 11 young Li Ka Shing Fellows have undertaken Master’s degrees and some have now started their DPhil. In addition, 100 research publications or presentations have been made possible through the support of the Programme. New partnerships have been forged between Shantou University, the University of Oxford, and institutions across Asia. It has been an incredibly busy year, but one which has laid a wonderful foundation on which the University of Oxford–Li Ka Shing Global Health Programme can grow and flourish in the years to come.

“To be able to contribute to society and to help those in need to build a better life, that is the ultimate meaning in life. I would gladly consider this to be my life’s work.”
Sir Ka-shing Li

Executive Summary by Professor Jeremy Farrar
Programme One

Shantou Oxford Training Courses

The aim of the Shantou Oxford Training Course Programme is to link Faculty staff from the University of Oxford with Faculty staff and students from Shantou University Medical College as well as Programme participants from across China. The training courses are co-ordinated by the Shantou Oxford Clinical Research Unit (SOCRU) and the aim is to arrange two to three courses per year. Each course will focus on a specific theme and will include lectures, seminars, workshops and small group teaching. On completion of the course, participants will receive a Certificate of Attendance.

During the first year of the Li Ka Shing donation in 2010, two training courses were organised at Shantou University Medical College. The first was held in May 2010 entitled “Clinical Infectious Diseases” and the second in January 2011 entitled “Public Health and Epidemiology”. The information on the following pages provides an overview of the course details, and the teachers, organisers and participants involved in the training.
This was the first course and was superbly organised by the Shantou-Oxford Clinical Research Unit team. It was very enjoyable teaching and the atmosphere was both warm and welcoming.” Jeremy Farrar
Public Health and Epidemiology Training Course
Date: 11 January 2011
Duration: 2 days
Number of participants: 37

Teachers and Organisers:
Dr Peter Horby, Oxford University Clinical Research Unit, Hanoi, Vietnam. Speciality subject: Public health
Ms Katherine Anders, Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam. Speciality subject: Epidemiology
Dr Vincent Chung, Chinese University of Hong Kong, Hong Kong. Speciality subject: Public Health, Epidemiology, Chinese Traditional Medicine
Dr Frieda Law, Li Ka Shing Foundation. Speciality subject: Paediatrics
Dr Binglin Cui, Shantou-Oxford Clinical Research Unit. Speciality subject: Paediatrics and Global Health
Dr Hui Pan, Shantou-Oxford Clinical Research Unit. Speciality subject: Clinical Medicine
Dr Dangui Zhang, Shantou-Oxford Clinical Research Unit. Speciality subject: Immunology
Ms Audrey Fang, Shantou-Oxford Clinical Research Unit. Speciality subject: Administration
Professor William Ba-Thein, Shantou-Oxford Clinical Research Unit. Speciality subject: Microbiology

Course details:
The aims of the second Shantou-Oxford training course were to promote an exchange of knowledge, ideas, and experiences between Chinese scientists and international experts on public health and epidemiology, and to strengthen the collaboration between the University of Oxford and Shantou University Medical College (SUMC).

The training course was held at SUMC and attended by 37 selected participants, including graduate students, scientists, and staff from Shantou University Medical College, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, Hubei Province), Anhui Medical University (Hefei, Anhui Province), and Ji’nan University Medical School (Guangzhou, Guangdong Province). The course was also attended by government officials from the Centres for Disease Control and Prevention of Shantou City and Guangdong Province.

The course covered important topics in public health and epidemiology, such as public health research methodology, effects of climate change and urbanisation on health, vaccine-preventable diseases and issues in immunisation programmes, zoonotic diseases, and dengue. The course was conducted in the form of lectures, practical sessions, and open discussion in English with Chinese translation of presentation materials and hand-outs. During tea breaks, the participants had face-to-face discussions and exchanged ideas with the course instructors and fellow participants. Certificates were presented to participants who completed the course.

Feedback from the participants was very positive, including comments that the course was very well conducted and it was informative, comprehensive, and stimulating. Most participants requested longer training courses in the future. The training course also opened up opportunities for the participants to collaborate with scientists from SUMC and Oxford Tropical Medicine Network.
As part of the Medical Elective Programme, Dr Brian Angus travelled to Patan Hospital, Nepal. Dr Angus and Professor Jeremy Farrar are both members of the Patan Academy of Health Sciences (PAHS) International Advisory Board and they contribute their diverse expertise and experience to the development of the Academy. They are committed to making PAHS an innovative and high-quality educational institution that will improve health care throughout rural Nepal. Oxford funds one medical student from Kathmandu each year to visit Oxford for their undergraduate medical elective, as part of the same programme for Shantou students.

Dr Angus arrived in Nepal to provide advice to assist the Patan Academy of Health Sciences (PAHS) with the set-up of their Medical MBBS Bachelor of Surgery and Bachelor of Medicine course. This course has now taken its first intake of 60 undergraduate medical students. The course is a novel one for Nepal and the curriculum focuses on problem-based learning (PBL) with an emphasis on strong community involvement. Students from rural areas are sponsored to attend in order to encourage greater engagement with rural communities and we hope for a long-term commitment to rural health from the graduates of the course.

The aim for Patan Hospital is to become the teaching hospital for the Patan Academy of Health Sciences. “Patan Hospital’s mission is to provide quality, compassionate health care to everyone who comes to the hospital, regardless of their ability to pay. It serves people from every district of Nepal, from the remote villages as well as from the Kathmandu valley.”

The visit was important to help encourage innovation in medical education in Asia and to be able to compare different models of medical education. It has strengthened the links between Oxford and PAHS.

Plans for year two of the Medical Elective Programme
Oxford will continue to support the programme of medical student electives within the Oxford Radcliffe Hospitals NHS Trust. Students from Bangladesh, Nepal and Shantou will visit Oxford, and we hope to host six students per year from Shantou University. Students will be given the opportunity to study surgery and infectious diseases, as well as internal medicine. Involvement by senior Oxford academics in medical education, particularly as it applies to the development of curriculum and assessment in Asia, will be a focus over the next few years with the sharing of expertise from Oxford University Medical School and Shantou Medical College. The exchange of undergraduate students between Oxford and Shantou will be an important part of the programme.
Programme Three

Shantou Oxford Clinical Research Unit

The Shantou-Oxford Clinical Research Unit (SOCRU) was established in May 2010 in order to strengthen the partnership between the University of Oxford and Shantou University Medical College. The aim of the collaboration is to bring together skills, expertise and ideas through research projects in the field of global health, as well as providing expert training to future scientists through collaborative training courses built around a specific theme, such as infectious diseases or epidemiology (as described in Programme Two).

The official opening ceremony was attended by Professor Jiang Gu, the Dean of Shantou University Medical College; Professor Jeremy Farrar, Director of the University of Oxford–Li Ka Shing Global Health Programme and the Oxford University Clinical Research Unit Vietnam; Professor Nick Day, Director of the Mahidol Oxford Clinical Research Unit, Thailand, and other senior SUMC staff.

The first Research Project to arise from the SOCRU collaboration is detailed below.

Etiology of upper respiratory tract infections in paediatric outpatients attending an urban Chinese hospital – a prospective descriptive study

This project involves collaboration between SUMC investigators:
• Professor William Ba Thein
• Dr Binglin Cui
• Dr Hui Pan
• Dr Dangui Zhang
and University of Oxford faculty:
• Professor Jeremy Farrar
• Professor Nick Day
• Dr Peter Horby
• Dr Rogier Van Doorn

The aim of this project is to investigate the prevalence and seasonality of respiratory viruses in the Chaoshan region of Southern China. This is investigated by identifying viral pathogens in paediatric patients attending the respiratory outpatient department in the first-affiliated hospital of Shantou University Medical College (SUMC), Shantou, Guangdong, China.

Regional epidemiological data on infectious diseases is not available. Therefore, the results of this project will provide baseline epidemiological data on respiratory infections which, in turn, will help clinicians improve their management of viral respiratory infections (for example, avoiding unnecessary use of antibiotics) and help local health authorities to respond better to seasonal outbreaks. This work will also document the causes of acute respiratory infection in Shantou and provide invaluable data on the respiratory viruses circulating in southern China including influenza, RSV.
and at least 12 other viruses. The results of this study will also enable us to develop future clinical studies and we hope to link with Shantou, Guangzhou and the Chinese Centre for Disease Control.

Development of this project involved:

- hiring an administrative assistant and three research assistants (two of them having Master’s degrees; one in paediatrics, and the other in immunology)
- training the research assistants in the clinical microbiology lab at the first SUMC-affiliated hospital and in the virology lab at the International Institute of Infection and Immunity at SUMC
- technology transfer from the Oxford University Clinical Research Unit (OUCRU), Ho Chi Minh City, Vietnam
- setting up a molecular diagnostic lab at the Shantou-Oxford Clinical Research Unit (SOCRU)
- implementing bioethics procedure in compliance with international practice and transport system for biological materials from overseas countries.

Project progress
A P2-level molecular diagnostic lab has been set up and is now fully functional, with two trained research assistants to run clinical specimens. Specimen preparation, pathogen isolation, nucleic acid extraction, and PCR-based diagnosis testing are currently only available for research purposes; we are hoping to provide these services to hospitals in the future.

One of the research assistants (sometimes two assistants during the peak season) has been assigned to collect clinical specimens (nasal/throat swabs) from paediatric outpatients on a daily basis, except national holidays, for one year at the participating hospital. Specimen collection began on 1 December 2010. A total of 652 specimens have been collected as of 29 March 2011; nucleic acids from the specimens were prepared and now they are ready for real-time RT-PCR detection of an array of viral pathogens – influenza virus (A and B), adenovirus, enterovirus, respiratory syncytial virus (A and B), human metapneumovirus, rhinovirus (A, B, and C), parainfluenzavirus 1-4, coronavirus (subtypes 229E, OC43, HKU1, SARS cov & NL63), bocavirus, and parechovirus.

Partnerships and collaborations formed
The setting up of the molecular diagnostic lab was made possible by generous technical and operational support from the OUCRU, Ho Chi Minh City, Vietnam. We have established collaboration with the International Institute of Infection and Immunity for joint specimen collection and real-time RT-PCR detection of pathogens.

Over the last few months, we have strengthened our personal relationship with the first SUMC-affiliated hospital and local health authorities at various levels and we are confident that they will co-operate with us for future clinical studies. In particular, the paediatric department and clinical laboratory department in the first-affiliated hospital are very co-operative and we are in the process of launching the second project in collaboration with these departments.

Impact on other research
This study is the first in a series of projects planned for the Shantou-Oxford Clinical Research Unit (SOCRU). Conducting clinical studies in Shantou hospitals is sensitive and can be a challenge; the scientific data from this project will greatly strengthen our relationship with local health authorities and provide the political leverage required to launch subsequent clinical studies in hospitals across Shantou in coming years. More importantly, this project and future studies will open up opportunities for Chinese clinicians to collaborate with scientists in the Oxford Tropical Network and, we hope, with the China Centre for Disease Control, Beijing, China in the future.
The aim of this programme is to bring Shantou University fully into the Oxford University Asia Research Network. The Network is based around the Beneficiary’s Centres in Thailand, Vietnam and now Shantou, China.

The funding supplied by the Li Ka Shing Foundation will support research projects in global health that involve University of Oxford researchers (based in Asia and the UK) collaborating with research groups in Shantou University and across Asia.

The research groups funded under this programme were split into two groups of Strategic Awards and Seed Awards. During the first year of the Programme, 15 research groups were awarded strategic grants of up to £100,000 to cover projects for up to two years, and 21 research groups were granted Seed Awards of up to £5,000 to cover research projects of up to one year.

The following reports detail the strategic and seed award research projects supported by the Li Ka Shing Foundation under the Asia Research Network.

**Strategic Awards**
Projects 1 to 10 began in 2010; the reports below describe the activities and results during the first year of their research. Projects 11 to 15 began in 2011 and their reports describe their planned research activities and expected outcomes for the coming year(s).

**Seed Awards**
The majority of the 21 seed awards began their projects in 2010 and for those groups, we report on their activities and the progress of their project since the start-date. For the few seed awards which began in early 2011 (four in total), we report on their aims, objectives and planned activities for the coming year.
1. INVESTIGATION OF FEBRILE DISEASES AMONG HOSPITALISED PATIENTS IN JAKARTA AND BANDUNG, INDONESIA (LG01)

Investigators
Dr Antonius Pudjiadi, Department of Child Health, University of Indonesia, Jakarta
Dr Emmy Pranggono, Department of Infectious Diseases, Hasan Sadikin Hospital, Bandung, Indonesia
Dr W Robert Taylor, Mahidol-Oxford Tropical Medicine Research Unit (MORU), Bangkok, Thailand
Dr Stuart Blacksell, Mahidol-Oxford Tropical Medicine Research Unit (MORU), Bangkok, Thailand
Dr Kevin Baird, Eijkman-Oxford Clinical Research Unit, Jakarta
Dr Steve Wignall, Eijkman-Oxford Clinical Research Unit, Jakarta
Dr Iko Safika, Eijkman-Oxford Clinical Research Unit, Jakarta
Decy Subekti, Eijkman-Oxford Clinical Research Unit, Jakarta

Project background
Data on febrile illnesses in Indonesia is limited. The small number of published studies have documented significant morbidity and mortality associated with leptospirosis, rickettsiae, salmonella sp. and haemophilus influenzae [Anderson et al., 1976; Laras et al., 2002; Lolekha, 2000]. However, these studies have focused on specific pathogens. To date, no published work has systematically surveyed the causes of febrile disease among admitted patients in hospitals in Indonesia. Consequently, we have almost no definitive data documenting the burdens of infectious disease, their aetiologies and their clinical outcomes in any Indonesian setting. Such data would permit the rational selection and design of clinical studies, inform local clinicians, lead to the rational prescribing of antimicrobial drugs, and inform local policy makers.

Project aims
This study aims to:
• document the causes of acute, community-acquired fevers in hospitalised patients at the Cipto Mangunkusumo General National Hospital (RSCM), Jakarta, and at Hasan Sadikin Hospital (RSHS), Bandung
• evaluate rapid diagnostic tests
• develop treatment algorithms and guidelines
• familiarise the teams with conducting hospital-based research.
Planned activities
We will classify patients admitted with a febrile illness according to a clinical syndrome (haemorrhagic, respiratory, gastrointestinal, etc.) based on the (dominant) clinical picture. This classification will set in motion a laboratory diagnostic algorithm specific to each syndrome which may lead to a laboratory-confirmed diagnosis. This will include routine tests (e.g. bacterial culture, paired serological samples) as well as a number of rapid diagnostic tests. All relevant clinical data will be recorded on a standardised case record form (symptoms, signs, clinical lab findings, treatments administered, duration of hospitalisation, clinical outcome, etc.), and an archive of specimens linked to those data and the ultimate diagnosis will be established to enable subsequent, more detailed microbiological investigation of any given aetiological pathogen.

The collection of demographic and clinical history, specimens and laboratory findings will be subject to rigid quality assurance measures which will enable us to demonstrate not only the high degree of credibility of the findings, but also of the capabilities of the clinical research team as a means of supporting subsequent applications for research support.

Project progress
The study has recruited 188 patients, 87 in Jakarta and 101 in Bandung. The recruitment phase has now stopped. We are continuing to manage and analyse the data, and prepare manuscripts for publication in peer-reviewed journals. Importantly, we intend to communicate the results of the study within Indonesia.

Expected outcomes
At the end of this study we will be able to report, for the first time, laboratory-confirmed causes of the important acute infectious disease among patients hospitalised at two major hospitals in Indonesia. The data collected will provide the first steps to developing a clinical decision tree for clinicians. We will also gather detailed information about the clinical presentation of several important infections and these basic descriptions will be useful for clinicians. Additionally, we intend to publish descriptive papers in journals of clinical medicine.

New collaborations
This is the first study between the University of Oxford and the Eijkman Institute and the Cipto Mangunkusumo hospital in Jakarta. New links have also been established with the University of Western Australia.

2. The Malaria Atlas Project in the Asia Pacific region (LG02)

Investigators
Dr Simon Hay, Department of Zoology, Oxford
Professor Sangkot Marzuki, Eijkman Institute, Indonesia
Dr Frédéric B Piel, Department of Zoology, Oxford
Professor Inge Sutanto, Faculty of Medicine, University of Indonesia
Professor Robert W Snow, Malaria Public Health & Epidemiology Group, Nairobi
Professor Liquin Jin Department of Parasitology Shantou University Medical School
Dr J Kevin Baird, Eijkman-Oxford Clinical Research Unit, Indonesia
Dr Din Syafuddin, Eijkman Institute, Indonesia
Dr Rita Kusriastuti, Vector-Borne Diseases Division, CDC of Indonesia
Dr Peter Horby, Hanoi Unit, Oxford University Clinical Research Unit, Vietnam
Mr Iqbal Elyazar, Eijkman-Oxford Clinical Research Unit, Indonesia

Project aims
The Plasmodium vivax malaria parasite infects several hundred million people each year, more than 90 per cent of whom reside in Asia. Treatment is complicated by the fact that many individuals possess inherited blood disorders that make the most common treatment for P. vivax malaria dangerous.
Disease and death associated with P. vivax is a significant problem in Asia and this project is playing an active and productive role in calling attention to this drain on the health of Asian people. We are doing this by mapping the distribution of the P. vivax parasite as well as mapping the level of disease and burden of illness. We are also mapping relevant inherited blood disorders and the distribution of the mosquitoes that carry P. vivax parasites. These maps are then widely disseminated to the Asian countries affected, to funders of malaria control measures and to groups working on the elimination of malaria.

