Display of the Tropical Epidemiology Group's work at the Group’s 40th anniversary Symposium, March 2012
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Photographs have been provided by members of the Tropical Epidemiology Group, other LSHTM staff members and researchers from collaborating institutions, with additional images courtesy of Frank Collins/CDC, Anne Goerber, Audrey Lenhart, David Tomlinson, Peter Vowles/DfID, Rita Willaert, Shunmay Yeung, the ACT Consortium, the Arthropod Control Product Test Centre (arctec), the BMGF, the CREATE team, Wellcome Images, Novartis AG and iStockphoto. We thank all those who have contributed to this publication.
For the past 40 years, the MRC Tropical Epidemiology Group (TEG) at the London School of Hygiene and Tropical Medicine (LSHTM) has focused on designing rigorous epidemiological studies to identify and evaluate effective interventions against diseases of major public health importance in developing countries.

This Biennial Report covers the work conducted by TEG in 2011-12, describing a broad range of studies on diseases inflicting a high burden of morbidity and mortality in many low-income countries. Research continues to be centred in sub-Saharan Africa, the region with the highest per-capita burden of disease. The portfolio is in line with the findings of the recently published Global Burden of Disease, which highlighted the need for continued focus on the major infectious diseases (HIV, malaria, TB), alongside important shifts in health priorities towards non-communicable diseases, including common mental disorders. TEG is also continuing its long-standing research into neglected tropical diseases, including trachoma, helminth infections and leishmaniasis, which should benefit from a new global strategy to control, eliminate or eradicate these diseases.

The 40th anniversary of TEG in 2012 was marked with a stimulating two-day symposium, which provided an opportunity to reflect on the progress made, but also on the future challenges for intervention research in developing countries. It is clear that the core expertise of the Group, applying rigorous quantitative methods to the design and analysis of epidemiological and intervention research studies on major disease problems in developing countries, is likely to be in continuing demand. The renewal of the Group’s core funding from the Medical Research Council, for the period 2013-18, was therefore particularly welcome. We look forward to seeing the continuing impact of the Group’s research in coming years.

Peter Piot
Director, LSHTM
An Ethiopian family
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Introduction

The MRC-funded Tropical Epidemiology Group (TEG) initiates epidemiological research and provides epidemiological and statistical expertise for research projects in resource-poor settings. This Biennial Report summarises the portfolio of research conducted in 2011-12. The Report is organised by our major themes: malaria, HIV, tuberculosis (TB), neglected tropical diseases, non-communicable diseases and methodological research. Our work on neglected tropical diseases and non-communicable diseases (including mental health) has expanded considerably in the past few years, in line with the growing burden of these diseases in developing countries.

The past two years have been a period of growth for the Group, and we now number 34 academic staff and two coordinators, with an annual grant income of over £1.5m. One of the highlights of 2011-12 was the celebration of our 40th anniversary, in March 2012. To mark this event, we held a two-day symposium, on progress and future challenges in intervention research in developing countries, and we were pleased to welcome about 250 colleagues, students, TEG fellows, and representatives from funding bodies to join us (p10).

The mission of the Group has remained the same over the past 40 years – to conduct research on the epidemiology and control of diseases of major public health importance in developing countries. We have an emphasis on conducting rigorously designed intervention studies, including (i) randomised controlled trials (RCTs) to identify effective interventions against these diseases and (ii) research strategies to implement such interventions. The latter increasingly focuses on overcoming barriers to scaling up proven interventions, including the use of task-shifting to tackle the lack of trained healthcare workers in many settings.

The aim of the Group is to contribute to improvements in health in developing countries through epidemiological research aimed at identifying and evaluating effective interventions.
i) Key studies to identify effective interventions:
- The ZAMSTAR trial of TB treatment, part of the Bill and Melinda Gates Foundation-funded CREATE Consortium, in which members of the Group co-direct the Biostatistics Core. The trial, in Zambia and South Africa, showed that interventions targeted at households of a person with TB, such as testing for HIV and screening for TB, were associated with a substantial reduction in TB transmission, and reduced prevalence of active TB by approximately 20% (p44).
- A multi-pronged malaria control intervention on Bioko Island, Equatorial Guinea, demonstrated a two-thirds reduction in all-cause mortality in children under 5 years of age, confirming the important indirect effects of malaria on other causes of death (p14).
- An RCT in Uganda showed that anthelminthics given to pregnant women had few benefits in their infants and some adverse effects (p54).
- Clinical trials of paramomycin for the treatment of visceral leishmaniasis in East Africa showed that larger doses were required to achieve the efficacy observed in studies in India (p52).
- Studies on human papillomavirus (HPV) showed for the first time that the bivalent HPV vaccine is safe and immunogenic in girls and young women in Africa, and that uptake varied according to different strategies of vaccine delivery in primary schools in Tanzania, but that vaccine uptake of over 80% was possible (p41).
- A major new cluster RCT, the HPTN 071/PopART trial, funded by NIH, PEPFAR and the Gates Foundation (through 3ie), will test the hypothesis that a combination HIV prevention package, including universal HIV testing with immediate treatment for all individuals who test HIV positive, will substantially reduce HIV incidence at a population level (p36).

ii) Key studies to evaluate strategies to implement or scale-up interventions:
- A series of studies of the safety, tolerability and effectiveness of alternative drug regimens for seasonal malaria chemoprevention (SMC), and effective methods of its delivery (p18).
- Operational research to evaluate strategies to increase uptake of male circumcision for HIV prevention in sub-Saharan Africa (p30).
- The ZENITH project, to evaluate the effect of a community-led intervention delivered by trained voluntary lay workers on retention in care and adherence to HIV treatment, compared with standard care in Zimbabwe (p37).
- Trials of the effectiveness of using trained lay health workers to deliver psychological therapy for common mental disorders (p60).
- A cluster RCT of community case management for malaria using trained volunteers (p20).[1]

Helen Weiss
Head, Tropical Epidemiology Group
Translating research into policy

The Group has a major focus on intervention research that will have an impact on international health policy and implementation, with studies generating data to enable policy-makers to make decisions about cost-effective strategies for rolling out proven interventions (e.g. for male circumcision), or for accessing new technology (e.g. TB diagnostics, including Xpert MTB/RIF).

Examples of where our research has had impact on policy in 2011-12:
- the WHO Malaria Policy Committee reviewed evidence including our studies on SMC, and recommended SMC for children under 5 years of age in areas of highly seasonal malaria transmission across the Sahel;
- research on visceral leishmaniasis led to a new standard treatment regimen for affected patients in national treatment guidelines in Ethiopia, Kenya, Sudan, and Uganda; and
- a study of HPV vaccination delivery strategies in Tanzania assisted the Tanzanian national HPV vaccination programme to plan its roll-out.

We also play an active role in influencing global health policy through participation in international technical and policy advisory groups to help to ensure that results from our research and other important studies can inform new policies and guidelines.

Strengthening research capacity in resource-poor settings
The Group provides major epidemiological and statistical support to the main MRC-funded research centres in Africa, including the MRC research units in Uganda and The Gambia and the MRC-supported Mwanza Intervention Trials Unit (MITu) in Tanzania. This includes collaborating with Unit researchers in applications for funding for field studies and in designing and conducting studies; advising and guiding locally employed statisticians; and teaching on training courses in epidemiology, statistics and research methods, which are organised at the Units for local scientists.

We are particularly proud of our TEG Training Fellowship scheme (p89), which provides support each year for a promising African scientist to undertake MSc training in Medical Statistics at LSHTM followed by a second year working as a statistician at one of our partner centres in Africa with continued mentoring and supervision by staff of our Group. All our fellows to date have completed this training programme successfully, and all are either working in relevant posts in research institutions in Africa or are engaged in PhD studies.
Celebrating 40 years of the MRC Tropical Epidemiology Group

In March 2012, TEG celebrated its 40th anniversary. Over 250 researchers and funders gathered at the LSHTM for a two-day symposium to reflect on progress and future challenges for intervention research in developing countries.

The symposium saw a distinguished panel of speakers review the state-of-the-art of intervention research in developing countries across the Group’s broad range of research areas, including malaria, HIV, TB, vaccine-related diseases, maternal, neonatal and child health, non-communicable diseases, and methodology of cluster RCTs. It also provided an opportunity to meet with friends and colleagues with whom the Group has worked closely over the years, and brought former TEG fellows from across Africa together to share their experiences.

The timeline below provides highlights of studies that the Group has been involved with over the years.

**1970**: Patrick Hamilton awarded a grant from the Wellcome Trust to set up the Tropical Epidemiology Group to provide expertise in epidemiology and statistical analysis for diseases that devastate the world’s tropical regions.

**1972**: Patrick Vaughan takes over leadership of the Group, which is awarded the first grant from the MRC. Funding support from MRC continues for the next four decades.

**1975**: Patrick Vaughan pioneers a new trial design called the ‘stepped wedge’ to measure the impact of hepatitis B vaccination. The vaccine is shown to have a major impact on hepatitis B carrier state, a major precursor of chronic liver disease and liver cancer. This paved the way for the successful establishment of hepatitis B vaccination programmes in many of the world’s poorest countries.

**1987**: Together with the MRC Unit in The Gambia, TEG pioneers a new trial design called the ‘stepped wedge’ to measure the impact of hepatitis B vaccination. The vaccine is shown to have a major impact on hepatitis B carrier state, a major precursor of chronic liver disease and liver cancer. This paved the way for the successful establishment of hepatitis B vaccination programmes in many of the world’s poorest countries.
1992: Insecticide-treated nets are shown to reduce child mortality by 20% in a trial in northern Ghana; one of four similar trials overseen by TEG for the WHO.

1995: The landmark Mwanza trial is carried out in Tanzania, showing that improved management of sexually transmitted infections at clinics reduces the incidence of HIV infection in the community by 42%.

1997: Insecticide-treated nets are shown to reduce child mortality by 20% in a trial in northern Ghana; one of four similar trials overseen by TEG for the WHO.

2000: A systematic review conducted by TEG finds a strong association between lack of male circumcision and HIV infection in sub-Saharan Africa. Later trials confirm that circumcision provides around 60% protection against HIV.

2004: TEG collaborates on research on various drug regimens for SMC, which involves giving all people in a community a monthly dose of an effective anti-malarial drug during the season of highest malaria risk.

2005: With statistical and epidemiological support from the Group, a trial in 9000 Gambian children shows that pneumococcal conjugate vaccine reduces radiographically proven pneumonia by 37% and reduces total mortality by 16%.

The MRC TEG Fellowship scheme is launched to enable African statisticians to undertake an MSc in Medical Statistics at LSHTM.

2006: A major trial is initiated with the MRC Unit in Uganda and shows that home-based care can play a major role in the delivery of antiretroviral therapy to patients in rural areas, reducing the demand for scarce medical supervision.

MITU in Tanzania is established in partnership with the National Institute of Medical Research (NIMR), with MRC funding. The new MITU building is completed and launched with an international symposium on HIV prevention.

2009: A major trial is initiated with the MRC Unit in Uganda and shows that home-based care can play a major role in the delivery of antiretroviral therapy to patients in rural areas, reducing the demand for scarce medical supervision.

2010: A trial of the vaginal microbicide PRO 2000, carried out with the MRC Clinical Trials Unit, UK, the MRC/UVRI Unit in Uganda, MITU/NIMR, Tanzania, and other sites, shows that there is no evidence that it reduces the risk of HIV infection in women.

2012: Looking forward
Looking forward to the next 40 years, the Group’s future challenges are encapsulated by the MRC Strategic Plan, the Millennium Development Goals to reduce child mortality and to combat HIV/AIDS, malaria and TB, and the recent WHO roadmap to control, eliminate or eradicate neglected tropical diseases, including dengue, trachoma, leishmaniasis and soil-transmitted helminths. Further challenges are presented by the changing patterns of morbidity and mortality in developing countries. The prevalence of conditions such as hypertension, diabetes and mental illnesses is increasing, especially in growing urban centres in developing countries, and this requires innovative approaches to prevention and control.
Malaria

The Group has an expanding research programme in malaria. In 2011-12, this ranged from trials of malaria vaccines, malaria vector control tools, seasonal malaria chemoprevention, delivery systems for effective treatment drugs and long-lasting insecticidal nets, to studies on the impact of insecticide resistance on malaria vector control, the evaluation of programmatic interventions, and the epidemiology of malaria elimination.

We collaborate closely with scientists in the UK and malaria endemic countries, with international agencies and with national malaria control programmes and other local implementing partners.

14 Bioko Island Malaria Control Project, Equatorial Guinea, Phase II and III

14 Equatorial Guinea Malaria Control Initiative (EGMCI): a 5-year project

15 The impact of insecticide resistance on the effectiveness of malaria vector control interventions, and combining indoor residual spraying and long-lasting insecticidal nets

15 Can combined use of indoor residual spraying and use of long-lasting insecticidal nets be replaced with use of nets alone in Tanzania? A cluster RCT

16 Cluster RCT of targeted malaria control to eliminate malaria in central Senegal

16 Strategies for delivering insecticide-treated nets at scale for malaria control in endemic countries: a systematic review

17 The effectiveness of interventions delivered at scale to improve the delivery of health services by front-line workers in low-income countries: a systematic review

18 Safety and effectiveness of seasonal malaria chemoprevention when delivered on a large scale by district health staff in Senegal

18 The costs of delivering seasonal malaria chemoprevention in Senegal

19 Maximising the impact of chemoprevention on malaria burden in children in areas of seasonal transmission

19 RCT of dihydroartemisinin-piperaquine for seasonal malaria chemoprevention in children from Burkina Faso

20 A cluster RCT of seasonal malaria chemoprevention combined with community case management in Senegal

20 The ACT Consortium

21 Evaluating the impact of enhanced health facility-based care for malaria and febrile illnesses in children in Uganda (ACT PRIME study)

22 IMPACT 2: Monitoring interventions to improve artemisinin combination therapy access and targeting in Tanzania

22 Multi-country evaluation of the Affordable Medicines Facility – Malaria

23 Multi-centre Phase IIb efficacy trials of the GMZ2 and the MSP3-LSP malaria vaccines

23 An RCT of a prophylaxis regimen for the prevention of malaria and related complications, in patients with sickle cell anaemia from Nigeria

24 Role of rapid diagnostic tests for malaria for the targeting of ACTs at community level in Ghana

24 Interventions to improve community case management of malaria in sub-Saharan Africa: a systematic review

25 Epidemiology of pre-elimination border malaria in northern Namibia
Girl collecting mosquito nets, central Africa © Pete Vowles, DFID
Bioko Island Malaria Control Project, Equatorial Guinea, Phase II and III

**TEG investigators:** John Bradley, Immo Kleinschmidt (Co-PI), Andrea Rehman

**Other LSHTM investigators:** Chris Drakeley

**External investigators/collaborators:** Christopher Schwabe (PI; Medical Care Development International), Janet Hemingway, John Vontas (Liverpool School of Tropical Medicine, UK), Hans Overgaard (Norwegian University of Life Sciences), Michel Slotman (Texas A&M University, USA), Mike Reddy (Yale University, USA)

**Funding:** Marathon Oil Co-operation and MoH, Equatorial Guinea, via Medical Care Development International

**Location:** Bioko Island, Equatorial Guinea

**Objective**
To evaluate critical aspects of malaria control and surveillance on Bioko Island, documenting the reduction in transmission from holo-endemic (very high prevalence) to pre-elimination phases.

**Description**
The Bioko Island Malaria Control Project, in collaboration with the Government of Equatorial Guinea, introduced an integrated malaria control programme in 2004. This consisted of (i) indoor residual spraying and long-lasting insecticidal nets (LLIN) delivered to all households, (ii) malaria case management using artemisinin combination therapy and definitive diagnosis, and (iii) intermittent preventive treatment for pregnant women, as well as training of health workers and information and education campaigns. Major reductions in malaria transmission and associated all-cause under-5 mortality were documented during the first 5-year phase of the project. Further transmission reduction is being extensively monitored through a surveillance system consisting of: (i) annual household surveys collecting a number of biomarkers and information on illness episodes, household wealth and health-seeking behaviour; (ii) patient information systems; (iii) entomological surveillance; (iv) serological surveys; and (v) assessment of all-cause child mortality. The third 5-year phase (2014-18) of the project is currently being planned. It is expected that malaria transmission will be at pre-elimination levels in many parts of the island by 2018.

**References:** 5, 10, 15, 29, 30, 32

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Equatorial Guinea Malaria Control Initiative (EGMCI): a 5-year project

**TEG investigators:** Immo Kleinschmidt (Co-PI), Andrea Mann, Andrea Rehman

**External investigators/collaborators:** Christopher Schwabe (PI; Medical Care Development International), John Vontas (Liverpool School of Tropical Medicine, UK and University of Crete, Greece), Michel Slotman (Texas A&M University, USA), Mike Reddy (Yale University, USA)

**Funding:** Global Fund to Fight AIDS, Tuberculosis and Malaria

**Location:** Equatorial Guinea

**Objective**
To evaluate the impact on malaria morbidity of using a reduced scale of the successful Bioko Island malaria control programme in the four mainland provinces of Equatorial Guinea.

**Description**
Malaria is the principal cause of morbidity and mortality in Equatorial Guinea, accounting for 31.5% of morbidity and 37.3% of mortality. The multiple malaria interventions that made up the EGMCI were initiated in 2007 and included both vector control and improving case management. Two provinces were targeted to receive LLINs and two to receive indoor residual spraying. All four provinces were targeted for improving case management. The initiative ended in 2011 and was evaluated by annual malaria indicator surveys from 2007-11. Findings showed that the prevalence of *P. falciparum* in children under 5 years reduced from 68% in 2007 to 52% in 2011.

**References:** 2, 25, 31

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The EGMCI found that vector control provided individual protection from malaria, in children.

References: 2, 25, 31
The impact of insecticide resistance on the effectiveness of malaria vector control interventions, and combining indoor residual spraying and long-lasting insecticidal nets

**TEG investigators:** John Bradley, Immo Kleinschmidt (Co-PI)

**Other LSHTM investigator:** Chris Drakeley

**External investigators/collaborators:**
- Martin Akogbeto (Benin), Jude Bigoga, Etienne Fondjo (Cameroon), Charles Mbogo (Kenya), Martin Donnelly (Co-PI; Liverpool School of Tropical Medicine, UK), Khalid El-Mardi, Hmooda Kafy, Bashir Ismail, Mohamed Ahmed Abass (MoH, Sudan), Kamaraju Raghavendra (National Institute of Malaria Research, India), Abraham Mnzava (Co-PI; WHO-GMP)

**Funding:** Bill and Melinda Gates Foundation and Global Environmental Facility, via UNEP

**Location:** Benin, Cameroon, India, Kenya, Sudan

**Objective**
To assess the impact of insecticide resistance on the effectiveness of malaria vector control tools (LLINs and indoor residual spraying (IRS)) and to evaluate the added protection of the combined use of LLINs and IRS for vector control in comparison with LLINs alone in a cluster RCT.

**Description**
In Sudan, a cluster RCT of universal coverage with LLINs compared with combined use of LLINs and IRS is being implemented. Baseline levels of insecticide resistance of the main malaria vector (*Anopheles arabiensis*) are balanced between the two study arms. In each cluster, resistance to the insecticide used is being monitored, and malaria incidence is estimated from cohorts of children followed over the duration of the study. This will provide (i) an estimate of the effect of the combined intervention (LLIN plus IRS) relative to LLINs alone, adjusted for the presence of insecticide resistance; and (ii) an estimate of the effect of insecticide resistance on vector control effectiveness.

In the other countries, clusters have been established and malaria vector mosquitoes in each cluster assessed for resistance to the insecticide used. Clusters with either very high susceptibility or very high resistance to the insecticides in use are retained for the study, and cohorts of children recruited for follow-up and estimation of malaria incidence. Resistance impact will be assessed from the ratio of incidence rates in clusters with high compared with low resistance. Resistance mechanisms will be determined in subsets of study clusters.

Can combined use of indoor residual spraying and use of long-lasting insecticidal nets be replaced with use of nets alone in Tanzania? A cluster RCT

**TEG investigator:** Immo Kleinschmidt (Co-PI)

**Other LSHTM investigators:** Matthew Kirby, Richard Oxborough, Natacha Protopopoff, Mark Rowland (Co-PI), Phillipa West

**External investigators/collaborators:**
- Reginald Kavishe, Jovin Kitau, Johnson Matowo, Franklin Mosha, Seif Shakaalaghe (Kilimanjaro Christian Medical College, Tanzania), Robert Malima, Patrick Tunga (NIMR, Tanzania)

**Funding:** US Agency for International Development

**Location:** Tanzania

**Objective**
To assess whether LLINs at high coverage provide as much protection against malaria infection as the use of LLINs and IRS combined.

**Description**
The project examined whether it is safe to withdraw IRS when high coverage and usage of LLINs has been achieved. Fifty clusters (villages or groups of hamlets) in northwest Tanzania were provided with
universal coverage of LLINs and IRS during the baseline year. Half of these clusters were randomly allocated to continue with both interventions, while the other half had IRS withdrawn. The primary outcome is malaria infection prevalence in children, assessed during cross-sectional surveys at the end of the trial. Results indicate that the combined use of the two interventions does offer additional protection compared with using LLINs alone, although the duration of this effect is limited to the duration of insecticide residual on walls. National malaria control programmes should consider the implementation of the combined intervention if their LLIN strategy is not effective.

Reference: 40

Cluster RCT of targeted malaria control to eliminate malaria in central Senegal

TEG investigators: Paul Milligan (PI), Matthew Cairns, Immo Kleinschmidt

Other LSHTM investigators: Badara Cisse (Co-PI), Chris Drakeley, El Hadj Ba (Co-PI), Catherine Pitt, Colin Sutherland

External investigators/collaborators: Cheikh Sokhna, Jean Francois Trape (Institut de Recherche pour le Developpement, Senegal), Boniface Mutombo (MACEPA, Senegal), Mady Ba, Fatou Ba Fall (PNLP, Senegal), Ousmane Faye, Oumar Gaye (University Cheikh Anta Diop, Senegal), Jean Gaudart, (University of Aix-Marseille, France)

Funding: MRC, DfID, Wellcome Trust

Location: Senegal

Objective
To evaluate the targeted use of existing tools to eliminate malaria, and to compare the effectiveness and acceptability of mass drug administration (MDA) and mass screening and treatment (MSAT).

Description
In Senegal, as in some other parts of Africa, there has recently been a sharp decline in the incidence of malaria coinciding with increased control efforts, primarily the large-scale distribution of free and highly subsidised LLINs. This raises the prospect that malaria could be eliminated, but despite scaling up of control methods transmission persists in foci that provide a continuing source of infection. Additional strategies are needed to eliminate these foci.

A new trial is being set up in which 40 health posts will be randomised. 10 posts will serve as controls, 15 will operate targeted malaria control with IRS followed by MDA, and 15 will use IRS followed by MSAT. All households in villages with evidence of transmission will receive IRS with the insecticide pirimiphos-methyl in June, followed by chemotherapy by either MDA or MSAT. In MDA clusters, treatment with dihydroartemisinin-piperaquine plus a single dose of primaquine will be administered to all persons in the target villages in September and again in October. In MSAT clusters, all persons will be screened for malaria infection using a sensitive rapid diagnostic test and those who test positive will be treated with dihydroartemisinin-piperaquine plus primaquine. In all three arms of the trial, efforts will be made to maintain high coverage of LLINs, and any individuals diagnosed with malaria at health facilities will be treated with artemether-lumefantrine plus a low dose of primaquine, and provided with an LLIN. The trial starts in June 2013 and results will be available in July 2015.

Strategies for delivering insecticide-treated nets at scale for malaria control in endemic countries: a systematic review

TEG investigators: Joanna Schellenberg (PI), Barbara Willey

Other LSHTM investigators: Lindsay Mangham-Jeffries, Lucy Paintain

External investigators/collaborators: Josip Car (ICL, UK)

Funding: WHO/TDR

Objective
To synthesise findings from recent studies of strategies to deliver insecticide-treated nets at scale in malaria endemic areas.

Description
A total of 32 papers describing 20 African studies were identified. Many delivery strategies involved health sectors and retail outlets, antenatal care clinics and campaigns. Strategies that delivered insecticide-treated nets free through campaigns achieved highest usage. Costs were comparable across strategies, with the nets being the main cost. Cost-effectiveness estimates were most sensitive to the assumed net lifespan and...
leakage. Common barriers to delivery included cost, stockouts of nets at distribution points, and poor logistics. Common facilitators were staff training and supervision, cooperation across departments or ministries and stakeholder involvement.

Reference: 43

The effectiveness of interventions delivered at scale to improve the delivery of health services by front-line workers in low-income countries: a systematic review

**TEG investigators:** Barbara Willey (PI), Joanna Schellenberg

**Other LSHTM investigators:** Lindsay Mangham-Jeffries, Lucy Paintain

**External investigator/collaborator:** Josip Car (ICL, UK)

**Funding:** DFID

**Objective**
To identify evidence for the effectiveness of interventions to strengthen national health service delivery in countries with low and lower-middle incomes. The focus was on supply-side interventions to improve the ability of front-line workers to deliver health services, and evidence from evaluations of interventions delivered at scale.

**Description**
In total, 21 papers covering 12 studies were included. The evidence base for quality outcomes was the largest (11 studies). Evidence for survival impact was limited to two studies of integrated management of childhood illness; both found weak evidence of a positive effect on under-5 mortality but neither reached statistical significance. Between-study heterogeneity precluded meta-analysis. However, studies of interventions that strengthened management, supervision and wider systems management (e.g. record keeping, supplies monitoring) at the health facility and district levels tended to show more consistently improved outcomes than those strengthening technical guidance alone.

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Mapping the availability of evidence to the logic framework: linking strengthening health service delivery and mortality

- **Access**
  - 0/12 studies
  - Weak evidence base
  - 5/12 studies
  - 3/12 with outcomes closely linked to morbidity or mortality

- **Coverage**
  - Good evidence base
  - 11/12 studies
  - Weak evidence base
  - 1/12 studies
  - Sparse evidence base
  - 1/12 studies

- **Quality**
  - Weak evidence base
  - 2/12 studies

- **Equity**
  - Addressed by this review, good evidence base
  - Addressed by this review, weak evidence base

- **Under 5 mortality**
  - Addressed by this review, sparse or no evidence base
  - Not addressed by this review

- **Weight for age and weight for height**
  - Good evidence base
  - 11/12 studies
  - Sparse evidence base
  - 1/12 studies

- **Mapping the availability of evidence to the logic framework: linking strengthening health service delivery and mortality**
Safety and effectiveness of seasonal malaria chemoprevention when delivered on a large scale by district health staff in Senegal

TEG investigators: Paul Milligan (PI), Matthew Cairns

Other LSHTM investigators: Badara Cissé (Co-PI), El Hadj Ba, Brian Greenwood, Catherine Pitt

External investigators/collaborators: Cheikh Sokhna, Jean Francois Trape (Institut de la Recherche pour le Development, Senegal), Yankouba Dial, Oumar Faye (MoH, Senegal), Babacar Faye, Ousmane Faye, Oumar Gaye, Jean Louis NDiaye (University Cheikh Anta Diop, Senegal)

Funding: Bill and Melinda Gates Foundation

Location: Central Senegal

Objective
To establish the safety of seasonal malaria chemoprevention (SMC), and the feasibility and effectiveness of delivering SMC on a large scale.