Progress
The first objective was to improve the quantity and quality of data on P. vivax malaria in the Asia Pacific region by engaging with leaders in the region. Working with the new partnerships described below and with our existing network of contributors, we have obtained new data from China, Indonesia, Malaysia, the Philippines and Sri Lanka to-date. Data collected by National Programmes in 2010 will bring our malaria maps up-to-date and we have also been able to obtain more complete datasets at a finer resolution to improve the maps further. Work collating new data on the mosquito carriers of malaria in the region and on the frequency of inherited blood disorders is also ongoing.

Working with the Asia Pacific Malaria Elimination Network (APMEN), we are using the malaria data collated up to 2010 to produce a malaria elimination atlas covering Bhutan, China, the Democratic People’s Republic of Korea, Indonesia, Malaysia, the Philippines, the Republic of Korea, the Solomon Islands, Sri Lanka, Thailand, Vanuatu and Vietnam. The first draft was presented at the annual APMEN meeting in May 2011 and will be used as a tool for malaria elimination planning by these countries.

Additional support secured as a result of this project
We are combining the training component of our Li Ka Shing grant with funds available within the Asia Pacific Malaria Elimination Network (APMEN) to provide a training course on using Geographical Information Systems for public health managers. Training will be provided to individuals from Bhutan, China, the Democratic People’s Republic of Korea, Indonesia, Malaysia, the Philippines, the Republic of Korea, the Solomon Islands, Sri Lanka, Thailand, Vanuatu and Vietnam. We have offered to run the course in China at Shantou University or one of the other locations where the University of Oxford–Li Ka Shing Global Health Programme is active. Training will be provided by our group, and travel funds will be provided by APMEN.

New partnerships and collaborations
As a result of our efforts to secure new partners in the Asia Pacific region, we are now working with the National Institute of Parasitic Disease in Shanghai and are running a Geographical Information Systems training course specifically for this group in August 2011.

We have also established extensive new links with Malaria Control Programmes in Indonesia and the Universities of Indonesia, Gadja Mada and Hassanudin.
Publications


3. The mathematics of artemisinin resistance (LG03)

Investigators
Dr Lisa J White, Mahidol Oxford Research Unit
Professor Nicholas P J Day, Mahidol Oxford Research Unit
Professor Nicholas J White, Mahidol Oxford Research Unit
Dr Arjen M Dondorp, Mahidol Oxford Research Unit
Dr Duong Socheat, National Centre for Malaria Control, Cambodia
Dr Shunmay Yeung, Mahidol Oxford Research Unit

Project aims
This project aims to:
• develop mathematical models for artemisinin resistant infections
• develop spatial models for malaria transmission and containment
• combine important elements of population movement as well as realistic natural history of infection submodels for sensitive and resistant infections
• use the models to develop pragmatic recommendations for the elimination of artemisinin resistant malaria in Cambodia

The impacts of this work are:
• the characterisation of the in vivo artemisinin resistance phenotype
• the creation of one of the first malaria elimination models to include population movement
• the provision of pragmatic recommendations for the containment of artemisinin resistant malaria within Cambodia and other countries
The first in vivo characterisation of artemisinin resistance has been developed. We show that given the pharmacokinetic-pharmacodynamic (PKPD) data and knowledge of the mechanisms of parasite growth and death from drug action, resistance is most likely to be a reduction in the killing effect at the ring stage of the parasite. We continue to develop new models for in vivo and in vitro dynamics to further characterise artemisinin resistance.

A prototype of a spatial model for the transmission of any infectious disease has been developed. The model requires input data on population distribution and surveillance. The model is written in a general form which will allow the easy extension to other regions and countries as well as other infectious diseases. The model is currently being run for P. falciparum malaria in Cambodia and it will be modified in collaboration with the Cambodian centre for malaria control (CNM) to design intervention programmes.

The inclusion of artemisinin resistance and P. vivax malaria is planned for the coming months. Population movement structure has been included in the spatial model and we are now awaiting data in order to predict and correct the effects of population movement in Cambodia on the elimination programme.

Additional support secured as a result of this project
Dr Lisa White submitted a proposal on modelling the effect of village malaria workers in Cambodia for the National University of Singapore NIHA funding; she is currently waiting for a decision. In addition to this proposal, Lisa is also applying for an HSFP Program Grant on the mathematics of artemisinin resistance and for an MRC Industry Collaboration Award with GSK Biologicals (Glaxo Smith Kline) on the optimal combination of their antimalarial vaccine currently in the final stages of development (RTS,S/AS vaccine) with other interventions for malaria elimination strategy. Furthermore, Dr White has initiated a network of mathematical modellers of infectious diseases based in the tropics and they plan to apply for more funds in the future.

New partnerships and collaborators
Dr White was invited to attend a meeting with ACT Malaria (Asian Collaborative Training Network for Malaria) which is an inter-country training and communication network which includes National Malaria Control Programmes of Bangladesh, Cambodia, PR China, Republic of Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Thailand, Timor-Leste, and Vietnam. In preparation for the meetings, Dr White will develop mathematical models to suit the specific public health needs of these countries and assist in capacity building.

In addition, Dr White has developed a productive collaboration with GSK-biologicals to use modelling in order to fully characterise the action of the RTS,S/AS vaccine and to determine its role in malaria elimination strategies.

Influencing other studies
Dr White and her collaborators in Cambodia (Dr Duong Socheat and Dr Chea Nguon, the director and vice-director of CNM) have initiated a new project to assess the national impact of the Cambodian village malaria worker scheme.
4. Study of the Epidemiological, Virological, and Immunological Features of Rabies Virus Infections in Humans in Bali, Indonesia (LG04)

Investigators
Professor A A Raka Sudewi, Neurology Department, Faculty of Medicine, Udayana University
Dr Nyoman Sri Budayanti, Microbiology Department, Faculty of Medicine, Udayana University
Professor DVM Gusti Ngurah Mahardika, Biomedical and Molecular Biology, Udayana University
Dr Made Susilawathi, Neurology Department, Udayana University, Sanglah Hospital
Dr Steve Wignall, Eijkman-Oxford Clinical Research Unit, Jakarta, Indonesia

Project aims
The Indonesian island province of Bali, previously considered rabies-free, has been experiencing an ever-widening animal and human rabies outbreak since November 2008. As of November 2010, over 22 animal and 104 human cases have been detected. Control has been challenged by an estimated dog population of 403,000 (density 890/sq km), most of which have never been vaccinated, and over 48,000 reported dog bites in 2010. An island-wide animal vaccination programme has begun. Animal bites continue, however, and human vaccine and hyperimmune globulin resources have been limited and expensive. Current policy requires large-dose intramuscular post exposure prophylaxis. This project aims to determine the epidemiological, virological,
and immunological features of rabies virus infections in humans in Bali. In addition, we will determine the immune response to low-dose intradermal rabies vaccination in an Indonesian population with an aim of reducing the overall burden of vaccine costs and increasing vaccine availability.

The short-term impacts of this project are:
- a clearer understanding of how the rabies virus was introduced to Bali
- a better understanding of how and where animal bites occur in Bali and who is most affected
- antibody response data as a result of intradermal administration of rabies vaccine
- improved human rabies diagnostic capacity in Bali

The medium-term impacts of this project are:
- potentially reducing the cost of vaccination through low-dose intradermal vaccination making more vaccines available
- development of evidence-based public awareness programme to reduce dog bite risk and improve first aid
- reduced inter-island importation risk through better control using molecular epidemiological data

Rabies diagnostic lab capacity has been improved with the development of a genetic (PCR) rabies test.

Progress
Clinical data from 104 rabies cases hospitalised at the Sanglah Provincial Hospital from November 2008 through November 2010 has been collected and analysed. Clinical presentation varied, with patients often manifesting non-specific signs or symptoms but then evolving to more classical paralytic (21 per cent) or furious (spasms of throat and diaphragm) (79 per cent) rabies. Most patients had not received appropriate first aid or post-exposure prophylaxis. The high incidence of dog bite and lack of awareness of the animal rabies epidemic may have led to poor post-bite wound management and care-seeking behaviour by patients.

A genetic test (PCR) for diagnosing rabies was initially developed at the outset of the epidemic based on the rabies NP gene but was not sensitive. New reagents (primers) have been designed based on the NP and G genes and the results are now being evaluated.

For molecular epidemiological and virological purposes, 40 virus specimens have been collected and examined. Viral sequencing of these samples for molecular epidemiological purposes is currently underway at the Indonesian National Institutes for Health Research and Development.

Prior to Indonesian government policy change on high-dose intramuscular post-exposure prophylaxis recommendations, data on the serological response from low-dose intradermal vaccination is required. We vaccinated the 40 volunteers (20 intradermal and 20 intramuscular) and have collected sera from all volunteers and controls on days 0, 7, 14, 28, 90. The last serum collection (day 180) was collected on 28 May 2011. Serological testing will be done after the collection of last serum. Data will be analysed and shared with the Indonesian National Vaccine Program Office.

New partnerships and collaborators
Discussions are underway with the Indonesian National Institute for Health Research and Development for rabies virus sequencing and with the Indonesian National Vaccination Program.

Publications
A draft of the manuscript *Epidemiological and Clinical Features of Human Rabies in Bali 2008 -2010* is currently being reviewed locally.
5. CLINICAL INFECTIOUS DISEASES RESEARCH IN SOUTHERN VIETNAM (LG05)

Investigators
Dr Ngo Thi Hoa, Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Vietnam
Dr Ngo Thanh Long, Regional Animal Health office 6
Dr Pham Phong Vu, Regional Animal Health office 6
Dr Tran Thi Bich Chieu, Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Vietnam
Dr Katherine Anders, Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Vietnam
Dr Tran Nguyen Bich Chau, Oxford University Clinical Unit, Hospital for Tropical Diseases, Vietnam
Dr Thomas Pouplin, Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Vietnam
Dr Pham Van Toi, Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Vietnam
Dr Maciej Boni, Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Vietnam
Dr Rogier Van Doorn, Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Vietnam
Dr Marcel Wolbers, Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Vietnam

Aims and progress
This project focuses on six main areas.

1. Implementation of paediatric formulations for childhood Tuberculosis in Vietnam
   (Lead investigator: Thomas Pouplin)
   The focus of this project is the implementation of paediatric formulations for childhood tuberculosis (TB). The paediatric dose regimen for tuberculosis is extrapolated from adults and adjusted to the body weight of the child. The situation is complicated by the fact that caregivers have to split tablets to make suspensions to treat children, leading to potential inaccuracies in dose delivery and poor compliance over the six months of therapy. This may contribute to the effective under-dosing of TB drugs observed in childhood TB. The first step in the project was to study the uniformity and accuracy of drug content in split portions (halves and thirds) of the fixed-dose combination. A bio analytical assay was developed and validated to measure Rifampicin (RIF), Isoniazid (INH) and Pyrazinamide (PZA) from the whole and split portions of tablets. Dose variation, measured as the difference between the actual values and the labelled target drug content, exceeded the USP specifications in a range of 6.7 per cent to 46.7 per cent in halves and 33.3 per cent to 50 per cent in third tablets. The second phase in year two of the award will be the bioequivalence clinical trial focused on blood exposure, using pharmacokinetics, at an early stage of the disease between young children treated with split tablets and those treated with a reference child-friendly formulation.

2. Epidemiology of dengue virus transmission in and around households in Ho Chi Minh City
   (Lead investigator: Katherine Anders)
   This project aimed to establish collaborative links with the Preventive Medicine Centre of Ho Chi Minh City (PMC HCMC) and develop data collection tools for the conduct of a prospective epidemiological study of dengue transmission. This study aims to determine the degree to which dengue risk in an urban setting is clustered in time and space at the level of the household. Over a four-month period from June-September 2010, the study protocol and processes were developed and training was conducted for PMC fieldworkers and entomological staff. A web-based database and data collection tools were developed by the Oxford University Clinical Research Unit-Vietnam data group, which facilitates data entry in the field using smart phones. A separate major grant from the University of Oxford–Li Ka Shing Global Health Programme was awarded to fund the fieldwork and laboratory diagnostics for
this study. This project has led to a new collaboration with the Preventive Medicine Centre HCMC. Following on from this new collaboration with PMC HCMC, we are discussing potential future research projects on dengue transmission utilising routinely collected surveillance data, or evaluations of vector control interventions.

Dr Katherine Anders taught on the Epidemiology Course at Shantou University Medical College in January 2011 and, in the future, would be interested in using the expertise developed on this project, particularly in relation to data capture, to facilitate work being developed by the Shantou Oxford Clinical Research Unit.

3. Socioeconomic impacts of using poultry culling to control of avian influenza (Lead investigator: Maciej Boni)

The aim of this project is to assess how avian influenza epidemiology interacts with small farm microeconomics. This has been done by reviewing literature, building theoretical models of the interactions, developing collaborations with economists, and using standard surveys to determine the importance of poultry farming to individual and local microeconomics. The focus will be on small poultry farms. These farms may be very sensitive to natural exposure to avian influenza, changes in the price of poultry, and perceptions of government plans for culling.

Progress has mainly occurred in the development of mathematical models, which have looked at
- factors that affect an individual farmer’s micro-economic optimisation of his poultry management
- possible effects of government culling policies on poultry prices and poultry production
- effect of farm size elasticity on avian influenza prevalence and the resulting overall risk to humans

A pilot set of surveys has been sent out and preliminary results were presented at a mathematical modelling workshop in Canada. This project has interested many economists and led to a potential new collaboration with a research team from the University of Toronto in economic analyses.

4. Use of probiotics in paediatric clinical management (Lead investigator: Rogier Van Doorn)

This laboratory research project on probiotics, funded by the University of Oxford–Li Ka Shing Global Health Programme, was put together into a PhD project with a clinical trial on probiotics, funded by a fellowship grant from one of our senior researchers (Stephen Baker). We have gathered retrospective data from the children’s hospitals in Ho Chi Minh City on the use of probiotics and for which indication these were prescribed. These preparations will be characterised molecularly in the laboratory research project, susceptibility will be assessed, and if resistance is found, the molecular mechanisms causing this will be characterised. The protocol for the randomised trial with probiotics in children with infectious diarrhoea is currently being drafted.

5. Prognostic models for infectious disease data (Lead investigator: Marcel Wolbers)

This project aims to develop statistical methodology and prognostic models, primarily in tuberculous meningitis. As biostatistics and prognostic modelling are relatively underdeveloped fields in Vietnam, part of the grant will be used for capacity building and attendance of young Vietnamese researchers at international conferences and workshops. A collaboration to share data from three major randomised controlled trials and one prospective observational study in tuberculous meningitis was established at a clinical research and CNS infections meeting in Berlin on 15-16 November 2010. Together, these studies comprise data from more than 900 patients with a clinical diagnosis of tuberculous meningitis. We are currently in the process of pooling the databases and finalising the analysis plan for the first project from this collaboration. To build biostatistics capacity, three Vietnamese biostatisticians attended a four-day course on prognostic models taught by Professor Tuan Nguyen from The Garvan Institute of Medical Research with funding from this grant. This training has significantly impacted an ongoing prognostic study to predict the severity of dengue shock syndrome. Dr Wolbers hopes to teach at the Shantou University Medical College and at Shantou Oxford Clinical Research Unit later in 2011.

6. Co-infection of S. suis in pigs infected with Porcine Respiratory and Reproductive virus (PRRSV) in Vietnam (Lead investigator: Hoa Ngo)

This project aims to understand if there is an increased risk for human infection during the outbreak of PRRSV-infected pigs (also known as blue ear diseases in pig images).

The results of this project could play an important role in the effort to enforce the safe handling of pigs/pork in South East Asia. We completed the sample collection, isolation and identification of co-infection bacterial pathogens.
Real-time PCR for detection of S. suis in pig blood was optimised for application to all samples. The Li Ka Shing Fund ensured we were able to commence this study during the blue ear outbreak in pigs in 2010. We have successfully secured the 550 million VND (~25K USD) research fund from the Department of Science and Technology in Ho Chi Minh City to complement this funding. This project enables research assistants from Oxford University Clinical Research Unit and Regional Animal Health Office 6 (RAHO 6) to work in the same laboratory and share research skills, which has provided the opportunity to strengthen our collaboration with RAHO 6 and Sub-Department of Animal Health (SDAH) in Tien Giang and led us to develop a new collaboration with SDAH in Thai Binh, Soc Trang and RAHO 7. Two MSc and BSc students of the University of Science have been trained and are writing their theses on this project.

**Additional support secured as a result of this project**

All of the projects in this report have received matched funds from the University of Oxford. The project on Streptococcus suis has led to a research grant from the Vietnamese government awarded to Dr Hoa for work on human and animal health, in collaboration with Professor George Gao, Beijing, China and with Dr Xu from the Chinese Centre for Disease Control, Beijing, China. Also, linked to this work, there are currently two applications pending at the Wellcome Trust; a Fellowship application from Dr Maciej Boni and a Strategic Award WT-VIZIONS.

**New partnerships and collaborations**

These projects have enabled us to develop new partnerships with Professor George Gao, Institute of Microbiology, Chinese Academy of Sciences, Beijing, China; Dr Xu from the Chinese Centre for Disease Control, Beijing, China; and Professor Marcello Gottschalk, Centre for Research on Infections of Pigs, University of Montreal, Canada for research on Streptococcus suis.