Description
Across the Sahel subregion, most childhood malaria mortality and morbidity occurs during the rainy season, which is generally short. SMC comprises giving effective malaria treatment at intervals during this period. In this study, SMC with sulfadoxine-pyrimethamine plus amodiaquine was introduced into three districts in central Senegal, using a stepped-wedge design. Community health workers visited each household monthly during the 2008-10 transmission seasons to deliver SMC to children aged 3-59 months in 2008, and to children aged up to 10 years of age in 2009 and 2010. A surveillance system was established to record all deaths, malaria cases diagnosed at health facilities and to detect adverse drug reactions. Surveys were conducted at the end of each transmission season to estimate the prevalence of parasitaemia and anaemia, for monitoring molecular markers of drug resistance, insecticide-treated net use, and for independent assessment of coverage of SMC. Almost 800,000 documented courses of SMC were administered. Coverage was high (80-90% each month) and was similar across all socioeconomic groups. No serious adverse events attributable to the intervention were detected despite a high level of surveillance, and the treatments were well tolerated. SMC was found to reduce the incidence of outpatient malaria confirmed by rapid diagnostic tests by 56%.

The costs of delivering seasonal malaria chemoprevention in Senegal

TEG investigator: Paul Milligan (PI)

LSHTM investigators: Catherine Pitt (PI), Badara Cisse, El Hadj Ba

External investigators/collaborators: Lesong Conteh (ICL, UK), Mouhamed N’Diaye (University Cheikh Anta Diop, Senegal)

Location: Senegal

Funding: Bill and Melinda Gates Foundation

Objective
To estimate the economic cost of SMC.

Description
In March 2012, the WHO-recommended SMC as an additional malaria control tool. This study to assess the costs of SMC on a large scale formed part of the evidence on which this recommendation was based. We evaluated the costs of delivering SMC in a population of 180,000 children aged 3 to 120 months across four districts of central Senegal in 2010. The financial cost to administer SMC to this population over one malaria season, achieving an average monthly coverage of 90%, was US$0.50 per course. This is substantially lower than in previous estimates from clinical trials, which is likely attributable to economies of scale but also to the leading role of the MoH in implementation and the economies achieved in extending the
usual age range of SMC from children under 5 to children under 10. The main cost drivers were the incentives paid to community health workers and the costs of the SMC drugs.

References: 27, 28

Maximising the impact of chemoprevention on malaria burden in children in areas of seasonal transmission

**TEG investigators:** Matthew Cairns (PI), Paul Milligan

**Other LSHTM investigators:** Daniel Chandramohan, Brian Greenwood

**External investigators/collaborators:** Azra Ghani (ICL, UK)

**Funding:** MRC Population Health Scientist Fellowship and Sir Halley Stewart Trust

**Location:** Burkina Faso, Ghana, Mali, Senegal

**Objective**

To identify the epidemiological situations and geographical areas in which extended SMC and/or replacing standard anti-malarials with long-lasting artemisinin combination therapy (ACT) would be useful in Africa, and to estimate their potential impact.

**Description**

As described previously, SMC is now recommended as policy by the WHO for certain areas of Africa with highly seasonal malaria transmission. SMC may also be useful in places where malaria is transmitted for a longer period each year, but the effectiveness and impact in such areas is not well understood. A more feasible form of chemoprevention in these settings would be treating malaria patients with long-lasting ACT. This prevents further malaria infections for several weeks. As some children repeatedly experience malaria, while other children remain healthy, treating children with long-lasting ACT may have a disproportionate impact on the malaria burden. Understanding the timing and frequency of repeat malaria attacks is necessary to estimate this benefit.

These two forms of chemoprevention will be evaluated using a combination of approaches, including a clinical trial currently underway in Ghana, reanalysis of data from previous clinical trials and epidemiological studies, and mathematical modelling.

**Reference:** 7

**RCT of dihydroartemisinin-piperaquine for seasonal malaria chemoprevention in children from Burkina Faso**

**TEG investigators:** Issaka Zongo (PI), Paul Milligan

**Other LSHTM investigators:** Daniel Chandramohan, Brian Greenwood, Colin Sutherland

**External investigators/collaborators:** Jean Bosco Ouedrago (Institut de Recherche en Sciences de la Santé, Burkina Faso), Francois Nosten (Shoklo-Malaria Research Unit, Thailand), Philip Rosenthal (University of California, USA)

**Funding:** Holley Cotec

**Location:** Burkina Faso

**Objective**

The drugs currently recommended for SMC, sulfadoxine-pyrimethamine plus amodiaquine (SP-AQ) are highly effective but alternative drug regimens may be required if these drugs lose their efficacy. Previous studies indicated that dihydroartemisinin-piperaquine (DHA-PQ) is a potentially suitable alternative. The aim of this 1-year non-inferiority study was to compare the safety, tolerability and efficacy of DHA-PQ and SP-AQ when used for SMC in children. The trial took place in Lena district where 1500 children were randomised to receive SMC with one of the two regimens. Outside the trial, a cohort of untreated children was followed to determine malaria incidence without SMC. Four fingerprick blood samples were taken each month from a subset of children for measurement of piperaquine concentrations and venous samples were taken from a second subset each month to measure the effect of SMC doses on haematological and biochemical parameters. Results will determine whether DHA-PQ is an effective alternative regimen for SMC.
A cluster RCT of seasonal malaria chemoprevention combined with community case management in Senegal

TEG investigator: Paul Milligan (PI)

Other LSHTM investigators: Badara Cisse Rachel Hallett, Colin Sutherland

External investigators/collaborators: Jean Louis NDiaye (PI), Youssoupha NDiaye (Ministère de Santé et de la Prévention, Senegal), Oumar Gaye (UCAD, Senegal)

Funding: EDCTP

Location: Saraya District, Senegal

Objective
The relative advantage of adding SMC in villages that have access to prompt effective treatment through community case management schemes has not been evaluated. The aim of this study was to determine effectiveness of SMC when delivered to children under 10 years of age as part of a community case management scheme in southern Senegal.

Description
In Saraya district, Senegal, where many communities are more than 15 km from the nearest health post, community case management for malaria has been introduced. Lay workers are trained to recognise the signs and symptoms of uncomplicated and severe malaria, to use rapid diagnostic tests, and to treat malaria with artemisinin combination therapy (ACT). Of the 24 villages randomised, 12 had SMC delivered over 2-4 days each month during the high transmission period to all eligible children. If a child was unwell, they were tested with a rapid diagnostic test and treated with ACT if positive. In the remaining 12 villages, case management was provided in the same way but SMC was not delivered. The primary endpoint is the incidence of clinical malaria. Secondary endpoints are incidence of severe malaria, and the prevalence of anaemia and of parasitaemia at the end of the transmission season. The impact of SMC on drug resistance is being evaluated by analysis of the rapid diagnostic tests used and from blood samples taken from a sample of children at the end of the transmission season.

The ACT Consortium

TEG investigators: Matthew Cairns, Bonnie Cundill, Emily Webb

Other LSHTM investigators: Multi-departmental collaboration led by David Schellenberg (Consortium Director)

External investigators/collaborators: Including researchers from the CDC, USA; Dangme West District Health Directorate, Ghana; Georgia Institute of Technology, USA; Health Protection and Research Organisation, Afghanistan; Ifakara Health Institute, Tanzania; Karolinska Institute, Sweden; Kilimanjaro Christian Medical Centre, Tanzania; Kintampo Health Research Centre, Ghana; MoH Uganda; NIMR, Tanzania, and the universities of California, Cameroon, Cape Town, Copenhagen, Liverpool School of Tropical Medicine, UK, Malawi, Nigeria, Oxford and Yaoundé

Funding: Bill and Melinda Gates Foundation

Location: Afghanistan, Cameroon, Ghana, Malawi, Nigeria, South Africa, Tanzania, Uganda

16 Community health workers delivering SMC in Senegal © Paul Milligan, LSHTM

ACT Consortium: 16 projects across 9 countries
Objective
The ACT Consortium is an international research collaboration formed to answer key questions on malaria drug delivery in Africa and Asia (further details at www.actconsortium.org).

Description
The Consortium, established in 2007, sponsors 16 main research projects and takes a multi-disciplinary approach to evaluating ways to improve access and targeting of ACT in public and private sectors and in the community. A number of TEG investigators are involved in projects led by the Consortium and provide core statistical support to the Consortium and to individual projects (e.g. IMPACT2 and ACT PRIME, (p21-22).

Data collection across all Consortium projects is due to complete by July 2013 and the work of the Consortium is now intensifying in the areas of data sharing and communication, to incorporate outputs into the larger landscape of malaria research and control.

References: 18, 21, 22, 44, 45

Evaluating the impact of enhanced health facility-based care for malaria and febrile illnesses in children in Uganda (ACT PRIME study)

TEG investigator: Emily Webb

Other LSHTM investigators: Sarah Staedke (PI), Clare Chandler (Co-PI), Deborah DiLiberto

External investigators/collaborators: Heidi Hopkins, Ambrose Talisuna (FIND Diagnostics), Moses Kamya, Fred Wabwire-Mangen (Makere University, Uganda), Grant Dorsey, Philip Rosenthal (University of California San Francisco, USA)

Funding: ACT Consortium, via Bill and Melinda Gates Foundation

Location: Uganda

Objective
To evaluate enhanced facility-based care compared with standard care for malaria and febrile illnesses in children, at lower-level government-run health facilities.

Description
Given the barriers to accessing good quality care through the formal healthcare sector, there may be scope for community-based interventions to deliver anti-malarial treatment. However, it is not clear whether resources should be put into community-based programmes or towards improving quality and delivery of healthcare through existing public facilities. A cluster RCT is being conducted to (i) compare the impact of enhanced facility-based care with standard care in 20 health facilities on key health indicators (ii) assess the safety and tolerability of anti-malarial drugs when dosed repeatedly and (iii) evaluate the cost-effectiveness of the interventions. The enhanced care has three components including (i) training of staff in health centre management, (ii) training health workers in fever case management and patient-centred services, and (iii) ensuring adequate supplies of artemether-lumefantrine and rapid diagnostic tests. Evaluation activities include annual cross-sectional surveys, follow-up of a cohort of children under 5 years of age, and monitoring and evaluation of the facility-based care. A process study has also been conducted to evaluate the process, context and impact of the health facility intervention to further our understanding about why the facility-based care was effective, or not. The PRIME study began in December 2010 and is scheduled to complete in July 2013.
**IMPACT 2: Monitoring interventions to improve artemisinin combination therapy access and targeting in Tanzania**

**TEG investigators:** Matthew Cairns, Immo Kleinschmidt

**Other LSHTM investigators:** Katia Bruxvoort, Catherine Goodman (Co-PI), Rebecca Thomson

**External investigators/collaborators:** Including investigators from the CDC, USA and Ifakara Health Institute, Tanzania

**Funding:** ACT Consortium, via Bill and Melinda Gates Foundation

**Location:** Tanzania

**Objective**

To evaluate the impact of the roll-out of rapid diagnostic tests in health facilities and subsidised ACT in the private sector in Tanzania mainland.

**Description**

The Tanzanian Government has implemented strategies to address both ACT access and targeting on a national scale. It aimed to improve access through the distribution of subsidised ACT at private facilities and retail drug shops under the Affordable Medicines Facility – Malaria (AMFm). Targeting was to be addressed through introducing rapid diagnostic tests in health facilities at every level of the system. This study has conducted an evaluation of these two interventions in three rural Tanzanian regions. Intervention effectiveness has been assessed through household, health facility and outlet surveys in terms of coverage, equity, quality, adherence and public health impact. Qualitative data have been collected throughout to explore provider and patient perspectives.

**Multi-country evaluation of the Affordable Medicines Facility – Malaria**

**TEG investigators:** Immo Kleinschmidt, Andrea Mann, Barbara Willey

**Other LSHTM investigators:** Kara Hanson (PI), Katia Bruxvoort, Diadier A Diallo, Catherine Goodman, Ben Palafox, Rebecca Thomson, Sergio Torres Rueda, Sarah Tougher

**External investigators/collaborators:**

Including researchers from African Population and Health Research Center, Kenya; Centre de Recherche pour le Développement Humain, Senegal; Centre International d’Etudes et de Recherches sur les Populations Africaines, Niger; DNDi, Geneva; ICF International; Ifakara Health Institute, Tanzania; Institut National de la Statistique, Niger; KEMRI, Kenya; Komfo Anokeye Teaching Hospital, Ghana; Phar-Mark Consultants, Nigeria

**Funding:** Global Fund to Fight AIDS, Tuberculosis and Malaria

**Location:** Ghana, Kenya, Madagascar, Niger, Nigeria, Tanzania mainland, Uganda, Zanzibar

**Objective**

To evaluate the effect of the AMFm on the price, availability, market share and use of quality-assured ACT 6-15 months after the delivery of subsidised ACTs.

**Description**

The AMFm aimed to improve access to quality-assured ACT and to reduce use of artemisinin monotherapies, which may contribute to drug resistance. It used an innovative financing mechanism to subsidise ACTs at the factory gate for distribution to the public, private for-profit and non-profit-making sectors, with additional interventions to ensure safe and effective drug use. AMFm has been implemented since mid-2010 in eight national-scale pilots, with over 220 million subsidised treatments ordered by March 2012.

Anti-malarial subsidies combined with supporting interventions can be effective in rapidly improving availability, price, and market share of quality-assured ACTs, particularly in the private for-profit sector. AMFm was an innovative financing mechanism, piloted and evaluated on a national scale under ‘real life’ conditions. Evaluation methods for such interventions need to account for intervention complexity and the implementation environment.

**References:** 37, 47
Multi-centre Phase IIb efficacy trials of the GMZ2 and the MSP3-LSP malaria vaccines

**TEG investigators:** Paul Milligan, Andrea Rehman

**Other LSHTM investigators:** Samuel Bosomprah

**External investigators/collaborators:** Tiono Alfred, Sodiomon Sirima (Centre National de Recherche, Burkina Faso), Saadou Isifou (Lambarène, Gabon), Fred Kironde (Makerere University, Uganda), Kalifa Bojang (MRC, The Gambia), Ogobara Doumbo (Co-PI), Issaka Sagara, Mahamadou Sissoko (MRTC, Mali), Frank Atuguba (Navrongo Health Research Centre, Ghana), Dawit Ejigu, Soren Jepsen, Brenda Okech, Michael Thiesen (Co-PI) (Statens Serum Institut, Denmark), Benjamin Mordmüller (University of Tubingen, Germany), Pierre Druihle, Zarifah Reed (Vac4All)

**Funding:** EDCTP, Vac4All

**Location:** Burkina Faso, Gabon, Ghana, Mali, Uganda

**Objective**
To assess whether two similar vaccines (GMZ2 and MSP3-LSP) can protect against clinical attacks of malaria in children aged 1-5 years in different epidemiological settings.

**Description**
GMZ2 and MSP3-LSP are two malaria vaccines that are designed to prevent malaria illness by eliciting immune responses that block invasion of red blood cells by the parasite. These are the first large-scale efficacy trials of malaria vaccines that target the blood-stage of the parasite.

GMZ2 is a recombinant fusion protein of *Plasmodium falciparum* glutamate-rich protein and merozoite surface protein 3, adjuvanted with aluminium hydroxide. A cohort of 1840 children have been enrolled into a Phase IIb trial, and randomised to receive three doses of GMZ2 or rabies vaccine. Follow-up will be for 22 months from the third vaccination.

The primary endpoint is the incidence of clinical malaria detected by passive surveillance over a 6-month period from the third vaccination.

The MSP3-LSP is a synthetic peptide of 95 amino acid residues. Phase I trials have shown the vaccine is safe and immunogenic and have provided preliminary evidence of efficacy. This Phase IIb efficacy trial is being conducted in two sites in Mali: Doneguebougou, which has a short transmission season, and Bougoula, with a longer wet season. In 2011, 400 children aged 12-48 months were enrolled in each site and randomised to receive three doses 1 month apart of 30 μg MSP3-LSP adjuvanted in aluminium hydroxide, or rabies vaccine, followed by a fourth dose 3 months after the third dose. Follow-up will be for 2 years. Preliminary efficacy results expected in mid-2013 will determine whether these vaccines can protect against malaria and should be developed further.

**Reference:** 3

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An RCT of a prophylaxis regimen for the prevention of malaria and related complications, in patients with sickle cell anaemia from Nigeria

**TEG investigators:** Paul Milligan (PI), Andrea Rehman

**Other LSHTM investigator:** Brian Greenwood

**External investigators/collaborators:** Rasaq Olaosebikan (PI), Kalifa Bojang (MRC, The Gambia), Ernest Kolade, Olugbenga Mokuolu (University of Ilorin Teaching Hospital, Nigeria)

**Funding:** Wellcome Trust

**Location:** Nigeria

**Objective**
To compare the safety, tolerability and acceptability of supervised bimonthly treatment with either sulfadoxine-pyrimethamine plus amodiaquine or mefloquine plus artesunate, with
unsupervised daily proguanil, for preventing malaria in children with sickle cell anaemia.

**Description**
Effective prophylaxis should be provided for people with sickle cell disease in malaria endemic areas. In Nigeria, daily proguanil or weekly pyrimethamine are the most commonly prescribed regimens, but the effectiveness of this policy is limited by poor compliance and drug resistance. Patients with sickle cell disease who are stable are recommended to visit the clinic every 2 months. A long-acting drug regimen that could provide prophylaxis for 2 months could be administered under supervision at each clinic visit. This might be more effective than the current practice that relies on patients remembering to take their prophylaxis regularly.

In this trial, 270 patients with sickle cell disease attending the paediatric sickle cell disease clinic in Ilorin hospital were randomised to one of the three prophylactic regimens and were asked to return to the clinic every 2 months and whenever they were sick. This study is ongoing, and participants will be followed for 1 year. Results should be available later in 2013.

**Interventions to improve community case management of malaria in sub-Saharan Africa: a systematic review**

**TEG investigator:** Barbara Willey

**Other LSHTM investigators:** Lucy Paintain (PI), David Schellenberg, Jayne Webster

**External investigators/collaborators:** Valentina Buj, Julia Kim, Ngashi Ngongo, Alyssa Sharkey (UNICEF, New York)

**Funding:** UNICEF

**Location:** Sub-Saharan Africa

**Objective**
A systematic review to update a previous review from the era before artemisinin combination therapy and rapid diagnostic testing, to expand the knowledge base on community case management (CCM) of malaria in sub-Saharan Africa.

**Description**
In total, 33 papers covering a total of 36 studies in 15 African countries were reviewed. Overall, 27 studies evaluated malaria CCM alone, 16 of these by presumptive diagnosis and 11 by confirmed diagnosis; the other nine studies evaluated malaria CCM integrated with other basic health services. Six main strategies emerged from the review as being important determinants of the success of malaria CCM for children:
1. practical and interactive training;
2. clear guidelines with simple algorithms;
(iii) pre-packaging of medicines in appropriate doses; (iv) regular supportive supervision; (v) a functional referral system from the community to health facility level; and (vi) appropriate demand generation.

Due to the multi-faceted nature of many of the community health worker studies, it is difficult to directly link outcomes to individual components of the intervention. Nevertheless, all of these strategies play some part in the success of a community health worker programme and their impact if implemented in combination is likely to be greater.

Epidemiology of pre-elimination border malaria in northern Namibia

TEG investigator: Immo Kleinschmidt (Co-PI)

External investigators/collaborators:
Roly Gosling (PI), Hugh Sturrock (University of California San Fransisco, USA), Stark Katokele (MoH, Namibia), Davis Mumbengegwi, Ronnie Bock (University of Namibia, Windhoek)

Funding: Bill and Melinda Gates Foundation

Location: Namibia

Objective
To identify key risk factors associated with having confirmed malaria, to pilot active case detection in Namibia, and to determine whether infections cluster around confirmed cases (i.e. whether hotspots of infection exist around passively identified cases).

Description
Malaria incidence has declined to low levels in Namibia, and the country has set 2020 as the target for malaria elimination. Many of the residual cases occur in the border regions with Angola. It is possible that malaria transmission is associated with cross-border movements of people between Angola and Namibia. This study will document the epidemiology of malaria in northern Namibia and strengthen the malaria surveillance system in one of the border districts with Angola. A case-control study is being conducted to assess risk factors for malaria, including cross-border travel, intervention coverage and compliance, and other local factors. By mapping cases and controls, and testing for subpatent infections and antibody seroconversions in the neighbourhood of each participant, the study will investigate the existence of any hotspots of transmission, and the extent to which recent cross-border travel poses a risk of infection. Data collection is currently underway.

Results of the study in northern Namibia will help the National Malaria Control Programme of Namibia to optimise its strategies for malaria elimination.
HIV and other sexually transmitted infections

The main aim of the Group’s work on HIV research is to evaluate prevention and treatment strategies. In 2011-12, we have continued long-standing collaborations with the MRC/UVRI Unit in Uganda and MITU/NIMR in Tanzania, for example through the EDCTP/MRC-funded cohort of women at high risk, which highlighted the need for interventions to treat sexually transmitted infections (STIs), and to address alcohol use disorders in these vulnerable populations.

There is increasing emphasis on the need for combination HIV prevention strategies, and the role of treatment as prevention. Mathematical models have predicted that test-and-treat interventions, in which the entire community is encouraged to access voluntary HIV testing with immediate onset of antiretroviral therapy (ART) for those infected (irrespective of CD4 count) may lead to steep reductions in HIV incidence. TEG has secured a major grant for the PopART trial, a three-arm cluster RCT in Zambia and South Africa that will evaluate the effectiveness of offering household-based HIV testing and offering immediate ART to all those testing positive.
HIV/AIDS prevention projects in Mozambique
© Sarah Bandali, LSHTM
HIV epidemiology

General Population Cohort

TEG investigators: Kathy Baisley, Sian Floyd, Heiner Grosskurth (MITu/NIMR, Tanzania), Richard Hayes, Natasha Larke, Helen Weiss

External investigators/collaborators: Anatoli Kamali (PI), Gershim Asiki, Samuel Biraro, Jonathan Levin, Dermot Maher, Billy Mayanja, Jessica Nakiyingi-Miiro, Rebecca Nsubuga, Janet Seeley, Laban Waswa (MRC/UVRI Unit, Uganda)

Funding: MRC

Location: Uganda

Objective
To examine the social and behavioural factors that determine the changing course of the HIV epidemic and the epidemiology of risk factors for non-communicable diseases in rural Uganda.

Description
The General Population Cohort was established in 1989 as an open community-based cohort in Masaka district, Uganda. The annual surveys have provided data on HIV prevalence and incidence, and the sociodemographic impact of the HIV epidemic in this population for over 20 years. Recent studies with TEG involvement include the epidemiology of sexual behaviour patterns, HIV and herpes simplex virus type-2 infections, evaluation of respondent-driven sampling (p71), and prevalence of indicators for selected non-communicable diseases and mental illness. The General Population Cohort is one of 10 population-based cohorts in sub-Saharan Africa in the Analysing Longitudinal Population-based HIV/AIDS data in Africa (ALPHA) network, which contributes to the development of evidence-based policy on HIV prevention.

References: 53, 84, 87, 88, 91, 102, 104, 105, 131-133, 179, 231, 243, 244, 300

Good Health for Women Project, Kampala

TEG investigators: Heiner Grosskurth (Co-PI; MITu/NIMR, Tanzania), Richard Hayes, Helen Weiss

External investigators/collaborators: Peter Hughes, Pontiano Kaleebu, Yunia Mayanja, Janet Seeley, Judith Vandepitte (Co-PI) (MRC/UVRI Unit, Uganda)

Funding: MRC

Location: Uganda

Objective
To investigate the epidemiology of HIV and other STIs in a cohort of women at high risk in Kampala.

Description
A cohort of 1027 women involved in high-risk sexual behaviour in Kampala was enrolled between April 2008 and May 2009. Participants were seen every 3 months, and data were collected on sociodemographic variables and risk behaviour. Blood and genital samples were tested for HIV and other STIs. HIV prevalence at baseline was 37%, and STIs were also highly prevalent. During the first 3 years, HIV incidence was 3.66/100 person-years and was independently associated with younger age, number of paying partners, inconsistent condom use, alcohol use and STI infections. Most (78%) participants reported using alcohol, and over two-thirds of users were classified as problem drinkers. Baseline prevalence of Mycoplasma genitalium infection was 14%, and was significantly associated with HIV prevalence and incidence. For almost half the women, the infection persisted for at least 3 months after enrolment, and 39% of those who spontaneously cleared the infection retested positive within 3-6 months.

References: 143-146

The high prevalence of HIV and STIs in this vulnerable population of women in Kampala calls for focused interventions, including alcohol-reduction interventions and intensification of STI screening and treatment.
HIV and ageing in South Africa

**TEG investigator:** Helen Weiss

**Other LSHTM investigators:** Sophia Pathai (PI), Leris D’Costa, Clare Gilbert, Stephen Lawn

**External investigators/collaborators:**
- Tien Wong (National University of Singapore)
- Tunde Peto (UCL, UK)
- Colin Cook (University of Cape Town, SA)
- Paul Shiels (University of Glasgow, UK)

**Funding:** Wellcome Trust

**Location:** South Africa

**Objective**
To assess whether HIV-infected individuals demonstrate greater levels of ocular ageing, systemic frailty and cellular senescence than a HIV-uninfected group of similar age.

**Description**
HIV infection is associated with an increased risk of age-related morbidity mediated by immune dysfunction, atherosclerosis and inflammation. Changes in retinal vessel calibre may reflect cumulative structural damage arising from these mechanisms. This case-control study enrolled 242 HIV-infected adults and 249 age- and gender-matched HIV-negative controls, aged ≥30 years, from a community-based HIV treatment centre in Nyanga District of Cape Town. Retinal vessel calibre was measured using computer-assisted techniques to determine mean arteriolar and venular diameters of each eye. Frailty was defined by standardised assessment comprised of three or more of weight loss, low physical activity, exhaustion, weak grip strength, and slow walking time.