**Influencing other studies**

The work on Streptococcus suis and zoonosis has led to a Workshop in Human and Animal Health held in Ho Chi Minh City in February 2011 and a Strategic Award Application entitled “Vietnam Initiative on Zoonosis” (WT-VIZIONS).

**Publications and Presentations**

Boni M. Oral presentation on 2 March 2011 at Control of Infectious Diseases workshop in Banff, Canada, at Banff International Research Station.


4. Hoa, N. Streptococcus suis, the story from Vietnam. Oral presentation at Centre for Research on infection of Pigs (CRIP), University of Montreal, Canada (2 Mar 2011).
6. UNDERSTANDING THE HUMAN GENETIC FACTORS RESPONSIBLE FOR VIRAL CONTROL IN A CHINESE COHORT INFECTED WITH A SINGLE STRAIN OF HIV-1 (LG06)

**Investigators**
Professor Sarah Rowland-Jones, Nuffield Department of Medicine, University of Oxford
Dr Tao Dong, Nuffield Department of Medicine, University of Oxford
Dr Linghang Wang, Nuffield Department of Medicine, University of Oxford, Ditan Hospital, Beijing
Professor KeYi Xu, Ditan Hospital, Beijing
Dr Yonghong Zhang, YouAn Hospital, Beijing
Professor Huiping Yang, YouAn Hospital, Beijing

**Aims**
The main aim of the project is to learn about host genetics influencing disease outcome in the unique setting of the Chinese plasma donor cohort in a village in Henan province (referred to as SM) where the infecting virus is very similar in all subjects, so the impact of host genetics should be magnified. We are particularly interested in the subset of infected people who have now survived 16-17 years without treatment or disease and still have low or undetectable viral load: we have termed these “elite non-progressors”. We are also aiming to expand the cohort by recruiting healthy HIV+ patients from other villages in the region who may also meet the definition of long-term non-progressor.

The key person for these studies is a new DPhil student selected by our colleagues in Ditan hospital: Dr Linghang Wang, an infectious diseases physician from Ditan who is supported by funds from an MRC strategic grant awarded to Sarah Rowland-Jones. Dr Wang registered for his DPhil in October 2010 and has been working on characterising the Killer Immunoglobulin Receptor (KIR) gene types in the SM cohort; these genes have been shown to affect clinical outcome in HIV-1 infection in Caucasians and Africans but have not previously been studied in the Chinese. In addition, Dr Wang has worked with Professor Xu to identify and recruit more non-progressors from elsewhere in Henan province. His work is going very well and he is now in a position to characterise novel KIR alleles found only in Chinese people, as well as to start analysing the impact of KIR gene haplotype on clinical course in HIV infection. He will also take the lead in genetic studies on genome-wide association and exome sequencing studies with expert collaborators. The exome sequencing work will take place at the Sanger centre under the leadership of Dr Manj Sandhu and Dr Paul Kellam and the genome-wide association studies will be part of a European consortium led by Dr Amalio Telenti in Lausanne.
Progress
The project is still at an early stage but we hope to have concrete results in time for next year’s report. In addition, a manuscript describing the Human Leucocyte Antigen (HLA) associations in the SM cohort with clinical outcome is almost ready for submission.

Additional support secured as a result of this project
Applications have been submitted to the MRC Programme Grant by Sarah Rowland-Jones (decision expected June 2011), and also to the European Union proposal for genome-wide association studies in HIV infection by Dr Amalio Telenti.

New partnerships and collaborations
Collaboration has been established with Dr Manj Sidhu and Dr Paul Kellam at the Sanger Institute in Cambridge for full exome sequencing of “extreme phenotypes” in HIV-1 infection, focusing on the non-progressors with undetectable viral load in the cohort. Another partnership has developed with Dr Amalio Telenti in Lausanne who is co-ordinating an EU programme-project on genome-wide associations studies on non-progression in HIV infection. In addition, we are collaborating with Dr Mary Carrington, National Cancer Institute Frederick, USA, on the KIR/HLA associations with clinical outcome in the cohort.

Influencing other studies
We are expanding our collaboration with Beijing, YouAn and Ditan infectious diseases hospitals in the area of HCV infection (with which most of the plasma donor cohort is infected) and on mucosal immunology. We are also currently hosting a Chinese gastroenterologist who is studying mucosal immunology in HIV infection in Oxford.

Presentations and publications


7. Urban influences on the transmission of dengue and influenza infection (LG07)

Investigators
Professor Nguyen Thi Kim Chuc, Hanoi Medical University, Vietnam
Dr Peter Horby, Oxford University Clinical Research Unit, Hanoi, Vietnam
Dr Tran Khanh Toan, Hanoi Medical University, Vietnam
Professor Max Petzold, Nordic School of Public Health, Sweden
Dr Heiman Wertheim, Oxford University Clinical Research Unit, Hanoi, Vietnam
Dr Annette Fox, Oxford University Clinical Research Unit, Hanoi, Vietnam

Project aims
It is estimated that the urban population of Asia will more than double in the next 40 years, and as urbanisation has been identified as the second most important environmental factor influencing infectious disease emergence, it is inevitable that urbanisation will play a central role in the evolution of infectious disease risks in Asia over the coming decades. Two infections of particular interest in the urban environment are dengue and influenza.

This study will be the first to directly link movement and contact data collected through diaries to the individual risk of dengue and influenza infection. The objectives of the study are:

- to estimate and compare the force of infection of dengue and influenza between urban and rural settings
- to quantify the association between the frequency and location of social contacts and travel, and the probability of infection with dengue and influenza in urban and rural settings
The study will provide data for testing the assumptions underlying a number of influenza and dengue control policies and will identify behavioural predictors of risk and provide improved parameters for mathematical models to predict the impact of strategies for control of transmission.

**Project progress**

Under a tripartite agreement signed between Hanoi Medical University (HMU), the Nordic School of Public Health, and the Oxford University Clinical Research Unit (OUCRU), the research will be conducted in two established field sites in Hanoi, Vietnam. The Dong Da demographic surveillance site (DoDaLab) is situated in a highly urban district of Hanoi with one of the highest incidences of dengue. It was established in 2007 and covers 37,308 inhabitants living in 10,608 households in three communes, and accounts for about 12 per cent of the total district population. FilaBaVi is an epidemiological field laboratory located in a rural district called Ba Vi, approximately 60 km west of the capital. The site was established in 1999 and consists of around 50,000 persons in nearly 13,000 households in 67 randomly selected clusters.

The detailed research protocol has been developed and laboratory methods are currently being validated. We have completed a pilot study of dengue seroprevalence in another rural field site, which indicates higher levels of dengue infection than previously thought (perhaps as high as 30 per cent). The protocol is now being submitted for ethical approval by Institutional Review Boards in Vietnam and the UK. Data from an earlier social contact and movement survey in 1,000 individuals living in DoDaLab and 1,000 in FilaBaVi have been entered, cleaned and analysed. Detailed information was collected on the frequency and nature of social contacts, the distance and frequency of travel, and household structures. Empirical data linking movement and contact behaviours from this earlier study to the risk of infection will be obtained through a dried blood spot survey (DBS) of all 2,000 individuals who completed the behavioural survey. Dengue and influenza antibody prevalence by age strata will be used to compare the intensity of transmission of these two infections in the urban and rural environments. The relationship between reported patterns of movement and social contacts and the probability of sero-positive status and sero-conversion will be analysed to determine the power of these variables to explain the observed pattern of infection. Geographical clustering of infection risk will also be explored since the location of participating households is known.

**Additional support secured as a result of this project**

This project has provided the framework for a separate study of Klebsiella pneumoniae carriage that will be nested within this study, but which has obtained separate funding (see below). The Nordic School of Public Health has provided additional funds to the DoDaLab field site in 2011 to support the collaborative research programme. A complementary application has been submitted to the Swedish Research Council for funds to explore the social aspects of urban vulnerability to infectious diseases in greater depth.

**New partnerships formed**

The project has strengthened the partnership between Hanoi Medical University and the University of Oxford. This strengthened partnership was recognised in October 2010 when Peter Horby was made an Honorary Professor at Hanoi Medical University.

**Influencing new studies**

This project has facilitated the development of a separate study of the prevalence of nasopharyngeal carriage of a respiratory pathogen, Klebsiella pneumoniae, in the two studied populations, and the relationship of Klebsiella pneumoniae carriage with alcohol consumption.
8. Defining severe acute infectious, central nervous system and toxin-related disease in children in Cambodia; an Oxford-Asia collaboration with Angkor Hospital for Children, Siem Reap, Cambodia (LG08)

Investigators
Dr Ngoun Pheaktra, Angkor Hospital for Children, Siem Reap, Cambodia
Dr Varun Kumar, Angkor Hospital for Children, Siem Reap, Cambodia
Dr Chheng Kheng, Angkor Hospital for Children, Siem Reap, Cambodia
Dr Yos Pagnarith, Angkor Hospital for Children, Siem Reap, Cambodia
Ms Lina Sin, Angkor Hospital for Children, Siem Reap, Cambodia
Mr Hor Putchhat, Angkor Hospital for Children, Siem Reap, Cambodia
Mr Bun Sen, Angkor Hospital for Children, Siem Reap, Cambodia
Ms Soeng Sona, Angkor Hospital for Children, Siem Reap, Cambodia
Mr Hip Viruth, Angkor Hospital for Children, Siem Reap, Cambodia
Mrs Vanaporn Wuthiekanun, Mahidol Oxford Research Unit (MORU), Tropical Medicine Faculty, Mahidol University, Bangkok, Thailand
Mrs Premjit Amornchai, MORU, Faculty of Tropical Medicine, Mahidol University, Thailand
Mr Sayan Langla, MORU, Faculty of Tropical Medicine, Mahidol University, Thailand
Dr Janjira Thaipadungpanit, MORU, Faculty of Tropical Medicine, Mahidol University, Thailand
Dr Narisara Chantratita, MORU, Faculty of Tropical Medicine, Mahidol University, Thailand
Dr Michael Carter, MORU Faculty of Tropical Medicine, Mahidol University, Thailand
Dr Kate Emery, MORU, Faculty of Tropical Medicine, Mahidol University, Thailand
Dr Catrin Moore, MORU, Faculty of Tropical Medicine, Bangkok, Thailand, University of Oxford
Dr Nicole Stoesser, MORU, Department of Medicine, University of Oxford
Dr Chris Parry, MORU, Department of Clinical Medicine, University of Oxford
Dr Daniel Paris, MORU, Department of Clinical Medicine, University of Oxford
Dr William Housworth, Angkor Hospital for Children, Siem Reap, Cambodia
Professor Nick Day, MORU, Department of Medicine, University of Oxford

Background to the study
The collaboration between Mahidol Oxford Research Unit (MORU) and the Angkor Hospital for Children (AHC), a provincial paediatric hospital in north-western Cambodia, was previously supported by an Oxford-Li Ka
Shing Collaborative Research Programme grant in 2007 for one year.

This grant enabled the setting up of a microbiology laboratory at AHC, the training of technicians and doctors in microbiology and microbiological laboratory techniques, and it allowed us to conduct a number of studies aimed at delineating the causes of infectious disease associated childhood morbidity and mortality in Siem Reap Province. This is a major priority as child mortality is unacceptably high in Cambodia, with nine per cent of all children dying before their fifth birthday. At the end of the period covered by the grant, after the requisite research training and capacity had been put in place, a fever study was initiated to provide systematic information on the causes of fever in children admitted to AHC, so that the treatment of children with serious infections could be improved.

This current (2010) strategic award builds on the successes of the previous LKS grant, which enabled us to initiate the project.

The specific aims of the project are to:

- support and develop further the clinical microbiology laboratory at AHC
- complete the fever study and initiate further targeted clinical studies on the causes of serious infections in children attending AHC and in the communities from which they come
- through training and long-term support, build capacity at AHC for the diagnosis and appropriate treatment of infections (a clinical microbiology service), and for the conduct of clinical research into clinical problems important in this clinical setting

Capacity building and training

With the initial LKS funding, a successful collaboration was established between the University of Oxford and AHC, and a number of epidemiological and clinical studies were completed or are currently underway.

Over the past year, staff at AHC have worked closely with collaborators from Thailand and Oxford to develop and expand the research agenda to address the most pressing clinical questions faced by this extremely resource-poor community. There are now three full-time microbiologists (Soeng Sona, Hip Viruth and Bun Sen) employed through LKS support who were trained in Thailand and Laos as part of the collaboration. The project has also attracted funding from the Oxford Tropical Network Fund and from the North London and Oxford Postgraduate Deaneries to place two research physicians (Dr Michael Carter and Dr Kate Emary) in AHC, a UK-trained microbiologist (Dr Catrin Moore), and a senior consultant clinical microbiologist (Dr Chris Parry) to help build sustainable research and microbiological capacity. To this end, a promising young Cambodian doctor, Dr Khun Peng An, has been identified for training as a clinical microbiologist. He is currently participating in a training course developed for him by Dr Parry.
The febrile illness study
For a comprehensive clinical and laboratory study of the causes of fever in children attending AHC, we recruited patients for a year from September 2009. In total, over 1,200 patients were enrolled in the study. The clinical data is currently being collated and patient samples are undergoing diagnostic reference testing. We hope to have a provisional analysis completed by June 2011.

This study will provide robust information on the causes of febrile illness in Cambodian children and, in the case of bacteria, their susceptibility to antibiotics. These results will inform decisions on the best empirical therapy for the treatment of these children in AHC and elsewhere in north-western Cambodia.

Additional support secured
The development of the microbiology laboratory at AHC has enabled the hospital to leverage charitable donations from individuals and organisations to support both the lab and the associated programmes. We have also secured support for new academic medical staff from the Oxford Tropical Network Fund and the North London Deanery.

New collaborations
This project has led to a great strengthening of the collaboration between AHC and the University of Oxford, leading to a number of important research projects and capacity-building initiatives. We are also in active collaboration with the Cambodia-based and US-funded “Diagnostic Laboratory Development Program” (DMDP).

Impact on other research
The development of the microbiology laboratory and associated research projects has catalysed the development of an active research agenda and a whole range of new projects at AHC.

Presentations and publications

In addition, four previous publications have arisen from this project as a result of previous LKS funding (please see the 2007-2010 Final Report). We anticipate several publications from the current funding, principally related to the febrile illness study.

9. DOES STRUCTURED IMPLEMENTATION OF ADAPTED EVIDENCE-BASED INTENSIVE CARE PRACTICE IN RESOURCE-POOR COUNTRIES IMPROVE PERFORMANCE? (LG09)

Investigators
Dr Arjen M Dondorp, Nuffield Department of Clinical Medicine, University of Oxford
Dr Saroj K Mishra, Ispat General Hospital, Rourkela, Orissa, India
Professor Shamsul Alam, Chittagong Medical College Hospital, Chittagong, Bangladesh
Dr Arjun Karki, Patan Hospital, Kathmandu, Nepal

Projects aims
The aims of this project are to
• define an effective implementation tool for cost-effective intensive care therapies and strategies tailored for developing countries
• assess the impact of defined modules of setting tailored therapies and strategies on patient outcome and performance of intensive care

Project progress
The training part of the project consists of six modules, each covering specific aspects of Intensive Care Unit (ICU) care. Training consists of classroom lectures, but the majority of time is spent on bedside training and implementation of the treatment strategies taught during the classroom sessions. As of 1 April 2011 half of the training programme had been completed and it was very well received by the doctors and nurses in all three study sites. During the courses, adjusted guidelines have been developed in close collaboration between trainers and local
staff; an example is an adjusted ‘surviving sepsis’ guideline. Another part of the programme is to assess the success of implementation and to measure the effects of the programme and their specific parts on ICU performance. The aim of the projects is to improve survival. For this purpose, an adjusted severity scoring system had to be developed, in order to measure severity adjusted mortality rates. This scoring system is now close to being finalised.

Additional support secured as a result of this project
Dr Arjen Dondorp and Professor Marcus Schultz have been invited as members of a new working group within the European Society of Intensive Care Medicine on the development of intensive care medicine in developing countries. The group may act as a sounding board for future plans and grant applications, it could also be a source of manpower for future projects. Our next grant application for a follow-up project, planned for the end of 2011, would not have been possible without the current Li Ka Shing award.

New partnerships and collaborations
Close relationships have formed between the Mahidol-Oxford Research Unit, the Academic Medical Centre in Amsterdam and the intensive care units in Ispat Hospital in Rourkela, Orissa, India, Chittagong Medical Centre Hospital in Chittagong, Bangladesh, and Patan Hospital in Kathmandu, Nepal. In addition, the training programme has established strong links between the institutions providing the teachers, including the John Radcliffe Hospital in Oxford, the University of Washington, Seattle, USA, and the Academic Medical Centre in Amsterdam, The Netherlands.

Influencing new studies
The project improves the general standard of ICU care in the participating institutions (Chittagong Medical College Hospital in Chittagong, Ispat Hospital in Rourkela, Orissa, India, and Patan Hospital in Kathmandu), and it will facilitate and improve all other clinical studies that are performed and will be performed there. A concrete example of this is how it helps clinical research in the ICU in Ispat Hospital, where we study the microcirculatory changes in patients with severe malaria using several techniques. If we study correlations between abnormalities and patient outcome, it is obviously important that these patients receive optimal standard care.