There was little evidence of a difference in retinal diameters between HIV-infected and control cases, but among the HIV-positive cases, narrowing of retinal arteriolar diameters was associated with duration of use of highly active antiretroviral therapy (ART) and viral load. Frailty was associated with HIV infection, especially in women, and among HIV-infected individuals, frailty was most prevalent among those with lower CD4 counts. The corneal endothelium also showed features consistent with HIV-related accelerated senescence (biological ageing), especially among those with poor immune recovery.

**References:** 118, 120-122

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Male circumcision for HIV prevention

**Male circumcision and risk of human papillomavirus infection, genital warts and penile cancer in men: a systematic review

**TEG investigators:** Helen Weiss (PI), Natasha Larke

**Other LSHTM investigators:** Isabel dos Santos Silva, Sara Thomas

**Funding:** WHO

**Objective**
To systematically review the evidence for an association between male circumcision and male HPV infection, genital warts and penile cancer.

**Description**
We identified 23 papers on the association of male circumcision and HPV DNA and 8 papers on the association with penile cancer. Circumcised men were less likely to have prevalent genital HPV infection than uncircumcised men. There was weak evidence that circumcision was associated with decreased HPV incidence and increased HPV clearance, and no evidence of an association with prevalent...
Male circumcision reduces the risk of penile cancer, and to a lesser extent, HPV infection.

References: 93, 94

Increasing uptake of voluntary medical male circumcision among men in Tanzania

TEG investigators: Richard Hayes, Helen Weiss

Other LSHTM investigators: Saidi Kapiga (MITU/NIMR, Tanzania), Fern Terris-Prestholt

External investigators/collaborators: Wambura Mwita (PI), Jonathan Grund, Naomi Bock (CDC, USA), Hally Mahler, Marya Plotkin (Jhpiego, USA), John Changalucha, Gerry Mahana (NIMR, Tanzania)

Funding: CDC

Location: Tanzania

Objective
To evaluate a strategy to increase uptake of voluntary medical male circumcision among men aged 20-34 years in Tanzania, to provide greatest population-level benefit for HIV prevention and to meet national targets.

Description
Male circumcision provides partial protection against HIV in heterosexual men. In 2010, Tanzania launched a national strategy for scaling-up male circumcision and aims to circumcise 2.8 million males by 2015. However, most circumcision clients are aged 10-19 years yet the greatest population-level benefit of circumcision on HIV incidence will be achieved by men in their 20s and 30s being circumcised, when HIV incidence is highest.

We are conducting qualitative studies to identify barriers and facilitating factors to the uptake of male circumcision services among males aged 20-34 years in Iringa and Tabora regions and will use these findings to develop an intervention to increase circumcision uptake in this age group. We will then evaluate the effectiveness of the intervention using a cluster RCT. Sixteen facilities providing circumcision services will be randomised into either the intervention group (implementing the piloted intervention) or the control group (providing the standard circumcision package). The primary outcomes will be the proportion of circumcision clients who are aged 20-34 years, and the mean number of clients in this age group who attend each week. Results are expected in 2014.

Early Infant Male Circumcision study

TEG investigators: Natasha Larke, Helen Weiss

External investigators/collaborators: Gerald Gwinji (PI), Frances Cowan (CeSHHAR, Zimbabwe and UCL, UK), Webster Mavhu (CeSHHAR, Zimbabwe), Cynthia Chasokela, Notando Motobi, Owen Mugurungi, Getrude Ncube, (Ministry of Health & Child Welfare, Zimbabwe), Karin Hatzold (Population Services International, USA), Harsha Thirumurthy (University of North Carolina, USA), Christopher Samkange, Ismail Ticklay (Co-PI; University of Zimbabwe)

Funding: Bill and Melinda Gates Foundation

Location: Zimbabwe

Objective
To assess the feasibility, safety and acceptability of implementing early infant male circumcision (EIMC) by comparing a standard clamp with a new disposable device.

Description
Zimbabwe intends to roll-out EIMC alongside adult circumcision for sustainable HIV prevention. Although the effect of EIMC on HIV acquisition will take longer to realise, it is less expensive than adult circumcision and easier, faster and safer to perform. EIMC can be conducted surgically or with a device. One EIMC device that has been approved for...
use in the USA and Europe is the AccuCirc. This disposable device has the potential advantage that it does not involve any cutting so there is no possibility of penile amputation and it does not require re-use/sterilisation. By contrast, the standard Mogen clamp needs to be sterilised between clients and requires a highly skilled operator to minimise the (small) risk of distal tip amputation or inadequate foreskin resection.

This study is piloting roll-out of EIMC in Zimbabwe, comparing AccuCirc and the Mogen clamp. If AccuCirc has an acceptable safety profile, it will be evaluated in a larger field study to explore use of the device in various health facility settings by nurses and midwives.

The study will provide information about future scale up of EIMC in southern Africa utilising a new device which can be used by non-surgically trained staff.

Male Circumcision Uptake Trial (MCUTS)

TEG investigators: David Ross (Co-PI), Helen Weiss

External investigators/collaborators:
Kenneth Bhauti, Jeff Decelles (Grassroot Soccer, Zimbabwe), Paul Makoni (National University of Science and Technology, Zimbabwe), Zachary Kaufman (Co-PI; Wits Reproductive Health and HIV Institute, SA and LSHTM PhD student)

Funding: Doris Duke Foundation and Bill and Melinda Gates Foundation

Location: Zimbabwe

Objective
To evaluate the effectiveness of one 90-minute football-themed group session to promote voluntary medical male circumcision (VMMC) among football teams in terms of uptake of VMMC.

Description
Grassroot Soccer’s (GRS) Make-The-Cut intervention is the first VMMC promotion strategy in Africa to use football as an entry point. One 90-minute interactive, football-themed session, delivered to teams involving men aged 18 years and older, will be led by trained, circumcised GRS coaches. After the session, participants will receive a poster and subsequently a series of text (SMS) reinforcing messages from the session, telling them where they can go for VMMC. GRS coaches will have referral cards to directly refer participants seeking VMMC after the session.

The effectiveness of the intervention in increasing VMMC uptake over 3 months will be evaluated through a cluster RCT. Participating teams have been randomly allocated to intervention (43 teams) and control (21 teams) groups. The intervention teams have been further randomised to either have the intervention delivered by well-known, circumcised local professional soccer players (22 teams) or by circumcised men who are not professional soccer players (21 teams). Baseline and 3-month follow-up surveys assessing VMMC-related knowledge, attitudes and reported sexual behaviour will be self-administered via android-enabled mobile phones using Open Data Kit. Results should be available by mid-2013.

MCUTS is the first RCT of a sport-based VMMC promotion intervention.
Vaginal microbicides

Microbicide feasibility study

**TEG investigators:** Richard Hayes (PI), Kathy Baisley, Fiona Ewings (MITu/NIMR, Tanzania), Suzanna Francis, Heiner Grosskurth (MITu/NIMR, Tanzania)

**Other LSHTM investigators:** Aura Andreasen, Tony Ao, Saidi Kapiga, Deborah Watson-Jones (all MITu/NIMR, Tanzania)

**External investigators/collaborators:** Aika Mongi (MITu/NIMR, Tanzania), Justine Bukunya, Judith Vandepitte (MRC/UVRi Unit, Uganda)

**Funding:** MRC and EDCTP

**Location:** Tanzania, Uganda

**Objective**
To enrol a cohort of 970 HIV-negative women working in bars and other facilities in three towns in northwestern Tanzania and 646 HIV-negative female sex workers in Uganda were enrolled in the study and followed every 3 months. Retention rates at 12 months were high (84% in Tanzania and 77% in Uganda). Preliminary results showed HIV incidence of 4.1/100 person-years in Tanzania and 4.3/100 person-years in Uganda, and there was a high prevalence of other STIs and high-risk sexual behaviour. Pregnancy rates were high, pointing to the need for more intensive measures in future trials to promote the use of effective contraceptive methods.

**Description**
A cohort of 970 HIV-negative women working in bars and other facilities in three towns in northwestern Tanzania and 646 HIV-negative female sex workers in Uganda were enrolled in the study and followed every 3 months. Retention rates at 12 months were high (84% in Tanzania and 77% in Uganda). Preliminary results showed HIV incidence of 4.1/100 person-years in Tanzania and 4.3/100 person-years in Uganda, and there was a high prevalence of other STIs and high-risk sexual behaviour. Pregnancy rates were high, pointing to the need for more intensive measures in future trials to promote the use of effective contraceptive methods.

Further analysis of data from the Tanzanian cohort and women recruited to an HIV vaccine feasibility study in Moshi, Tanzania, has evaluated the prevalence, incidence and risk factors for HIV and herpes simplex virus type-2 (HSV2) infection. Overall incidence rates were 3.7 and 28.6/100 person-years for HIV and HSV2, respectively. Related work in the same cohorts has shown high rates of problem drinking and demonstrated significant associations between alcohol use and risky sexual behaviour.

**References:** 54, 144

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Characterisation of microbicide safety biomarkers in sub-Saharan Africa

**TEG investigators:** Kathy Baisley, Richard Hayes (Co-PI), Suzanna Francis

**Other LSHTM investigators:** Aura Andreasen, Saidi Kapiga, Deborah Watson-Jones (all MITu/NIMR, Tanzania)

**External investigators/collaborators:** Carolina Herrera, Robin Shattock (Co-PI) (ICL, UK), Vicky Jespers (ITM Antwerp, Belgium), Gary Coulton, Yanwen Hou (St George’s Hospital, UK), Janneke van de Wijgert (University of Liverpool, UK)

**Funding:** EDCTP, MRC, the International Partnership for Microbicides, European Community (Grant EU-FP7)

**Location:** Tanzania

**Objective**
To characterise 41 biomarkers in the cervicovaginal environment of HIV-negative adult women at increased risk for HIV, to investigate variations with menstrual cycle, hormonal contraception, semen exposure and intravaginal practices, and to report associations with reproductive tract infections or STIs.

**Description**
One hundred women from the Tanzanian Microbicide feasibility study were
purposively recruited according to reported intravaginal practices at enrolment into the cohort. Consenting participants were followed three times per week for 4 weeks (12 visits). Colposcopy and tests for *Chlamydia* infection, gonorrhoea and trichomoniasis were conducted at the first and last visits. Samples for the measurement of biomarkers and bacterial vaginosis were obtained at all 12 visits. Biomarkers were tested using Luminex Multiplex at St George’s Hospital, UK. Results will be available in 2013.

### Intravaginal practices project

**TEG investigators:** Richard Hayes (PI), Kathy Baisley, Suzanna Francis, Heiner Grosskurth (MITu/NIMR, Tanzania)

**Other LSHTM investigators:** Aura Andreasen, Tony Ao, Saidi Kapiga, Deborah Watson-Jones, (all MITu/NIMR, Tanzania), Shelley Lees

**External investigators/collaborators:** Justine Bukunya, Janet Seeley, Judith Vandepitte, Flavia Zalwango (MRC/UVRi Unit, Uganda), Bahati Andrew, John Changalucha, Joseph Chilongani, Clemens Masesa, Kaballa Maganja (NIMR, Tanzania), Janneke van de Wijgert (University of Liverpool, UK)

**Funding:** EDCTP, MRC and the International Partnership for Microbicides

**Location:** Tanzania, Uganda

**Objective**

To investigate the epidemiology of intravaginal practices (IVP), changes in the vaginal microbiota, and risk of HIV/STIs among women at high risk of HIV in Tanzania and Uganda.

### Bacterial vaginosis among women at high risk of HIV in East Africa

**TEG investigators:** Suzanna Francis (PI), Kathy Baisley, Richard Hayes

**Other LSHTM investigators:** Aura Andreasen, Saidi Kapiga, (both MITu/NIMR, Tanzania) Martin Holland, David Mabey

**External investigators:** Rita Verhelst (ICRH, Belgium), Tania Crucitti, Vicky Jespers (ITM Antwerp, Belgium)

**Funding:** MRC Population Health Scientist Fellowship

**Location:** Tanzania

**Objective**

To investigate the role of host behaviour, immune response, genetics and the vaginal microbiome in bacterial vaginosis (BV) and to develop a framework to design future interventions against BV.

### Intravaginal practices project

**Description**

The prevalence of IVP and effects on HIV incidence were prospectively measured among 970 women at increased risk for HIV participating in the Microbicide Feasibility Study (p32) in Tanzania and Uganda. Intravaginal cleansing was highly prevalent in both cohorts (Tanzania, 92%; Uganda, 94%). However, insertion of cleaning substances was more common among Ugandan women than Tanzanian women (50% vs. 13%). Cleansing was not a predictor of HIV in this study and may be protective. However, some substances used for insertion may be harmful. These rarer and more harmful types of IVP warrant further investigation.

A substudy investigated IVP behaviours further, using a daily self-administered diary to record vaginal practices and sexual behaviour among 200 women. A comparison of diary results and answers in a face-to-face interview found that recall of IVP was improved using the diary, especially for frequency of cleansing and cleansing in proximity to sexual intercourse. The vaginal practices diary can provide a more detailed understanding of IVP and aid in the interpretation of findings from the face-to-face interview. Additionally, in this detailed substudy, differences in IVP between the cohorts reflected differences in sexual behaviour between populations, and may warrant different approaches to interventions targeting IVP.