Presentations
Dondorp AM. Improving Critical Care Management in Developing Countries – Clinical Practice, Medical Education, Evaluation. East West Alliance Meeting, Winnipeg, Canada, June 2010. There will be many more to follow when the project progresses.
Institutors
Dr Nguyen Van Vinh Chau, Hospital for Tropical Diseases, Vietnam
Ms Katherine Anders, Oxford University Clinical Research Unit, Vietnam
Dr Nguyen Dac Tho, Preventive Medicine Centre HCMC, Vietnam
Dr Phillippe Buchy, Institute Pasteur, Cambodia
Dr Sirenda Vong, Institute Pasteur, Cambodia
Dr Cameron Simmons, Oxford University Clinical Research Unit, Vietnam

Project aims
This project aims to determine the degree to which the risk of dengue in an urban and semi-rural setting is clustered in time and space at the level of the household. In many dengue endemic settings, disease intervention programmes rely on vector control, much of which is reactive and focused around the households of index cases on the assumption that most infections are acquired in the home. What remains poorly understood, particularly in high-incidence, densely populated urban settings with mobile populations of viraemic index cases, is how dengue infection and disease risk is distributed in space and time, and the degree to which households are foci of dengue virus transmission. This project is addressing these questions through a prospective epidemiological study conducted in a high incidence urban setting in Ho Chi Minh City, Vietnam and in a semi-rural setting in Kampong Cham, Cambodia.

Project progress
During the first phase of this study, a collaboration was established between the Oxford University Clinical Research Unit, Vietnam (OUCRU-VN) and the Preventive Medicine Centre in Ho Chi Minh City (PMC HCMC), which is responsible for dengue control activities in the city. Following a four-month period of protocol development and training, enrolment began in October 2010 in HCMC.

Six index cases with a clinical diagnosis of dengue were enrolled at a general practice clinic in central HCMC between October 2010 and January 2011, with PMC staff visiting their homes within 48 hours to enrol family members and neighbours. In total, 176 community participants have been enrolled across the six clusters, of whom 160 (91 per cent) completed the two-week follow-up period. PMC staff collected three finger-tip blood samples from participants at weekly intervals, monitored participants for febrile illnesses, and collected mosquitoes from the houses of index cases. Five of the six index cases had laboratory-confirmed acute dengue, and one had inconclusive serology results that are being investigated further. Preliminary serological results suggestive of recent dengue exposure were observed in 10/176 household and community participants.

Study enrolment in HCMC paused over the dry season, when dengue incidence is low, and continued from June 2011 for two dengue seasons until the sample size of 150 clusters is met.

New collaborations
A new collaboration has been established with the Preventive Medicine Centre HCMC, which is providing expertise in fieldwork and entomological collections for this study.

Influencing new studies
The new partnership between OUCRU-VN and PMC HCMC has resulted in dialogue on potential areas for future applied research on dengue transmission and control in HCMC and southern Vietnam.
The following five Collaborative Research projects were awarded funds in the first year (2010) of the University of Oxford–Li Ka Shing Global Health Programme and began their projects in early 2011; the reports below provide information on each project’s research objectives, background, planned activities and expected outcomes. Results will be reported in next year’s report.

1. **Environmental Stress, Health, and Migration: A Study of the Mekong Delta and Ho Chi Minh City, Vietnam (LG11)**

**Investigators**
Professor Emily Chan, Chinese University of Hong Kong
Ms Jane Chun, Oxford University Clinical Research Unit, Vietnam
Professor Tran Tinh Hien, Oxford University Clinical Research Unit, Vietnam
Dr Peter Horby, Oxford University Clinical Research Unit, Vietnam
Professor Roger Zetter, International Development, University of Oxford

**Project objectives**
The three main objectives of this research are

- to gain empirical knowledge of the management of household assets (in particular health and the human body), and coping and adaptation strategies employed by poorer households that are experiencing environmental stress in Vietnam
- to understand the relationships between household assets, environmental stress, and migration, and identify patterns including cause and effect where possible
- to measure health and migration as benchmark variables within a sustainable livelihoods framework

**Project background**
If scientific forecasts are true, we will witness anthropogenic climate change at a rate and intensity surpassing any in the last 10,000 years of recorded meteorological history. While the necessity for human adaptation to climate change is well-established, its processes are not well understood and infrequently empirically examined.

Most of the existing research on vulnerability to environmental hazards focuses on the economic and physical resource dimensions of livelihoods, while health dimensions remain largely understudied. However, understanding health dynamics is critical to the achievement of human development. Numerous reports and articles have also highlighted that widely varying estimates of people will be displaced due to climate change. While there is a critical need for greater knowledge regarding the relationship between climate change and migration, as well as understanding environmental impacts at the community level, a large evidence gap remains to be filled.

This research will focus on the health, migration, and surrounding socioeconomic effects of environmental change on poor households, with flooding in the Mekong Delta serving as a proxy.

**Planned activities**
The research will have two parallel study sites - one in a rural, migrant-sending area experiencing environmental change / stress in the...
Mekong Delta and one in a poor urban, migrant-receiving area in HCMC. The study will have two complementary groups for data collection. The first will comprise a sample number of 200 households, utilising semi-structured questionnaires. The second group will be a smaller sample of 60 households from the larger group, with data collection carried out by the principal investigator and an interpreter. Collected data will be further analysed and superimposed with GIS and meteorological data to look for any patterns of vulnerability, migration, and health impacts correlating with climate events. Should the generated data from the larger sample of 200 households prove to be sufficient, mathematical modelling will then be used to forecast future scenarios of vulnerability, migration, and health impacts and behaviour for climate scenarios relevant to the selected study sites.

Expected outcomes
Following this research project, we expect to answer the following research questions:

1. How do poor households conceive and operationalise health as a household asset?
2. What is the interaction between environmental stress and the management of assets in poor households?
3. What health and health-seeking strategies do poor households use when exposed to external environmental stress?
4. To what extent is migration a coping and adaptation strategy for poor households exposed to external environmental stress (e.g. flooding, storms, drought), which impacts their health and health seeking objectives?
5. How are health and health-seeking priorities balanced against other household assets in the context of migration strategies?
6. Are there differences between urban and rural decision making and behaviour patterns?

2. Climate change and health in an Asian urban setting: community health risk literacy and response (LG12)

Investigators
Professor Emily Ying Yang Chan, Chinese University of Hong Kong
Dr William B Goggins, Chinese University of Hong Kong
Dr Peter Horby, Oxford University Clinical Research Unit, Vietnam, University of Oxford, Nuffield Department of Clinical Medicine
Ms Jane Chun, Oxford University Clinical Research Unit, Vietnam, University of Oxford, Nuffield Department of Clinical Medicine

Project objectives
The main objective of this project is to examine how the urban environment might affect socio-demographic characteristics, health, and community perceptions to health risk. Specifically, the impact of urban planning and thermal environment will be studied through interdisciplinary scientific efforts. We will aim to identify socio-demographic predicting factors that are associated with the awareness of heat weather warnings.

Project background
While there is mounting evidence of the adverse consequences of global climate change on human health, studies related to its health impact in the urban Asian environment, population mitigation behaviour and responses are very limited. The population of Hong Kong, as a subtropical city, experiences wide seasonal variations in temperature and precipitation, and is reported to have experienced the highest urban ambient temperature increase. A previously published study on temperature-mortality/morbidity model (Chan & Goggins 2010) indicates that mortality is disproportionally associated among socio-demographic characteristics and variation of ambient temperature. In an attempt to mitigate the adverse impact of climate change on health, this research project aims to examine community-based perceptions and associated behaviour responses (e.g. to weather warnings) to climate change and health risk literacy in the urban Chinese population.

The Climate Change and Health study group of the School of Public Health and Primary Care of the Chinese University of Hong Kong was established in July 2007. It is one of the few public health research study teams examining the health impact of, and issues related to, climate change and variability in Hong Kong and the Asia-Pacific Region. The team received a generous donation from the Li Ka Shing Global Health Research Programme (2007-2010) and has gained experience in constructing climate and health outcome models. This proposed project will continue with efforts to examine health risk literacy and community health-related behaviours that might be associated with climate change.
Planned activities
Data will be collected through a general population telephone survey (n=1,000) and community stakeholder interviews. Statistical analysis, e.g. step-wise multiple logistic regression and structural equation modelling (SEM), will also be conducted to examine socio-demographic and behavioural risk factors. Study results will identify socio-demographic population subgroups, their respective sensitivity towards warnings, behaviour changes and the adapted mitigation responses.

Expected outcomes
The study outcome will provide scientific evidence to understand human behaviour associated with climate change. The findings will support public health policy development to mitigate and protect the general public from the adverse health impact of climate change in Asian urban settings. The research team will also conduct knowledge transfer skills workshops, graduate academic training and public seminars to share the technical expertise gained from the research process.

3. THE DEVELOPMENT OF SNP ASSAY FOR TRACKING SHIGELLA SONNEI (A CAUSE OF DYSENTERY) IN THE FIELD (LG13)

Investigators
Dr Ha Vinh, Hospital for Tropical Diseases, Vietnam
Dr Stephen Baker, Oxford University Clinical Research Unit, Vietnam, University of Oxford
Professor Tran Tinh Hien, Oxford University Clinical Research Unit, Vietnam, University of Oxford
Dr Kathryn Holt, Melbourne University, Australia

Project objectives
Each year, over 150 million people, most of them children in developing countries, develop bacillary dysentery (Shigellosis). The majority of cases in Vietnam are caused by a single bacterial clone, Shigella sonnei, which displays a vast repertoire of resistances to antimicrobial drugs. Attempts to trace transmission patterns and the evolution of drug resistance within the S. sonnei population have been hampered by a lack of robust methods for detection and high-resolution subtyping of the pathogen.

We hypothesise that sequence-based approaches to detection and subtyping of S. sonnei will facilitate a better understanding of disease transmission and the evolution of drug resistance, which may be used to improve treatment and prevention regimes.

The specific aims of the project are to:
• develop a high-throughput SNP typing assay for S. sonnei
• apply the SNP assay to study the phylogenetic structure of S. sonnei populations in Vietnam and how this relates to spatial and epidemiological patterns of infections
• use this phylogenetic structure to study the evolution of drug resistance in S. sonnei
• develop a sequence-based assay to detect the presence of S. sonnei and other bacterial agents of dysentery directly from stool samples

Project background
Acute bacillary dysentery (Shigellosis) is a diarrheal disease characterised by severe watery diarrhoea (often blood- or mucous-streaked), abdominal cramping, rectal pain and fever. The major cause of dysentery is a bacteria known as Shigella, for which the clinical infection is named Shigellosis. Humans are the only known reservoir for Shigella, which are transmitted from person to person by the faecal-oral route. Unlike other gastrointestinal pathogens (e.g. Salmonella), ingestion of just a few Shigella bacteria is enough to establish an infection. Antimicrobials shorten the duration of disease, which is important for limiting disease spread, however many infecting organisms are now resistant to multiple antimicrobials. Ninety-nine per cent of the Shigellosis disease burden falls in developing
countries. At the Hospital for Tropical Diseases (HTD) in Ho Chi Minh City (HCMC), Shigellosis is the leading cause of paediatric diarrheal admissions with culture-confirmed bacterial origin. We recently reported an increase in the proportion of Shigellosis cases in HCMC caused by S. sonnei, from 29 per cent in 1995-1996 to 78 per cent in 2007-2008. This appears to mirror the situation in industrialised areas of Thailand, where S. sonnei accounted for 33 per cent of infections in 1993-1994 and 63 per cent-91 per cent in 2000-2006. Thus, this serotype shift may be an indicator of economic change. However, the majority of cases may be culture negative; thus, we do not yet have a complete picture of the etiology or incidence of bacterial dysentery in HCMC.

Planned activities
SNPs will be detected by comparison of whole genome sequences from S. sonnei (including the large virulence plasmid, essential for pathogenesis). It is important that a large sample of genomes is included to avoid the recognised problems of selection bias. In addition to the two finished genome sequences, Ss046 and 53G [68], we are nearing completion of whole genome re-sequencing of 98 HCMC S. sonnei isolates from 1995-2008 with a variety of antimicrobial resistance profiles. SNPs will be identified by comparison to the reference genome (strain 53G) using previously described methods. These SNPs will be used to build a phylogenetic tree for S. sonnei using maximum likelihood phylogenetic inference.

A subset of 100 SNPs will be selected so as to include ≥1 representative SNP from each major branch in the phylogenetic tree, referred to as “canonical SNPs” [69]. The selected SNPs will be separated by at least 100 bp of SNP-free sequence, to minimise potential problems with false positive SNP identification and SNP typing assays. Based on prior experience with S. Typhi we expect that two to three per cent of SNPs detected from Solexa sequence data will be revealed as errors upon validation with an independent SNP typing platform (unpublished data). We have previously used this method in typing S. Typhi [8] and we predict that S. sonnei will display a similar level of variation. Thus, by selecting 100 SNPs and ensuring that major branches of the tree are represented by multiple SNPs, we predict we will retain enough resolution to discriminate within the S. sonnei population even if some SNPs fail to validate, while keeping costs within reason.

Expected outcomes
This project will generate novel insights into the S. sonnei population in Vietnam which may be used to inform preventative and therapeutic interventions. Outputs will include a detailed analysis of the population structure in each location, and, potentially, links between strains and/or drug resistance mechanisms present in both locations. In Vietnam, the genetic data will be combined with epidemiological and spatial data for each S. sonnei infection, which may provide insights into disease transmission. New knowledge of the mechanisms and rate of evolution of drug resistance in S. sonnei in Vietnam may be used to inform the establishment of more effective treatment regimes, e.g. by identifying combinations of therapies that provide barriers to the rapid evolution of resistance.

The SNP typing methodology developed will offer significant improvements in discriminatory power compared to current serotyping and subtyping tools for S. sonnei. Once established, it will be available for use in future studies of disease transmission and resistance and will serve as a model for molecular analysis of pathogen populations in the region. The PCR-based diagnostic assay for bacillary dysentery will generate novel insights into the pathogens causing diarrheal disease in HCMC, which will be informative for targeting research efforts in the future. The assay is expected to offer improved sensitivity and specificity over culture and serotyping and can be used in future studies of diarrheal disease in Vietnam and elsewhere.

4. Enteric fever in Nepal (LG14)

Investigators
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Ms Abhilasha Karkey, Patan Hospital, Nepal
Dr Stephen Baker, Oxford University Clinical Research Unit, Vietnam, University of Oxford
Mr James Campbell, Oxford University Clinical Research Unit, Vietnam, University of Oxford
Dr Christiane Dolecek, Oxford University Clinical Research Unit, Vietnam, University of Oxford

Project objectives
The objective of this project is to conduct a randomised controlled trial (RCT) evaluating the efficacy of gatifloxacin versus ofloxacin in adult and paediatric patients with uncomplicated enteric fever.
Project background
Enteric fever (typhoid and paratyphoid fever) is a systemic infection caused by the bacterium Salmonella enterica serovar Typhi (S.Typhi) or Salmonella enterica serovar Paratyphi (S. paratyphi) which gains access in human beings through faecal oral transmission (Parry, 2002; Bahn, 2005). Today, the vast burden of disease is encountered in the developing world where sanitary conditions remain poor. The best global estimates are of at least 22 million cases of typhoid fever each year, resulting in 200,000 deaths (Crump, 2004). Crucially, these are almost exclusively confined to resource-poor countries. A recent Cochrane review (Thaver) on typhoid treatments underscored the need for large sample size drug interventional trials especially in children, in whom this disease predominates. This study will assess whether or not the new generation fluoroquinolones (Gatifloxacin) improves the clinical outcome of patients with enteric fever.

Planned activities
The study physicians will enrol patients from the outpatient or emergency department of Patan Hospital, Lalitpur, Nepal. Patients with fever for more than three days, who were clinically diagnosed to have enteric fever (undifferentiated fever with no clear focus of infection on preliminary physical exam and laboratory tests), whose residence was in a pre-designated area of approximately 20 square kilometres in urban Lalitpur and who gave fully informed written consent, will be eligible for the study. Exclusion criteria will be pregnancy or lactation, age under two years, weight less than 10 kg, shock, jaundice, gastrointestinal bleeding or any other signs of severe typhoid fever, previous history of hypersensitivity to either of the trial drugs, known previous treatment with a quinolone antibiotic or third generation cephalosporin or macrolide within one week of hospital admission. Patients who have received amoxicillin or cotrimoxazole will be included as long as they did not show evidence of clinical response. Each patient recruited into the study was randomised to treatment with either gatifloxacin 10mg/kg/day in a single oral dose (BroadbandTM, Novartis AG Basel, Switzerland) for seven days or ofloxacin 20mg/kg/day in two divided oral doses for seven days.

Prior to admission to the study, a full history and clinical examination will be taken at Patan hospital and informed written consent obtained from patients who fulfilled inclusion and exclusion criteria. Laboratory tests on day one will include haematocrit, white cell count/differential, platelet count, AST, ALT, creatinine, bilirubin, random blood glucose, and blood stool cultures. Once the study physicians enrol the patient, they will be managed as outpatients.

Expected outcomes
The primary endpoint of this study will be the composite endpoint of treatment failure which consists of
A) persistence of fever of more than 37.5 degrees Celsius at day 10 of treatment
B) the need for rescue treatment with ceftriaxone or ofloxacin as judged by the treating physician
C) microbiological failure, that is a positive blood culture for S. Typhi or S. Paratyphi A on day 8
D) relapse, that is reappearance of culture confirmed (including mismatch of serovars, e.g. day 1 blood culture positive for S. Typhi
and relapse blood culture positive for S. Paratyphi A or vice versa) or syndromic enteric fever on or after day 11 to day 31 in patients who were initially categorised as successfully treated, and
E) occurrence of enteric-fever related complications (gastrointestinal bleeding, fall in the Glasgow Coma Score, perforation of the gastrointestinal tract, or admission to hospital within one month of starting therapy due to a complication thought to be related to enteric fever).

Time to treatment failure is defined as the time from the first dose of treatment until the date of the earliest failure event of that patient, and patients without an event were censored at the date of their last follow-up visit or on day 9 (for culture confirmed patients without a blood culture on day 10).

Secondary endpoints are
A) fever clearance time (FCT) (time from the first dose of treatment given until the temperature was for the first time ≤37.5°C and the patient remained afebrile for at least 48 hours)
B) time to relapse until day 31, day 62, or month 6 of follow-up
C) faecal carriage at the follow up visits at 1, 3 and 6 months. Patients without recorded fever clearance or relapse were censored at the date of their last follow-up.

5. Investigating the evolutionary pathways of SARS-like coronavirus from bats in southern China and Vietnam (LG15)

Investigators
Professor Yi Guan, International Institute of Infection and Immunity, Shantou University, China
Dr Huachen Zhu, International Institute of Infection and Immunity, Shantou University, China
Dr Jia Wang, International Institute of Infection and Immunity, Shantou University, China
Dr Lian Duan, International Institute of Infection and Immunity, Shantou University, China
Professor Jeremy Farrar, Oxford University Clinical Research Unit Vietnam, University of Oxford
Dr Wei Liu, Guangxi Centre for Diseases Control and Prevention, China
Professor David K Smith, International Institute of Infection and Immunity, Shantou University, China

Project objectives
The objectives of this proposal are:
• to understand the evolution of SARS-like-Cov at its natural reservoirs
• to identify whether there are any other bat species which carry SARS-like-Cov
• to understand the evolutionary behaviour of other coronaviruses detected from different bat species

The information generated by this proposal would be vital for fully understanding the emergence pathway of SARS, and to define its whole zoonosis.

Project background
SARS (severe acute respiratory syndrome) was the first emerging infectious disease in the 21st century that caused great epidemics in more than 30 countries in 2003. Etiological studies revealed that SARS was caused by the SARS coronavirus (SARS-Cov). Genetic and epidemiological investigation revealed that SARS-Cov was directly derived from SARS-like coronaviruses (SARS-like-Cov) infecting wild mammals in live markets in the Guangdong region by interspecies transmission. As the sequence identity between SARS-Cov and the SARS-like-Cov from market wild animals was as high as 99.8 per cent over their entire genome, the wild animals were recognised as the infectious source of the disease. This was further confirmed in early 2004 when the second SARS outbreak was averted by removing wildlife from the markets.

Further ecological surveillance studies suggested that bats (Rhinolophus spp.) were very likely the natural reservoirs of SARS-like-Cov, as viruses belonging to this subgroup were found in bats from different regions, including different provinces of China, European countries and even an African country. The most closely related SARS-like-Cov was found in the bats from China (93 per cent identical), while other SARS-like-Cov found in other countries had lower similarity (ranging from 80-90 per cent identical). These findings plausibly suggested that the SARS-Cov was more likely directly derived from the SARS-like-Cov prevalent in bats in China. However, the bats could migrate to different regions, and there were reports to show that many wild animals in Guangdong markets were smuggled into China from south-eastern Asian countries. Thus, we hope to conduct long-term surveillance on bat-borne viruses in southern China and Vietnam.
Planned activities
From 2006 to present, we have collected 5,951 bat oral or rectal swabs; 407 of them were sampled from Rhinolophus spp. bats. All swabs were well stored in -80°C freezers. In 2010, we also set up a GS FLX sequencing system at SUMC. It is feasible to get viral full-length genome sequences by routine sequence techniques or current deep sequencing approaches. We are looking forward to having a novel and deeper understanding of coronavirology and also finding other new viruses that have potential to infect humans.

We will identify two postdoctoral research fellows, two Master’s students, and two technicians from Shantou University who will be funded with this study. We would hope that one of these individuals would be able to apply for PhD training in Global Health during Year Three of this proposal as part of a separate application to the University of Oxford–Li Ka Shing Global Health Programme.

Expected outcomes
We expect to:
1. Understand how the SARS-like-coronavirus evolves in its natural hosts
2. Document the prevalence of SARS-like-coronavirus in specific bat species
3. Understand the evolutionary pressures on SARS-like-coronavirus in different bat species
4. Understand the drives of the emergence of novel coronaviruses in South East Asia.

SEED AWARDS COMMENCING 2010

The following 21 research projects were granted seed awards of up to £5,000 to cover a period of up to one year. Eighteen of the seed grants began their projects during 2010 while four began in early 2011.

The seed awards cover a variety of projects from laboratory and clinical research, retrospective studies, information exchange and software development to workshops and training.

1. PLACE OF CHANGE (SM01)

Investigators
Dr Mary Chambers, Oxford University Clinical Research Unit, Vietnam, University of Oxford
Dr Thuy Chau Tran, Oxford University Clinical Research Unit, Vietnam, University of Oxford
Professor TT Hien Oxford University Clinical Research Unit, Vietnam, University of Oxford
Mr Nicholas Fernandez, Fact, Fiction and Films, Vietnam
Mr Hung Vu, Fact, Fiction and Films, Vietnam

Project aims
The aim of this project is to develop unique, media-led techniques for engaging Vietnamese communities with science and health issues that affect them. The project will encourage deeper thinking on health and science issues within Vietnamese communities not typically connected to health research; it will encourage local participants and audiences to understand and more readily interact with the health concerns most significant in their communities. The project also has a dual purpose in that the stories and media generated by the project can be used to educate and engage broader sectors of the community than those creating the content. It is intended that the final results will be deployed in developed-country settings at junior secondary school level, in the form of an interactive website.

In the short term, we have been building a dedicated skill base in the region to support media engagement for health and science, while also developing and nurturing relationships with appropriate government bodies. These bodies will ultimately support the project by seeking permissions for the project, linking to key audiences/participants, and allowing us to integrate our project with national policy and regional health concerns.

In the medium term, we will begin our community-based activities by working with target groups of participants to build a body of stories that we will develop into an interactive website in the longer term.

Project progress
Since the commencement of this project we have identified the appropriate government partners to develop the
project with and commenced a dialogue about priority areas and themes of investigation. We have also connected with several Non-Governmental Organisations (NGOs) and local organisations with whom we can deliver projects in the field. We have significantly progressed in completing an agreement with the Ho Chi Minh City Health Services Department of Health Information and Education (T4G) that will secure our ability to work in various communities. Together with these bodies, we have made progress in determining the issues and relevant participant groups for the project.

The project has also established a training scheme and coursework to assist in building the right media and engagement skills in Vietnam. We see that such skills have not been readily available locally and we are significantly contributing to local capacity by training young media and health practitioners around public health engagement with media making technologies. To build local government capacity, four staff from T4G will be trained in media engagement skills and will join as facilitators in the project, and will return to their department with a new skill set. We are currently in early stage training with select individuals and we are in the process of scaling up that programme.

Additional support secured as a result of this project
The project has already received a large grant from the Wellcome Trust (WT International Engagement Award), and we are currently in the process of seeking further funds so the project can plan for its long-term goal of becoming an ongoing activity and resource.

New partnerships
The project has led to new partnerships between the key health information unit (T4G) of the central government health services, while also bringing together various NGO community organisations. The project is currently preparing to train government staff in media engagement theory and practice, ensuring a long-term collaboration between the project and the key relevant government body and adding a capacity building element. We are also in discussions about various ways to extend the remit of the project to incorporate a number of other organisations, including a specific interest in a project collaborating with the Oxford University Clinical Research Unit in Ha Noi.

Influencing new studies
Although it is only at a very early stage, the unique and far-reaching potential of this model we have developed through the grant is already encouraging further submissions by us to develop new and specific “micro-projects” to explore different themes. It is intended that we will then be able to plug the results of those projects in to our greater web-based portal. Also, our ongoing discussions with several unit staff are ensuring that similar public engagement activities will already be included in new grant submissions to be decided throughout 2011.
2. Dengue in Africa: the beginning of a new era? (SM02)

Investigators
Dr Cameron Simmons, Oxford University Clinical Research Unit, Vietnam, University of Oxford
Dr Katherine Anders, Oxford University Clinical Research Unit, Vietnam, University of Oxford
Professor Jeremy Farrar, Oxford University Clinical Research Unit, Vietnam, University of Oxford
Professor Joshua Dawurung, WHO National Polio Laboratory, University of Maiduguri, Borno State, Nigeria

With current estimates of 100 million cases annually and 2.5 billion people at risk in tropical and subtropical regions, dengue is one of the most important vector borne diseases, distributed worldwide and a leading cause of morbidity among urban and peri-urban populations of Asia and South America. Dengue encompasses a clinical syndrome characterized by fever, generalized pains, rash, lymphadenopathy, haemostatic dysfunction and a marked increase in vascular permeability leading to plasma leakage and dengue shock syndrome (DSS) with a case fatality rate of 1-5%. The etiologic agents of dengue are the 4 serotypes of dengue virus (DEN) of the Flaviviridae family, genus flavivirus. Infection with one serotype confers long-term protection for that same serotype but secondary infection with a different serotype is hypothesized to lead to severe dengue through antibody dependent enhancement (ADE).

Over the last fifty years dengue has become endemic across most of South and South East Asia and South America and in many countries is the commonest cause of hospital admission during the rainy seasons. However dengue was thought to be rare in Africa, despite the name probably deriving from a Swahili word and the first laboratory confirmed epidemic reported in 1927 (ref) and evidence of DEN circulation traced back to 1845 and 1870 in West Africa and East Africa (ref) respectively. However recent outbreaks suggest that substantial parts of Africa may be at a tipping point in terms of dengue transmission with enhanced activity, increasing severity of cases, changing epidemiology with the introduction of new serotypes and geographic expansion. In the last two years Cote d’Ivoire, Senegal, Mali, Sudan, Benin, Nigeria, Ghana, Togo and Guinea have all reported an increase in the number of patients with dengue and the European Network for Imported Viral Diseases have reported an increase in dengue patients returning from Africa. Between October and December 2009, a major urban dengue 3 epidemic occurred in Cape Verde with 25,000 suspected cases among a total population of 500,000 people. With the recent emergence of dengue 3 virus in West Africa, all four serotypes are now known to be circulating in West Africa. With the unusual transmission dynamics and underlying pathogenesis of dengue driven by the need for the coexistence of multiple serotypes it often takes a few years for dengue to become established in a new community and cause an overt clinical and public health problem. We may have now reached that tipping point.

As part of an overall risk assessment of potential yellow fever epidemics in Africa an entomological survey of urban yellow fever vectors – Aedes aegypti was conducted in several countries between 2004 and 2010. The aquatic stages of Ae. aegypti were sampled in domestic and peridomestic environment in different ecological contexts in the selected cities. These results indicate persistently high levels of Ae. aegypti with risk indices (Bretau index and container index) in all countries consistently over the threshold used to classify them as areas of high risk of dengue transmission.

In many ways the current situation in parts of Africa mirrors the situation in Asia and South America in the 1960s and 1980s respectively with initially isolated reports of relatively limited outbreaks gradually increasing in scale and distribution as the virus becomes increasingly established in the competent vector population. Three other relatively recent changes in Africa may also have contributed to the upsurge in the number of cases of dengue; the massive increase in trade between Asia and Africa over the last decade and hence increased opportunity for the dengue virus and the vector to spread from Asia (the DEN3 virus causing the epidemic in Cape Verde was most like the strain circulating in Cambodia) and the increasing urbanization in many African countries. The principle vector Aedes aegypti is predominately an urban mosquito and the growth of megacities and dramatic demographic shifts serve as the perfect environment for the increased transmission of dengue.

Three potentially unique and important features of dengue transmission in Africa are the coexistence of active sylvatic and epidemic dengue transmission in several countries (Senegal, Cote d’Ivoire, Burkina Faso), the coexistence of multiple other flaviviruses and the high prevalence of other infections. Although the true impact of sylvatic dengue on human health is not completely understood recent data from Asia suggested a link between sylvatic isolates and the outcome of severe dengue (Cardosa, 2008). The dengue outbreak in Mali and Senegal in 2008 highlighted the epidemic character of sylvatic dengue 2 strains. The presence of multiple other flaviviruses including Yellow Fever, West Nile and Zipo complicates the transmission dynamics of infection and complicates diagnostic testing. Although it is well established that comorbidities can worsen the clinical outcome of dengue infection it is unknown what influence coinfection with malaria, TB, HIV, may have on the severity of dengue.
In response to the H1N1 2009 pandemic there has been significant investment in virological diagnostic capacity across much of Africa. This represents an opportunity for enhanced surveillance for dengue through existing laboratory networks already dealing with yellow fever, measles, poliomyelitis and influenza and addressing diagnostics issue in the specific context of high diversity of circulating flaviviruses closely related to dengue. Particularly in the setting of rapidly expanding cities vector control could play a crucial role in reducing the chance of major dengue epidemics. Careful and well organised clinical triage and management is critical in dengue. Experience from major dengue epidemics in New Delhi (1998), Sao Paulo (2008) and Cape Verde (2009) demonstrated the sudden dramatic surge in the number of patients with many requiring labour intensive judicious fluid resuscitation and careful clinical care can easily overwhelm health care facilities and the public health system. Mortality rates during such unexpected surges particularly in areas with little clinical experience of dengue are always high. Epidemics are inevitably accompanied by fear among the public and ensuring the best care is available to those who need it most through established triage systems is critical in ensuring morbidity and mortality is kept to a minimum. This is extraordinarily difficult when faced with an unexpected and unplanned for epidemic and the huge surge in patients that accompanies such outbreaks.

Based on what appears to be increasing transmission of dengue across many parts of Africa it would be timely to give consideration to a systematic risk assessment and seek through vector control, clinical education and public health preparedness to prevent further increases in transmission and the inevitable increase in the number of patients with dengue.

DENGUE IN NIGERIA

Dengue viruses (DENs) are etiologic agents of Dengue. This study was designed to serologically determine the significance of these viruses in febrile illness and provide some of the first systematic data on dengue in Nigeria.

The main objectives were:
1. To epidemiologically obtain base-line information of Dengue infection in Jos, Plateau State Nigeria.
2. To create awareness of and the need for dengue viral diagnosis in the Plateau state Specialist Hospital and other health centres on the Plateau Nigeria.
3. To establish the current status and/or prevalence rate of Dengue fever in febrile cases of unknown origin in patients attending Plateau State Specialist Hospital, Jos Nigeria.

Materials: 283 serum samples from suspected cases of malaria and typhoid were collected in January – December 2009 from patients attending the Plateau state Specialist hospital Plateau State Nigeria. ELISA was used to test all the sera for IgM, IgG and NS1.

Results
The serological evidence of acute dengue virus infection was assessed in 283 sera of male 54 (19%) and female 229 (80%) , with febrile complaints attending the Plateau State Specialist Hospital Jos. The age range of subjects in the study is 2-67 (mean of 33.38±13.85) years. 37 (13.7%) of the sera were positive for Den IgG, 12 (4%) of the sera were positive for IgM and 4 (1.4%) (1.2%) of the sera were positive for NS1. 4 of the sera were both positive for IgG and IgM, 1 serum was positive for both IgG and NS1 and 1 was positive for Both IgM and NS1, while none were positive for all the three (IgM, IgG and NS1).

Conclusion
The prodromal phase of DEN infection could be mistaken for malaria/typhoid. There is a need to include DENs and other endemic arboviruses routinely in the differential diagnosis of febrile illness in Nigeria.

Recommendations
1. Dengue virus routine investigation should be recommended in all hospitals in Nigeria, to enable the early detection and appropriate management for patients
2. A surveillance system should be instituted for dengue virus in Nigeria, in order to create awareness to the public and to aid control.
3. Research work should be establish for dengue virus in Nigeria
4. In order to establish the seasonality of dengue virus infection, we need to begin a study on dengue virus detection during two seasons of the year.

We are deeply grateful to the Li Ka Shing Foundation for their support without which this would not have been possible.
3. RESEARCH ETHICS IN EMERGING INFECTIOUS DISEASES: THE CASE OF INFLUENZA PANDEMIC (SM03)

Investigators
Professor Jeremy Farrar, Oxford University Clinical Research Unit, Vietnam
Professor Michael Parker, Ethox Centre, University of Oxford
Dr Philippe Calain, Medecins sans frontieres, Switzerland
Dr Thuy Le, Oxford University Clinical Research Unit, Vietnam
Ms Nguyen Thi Cam Binh, Oxford University Clinical Research Unit, Vietnam

Project type: Research, exchange and workshops.

Project background
The world faces a number of major global threats including the emergence of epidemic and pandemic infectious diseases, bioterrorism and natural emergencies including earthquakes, tsunamis and climate change. Many of these threats occur in parts of the world which are least able to deal with the consequences.