### Differences in intravaginal practices between cohorts were likely to reflect differences in sexual behaviour and may warrant different approaches to interventions targeting intravaginal practices in different populations.

**References:** 99, 295

**Developing novel strategies for the treatment or prevention of BV may reduce reproductive health burden and HIV transmission.**
Behavioural interventions

Effects of cash transfer for the prevention of HIV in young South African women (HPTN 068)

TEG investigator: James Hargreaves (PI)

External investigators/collaborators: Audrey Pettifor (PI; University of North Carolina, USA), Kathleen Kahn, Catherine MacPhail (University of the Witwatersrand, SA)

Funding: US National Institute of Mental Health and HIV Prevention Trials Network

Location: South Africa

Objective
To determine whether providing cash transfers to young women and their household, conditional on school attendance, reduces young women’s risk of acquiring HIV.

Description
School attendance can reduce young women’s vulnerability to HIV infection. The overall aim of the Conditional Cash Transfer intervention is to reduce structural barriers to education with the goal of increasing school attendance of young women, and thus decrease their HIV risk. Young women and their households in 24 villages in South Africa have been randomised 1:1 to receive monthly cash transfer payments, or not (those not receiving cash transfer forming the control arm). The study, which will last approximately 4 years, completed enrolment at the end of 2012 with 2430 young women enrolled. Follow-up visits will take place throughout 2013 with assessments of participants and parents/legal guardians taking place at 12, 24 and 36 months from baseline. The primary outcome is HIV incidence, with additional outcomes of herpes simplex virus type-2 incidence and reported sexual behaviour.

In South Africa, by the time a woman reaches age 21 years, she has a 30% chance of being infected with HIV. Attention to structural factors, such as education and poverty, is key to preventing transmission in young women.

The GOAL trial

TEG investigators: David Ross (Co-PI), Helen Weiss

Other LSHTM investigator: Zachary Kaufman

External investigators/collaborators: Elise Braunschweig, Tommy Clark, Jeff Decelles (Grassroot Soccer), Sinead Delany-Morettwe (Co-PI; Wits Reproductive Health and HIV Institute, SA)

Funding: Comic Relief, MAC AIDS Fund

Location: South Africa

Objective
To evaluate the effectiveness of a Grassroot Soccer’s sport-based HIV prevention intervention (Generation Skillz) on self-reported sexual risk behaviours, perpetration of gender-based violence, attitudes and knowledge in secondary schools in South Africa.

Description
Previous research shows high levels of reported rape and intimate-partner violence perpetration in South Africa, and a strong association with increased HIV risk among both male perpetrators and female victims. We are collaborating on a cluster RCT in which 46 high schools in Cape Town and Port Elizabeth, South Africa, were randomised to receive either the Generation Skillz intervention in School Year 9 with a booster in Year 10 led by trained Grassroot Soccer coaches, or standard life-orientation classes led by teachers. Generation Skillz uses soccer themes, activities and metaphors to start discussions on sexual risk behaviour and gender-based violence. The 23 intervention schools have been further randomised into two groups, with one receiving fortnightly short text messages to reinforce the intervention. A total of 4485 grade nine students (median age 15 years) have been enrolled. Key outcomes at 12-month and 24-month follow-up include measures of reported age-disparate sex, multiple partners, perpetration of intimate-partner violence and perpetration of rape. Preliminary results are expected in 2013 and final results in 2014.

Reference: 89

In South Africa, by the time a woman reaches age 21 years, she has a 30% chance of being infected with HIV. Attention to structural factors, such as education and poverty, is key to preventing transmission in young women.
HIV prevention in Tanzania: the role of types of sexual partnership, early sexual history and community factors

TEG investigators: Aoife Doyle (PI), James Hargreaves, Richard Hayes, Immo Kleinschmidt, David Ross, Helen Weiss

Other LSHTM investigator: Basia Zaba

External investigators/collaborators: Mary Plummer (Freelance Social Scientist, Dar es Salaam), John Changalucha, Joyce Warnoi (NIMR, Tanzania), Danny Wight (University of Glasgow, UK)

Funding: MRC Population Health Scientist Fellowship

Location: Tanzania

Objective
To investigate factors associated with the prevalence of HIV and STIs among youth in rural Tanzania in order to improve HIV prevention intervention design and evaluation.

Description
Prevention interventions such as sex education in schools can increase knowledge about HIV and sexual and reproductive health. However, such interventions have not been demonstrated to reduce the number of young people infected with HIV and other STIs. There is a gap between knowledge of how to avoid HIV and other sexual risks among young people and actual behaviour change. We need to find effective ways to prevent HIV among young people in sub-Saharan Africa.

This research will use data collected during a survey of 13,000 young people in rural Tanzania. Participants reported sexual partnerships and described the type of relationship with each of their recent sexual partners. We will map the study population to see whether young people infected with HIV live in certain areas (e.g., near to a major road or town) and to increase our understanding of where and when a young person is most likely to take risks. We will also study the types of recent partnerships that are associated with being HIV infected. The results of this research will be used to design interventions that will help young people to reduce their risk of being infected.

Following young people through the transition from adolescence to adulthood provides an opportunity to understand the key geographical and behavioural factors that put young people at high risk of HIV in rural Tanzania.

HIV awareness seminar, Tanzania
© Mina Robert
HIV treatment as prevention

Population effects of antiretroviral therapy to reduce HIV transmission, PopART (HPTN 071)

TEG investigators: Richard Hayes (PI), Sian Floyd, James Hargreaves, Kalpana Sabapathy

Other LSHTM investigators: Helen Ayles (Director of ZAMBARt, Zambia), Peter Godfrey-Faussett, James Hargreaves, Deborah Watson-Jones (MITu/NIMR, Tanzania)

External investigators/collaborators: Leads: Sarah Fidler, Christophe Fraser, Peter Smith (ICL, UK), Nulda Beyers, Peter Bock (University of Stellenbosch, SA); in collaboration with the HIV Prevention Trials Network and Family Health International 360

Funding: NIH, PEPFAR and Bill and Melinda Gates Foundation (through 3ie)

Location: South Africa, Zambia

Objective
To test the hypothesis that a combination prevention package, including immediate antiretroviral therapy (ART) for all individuals who test HIV positive, will substantially reduce HIV incidence at a population level.

Description
PopART is designed to evaluate a universal testing and treatment prevention package using a combination of interventions including voluntary home-based HIV testing, promotion of proven HIV prevention methods (including medical male circumcision, prevention of mother-to-child transmission and condom distribution) and provision of ART irrespective of immune status for HIV-infected individuals in the main intervention arm. The three-arm, cluster RCT will be implemented in 21 communities, 12 in Zambia and 9 in South Africa. The prevention packages will be implemented throughout the communities randomised to the intervention arms, with a combined population of approximately 800,000 individuals (adults and children) in these arms. The primary outcome will be measured in a population cohort consisting of 2500 individuals randomly selected from each community (52,500 in total). The study will last approximately 6 years, with enrolment and follow-up of communities and delivery of the intervention occurring over 4 years. Assessment of the primary outcome (HIV incidence) in the population cohort will occur at 12, 24 and 36 months after recruitment. Several secondary outcomes will be measured to examine the impact of the interventions, and substudies will be carried out to access factors associated with uptake and the cost-effectiveness of the approach. Mathematical modelling using trial data will be undertaken.

PopART trial results will provide valuable information on the feasibility, acceptability and impact of this ambitious population-wide intervention strategy which will inform health policy in countries with generalised HIV epidemics.

References: 77, 130

HIV treatment and adherence

Adherence among refugees and host populations in Malaysia and Kenya

TEG investigators: Natasha Larke, David Ross (Co-PI)

Other LSHTM investigators: Alison Grant, Joshua Mendelsohn, Tim Rhodes, Egbert Sondorp

* Interventions will be delivered community-wide in arms A and B (facilitated by CHiPs)

** The primary outcome will be measured in the Population Cohort, who will be surveyed at 12-monthly intervals up to 36 months

Distribution of participants across the three study arms of PopART (ART = antiretroviral therapy)

<table>
<thead>
<tr>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
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<tbody>
<tr>
<td>Full PopART intervention*</td>
<td>PopART intervention* except ART initiation according to current national guidelines</td>
<td>Standard of care at current service provision level including ART initiation according to current national guidelines</td>
</tr>
<tr>
<td>including immediate ART irrespective of CD4 count</td>
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Primary Outcome Measure: HIV incidence measured at 36 months in randomly selected Population Cohort (52,500) i.e. 2,500 individuals per community in all 3 study arms **
External investigators/collaborators:
Susheela Balasundaram, John Burton, Nadine Corrner, Marian Schilperood, Paul Spiegel (Co-PI) (UN High Commissioner for Refugees)

Funding: UN High Commissioner for Refugees

Location: Kenya, Malaysia

Objective
To investigate adherence to highly active antiretroviral therapy (HAART) and virological treatment outcomes among refugees and host community members attending the same clinics in Kuala Lumpur, Malaysia, and Kakuma, Kenya.

Description
A total of 153 refugee and 148 host clients were recruited in Kuala Lumpur and 73 refugee and 86 host clients in Kakuma. A structured questionnaire with self-reported adherence measures, a pharmacy-based prescription refill measure, HIV viral loads, and in-depth interviews were administered to all participants. There were no significant differences in measures of HAART adherence or viral load between refugees and the host community in either setting, but a large difference between the settings. In Malaysia, 83% of clients taking HAART had HIV viral suppression while only 11% were suppressed in Kenya.

Refugees should have equal access to HIV treatment based on the principles of fairness, human rights and individual and population-based public health benefit. Since HIV-positive individuals on HAART with good adherence will rarely transmit HIV to their sexual partners, it is in the interest of host country governments to support HIV programmes that serve HIV-positive refugees and host clients equally.

Reference: 106

Zimbabwe Study to Enhance testing and Improve Treatment of HIV; the ZENITH project

TEG investigators: Richard Hayes, Helen Weiss

Other LSHTM investigators: Rashida Ferrand (PI), Joanna Busza, Liz Corbett

External investigators/collaborators: Peter Mason (Biomedical Research and Training Institute, Zimbabwe), Stanley Mungofa (Harare City Health, Zimbabwe), Owen Mugurungi (Ministry of Health & Child Welfare, Zimbabwe), Sarah Rowland-Jones (University of Oxford, UK), Hilda Mujuru (University of Zimbabwe)

Funding: Wellcome Trust Intermediate Fellowship

Location: Zimbabwe

Objective
To investigate whether a community-level intervention, delivered by trained voluntary lay workers, will improve retention in care and adherence to treatment of newly diagnosed vertically infected HIV-positive children and adolescents in Harare, Zimbabwe, compared with standard HIV care.

Description
The hypotheses for this study are three-fold. Firstly, that optimised routine opt-out HIV testing and counselling of children aged 8-15 years attending acute primary care services will provide near-complete and timely diagnosis of long-term survivors living in primary care clinic catchment areas. Secondly, that decentralised HIV care services are necessary but not sufficient to ensure good adherence and treatment outcomes, because of other factors in survivors of mother-to-child transmission, including their high risk of maternal orphanhood. Finally, that immediate initiation of antiretroviral therapy (ART) regardless of CD4 count may be indicated in this age group (as in infants), because of an otherwise unacceptably high risk of chronic complications, notably chronic lung disease and growth failure.

This study aims to estimate the proportion of HIV-infected children aged 8-15 years who are still undiagnosed after at least 2 years of provider initiated testing and counselling. Newly diagnosed HIV-infected children will be randomised to receive either the community-based intervention or the standard HIV care, with the aim of evaluating the effectiveness of the community-based intervention in improving retention in care and adherence to treatment. Children in HIV care will be enrolled into a 2-year cohort study, and lung function and growth will be evaluated longitudinally in the pre- and post-ART periods.
Reduction of early mortality among HIV-infected subjects presenting to health services with low CD4 counts (REMSTART): an RCT

**TEG investigators:** Christian Bottomley, Shabbar Jaffar (Co-PI), Victoria Simms

**Other LSHTM investigator:** Lorna Guinness

**External investigators/collaborators:** Saidi Egwaga (PI; MoH, Tanzania), Peter Mwaba (Co-PI; MoH Zambia), Sayoki Mfinanga (Co-PI; Muhumbili/NIMR, Tanzania), Tom Harrison (St George’s Hospital, UK), Duncan Chanda (uTH, Lusaka, Zambia)

**Funding:** EDCTP and MRC

**Location:** Tanzania, Zambia

**Objective**
To evaluate whether a complex intervention involving accelerated initiation of ART, increased involvement of lay workers in adherence and increased frequency of diagnostic testing for cryptococcal meningitis, leads to a reduction in mortality among patients initiating ART compared with current standard of care.

**Description**
Mortality of HIV-infected subjects is very high just prior to starting ART, and during the first 6-12 months. Health services in Africa have severe shortages of healthcare staff, particularly doctors and nurses. Lay workers are increasingly involved in healthcare, but evidence of their effectiveness is lacking, particularly in urban settings.

In this trial, 2500 participants with CD4 count <100 cells/μl are being randomised to the intervention strategy or control (standard care) in Dar es Salaam, Tanzania, and Lusaka, Zambia and followed for 12 months. The intervention comprises i) testing for cryptococcal infection using a point of care antigen test, ii) rapid initiation of antiretroviral therapy, iii) home-based adherence support during the first 4-6 weeks of therapy to supplement care provided at the clinic. The primary endpoint is all-cause mortality. Recruitment began in February 2012 and will close in 2013.