Conducting crucial medical research in emergency settings presents a range of complex challenges and difficulties including major ethical dilemmas. Guidance on obtaining informed consent for research is included in all international normative guidelines such as Council International Organizations of Medical Sciences (CIOMS), US Food Drug Administration (FDA), Declaration of Helsinki 2008, and the International Conference on Harmonization - Good Clinical Practice (ICH-GCP). However, there is no specific guidance on obtaining informed consent for research in emergency situations and this is often the situation when medical research is absolutely critical.

This project will bring together key partners in Asia and Europe to address these complex issues, including clinicians from Vietnam who have experience in clinical research in epidemics, the ETHOX centre in Oxford, Dr Philippe Calain from Medecins Sans Frontieres, Switzerland and Ms Binh, a DPhil student from Vietnam whose thesis is on Ethics and Emerging Infectious Diseases.

Project aims
The aims of this project are:
• to examine the ethical issues arising during medical research in emergency settings with a focus on infectious diseases including avian influenza, H1N1 influenza, and SARS
• to develop an ethical framework capable of addressing these issues in ways which take account of socio-cultural factors, the broader global perspective and the unpredictable nature of these disease outbreaks

Project progress
Details of work completed:
The first round of interviews consisted of a one-hour exploratory interview with nine study staff involved in H1N1 influenza research projects at the Hospital for Tropical Diseases, Vietnam in July 2010. Eleven unique ethical themes were identified from the interview including: research conduct, resources, review of Institutional Review Board, regulations, guidelines, compensation, recruitment, risk exposure, data and benefit sharing.

An interview strategy and questionnaires have been developed for the second round of interviews. The strategy consists of aims and objectives, methods and research sites. We are currently expanding our interview strategy to a larger number of study staff and to other research sites involved with research in disease outbreaks including H1N1, H5N1 and SARS; the aim of this is to explore new themes using examples from the study staff’s research practice, experience and perspectives. Issues and principles identified from the interviews will determine the main focus of the research project. In addition to this we are gathering information from relevant publications to assist with the study.

Additional support secured
The Li Ka Shing award for this project has provided Ms Nguyen Thi Cam Binh with a strong research basis to apply for a Wellcome Trust Doctoral Studentship at the University of Oxford. The studentship will cover the stipend, travel and research costs, and will act as additional financial support for Ms Binh’s doctoral research project for three years.

New partnerships formed
Partnerships have been formed with the Ethox Centre, University of Oxford; National Institute of Allergy and
Infectious Disease, Toronto; Vietnamese Ministry of Health; Medicine sans Frontiers; and the World Health Organization. We are also hoping to form links with Professor Emily Chan at the Chinese University of Hong Kong. Professor Chan is the Director of the Emergency and Disaster Centre, which involves collaboration between the Chinese University of Hong Kong, the University of Oxford and the Li Ka Shing Foundation.

Impact on other research
This project has stimulated a workshop on Research Ethics in Public Health Emergencies, which is due to be held in Geneva in February 2012; it will ensure ethical issues are central to the development of new paradigms for health research in rapidly emerging problems.

Presentations
Academic meeting at Oxford University Clinical Research Unit, Vietnam (OUCRU) 24 May 2010
Human genetics group presentation at OUCRU 12 January 2011

4. ROLE OF GATIFLOXACIN IN ENTERIC FEVER AND TUBERCULOSIS (SM04)

Investigators
Dr Buddha Basnyat, Patan Academy of Health Sciences, Kathmandu, Nepal
Dr Christiane Dolecek, Oxford University Clinical Research Unit, Vietnam

Project aims
The world is struggling with the spread of drug resistance and few new and affordable antibiotics have been developed over the last 30 years. This is a particular problem for the resource-poor world and we should therefore be particularly careful about discarding effective and affordable antibiotics unless their safety profile demands their withdrawal.

Recently, we have demonstrated that for young people with multidrug resistant typhoid fever, gatifloxacin is an effective and safe drug. Typhoid fever affects 22 million mostly young people annually, and resistance has developed against all the traditional treatments. Gatifloxacin has been shown to be effective and is used in clinical trials for the treatment of typhoid, tuberculosis and multidrug resistant shigellosis.

Shortly after gatifloxacin was introduced, reports of effects on glucose homeostasis began to emerge showing that gatifloxacin’s dysglycemic adverse effect profile varies in different settings.

We believe this drug should continue to be made available for young patients at low risk of adverse effects, but we should be very cautious about discarding safe and effective antibiotics based on adverse events in different patient populations. Unfortunately there are not many effective, safe and affordable antibiotics available to us.

Project progress
Enteric fever (Salmonella Typhi and S. Paratyphi) affects approximately 26 million (mostly) young people annually. Resistance has developed against all the traditional treatments and there are few options that both treat the patient effectively and prevent long term carriage.

Our research shows that:
- multidrug resistance (MDR – resistance to chloramphenicol, ampicillin and trimethoprim/sulfamethoxazole) is widespread; nalidixic acid resistance also occurs. Resistance causes higher failure rates and prolonged carriage, thus protracted infectivity.
- gatifloxacin can be applied universally in all endemic areas, irrespective of Salmonella susceptibility profiles. A seven-day gatifloxacin treatment is effective, safe and cost-effective.

This claim is supported by:
- in vitro, clinical (randomised controlled trials, RDTs and meta-analysis) and pharmacological (pharmacokinetics/pharmacodynamics, PK/PD) evidence that gatifloxacin is effective for the treatment of enteric fever, including multi-drug resistant and nalidixic acid resistant strains
- safety information based on RDTs of enteric fever and longer exposure for the treatment of tuberculosis
- cost and cost-effectiveness data – gatifloxacin is the least expensive option for treating enteric fever
A dossier on our findings has recently been submitted to the World Health Organization (WHO) on the use of gatifloxacin.

**Other support secured**
We hope to secure funding to develop new WHO Guidelines on the treatment of typhoid fever from the National Institute of Health or the Bill and Melinda Gates Foundation.

**New partnerships formed**
We have formed new partnerships between Patan Academy of Health Sciences, Nepal Health Research Council and the Public Health Foundation of Nepal, Vietnam, the World Health Organization, Liverpool University and the Cochrane Reviews.

**Impact on other research**
This project has influenced the recent Cochrane Review on the treatment of typhoid fever.

**Publications and presentations**

Thapa SD, Koirala KD. ‘Health in South East Asia’. *Lancet* 2011 May;377;1571.

Submission to the 18th Expert Committee on the Selection and Use of Essential Medicines on the availability of gatifloxacin in the essential medicines list of the World Health Organization.

**5. Evaluation of artemisinin-based combination treatments in an in-vitro model (SM05)**

**Investigators**
Dr Hoan Phu Nguyen, Hospital for Tropical Diseases, Vietnam  
Professor Tran Tinh Hien, Oxford University Clinical Research Unit, Vietnam  
Dr Christiane Dolecek, Oxford University Clinical Research Unit, Vietnam  
Dr Nguyen Than Thuy Nhien, Oxford University Clinical Research Unit, Vietnam

**Collaborators**
Professor Piero Olliaro, World Health Organization, Switzerland  
Dr Boubakar Ba, Université Victor Segalen Bordeaux2, France  
Professor Pascal Millet, Université Victor Segalen Bordeaux2, France  
Dr Karen Gaudin, Université Victor Segalen Bordeaux2, France
The overall objectives of this project are:

- to develop an in vitro pharmacokinetic/pharmacodynamic model that will allow the estimation of antimalarial activity of drug combinations
- to adapt current device control software to the simulation of drugs combination, taking into account the individual pharmacokinetic profile of each drug

Malarial treatment today is not based on solid pharmacological grounds. The selection of the components and the dosages for combination therapies is largely empirical. One of the reasons for this is the lack of convenient experimental models. Conventional static in vitro methods for the assessment of antimalarial activity can inform on dose treatment efficacy but not about dosage regimens, which requires a dynamic approach. In addition, animal models do not truly reflect human pharmacokinetics, because they have low-throughput and their use has ethical limitations.

In vitro pharmacokinetic/pharmacodynamic (PK/PD) models could be an alternative tool for these drawbacks and may allow us to identify and optimise drug combination and hence improve treatment regimens. The in vitro (PK/PD) model was developed and validated in our laboratory at the University of Bordeaux for antibiotic monotherapies; it is a two-compartment kinetic model designed to expose bacteria to varying antibiotic concentrations. The central compartment (CCp) consists in a thermostatable flask, containing the culture broth, tubing and the lumina of the capillaries within a disposable dialyser unit. The peripheral compartment (PCp) is in an extra-capillary space of the dialyser unit plus tubing, where the bacterial inoculum is confined. A computer-controlled peristaltic pump provides a fast equilibrium of antibiotic concentration between the CCP and the PCp in order to simulate blood levels in the PCp. Broth flow into and out of the CCP is adjusted according to reference pharmacokinetic parameters of the drug under investigation. Computerisation of pump speed control enables simulation of a multiexponential pharmacokinetic profile. Both intravenous and oral administrations are simulated using the same computer-controlled syringe pump. The system works using self-developed software.

Planned activities

On the basis of the existing model, we propose to develop a new system for *P. falciparum* using continuous cultivation and antimalarial drug combinations. We will develop mathematical models for programmable syringes to deliver drugs based upon the entire pharmacokinetic profile of each antimalarial drug for all the usual routes of drug administration. We will adapt current device control software for combination therapies.

We hope that the new model will be a tool for identifying and optimising combination treatments for subsequent clinical investigation.
6. ENVIRONMENTAL CHANGE, URBANISATION AND ITS EFFECT ON HEALTH IN ASIA (SM06)

Investigators
Professor Emily Chan, Chinese University of Hong Kong
Ms Jane Chun, Oxford University Clinical Research Unit, Vietnam
Professor Tran Tinh Hien, Oxford University Clinical Research Unit, Vietnam
Dr Peter Horby, Oxford University Clinical Research Unit, Vietnam

Project background
If scientific forecasts are true, we will witness anthropogenic climate change at a rate and intensity surpassing any in the last 10,000 years of recorded meteorological history. While the necessity for human adaptation to climate change is well-established, its processes are not well understood and infrequently examined.

Much of the existing research on vulnerability to environmental hazards focuses on the economic and physical resource dimensions of livelihoods, while health dimensions remain largely understudied. Understanding health dynamics is critical to the achievement of human development. Numerous reports and articles have also highlighted that varying estimates of people will be displaced due to climate change. This shows there is a critical need for a better understanding of the relationship between climate change and migration.

Project aims
The aim of this project is to understand the health, migration, and surrounding socioeconomic effects of environmental change on poor households in Vietnam. The project seeks to gain empirical knowledge of the management of household assets (in particular health and the human body), and coping and adaptation strategies employed by poor households experiencing environmental stress. We also aim to identify how policy makers and service providers can best intervene to improve the health and livelihoods of poor households.

Project progress
We have formed a partnership with the International Federation of the Red Cross (IFRC) who have enabled us to secure access to study sites and communities. In return, the data we collect from the study will be shared with the IFRC and Vietnam Red Cross to support their intervention for disaster-prone communities. A 27-page questionnaire has been developed and translated into Vietnamese, and study sites narrowed down to Ben Tre province and Ho Chi Minh City.

The award has also enabled Ms Jane Chun to attend conferences and workshops which have allowed her to keep up-to-date with the latest research in this field, exchange ideas and form new partnerships.
7. URBAN VULNERABILITY TO EPIDEMIC DISEASES IN THE RED RIVER, MEKONG AND PEARL RIVER DELTAS (SM07)

Investigators
Dr Peter Horby, Oxford University Clinical Research Unit, Hanoi, Vietnam
Professor Emily Ying Yang Chan, Chinese University of Hong Kong

Project aims
More than half of the world’s population lives in the Asia Pacific region; a region that is experiencing an unprecedented period of economic, environmental and social change. Rapid economic development has brought many benefits, but has also resulted in widening inequalities, environmental degradation, migration, urbanisation and social disruption. All of these factors have been clearly linked to the emergence of infectious diseases. River deltas are especially vulnerable to these forces as they attract a concentration of populations, industry and agriculture and are acutely vulnerable to the effects of climate change.

The Mekong River Delta in southern Vietnam, the Red River Delta in northern Vietnam and the Pearl River Delta in southern China together are home to over 90 million people and contain the rapidly evolving cities of Ho Chi Minh City, Hanoi, and Guangzhou. We are developing a proposal to conduct interdisciplinary research on the vulnerability of major cities in Asia to epidemic infectious diseases. Our goal is to develop a theoretical model of urban vulnerability to epidemic infectious diseases and to use this model to inform the design and testing of multi-faceted intervention packages.

This preliminary research phase will focus on developing inter-disciplinary partnerships, engaging stakeholders, defining key issues and research questions, and formulating an inter-disciplinary methodology.

Project progress
In August 2010, Dr Peter Horby visited Professor Tony McMichael, David Harley, and Colin Butler, of the Australian National University, and Simon Hales, of the University of Otago, Wellington. Professor McMichael is a leading authority on the impact of climate change on health and the visit successfully established an academic link with his research group.

In September 2010, Dr Horby and Professor Emily Chan met in Hong Kong to develop the project concept; and in April 2011, Professor Nguyen Tran Hien, Director of the National Institute of Hygiene and Epidemiology, Vietnam, travelled to the UK to meet with the UK Health Protection Agency to establish and strengthen research links between Vietnam and the UK.
Presentations and publications
Invited presentation: Effects of Climate Change and Urbanisation on Infectious Diseases at the UK-South East Asia Expert Meeting, 29 June 2010, Ho Chi Minh City, Vietnam.

Our work was also used as course content for training courses on Climate Change and Health and Urbanisation and Health at Shantou University Medical College, 11-12 January 2011.

8. AN EVALUATION OF DIAGNOSTIC TESTS FOR COMMON CAUSES OF FEVER IN THE TROPICS (SM08)

Investigators
Dr Paul Turner, Shoklo Malaria Research Unit, Thailand
Ms Wanitda Watthanaworawit, Shoklo Malaria Research Unit, Thailand
Dr Claudia Turner, Shoklo Malaria Research Unit, Thailand
Professor Francois Nosten, Shoklo Malaria Research Unit, Thailand
Dr Stuart Blacksell, Mahidol-Oxford Tropical Medicine Research Unit, Thailand

Project aims
The aim of this project is to assess diagnostic tests for common tropical infections, including dengue, leptospirosis and scrub typhus; it will focus on tests which can be used to rapidly guide clinicians in the field.

Around 1,000 patients will be recruited from three rural clinics on the Thailand-Burma border who have a fever with no clear cause. Blood samples will be collected from these patients and will be tested using “gold-standard” reference assays to determine the cause(s) of fever. These samples will then be used to evaluate new rapid diagnostic tests,
including bedside tests and rapid laboratory-based tests.

**Project progress**
Having received ethical approval to conduct the study from Mahidol and Oxford Universities, we started the recruitment of patients in March 2011.

Sample collection and testing is proceeding well and the culture of blood to identify bacterial causes of fever, along with blood count, c-reactive protein measurement, and rapid testing for dengue virus infection is occurring in real time. Further testing for dengue virus, murine and scrib typhus, and leptospirosis by rapid test, PCR (detection of pathogen genes), and serology (detection of antibodies) started in April 2011.

In addition, a bank of previously collected specimens from 152 patients with suspected dengue infection was used to assess a bedside dengue rapid test (SD Dengue Duo). In this small evaluation, the rapid bedside test did not perform as well as PCR detection of dengue virus (sensitivity 48 per cent vs 89 per cent), and a larger evaluation is currently ongoing.

**New partnerships and collaborations**
As a result of setting up this fever study, we have been able to establish a link with a US biotechnology company (Idaho Technologies Inc) and are testing a field-deployable PCR system to improve the diagnosis of scrub typhus.

9. AN EVALUATION OF METHODS TO DETECT NASAL CARRIAGE OF PNEUMONIA-CAUSING BACTERIA IN YOUNG INFANTS (SM09)

** Investigators**
Dr Paul Turner, Shoklo Malaria Research Unit, Thailand  
Ms Auscharee Jankhot, Shoklo Malaria Research Unit, Thailand  
Dr Claudia Turner, Shoklo Malaria Research Unit, Thailand  
Professor Francois Nosten, Shoklo Malaria Research Unit, Thailand

**Project background**
The bacterium Streptococcus pneumoniae (the pneumococcus) is a leading cause of childhood pneumonia and death globally. There are >90 pneumococcal types but only 7-13 can be prevented by current vaccines. Pneumococcus is always carried in the back of the nose (nasopharynx) before causing disease. Multiple pneumococcal types may be carried in the nasopharynx concurrently, and the use of vaccines promotes carriage and disease by previously unusual types. Understanding how different types of pneumococci interact in the nasopharynx is important to predict the outcomes of vaccination and to develop new vaccine strategies based on elimination of carriage.

Pilot work at Shoklo Malaria Research Unit has demonstrated that a cheap rapid pneumococcal typing method based on latex agglutination can be applied to nasopharyngeal swab (NPS) cultures to detect carriage of more than one
pneumococcal type, and that this method performs well compared to sophisticated molecular techniques.

This study will further evaluate the latex typing method on more than 8,000 longitudinal NPS specimens (from approximately 300 infants with monthly swabs from one month until 24 months of age) collected as part of the SMRU pneumococcal carriage study.

**Project aims**

We aim to conduct a large scale evaluation of a latex agglutination sweep method in order to determine the dynamics of carriage of the bacterium *Streptococcus pneumoniae*, one of the most important causes of childhood pneumonia globally, in a cohort of infants living on the Thailand-Burma border.

In the short term, this project aims to establish whether traditional methods used to determine the carriage of this bacterium are inadequate to identify the concurrent carriage of more than one serotype of this bacterium (of which, there are over 90 serotypes circulating). The medium-term goal of this project is to improve the understanding of nasopharyngeal carriage of this bacterium in infancy, which may influence immunisation development and strategy.

**Project progress**

The project is proceeding extremely well. The Shoklo Malaria Research Unit (SMRU) microbiology laboratory staff have optimised the latex agglutination sweep methodology for high-throughput work and to date over 3,500 specimens have been processed out of a total of around 8,500 planned. The interim results are very promising: significantly more episodes of multiple pneumococcal serotype colonisation have been detected using the latex agglutination sweep method compared to the standard culture method. This data is important and will permit a re-evaluation of our understanding of how this bacterium interacts with young infants. The method is very easy to perform and is extremely cost-effective compared with conventional culture, identification, and serotyping.

**Impact on other research**

Data generated from this study will be used in planned pneumococcal carriage modelling work.

### 10. Improving detection of a bacteria carried in the birth canal of women that can cause life threatening infections in new-born infants (SM10)

**Investigators**

Dr Claudia Turner, Shoklo Malaria Research Unit, Thailand  
Ms Linda Po, Shoklo Malaria Research Unit, Thailand  
Dr Paul Turner, Shoklo Malaria Research Unit, Thailand  
Professor Francois Nosten, Shoklo Malaria Research Unit, Thailand

**Project background**

Each year, four million infants less than four weeks of age die, approximately one third of these die from severe infections. Group B Streptococcus (GBS) causes the majority of neonatal infections in the developed world but its impact in the developing world is unknown. To cause an infection in an infant less than seven days of age, GBS must be carried by an expectant mother. If a mother is known to carry GBS she can receive antibiotics in labour which can prevent an infection. In Europe approximately 20 per cent of women carry GBS. Data about the number of women carrying GBS in South East Asia is lacking.

**Project aims**

The aim of this project is to improve the detection of Group B streptococcus (GBS). In a previous study a vaginal rectal swab was taken from 549 women and cultured for GBS using conventional microbiological methods (growing GBS in an incubator). For this project, we carried out more sensitive molecular tests - Polymerase Chain Reaction (PCR) – which look for the DNA from GBS in these swab cultures, thus giving us a more accurate picture of how many women carry this bacteria and how many infants are at risk.

In the short term, this study has enabled us to build capacity in the laboratory so that we now have the ability to detect GBS by PCR. In the medium term, this study means that we will be able to undertake further analysis to determine whether any intervention should be introduced to reduce infants’ risk of infection with GBS.
**Project progress**
The laboratory identified previously described methods for extraction of GBS DNA and PCR, and adapted these for use in the SMRU laboratory. The methods were evaluated with mock specimens before testing patient specimens. In total, 549 frozen swab cultures were re-tested by PCR and 66 were found to be positive for GBS. This was 29 per cent more GBS than previously found using conventional microbiological techniques. Using the new technique (PCR) we found 19 more positive swabs than we found when using the old technique (culture). Prior to this project the GBS carriage rate in the population was calculated to be nine per cent, but with the extra data from the PCR we now know the true carriage rate to be 12 per cent.

**Impact on other research**
This project has added more accurate data to the GBS carriage study and neonatal sepsis study undertaken at Maela Camp for displaced persons on the Thai-Myanmar border.

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**11. Mapping the epidemiology of tropical diseases (SM11)**

**Investigators**
Dr Richard Maude, Mahidol-Oxford Research Unit, Tropical Medicine, University of Oxford  
Dr Wirichada Pan-ngum, Department of Hygiene, Faculty of Tropical Medicine, Mahidol University

**Collaborating institutions**
Bureau of Epidemiology Department of Disease Control, Thai Ministry of Public Health, Thailand  
Cambodia National Malaria Control Programme, Cambodia  
Malaria Research Group of Chittagong, Bangladesh

**Project background**
The transmission and incidence of infectious diseases in the tropics (e.g. malaria and dengue) are highly spatially heterogeneous and dependent on many interacting factors from the environment, population density and behaviour. Spatial data has been collected in many tropical areas including Thailand, Cambodia and Bangladesh. The Geographic Information System (GIS) provides a platform for managing this data. High skills are required in order to visualise, manage and analyse data. We therefore identify a training requirement for working with GIS data in spatial analysis.

**Project aims**
The aim of this project is for two members of the Mahidol-Oxford Research Unit (MORU) mathematical modelling team to undergo training in Geographical Information Systems (GIS) data manipulation and subsequently train the rest of the modelling team.

The award will also support the purchase of software licenses for the GIS software packages. In the short term, the new skills acquired will be used for analysis and manipulation of spatial data, and in the medium term to produce transmission dynamic models of various infectious diseases, particularly malaria, in Thailand, Cambodia and Bangladesh.
In the medium to long term, GIS mapping will be used to communicate mathematical modelling results to health policy makers more effectively, and will help to identify gaps in epidemiological knowledge required for effective control of infectious diseases.

**Project progress**
The grant was spent on the attendance of two team members at GIS training courses, both at regional and international levels. The members learned extensive concepts of GIS from introductory data manipulation to advanced data analysis. Subsequently, the rest of the team members have been trained.

National malaria surveillance data for Cambodia has been analysed and manipulated using ARC GIS for parameterisation of a spatial model of malaria elimination, which is currently under development.

Government data on monthly malaria incidence, the results of new studies on the distribution of severe malaria in the southeast of Bangladesh and the geographical extent of seropositivity for melioid, scrub typhus and murine typhus in Bangladesh are currently being analysed and distribution maps produced using the software. These maps will be the first maps produced for Bangladesh. We are planning to apply GIS technology to further modelling work, both for inputting GIS data to mathematical models and showing model results with GIS mapping.

**Additional support secured**
The modelling and data analysis which GIS has enabled us to do is ongoing, and we envisage that it will greatly strengthen future applications for funding – both by increasing the validity of mathematical models through the incorporation of spatial heterogeneity and by greatly increasing the impact of modelling results by presentation in a map format.

**Impact on other research**
This project has influenced the analysis of the seroprevalence study by adding mapping of the geographical distributions and analysis to identify clustering of seropositive individuals. This is facilitating identification of ‘hot spots’ for further intensive study. GIS mapping of the changing distribution of malaria in Bangladesh over time is providing valuable insights on the effectiveness of the patient referral system and local malaria control activities. It is anticipated that this will influence malaria control planning and will be used to help parameterise models of malaria control/elimination and severe malaria management.

A project entitled “The impact of population movement in a Thai setting for epidemiological studies” has already started with the hope that the model outcomes would be expressed as GIS mapping. This would be relevant to designing national health policies.

**Presentations**
Severe malaria in Bangladesh. 13th ASCON meeting, Dhaka, 14-17 March 2011.
12. The impact of a globally common blood disorder (G6PD deficiency) that causes the breakdown of red blood cells in the new-born period (SM12)

Investigators
Dr Claudia Turner, Shoklo Malaria Research Unit, Thailand
Ms Raweewan Somsakchaicharoen, Shoklo Malaria Research Unit, Thailand
Dr Germana Bancone, Shoklo Malaria Research Unit, Thailand
Professor Francois Nosten, Shoklo Malaria Research Unit, Thailand

Project background
G6PD deficiency is an inherited blood disorder that affects more than 400 million people worldwide and can cause serious illness in the new-born period. The most common presentation in the new-born period is with jaundice. If the level of jaundice in an infant reaches a critical level, it can cause brain damage and death.

Project aims
The aim of this study is to determine the number of people in the population of refugees living in Maela Camp on the Thai-Myanmar border for displaced persons who have G6PD deficiency. In addition, we will investigate how many of the infants with G6PD deficiency need to be admitted to hospital in the first few weeks of life, and we will compare this with the number of infants who are admitted to hospital who do not have G6PD deficiency.

Project progress
The screening for G6PD deficiency began on 1 January 2011 and so far 250 infants have been tested (98 per cent of all the infants who were born to mothers following antenatal care at SMRU). Eighteen infants have been found to be deficient – seven per cent of all tested. Seven (38.9 per cent) infants who were found to be G6PD deficient needed to be admitted to hospital for the treatment of jaundice, an infant with G6PD deficiency was three times more likely to be admitted to hospital than an infant without G6PD deficiency.

Impact on other research
This project has identified the need for a more detailed study on the effect of G6PD deficiency in the neonatal period.
13. Experience of the members of the Tak Province Community Ethics Advisory Board — a qualitative study (SM13)

Investigators
Dr Phaik Yeong Cheah, Mahidol Oxford Research Unit, Tropical Medicine, Nuffield Department of Medicine, University of Oxford
Dr Khin Maung Lwin, Shoklo Malaria Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok Thailand
Dr Phaik Kin Cheah, Faculty of Arts and Social Sciences, University Tunku Abdul Rahman, Kampar, Malaysia
Professor Francois Nosten, Shoklo Malaria Research Unit, Mahidol Oxford Research Unit, Tropical Medicine, Nuffield Department of Medicine, University of Oxford

Project background and aims
The Shoklo Malaria Research Unit has been providing healthcare and conducting research on the Thai-Burmese border for many years. In January 2009, we formalised this process by facilitating the set-up of the Tak Province Border Community Ethics Advisory Board (T-CAB).

The objective of the T-CAB is to provide advice to researchers in the border area so that research activities can respond to the needs of the community while adhering to community standards and sensitivities.

The aim of this project is to understand the experiences of the T-CAB members to improve the effectiveness of the T-CAB in the future. The overall aim can be broadly broken down to three objectives:

• what are the motivations for serving in the T-CAB?
• what are the challenges given the risks involved and instability of the border?
• what strategies can be used to overcome these challenges?

The short-term impact of this project is the development of an action plan to improve the effectiveness of the T-CAB. The medium-term impact is the potential increase in the effectiveness of the T-CAB in helping researchers to develop study programmes that are responsive to the needs of the border community while adhering to community standards and sensitivities (i.e. the main objective of the T-CAB).

Project progress
Each T-CAB member who consented (12 of a total 14 members) was interviewed in their preferred language (Burmese or Karen). All the interview transcripts have been translated into English. (A copy may be viewed in the Appendix.)
Preliminary analysis suggests that:
1) Motivations: The members feel that being a member is beneficial to themselves, their families and their communities; they act as a bridge between medical researchers and the community, and they help to improve health literacy in their communities
2) Challenges: The fact that there is no singular common language in the T-CAB, hence there are multiple translations in each meeting; because the T-CAB members come from a wide geographical area, it is difficult to have frequent meetings; and there is a lack of medical/health knowledge.
3) To overcome these challenges: Change the membership criteria to include the ability to read and write in the chosen T-CAB language, whatever it may be; develop geographical clusters; introduce more training and capacity building activities to enhance the members’ health and research knowledge; and organise visits between sites.

Additional support secured
The Li Ka Shing award enabled us to provide background data on the T-CAB to form part of a Wellcome Trust Strategic Award application. The application includes funds for the capacity building and development of the T-CAB.

New partnerships and collaborations
This project has strengthened existing partnerships with, for example, the Ethox Centre, University of Oxford. Additionally, we are collaborating with the Faculty of Arts and Social Sciences, University Tunku Abdul Rahman, Kampar, Malaysia for the first time. A potential collaborator for future studies is the Forum for Ethical Review Committees in Asia and the Western Pacific Region (FERCAP).

Impact on other research
A new project is underway on the development of a tool for evaluating the effectiveness of community engagement and utilising the tool to evaluate the effectiveness of the T-CAB. The investigators for this study are: Khin Maung Lwin, Phaik Yeong Cheah, Francois Nosten, and Michael Parker.

Presentations and publications
Lwin KM, Cheah PY, Cheah PK, Nosten FN. Experience of the members of the Tak Province Border Community Ethics Advisory Board, abstract provisionally accepted at the FERCAP annual conference, Daegu, Korea, November 2011. Preliminary results were presented at the Workshop on Consent & Community Engagement in Research, Kilifi, Kenya in March 2011.

14. Development of open access clinical trials networks for clinical investigators in infections of the central nervous system and enteric infections (SM15)

Investigators
Professor Tran Tinh Hien, Oxford University Clinical Research Unit, Vietnam
Dr Ho Dang Trung Nghia, Hospital for Tropical Diseases and Oxford University Research Unit, Vietnam
Dr Jeremy Day, Oxford University Clinical Research Unit, Vietnam

Project type: Series of workshops and Internet development of online tools and resources.

Project background
Clinical trials are needed to improve public health as they allow the development and testing of new drugs and vaccines. They are fundamental for those who manage health as they allow treatment to be guided by evidence. Therefore trials based in developing countries offer the greatest potential as these regions have the greatest need as disease brings the largest burdens. However to initiate clinical research studies is becoming increasingly difficult. The development of a new study requires a great deal of time and effort developing the protocol, Case Record Forms, etc. and there are no standardised documents available.

Project aims
This project aims to increase the evidence base for treating central nervous system (CNS) infections by improving clinical trial design. The project aims to do this through increasing inter-investigator dialogue, identifying common research themes, identifying key methodologies and outcome measures, and increasing access to essential trial materials and tools in order to enable research to be done more effectively.
These workshops focused on CNS and enteric infections will bring together people from around the world to develop standard approaches to clinical trials. We hope to link with the Global Health Trials initiative led by Dr Trudie Lang, University of Oxford, and we anticipate this will lead to building an internet based resource for clinical researchers globally.

Project progress
Forty international researchers from Asia, South America, Europe, Africa and North America were invited to attend the inaugural meeting in Berlin in November 2010. All were enthusiastic and almost 30 attended. Professor Charles Warlow led the opening session and recounted his experiences of small and large national and international clinical trials in neurological disease. He emphasised the importance of the interplay between basic and clinical science, and the complementary and overlapping skill sets of basic and clinical scientists. Trudie Lang gave an excellent talk detailing the open access resources that are being developed for trialists through Oxford University, and Friedrich Theinemann demonstrated an electronic and comprehensive database that he has developed for capturing a wide variety of different clinical and laboratory data in differing formats. Following this there were short presentations where researchers presented their latest findings, and a lively discussion session.

Additional support secured
This meeting has led to one multicentre trial proposal that is currently under funding review.

Impact on other research
Relationships forged at this meeting have led to cooperation on multicentre trials and may lead to further collaboration in the areas of TB meningitis in children and encephalitis.

15. ‘Indivaria’: a computational software platform for studying the dynamics of malaria parasites in an infected patient (SM18)

Investigators
Dr Lisa White, Mahidol-Oxford Research Unit, Nuffield Department of Medicine, University of Oxford
Mr Sompob Saralamba, Mahidol-Oxford Research Unit, Mahidol University, Thailand
Mr Nantasit Luangasanatip, Mahidol-Oxford Research Unit, Mahidol University, Thailand

Project aims
With the present knowledge of malaria, we are able to estimate the number of parasites in a patient before and during treatment by using mathematical models. Mathematical models are used to study many aspects of malaria parasites to improve treatment.

The aim of this project is to form a collection of published models for the dynamics of malaria parasites in an infected patient before and during treatment with antimalarial drugs. The collection will be presented in the form of a computer software package which will allow the user to choose a model and apply it to a specific problem using their own data, such as parasite count data and drug concentration.

In the short term, some models for artemisinin resistance and dormancy will be tested using data from clinical trials at Pailin, Cambodia and Maesot, Thailand. In the medium term, the software will be used to study the dynamics of malaria parasites in a patient.
Project progress
The project has been progressing well; it can be divided into three main sequential stages:
1) literature review
2) coding and testing the computer programme
3) writing the programme manual.

A computer server and mathematical software were purchased at the start of the project and the main structure of the computer programme has been designed and written. Some published mathematical models for malaria parasite dynamics in an infected patient before and during treatment with antimalarial drugs were reviewed and implemented into the computer programme. The programme now has 20 models and is at the beta-testing stage.

Additional support secured
This award has contributed to preliminary work for an application for further funding to the AXA research fund with a decision expected in November 2011.

New partnerships formed
New collaborations have formed with Dr Julie Simpson from the University of Melbourne and with Dr Kasia Stepniewska from the Worldwide Antimalarial Resistance Network (WWARN) on the modelling of artemisinin resistance.

Publications and presentations

Saralamba et al., ‘Can dormancy explain prolonged parasite clearance time observed in Pailin?’ Poster presented at Oxford Tropical Network Meeting 2011, Vientiane, Laos.

16. The correlation of host genotype to disease susceptibility phenotype using a healthy cohort of Vietnamese adults (SM19)

Investigators
Ms Nguyen Thi Quynh Nhu, Oxford University Research Unit, Hospital for Tropical Diseases, Vietnam
Dr Maxine Caws, Oxford University Clinical Research Unit, University of Oxford, Vietnam
Dr Sarah Dunstan, Oxford University Clinical Research Unit, University of Oxford, Vietnam
Dr Guy Thwaites, Imperial College London, UK

Aim of the project
The aim of this Li Ka Shing seed award was to purchase a CO2 incubator to use in our Category III biosafety facility for a specific separately funded project. The aim of the project was to study the combined effect of the host and mycobacterial genotype on the innate immune response to Mycobacterium tuberculosis (M.tb) infection. The primary objectives of the project were:

- to examine whether macrophage gene expression levels, or other markers of gene function, ie. cytokine expression, following Mtb infection can be related to a specific host genotype
- to examine the relationship between the macrophage response to different bacterial lineages of M.tb and the host genotype

Understanding both the roles of human and bacterial genetic variation in the innate immune response to TB is central to
determining the mechanisms responsible for protective immunity.