**Evaluation of strategies for the treatment of HIV-associated cryptococcal meningitis: the ACTA trial**

**TEG investigators:** John Bradley, Shabbar Jaffar, Victoria Simms

**External investigators/collaborators:** Tom Harrison (PI), Tihana Bicanic, Angela Loyse, Sile Molloy (St George’s Hospital, UK)

**Funding:** MRC

**Location:** Cameroon, Malawi, Zambia

**Objective**
To evaluate different strategies for the treatment of cryptococcal meningitis in a phase III trial in Malawi, Zambia and Cameroon.

**Description**
Mortality from cryptococcal meningitis in Africa is very high, even among hospitalised patients. In developed countries, the current standard care for initial treatment comprises 2 weeks of amphotericin B-based therapy, but this is not practical in Africa as it requires intravenous administration and close monitoring for the duration of treatment.

We have been involved with phase II studies co-ordinated by St Georges Hospital Medical School, University of London, which compared various regimens; these findings were used to inform the present trial.

The present trial will compare an oral treatment (a combination of fluconazole and flucytosine), with a 1-week amphotericin B-based strategy, and with the standard of 2 weeks’ treatment with amphotericin B. A further comparison of fluconazole versus flucytocine is also nested within the trial. Results are expected to be available in early 2016.

**The ACTA trial will guide clinical practice for the management of HIV-associated cryptococcal meningitis.**
Nutritional support for African adults starting antiretroviral therapy (NUSTART)

**TEG investigators:** Natasha Larke, Andrea Rehman

**Other LSHTM investigators:** Suzanne Filteau (PI), Susannah Woodd

**External investigators/collaborators:** Paul Kelly (Barts & The London Hospitals, UK), Tsinuel Girma (Jimma University Specialised Hospital, Ethiopia), John Changalucha (NIMR, Tanzania), Henrik Friis (University of Copenhagen, Aase Bengaard Andersen (University of Southern Denmark), Jackson Kasonka, (UTH, Lusaka, Zambia), Douglas Heimburger, John Koethe (Vanderbilt University, USA)

**Funding:** EDCTP

**Location:** Tanzania, Zambia

**Objective**
To assess the effect of a two-stage micronutrient and electrolyte intervention on survival during the first 3 months of ART, among malnourished patients in sub-Saharan Africa.

**Description**
Micronutrient deficiencies and altered mineral metabolism associated with wasting malnutrition are potential risk factors for mortality among African patients referred for ART. This RCT compares a two-stage protocol, vitamin and mineral supplements versus placebo, given just after referral for ART for 6 weeks. In the first stage, the vitamins and minerals or placebo will be given with minimal calories from recruitment until 2 weeks after initiating ART, and then the same nutrients or placebo will be given in a calorie-rich supplement from 2 to 6 weeks after initiating ART. The primary outcome is survival from the time of referral for ART to 12 weeks after starting ART. Secondary outcomes include hospitalisation from referral to ART, gain in lean body mass and change in serum phosphate. Recruitment is due to be completed in August 2013.

Human papillomavirus-related studies

**HPV in Africa Research Partnership (HARP)**

**TEG investigator:** Helen Weiss

**Other LSHTM investigators:** Philippe Mayaud (PI), Lorna Gibson, Claire Gilham, Helen Kelly

**External investigators/collaborators:** Nicolas Nagot, Michel Segondy, Philippe Van de Perre (University of Montpellier, France), Joseph Drabo, Nicolas Meda, Bernard Sawadogo (University of Ouagadougou, Burkina Faso), Sinead Delany (University of Witwatersrand, SA)

**Funding:** European Community (Grant EU-FP7)

**Location:** Burkina Faso, South Africa

**Objective**
To improve cervical cancer prevention programmes for HIV-infected women in South Africa and Burkina Faso by evaluating the effectiveness and cost-effectiveness of alternative screening strategies, and by developing algorithms leading to earlier detection and management of cervical cancer in these high-risk populations. The study will evaluate CareHPV (a molecular diagnostic rapid HPV DNA test to screen for high-risk HPV designed for low-resource clinical settings) in an African environment.

**Description**
Every year, around a quarter of a million women die from cervical cancer, an almost entirely preventable disease, in part through lack of screening. Women living with HIV are at particular risk of being infected by high-risk HPV, and experience more rapid disease progression.

The study comprises three interlinked substudies: (i) a cross-sectional study of HPV and cervical neoplasia screening (using cytology, visual inspection (with acetic acid and with Lugol’s iodine) and a rapid HPV DNA test) among 1200 women attending HIV care centres in Johannesburg, South Africa and Ouagadougou, Burkina Faso; (ii) a cohort of 1200 women recruited in the cross-sectional study followed up for up to 18 months in order to evaluate the performance of screening tests in predicting the development or recurrence of cervical neoplasia; and (iii) a modelling study using data from the first two epidemiological studies to determine the cost-effectiveness and long-term impact of the various triage and screening strategies. Results are expected in 2014.

HARP is the first study with simultaneous evaluation of currently existing cervical cancer screening strategies against histological endpoints, conducted among HIV-infected African women.
Safety and immunogenicity of human papillomavirus vaccination in Tanzania

**TEG investigators:** Richard Hayes (PI), Kathy Baisley

**Other LSHTM investigators:** Aura Andreasen, Saidi Kapiga, Deborah Watson-Jones (Co-PI) (all MITu/NIMR, Tanzania), Joelle Brown, Philippe Mayaud

**External investigators/collaborators:** Kouro Bousso, Khadiata Diallo Mbaye, Papa Salif Sow (Co-PI), Macoumba Toure (CHU Fann, Dakar, Senegal), Dominique Descamps, Marjan Herazeh, Marie Lebacq, Florence Thomas (GSK Biologicals), John Changalucha, Bazil Kavishe (NIMR, Tanzania), Nancy Kiviat (University of Washington, USA)

**Funding:** GlaxoSmithKline Biologicals SA

**Location:** Senegal, Tanzania

**Objective**
To evaluate HPV-16/18 antibody response following HPV vaccination, among girls aged 10-25 years in sub-Saharan Africa, the region that bears the highest burden of cervical cancer.

**Description**
A Phase IIIb RCT of HPV-16/18 vaccine in girls aged 10-25 years old was undertaken in two sites, one in Tanzania and one in Senegal. Participants were randomised (2:1) to receive either active vaccine (450) or placebo (226) at 0, 1 and 6 months.

All initially seronegative girls in the vaccine arm had HPV-16/18 antibody at 7 months. Antibody was maintained at 12 months and was higher in younger girls. No participant withdrew owing to adverse events, and there were no vaccine-related serious adverse events.

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**Epidemiology and natural history of human papillomavirus in a cohort of adolescent Tanzanian girls**

**TEG investigators:** Kathy Baisley, Richard Hayes, David Ross

**Other LSHTM investigators:** Deborah Watson-Jones (PI), Aura Andreasen, Saidi Kapiga (all MITu/NIMR, Tanzania), Catherine Houlihan

**External investigators/collaborators:** Silvia de Sanjosé (Institut Catala d’Oncologia, Barcelona), John Changalucha (NIMR, Tanzania), Ivana Bozicevic (University of Zagreb, Croatia)

**Funding:** Wellcome Trust Clinical PhD Programme

**Location:** Tanzania

**Objective**
To assess the prevalence and incidence of HPV infection and clearance among young women in Tanzania.

**Description**
HPV infection is highly prevalent in many parts of Africa but the epidemiology and natural history of infection around the age of sexual debut are not well understood. A sample of 503 girls aged 15-16 years were enrolled into the cohort from 82 randomly selected primary schools in or near Mwanza. Of these, 481 reported not having commenced sexual activity. Participants are being followed every 3 months for 18 months, and self-administered vaginal swabs will be tested for the presence of HPV.

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Community social mobilisation about cervical cancer and HPV vaccination with a dance group in Mwanza, Tanzania © Deborah Watson-Jones, LSHTM
of HPV (genotyped by the polymerase chain reaction). The data will be used to estimate HPV prevalence at baseline; HPV incidence, persistence and clearance; and associated risk factors. A substudy will evaluate the use of audio computer-assisted self interview methods for the collection of sensitive behavioural data in this study population.

At baseline, HPV prevalence was 8.3% among girls reporting no sexual activity (5.3% prevalence of high-risk genotypes). Of these, half were infected with more than one genotype. HPV vaccine is usually given to young girls below the age of sexual debut as it is less effective in girls who have already been infected. The finding of a substantial prevalence of HPV among girls who do not report previous sexual activity is a cause for concern.

**Delivery of human papillomavirus vaccination in Tanzanian girls**

**TEG investigators:** Kathy Baisley, Richard Hayes (Co-PI), David Ross

**Other LSHTM investigators:** John Edmunds, Saidi Kapiga (MITU/NIMR, Tanzania), Francesca Lemme, Philippe Mayaud, Fern Terris-Prestholt, Deborah Watson-Jones (Co-PI; MITU/NIMR, Tanzania)

**External investigators/collaborators:** Silvia de Sanjosé (Institut Catala d’Oncologia, Barcelona), Julie Torode (International Union against Cancer, Geneva), Twalib Ngoma (Ocean Road Cancer Institute, Dar es Salaam), John Changalucha (Co-PI), Riziki Ponsiano (NIMR, Tanzania), Wilm Quentin (Technical University, Berlin), Pieter Remes, Daniel Wight (University of Glasgow, UK), Raymond Hutubessy (WHO, Geneva)

**Funding:** Wellcome Trust, Union of International Cancer Control and WHO; HPV vaccine donated via the GARDASIL Access Program

**Location:** Tanzania

**Objective**

To evaluate the vaccine coverage achieved by two school-based HPV vaccination delivery strategies in Tanzania.

**Description**

Tanzania has one of the highest rates of cervical cancer globally and is currently developing a national cervical cancer control strategy to introduce HPV vaccination of schoolgirls. The efficacy of these vaccines is highest if given before sexual debut, when HPV infection has not yet been acquired. Strategies for delivery of the vaccine need to be explored. A total of 134 primary schools (5532 schoolgirls) were randomised to class-based (3352; all girls enrolled in class 6) or age-based (2180; all girls born in 1998) vaccine delivery. Eligible girls were offered three doses of the quadrivalent (HPV 6-11-16-18) vaccine. The primary outcome was vaccine coverage by dose. HPV vaccine coverage was 85% for dose 1, 81% for dose 2 and 76% for dose 3. Coverage was significantly higher in the class-based strategy. There was no evidence that offering HPV vaccination increased absenteeism rates (i.e. no evidence of avoidance of the vaccine).

**This study is assisting with planning the Tanzanian national HPV vaccination programme, for which roll-out is planned in 2013.**

References: 126, 129, 150, 152
Tuberculosis

The TB research conducted by the Group consists of a broad range of studies, including large-scale trials of treatment strategies for patients co-infected with TB and HIV to reduce mortality; studies to assess how new TB diagnostics can improve outcomes among TB suspects and patients; and the effect of earlier initiation of antiretroviral therapy (ART) in HIV-positive individuals on the incidence and prevalence of TB.

Through its role as the Biostatistics Core of the Bill and Melinda Gates Foundation-funded Consortium to Respond Effectively to the AIDS and TB Epidemics (CREATE) programme, TEG was pivotal to the recent successful completion of two major cluster RCTs of interventions to control TB in HIV-endemic settings. Results of these trials, the ZAMSTAR and Thibela TB studies, were presented at international meetings in 2011 and 2012. The OFLOTUB study, a Phase III study of a TB treatment-shortening regimen, is nearing completion and trial results will be finalised in 2013.

The work of the Group continues to expand into 2013 with a new 6-year cluster RCT starting in Lima, Peru. This is a socioeconomic intervention aiming to reduce further TB and mortality in TB-affected households.

44 The CREATE Biostatistics Programme, including (i) the Thibela TB cluster RCT, South Africa, (ii) the ZAMSTAR cluster RCT, South Africa and Zambia and (iii) the TB Modelling Programme

45 OFLOTUB multi-centre Phase III trial

46 Contribution of genetic variation to pharmacokinetic variability and toxicity in patients undergoing multi-drug TB treatment in sub-Saharan Africa: RAFAgene

46 Use of innovative tools and delivery approaches to improve TB control in China: community randomised trial of mobile text messaging and medication monitor adherence measures

47 XTEND: Xpert for TB – a pragmatic cluster RCT to evaluate a new TB diagnostic

47 XPHACTOR study: Xpert MTB/RIF for people attending HIV care

48 TB Fast Track: a cluster RCT to guide TB care among HIV-infected adults in South Africa

48 MERGE: a cluster RCT of integrated HIV/TB care in South Africa

48 Investigation of potential nosocomial transmission of TB in TB wards of Mulago Hospital, Kampala, Uganda

49 Community-wide TB case finding and a cluster RCT of promotion of HIV testing and prevention of HIV-related TB in Malawi: ‘Hit TB hard’
Sputum smear reading for the OFLOTUB project, Conakry, Guinea
The CREATE Biostatistics Programme, including (i) the Thibela TB cluster RCT, South Africa, (ii) the ZAMSTAR cluster RCT, South Africa and Zambia and (iii) the TB Modelling Programme

TEG investigators: Katherine Fielding (Co-PI; CREATE Biostatistics and Thibela TB), Justin Fenty, Sian Floyd, Hannah Jeffery, Richard Hayes (Co-PI; CREATE Biostatistics, Thibela TB and ZAMSTAR), James Lewis, Albertus Schaap (ZAMBART, Zambia)

Other LSHTM investigators: Helen Ayles (Co-PI; ZAMSTAR, ZAMBART, Zambia), Liz Corbett (Co-PI; Thibela TB), Pete Dodd, Peter Godfrey-Faussett (Co-PI; ZAMSTAR), Alison Grant (Co-PI; Thibela TB), Emilia Vynnycky, Richard White (PI; CREATE Modelling)

External investigators/collaborators: Dick Chaisson (PI; CREATE), Susan Dorman (PI; Thibela TB Laboratory Substudies), Gavin Churchyard (PI; Thibela TB, Aurum Institute, SA), Larry Moulton (Co-PI; CREATE Biostatistics, Johns Hopkins University, USA), Azra Ghani (ICL, UK), Nulda Beyers (Co-PI; ZAMSTAR, University of Stellenbosch, SA)

Funding: Bill and Melinda Gates Foundation via Johns Hopkins University

Location: South Africa (ZAMSTAR and Thibela TB), Zambia (ZAMSTAR)

(i) Thibela TB cluster RCT, South Africa

Objective
To examine whether isoniazid preventive therapy (IPT) given to goldminers on a community-wide basis reduces TB incidence, TB prevalence and mortality, using a cluster RCT design.