The main impact of the Li Ka Shing funding is that we are now adequately resourced to perform cellular assays of M.tb infection, which previously we were unable to do due to the lack of appropriate equipment within the Category III bio-safety laboratory. During this project, partners from Imperial College in the UK came to OUCRU and trained Vietnamese investigators (Nguyen Thi Quynh Nhu and Nguyen Thuy Hang) in the necessary techniques to perform these cellular studies of TB.

**Project progress**
Since the start of this project, we have recruited 100 healthy volunteers to participate in our study. We have genotyped the host DNA from these volunteers and have currently performed M.tb infections of cultured primary cells from 29 volunteers. We have infected these primary cells (monocyte derived macrophages) with six different strains of M.tb representing three different bacterial lineages. We are assessing the cellular activation of the macrophages by performing cytokine and gene expression assays. This study is currently ongoing.

**Additional support secured**
This seed award enabled us to buy an essential piece of equipment to carry out a project funded jointly between Ms Nguyen Thi Quynh Nhu, Dr Maxine Caws, Dr Sarah Dunstan at OUCRU and Dr Guy Thwaites at Imperial College.

**Impact on other research**
This incubator has enabled M.tb infections of cultured primary cells from a group of healthy volunteers in this jointly funded project and is now a vital piece of equipment for future cellular studies of TB in our Category III biosafety facility.

17. Training in clinical science for interns at the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam (SM20)

**Investigators**
Associate Professor Dong Thi Hoai Tam, University of Medicine and Pharmacy, Vietnam
Dr Duong Bich Thuy, University of Medicine and Pharmacy, Vietnam
Dr Duong Minh Cuong, University of Medicine and Pharmacy, Vietnam
Dr Tran My Phuong, University of Medicine and Pharmacy, Vietnam
Dr Mary Chambers, Oxford University Clinical Research Unit, Department of Clinical Medicine

**Project aims**
The project aims are:
- to conduct three clinical research studies under one project umbrella
- to provide first hand clinical research training to three Vietnamese clinicians.

Throughout the project, the students will be mentored by senior Vietnamese clinical scientists: Professor Tran Tinh
Hien and Assistant Professor Dong Thi Hoai Tam. They will be required to attend a weekly academic and journal club and write a full report at the end of the project and take part in a viva on their work.

The three studies focus on the following research areas:

Study 1 will describe the epidemiological, clinical and laboratory features of Hand-Foot-and-Mouth (HFM) disease in children at the Hospital for Tropical Diseases. Children with HFM disease may present mild or benign clinical features or may have severe and fatal complications. We aim to uncover the real picture of this disease in cases with virological-confirmation by PCR investigation.

Study 2 will provide a comparison of the management of recurrent shock in children with dengue infection. One third of patients with dengue shock syndrome (DSS) develop recurrent shock during 24 to 48 hours of evolution. The management of this state requires treatment with colloids (dextran), which may lead to side effects such as bleeding or fluid overload. We will compare two groups of patients using either dextran or Lactated’s ringer in terms of efficacy and possible side effects.

Study 3 will produce a description of the epidemiological, clinical and laboratory features of severe dengue infection in adults at the HTD. Severe dengue infection in adults is a rather new entity because it is different from the classical presentation in children. We aim to describe the whole picture of this new entity, the frequency of the many complications such as bleeding, shock, myocarditis, renal failure, encephalitis etc. We also hope to look for risk factors by comparing two patient groups: moderate and very severe cases.

Project progress

Study 1: We have collected 132 cases of HFM disease from children, 95 per cent under five years old, from May 2009 to June 2010. Most of the cases were hospitalised with fever (87 per cent), pathognomonic skin lesions (73 per cent) and myoclonic jerk (40 per cent). Sixty-six per cent were classified as grade 1 (no specified treatment), 32 per cent classified as grade 2 (myoclonic jerk requesting phenobarbital) and three cases (neurological complications, requesting IV Immunoglobulin perfusion) as grade 3. Ninety-seven per cent had mouth and/or rectal swabs PCR (+) with enterovirus, in which 12 cases had EV71 infection.

Study 2: We have collected 55 cases with recurrent shock among 178 children with dengue shock syndrome (DSS) from December 2009 to September 2010. We aim to finish this study by December 2012, having increased our recruitment to 300 cases with recurrent shock. Preliminary findings show that using Dextran (58 per cent of cases) leads to a more rapid decrease of the hematocrite (positive indicator), prevents more episodes of re-shock (p=0,02) and the patients do not present signs of coagulation or biological disorders.

Study 3: We have collected 130 cases of adult severe dengue infection since January 2011 and we aim to finish recruiting by September 2011. The preliminary results are: 10 cases died due to massive bleeding (with coagulation disorders), irreversible shock or encephalitis.

Additional funds secured

The Li Ka Shing funding for these studies has enabled us to produce preliminary data which will allow us to design further studies and make our future funding applications more viable.

New collaborations formed

For study 1, we have developed new collaborations with the Hospital for Tropical Diseases enterovirus laboratory team, who will observe the sensitivity and specificity of their PCR results.

Impact on other research

The preliminary results from study 1 may lead to the design of a new study entitled: Evaluation of the specificity/sensitivity of enterovirus (and/or EV71) PCR. However, we would need to recruit a larger number of patients. The results of studies 1 and 2 will be used as a reference document for the management of dengue infection.

Presentations

Study 1 and 2 were written up by Dr Tran My Phuong and Dr Duong Bich Thuy for their final year theses presented at the end of 2010 at the Department of Infectious Diseases of the University of Medicine and Pharmacy, Ho Chi Minh City.
The following seed awards began their projects in early 2011. The reports below provide information on each project’s research objectives, background, planned activities and expected outcomes. The results and project progress will be reported in next year’s report.

1. Molecular detection of Burkholderia pseudomallei in crude soil samples for environmental surveys (SM14)

Investigators
Dr Piengchan Sonthayanon, Faculty of Tropical Medicine, Mahidol University, Thailand
Dr Direk Limmathurotsakul, Faculty of Tropical Medicine, Mahidol University, Thailand
Mrs Vanaporn Wuthiekanun, Mahidol Oxford Research Unit, Thailand
Professor Nicholas Day, Mahidol Oxford Research Unit, Thailand

Collaborating institutions
• Department of Clinical Tropical Medicine and Department of Tropical Hygiene, Mahidol University, Bangkok
• Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford
• Mahidol Oxford Research Unit (MORU), Faculty of Tropical Medicine, Mahidol University, Bangkok

Project details
Burkholderia pseudomallei, the causative agent of Melioidosis, is a soil-dwelling saprophyte. The disease is endemic in Southeast Asia, particularly northeast Thailand. The organism is present in the soil and surface water, and infection results from direct skin inoculation, inhalation or ingestion. Environmental sampling is important to identify the geographical distribution of this organism and related risk of infection to humans and livestock.

Our previous studies found that the B. pseudomallei is genetically diverse in agricultural land, and that the bacteria is not uniformly distributed in soil but rather randomly distributed with spatial autocorrelation. The conventional culture method for environment soil sampling has limitations in sensitivity and is time consuming when a large number of samplings are required. A PCR-based method has been developed to evaluate the presence of B. pseudomallei in water mixed overnight with soil samples. However, the number of bacteria from extracted soil may not reflect the true number of bacteria in the soil.

This study aims to validate new molecular tools to define B. pseudomallei load in crude soil samples, which will reduce the time taken for processing and can be performed on a large number of soil samples. This technique will be very useful for epidemiology surveys in the future.
2. Simple web application for Bayesian latent class models evaluating diagnostic tests with an imperfect gold standard (SM16)

Investigators
Mr Nuttapol Panachuenwongsakul, Mahidol Oxford Research Unit, Thailand
Dr Direk Limmathurotsakul, Mahidol Oxford Research Unit, Thailand
Mr Montri Ridjaibun, Mahidol Oxford Research Unit, Thailand
Dr Phaik Yeong Cheah, Mahidol Oxford Research Unit, Thailand

Project details
When determining the prevalence of a medical condition or when evaluating new medical diagnostic tests, it is often the case that neither could be considered as having a perfect reference test with 100 per cent accuracy. Moreover, the accuracy of the reference test is often unknown and if the true accuracy of the reference test is low, the estimation of prevalence and accuracy of new diagnostic tests will be critically inaccurate.

To overcome this problem, an advanced statistical model is required. Using Bayesian latent class models (LCMs), we have recently reported that accuracy of culture, the reference test in many bacterial and fungal infections, has very low sensitivity for diagnosis of Burkholderia pseudomallei infection (PLoS one, 2010). In addition, accuracy of the ELISA test was wrongly estimated, and ELISA could have been used widely for the diagnosis of this fatal bacterial infection.

Although, LCMs are very useful, they are not widely used. They are very difficult to perform and a specific programme is required. We aim to develop a simple and user-friendly web-based application, which can run LCMs for estimating the accuracy of diagnostic tests with an imperfect reference test easily. This webpage will be fully open, and can be equipped with user-friendly and more sophisticated models in the future.

3. Evaluation of antimalarial drug resistance on the Thai-Cambodian border (SM17)

Investigators
Dr Prakaykaew Charunwatthana, Mahidol Oxford Research Unit, Thailand
Professor Sasithon Pukritayakamee, Faculty of Tropical Medicine, Mahidol University, Thailand
Dr Arjen M Dondorp, Mahidol Oxford Research Unit, Nuffield Department of Clinical Medicine, University of Oxford

Project details
Antimalarial drug-resistance is a major global health problem. Malaria endemic countries in South East Asia are now faced with the increasing problem of multi-drug resistant P. falciparum.

In western Cambodia, it has recently been demonstrated that parasitological responses to artesunate/artemether containing treatment regimens for uncomplicated falciparum malaria are slower than elsewhere in the world. The rate of parasite clearance is a measure of the efficacy of antimalarial treatment; slow parasite clearance indicates the emergence of significant resistance. Both delayed parasite clearance and unusually high failure rates with artesunate-mefloquine and artemether-lumefantrine have been reported. Artemisinin-base combination therapies are central to current antimalarial treatment strategies, and so the spread of parasites with reduced artemisinin susceptibility outside this area would be a disaster.

This research proposal aims to evaluate the problem of artemisinin resistance in the malaria endemic area of the Thai-Cambodian border. We propose to conduct a 2005-2010 retrospective study comparing the parasite clearance time and rate of recrudescence following treatment regimens with artemisinin derivatives in patients who had contracted falciparum malaria. The study sites we plan to use are three malaria endemic provinces: Srisaket and Surin (Thai-Cambodian borders) and Ranong (a malaria endemic area in the south). Parasite clearance time and other clinical data will be obtained from all patients with microscopically proven malaria who were admitted to these provincial hospitals and nearby clinics. This information on the trend of parasitological responses will help to elucidate any reduced artemisinin susceptibility and may be useful for setting up a strategy to delay or eliminate artemisinin resistance from the Thai-Cambodian border and to help protect other parts of the world.
4. Causes of infections of the central nervous system in Vietnam (SM21)

Investigators
Dr Tran Thi Hong Chau, Oxford Clinical Research Unit, Hospital for Tropical Diseases, Vietnam
Dr Jeremy Day, Oxford Clinical Research Unit, Vietnam

Project details
In Vietnam (as in much of the developing world), it is extremely difficult to diagnose infections of the brain. Partially treated pyogenic meningitis is very common and can be confused with tuberculous meningitis, viral meningitis, encephalitis or fungal infections. Most of the available data comes from the developed world and there has been very little work reported from countries in South East Asia.

“Are the common pathogens, the clinical features of brain infection in Vietnamese patients, different from patients in developed countries or other parts of the world? And how can the diagnosis and management of these infections be improved to reduce the mortality and the sequelae?”

The mortality rate remains high and many patients who survive are left with severe problems which impact on their ability to go to school or return to their jobs or family lives. This project will bring together a series of studies conducted in Vietnam over the last 15 years and will document the most common causes of these infections of the brain and try to identify how we might improve the diagnosis and treatment in order to reduce the mortality and morbidity associated with these severe infections.
The aim of the DPhil Fellowship Programme is to provide funding in the form of scholarships for doctoral and clinical scientists to undertake a DPhil or Master’s at the University of Oxford.

In October 2010, the Programme awarded Fellowships to two outstanding students: Mr Laiwen Lu from Shantou, China and Miss Nguyen Thi Cam Binh from Vietnam.

**Miss Nguyen Thi Cam Binh**  
**Based at the Oxford University Clinical Research Unit, Vietnam**

Before starting her DPhil in Clinical Medicine, Miss Binh was the Co-ordinator of the Clinical Trials Unit at the Hospital for Tropical Diseases, Vietnam for three years. Her responsibilities included:

- assisting Principal Investigators with preparation of research protocols and ethical submissions
- maintaining regulatory files
- working with study staff to monitor quality assurance and quality control checks

She was involved in two major studies involving a new drug (IND); Typhoid Vaccine Trial and the multi-country study SEA 001. She has also been a member of Network Coordinating Centre (NCC) of the South East Asia Infectious Disease Network (SEAICRN).

The title of her DPhil thesis is: “Research ethics in emerging infectious diseases; an international perspective”, and the aims of her research project are to:

- examine the ethical issues arising during research practice in disease outbreak settings including avian influenza, H1N1 influenza, and SARS
- develop an ethical framework capable of addressing these ethical issues in ways which take account of both socio-cultural factors, the broader global perspective and the emergency and unpredictable nature of these disease outbreaks

The initial phase of her work will focus in Vietnam to develop a local perspective on issues from individuals and groups with direct experience in responding to recent epidemics. The second phase will engage partners outside the region to encompass a wider international perspective from experts in Bioethics.

“So far, the DPhil has provided me with many opportunities to meet and work with colleagues and experts from different regions and countries, and from that I have learned a wide range of valuable skills.”

Miss Nguyen Thi Cam Binh
Mr Laiwen Lu (Clark)  
Based at the Mahidol-Oxford Tropical Medicine Research Unit (MORU) and Shantou Oxford Clinical Research Unit

Before starting his DPhil, Laiwen Lu (also known as Clark, under his English name) studied for a Master of Science in Global Health at the University of Oxford. Clark won a Li Ka Shing MSc Scholarship to take part in this taught programme of study for one year.

For his DPhil research project, Clark plans to study the medical history of artemisinin (Qinghaosu). His project will summarise the discovery and isolation of artemisinin, it’s early clinical trials and the concept of artemisinin combined therapy in China and the rest of the world. Clark aims to demonstrate how artemisinin was discovered and introduced worldwide, he also aims to describe the influence of politics on the development of the medicine.

So far, Clark has spent several months in China visiting various institutions involved in the Qinghaosu development project in the early 1970s, he has interviewed retired scientists (including Professor Zhou Yiqing, winner of the European Inventor Award in the “non-European” category 2009, pictured with Clark at the top of this section) and explored Chinese archives. He was touched by the retired scientist’s dedication to science and their country, particularly under the anti-intellectual atmosphere of the Cultural Revolution; he says that they sacrificed and suffered to finish their work perfectly. This experience has given Clark the determination to work hard to record the history of artemisinin objectively and precisely.

Over the coming 12 months, Clark plans to spend some time in Oxford attending training courses in DPhil thesis writing.
APPENDIX

SM13 Experience of the members of the Tak Province Community Ethics Advisory Board — a qualitative study

Interview Guide

Part 1: Open question
Can you describe your experience in being a T-CAB member?

Part 2: This section is based on Maslow’s Theory of Needs.

Question 1
a. Why did you join T-CAB?
b. How long have you been a member of T-CAB?
c. Do you think you still want to be a member in the next few years? Why?
d. How do you feel being a part of T-CAB?
e. What are your achievements? What have you learned from joining the T-CAB? What have you done as a member in T-CAB so far?
f. What do you feel about your achievements so far?
g. Has your life been different after you joined T-CAB? Are you happy with these changes – why? Have you told your family and friends about your involvement in T-CAB? Why? How do you feel – being a member/associated with T-CAB?

Question 2
a. Is it safe to work in T-CAB? Do you feel comfortable working in T-CAB?
b. Does SMRU take care of your welfare? Are there any personal costs incurred being a member of T-CAB? For example, your reputation, respect from others, job security, status in society/family, etc.

Question 3
a. What is your relationship with the SMRU and T-CAB members? Eg. Do you meet amongst yourselves outside of T-CAB?
b. Are you happy with these relationships? Do you enjoy the meetings?
c. What changes would you like to see in these relationships?

Question 4
a. What is your job in T-CAB? What do you do in the T-CAB/T-CAB meetings?
b. Can you handle your job?
c. Do you feel that people appreciate what you do in T-CAB? If yes, who and how?

Question 5
a. What is your future in T-CAB?
b. What more do you think you can do for T-CAB?
c. What changes would you like to see in T-CAB? Why? How?
d. How would you feel if these changes were made?

Part 3: Miscellaneous
Do you think that the meetings are too long/too short?
Do you have a chance to voice your opinions?
What training do you need to do your job better?
How many members do you think the T-CAB should have?
What do you think of the membership criteria for T-CAB?
What do you think about the 500 bhat per diem?
For more information, please contact:

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