Description
In this trial, 15 clusters (comprising all miners at a mine shaft and associated hostels) were randomised to seven control or eight intervention clusters. In intervention clusters, all miners were offered TB screening and 9 months of IPT, after excluding active TB. The primary outcome was TB incidence measured after all miners had completed the IPT and secondary outcomes included mortality during the study, and TB prevalence (sputum culture positivity) measured at the end of the study. In intervention clusters, 27,126 (66%) miners consented, and 23,659 (87%) started IPT. Across the eight intervention clusters, the proportion of participants collecting ≥6 months of isoniazid ranged from 35 to 79%. At the population level the intervention did not reduce TB incidence (2.95/100 person-years for controls and 3.02/100 person-years for intervention), TB prevalence (2.14% controls and 2.35% intervention) or all-cause mortality (0.91/100 person-years in both arms). However, at the individual level, compared with a control group, the cohort who started IPT had a 58% reduction in TB incidence while on preventive therapy (adjusted rate ratio 0.42; 95% CI, 0.20-0.88), although incidence was similar in both arms following that period.

Laboratory substudies were also performed, to evaluate diagnostic tests for the detection of Mycobacterium tuberculosis.

For the first substudy, the accuracy of the Genotype MTBDRplus for direct detection of M. tuberculosis was assessed using sputum collected from mine workers suspected of TB. The sensitivity increased as smear grade increased, ranging from 14% (smear negative) to 89% (smear positive 3+). Overall, the study supports the current recommendation not to apply MTBDRplus testing to smear-negative respiratory specimens.

The second substudy assessed the performance of a molecular test, Xpert MTB/RIF, for detection of M. tuberculosis in the context of a prevalence survey conducted to measure a secondary endpoint of the Thibela TB study. In the context of a TB prevalence survey, the Xpert MTB/RIF diagnostic yield was considerably higher than that of smear microscopy, though lower than that of culture.

References: 166, 167, 169

(ii) ZAMSTAR cluster RCT, South Africa and Zambia

Objective
To reduce the burden of TB by facilitating rapid sputum diagnosis and by integrating TB and HIV services both within local health facilities and in the community.

Description
ZAMSTAR was a cluster RCT involving 24
communities with a total population of over 1 million people. Two interventions were implemented during 2006-9: one was enhanced TB case finding and the other was household-level TB and HIV care. The impact of the interventions was assessed in the general population using two endpoints. One was the prevalence of active TB among a random sample of 64,463 adults during 2010; the other was the incidence rate of new infection with *M. tuberculosis* among 8809 schoolchildren during 2005-9.

There was moderate evidence that the household-level intervention reduced both the prevalence of active TB (prevalence ratio 0.82; 95% CI, 0.64-1.05) and the incidence rate of new infection (incidence rate ratio 0.45; 95% CI, 0.20-1.05), while the enhanced case-finding intervention had no effect on either of these outcomes. The trial findings were presented in a symposium at the International Union against Tuberculosis and Lung Disease Conference in Lille in October 2011 and results will be published in 2013.

Reference: 165

The findings of the ZAMSTAR project have contributed to the formulation of WHO guidelines on TB case finding.

(iii) TB Modelling Programme

**Objective**
To develop mathematical models able to inform and assist effective decision-making by comparing the likely long- and short-term impact of alternative strategies for improving TB control.

**Description**
**Active case finding.** The burden of TB, proportion of incidence due to recent infection and case detection rate by routine services were identified as key determinants of the impact and cost-effectiveness of active case-finding interventions against TB. If applied over 10 years, there is the potential to reduce total case load where routine services are already reasonably effective. In situations where the burden is very high, treatments saved may even cover the intervention. More TB cases are averted by finding HIV-uninfected TB than finding those co-infected with HIV and TB. There is a rapid reduction in HIV-infected TB cases found as the screening period increases.

Combination prevention. Modelling exercises support the proposal that, in setting of high HIV prevalence such as South Africa, a narrow focus on a single new strategy (such as improved diagnostics alone) is unlikely to be sufficient to achieve the Millennium Development Goal targets. However, rapid scale up of a combination TB treatment and prevention approach, tailored to local epidemiology, has the potential to achieve a marked reduction in TB incidence in South Africa by 2016.

**OFLOTUB multi-centre Phase III trial**

**TEG investigators:** Kathy Baisley, Katherine Fielding (Co-PI), Hannah Jeffery, Corinne Merle, Emily Webb

**External investigators/collaborators:** Piero Olliaro (PI; WHO/TDR), Martin Gninafon (Co-PI; Centre National Hospitalier de Pneumo-Phtisiologie, Benin), Oumou Bah-Sow (Co-PI; Hospital Ignace Deen, Guinea), Francoise Portaels (ITM Antwerp, Belgium), Joseph Odhiambo (Co-PI; KEMRI, Kenya), Roxana Rustomjee (Co-PI; MRC, SA), Mame Bocar Lo (Co-PI; Programme National de Lutte contre la Tuberculose, Senegal), Denis Mitchinson (Co-PI; St George’s Hospital, UK)

**Funding:** European Commission and WHO/TDR

**Location:** Benin, Guinea, Kenya, Senegal, South Africa

**RCT of three strategies for the treatment of antiretroviral therapy-naive HIV-infected patients with TB: RAFA project**

**TEG investigators:** Corinne Merle (PI), Sian Floyd (Co-PI)

**Other LSHTM investigators:** Keith Branson, Judith Glynn

**External investigators/collaborators:** Tatiana Galperine (Hôpitaux de Paris),
Anandi Martin (ITM Antwerp, Belgium), Martin Gninafon (Co-PI; National TB Programme, Benin), Oumou Bah-Sow (Co-PI; National TB Programme, Guinea), Mame Bobacar Lo (Co-PI; National TB Programme, Senegal), Andre Furco (UCL, UK), Helen McIlleron (University of Cape Town, SA)

**Funding:** EDCTP, MRC, ITM, Antwerp, Belgium, National TB programme of Benin and Senegal

**Location:** Benin, Guinea, Senegal

**Objective**
To assess, using a three-arm approach, whether aggressive management of TB with a high dose of rifampicin during the first 2 months of TB treatment in HIV-infected patients might result in a decrease in early HIV/TB mortality, without the negative effects of the early severe complications that can arise from the use of early antiretroviral treatment (ART).

**Description**
In sub-Saharan Africa, around 30% of HIV-positive patients with TB die within 12 months of starting TB treatment. Half of these deaths occur during the first 2 months of starting TB treatment, and appear to be TB related, rather than HIV related. The RAFA project is a multi-centre, open-label randomised trial in West Africa, with a nested pharmacokinetic study in a subsample of patients. The trial aims to assess the efficacy for reducing mortality of three strategies for the treatment of ART-naive HIV-positive patients with TB: (i) ART initiation at week 2 combined with standard TB treatment; (ii) ART initiation at week 8 combined with standard TB treatment; and (iii) ART initiation at week 8 combined with a high-dose rifampicin regimen during the intensive phase of TB treatment (15 mg/kg). The trial will recruit 1125 patients.

The project also aims to create a West African platform able to conduct further international multi-centre TB and TB/HIV GCP-ICH compliant clinical trials.

**Contribution of genetic variation to pharmacokinetic variability and toxicity in patients undergoing multi-drug TB treatment in sub-Saharan Africa: RAFAgene**

**TEG investigator:** Corinne Merle (PI)

**External investigators/collaborators:**
Dissou Affolabi (PI; National TB Programme, Benin), Thuli Mtyani (MRC Durban, SA), Oumou Bah-Sow (Co-PI; National TB Programme, Guinea), Marie Saar (Co-PI; National TB programme, Senegal), Helen McIlirion (University of Cape Town, SA), Andrew Owen (University of Liverpool, UK)

**Funding:** NIH (H3Africa initiative)

**Location:** Benin, Guinea, Senegal, South Africa

**Objective**
To examine host genetic factors contributing to pharmacokinetic (i.e. drug concentration) and dynamic (i.e. treatment outcome) variability in patients with TB.

**Description**
The complex relationship between pathogen, host and drug exposure in the pathogenesis of TB is poorly understood. In recent years, there has been a rapid development in the understanding of the genetics underlying interindividual differences in drug metabolism and treatment efficacy. The field of pharmacogenetics encompasses the study of the heterogeneity in genes related to drug transporters, drug-metabolising enzymes and drug targets in the context of efficacy of treatment and adverse drug reactions. Few studies have been conducted to explore this field for TB. The RAFAgene study is a 4-year project nested within the OFLOTUB and RAFA trials. Patients enrolled in the pharmacokinetic studies within these two trials are sampled for genetic analysis (genome-wide and targeted screening for single nucleotide polymorphisms, with in vitro confirmation of the biological plausibility of the association between pharmacokinetic and genetic characteristics).

**Use of innovative tools and delivery approaches to improve TB control in China: community RCT of mobile text messaging and medication monitor adherence measures**

**TEG investigators:** Katherine Fielding, James Lewis

**External investigators/collaborators:**
Daniel Chin, Shitong Huan (Bill and Melinda Gates Foundation), Xin Du (Co-PI), Shuigao Jin (National Center for TB Control and Prevention, China)

**Funding:** Bill and Melinda Gates Foundation

**Location:** China

**Objective**
To determine whether the use of mobile phone text messaging and/or an electronic medication monitor can improve adherence to TB treatment in China.
Description
This large-scale cluster RCT is part of an innovative partnership between the Bill and Melinda Gates Foundation and the MoH of the People’s Republic of China to address the TB epidemic in China. In this trial, approximately 4000 subjects from 36 districts/counties were randomised to mobile phone text messaging and/or an electronic medication monitor. The primary endpoint is the proportion of months on TB treatment where at least three doses were missed in a month. Adherence is being measured using the electronic medication monitor and pill count.

XTEND: Xpert for TB – a pragmatic cluster RCT to evaluate a new TB diagnostic

TEG investigator: Katherine Fielding (Co-PI)
Other LSHTM investigators: Alison Grant (Co-PI), Anna Vassall (Co-PI)
External investigators/collaborators: Gavin Churchyard (Co-PI), Violet Chihota (Co-PI), Kerrigan McCarthy (Co-PI) (Aurum Institute, SA), Alan Karstaedt (Chris Han Baragwanath Hospital, SA), Hans Kinkel (Foundation for Professional Development, SA), Linda Erasumus (Co-PI), Wendy Stevens (Co-PI) (National Health Laboratory, SA), Helen Cox (Co-PI), Mark Nicol (Co-PI), Edina Sinanovic (Co-PI) (University of Cape Town, SA), Chris Dye (Co-PI; WHO)

Funding: Bill and Melinda Gates Foundation via the Aurum Institute, South Africa

Location: South Africa

Objective
To evaluate the effectiveness and cost-effectiveness of Xpert MTB/RIF in investigating TB and TB drug resistance, and its impact on patient and programme outcomes, and transmission at a population level.

XPHACTOR study: Xpert MTB/RIF for people attending HIV care

TEG investigator: Katherine Fielding (Co-PI)
Other LSHTM investigators: Alison Grant (PI), Anna Vassall (Co-PI)
External investigators/collaborators: Salome Charalambous (Co-PI), Violet Chihota (Co-PI), Gavin Churchyard (Co-PI), Kerrigan McCarthy (Co-PI) (Aurum Institute, SA), Alan Karstaedt (Chris Han Baragwanath Hospital, SA), Hans Kinkel (Foundation for Professional Development, SA), Linda Erasumus (Co-PI), Wendy Stevens (Co-PI) (National Health Laboratory, SA), Helen Cox (Co-PI), Mark Nicol (Co-PI), Edina Sinanovic (Co-PI) (University of Cape Town, SA), Chris Dye (Co-PI; WHO)

Objective
To evaluate whether an algorithm that prioritises immediate testing for HIV-positive clinic attendees at highest risk of TB mortality (based on CD4 cell count and BMI) and/or transmitting TB will reduce health service costs with minimal risk to patients.

Description
The XPHACTOR study is a cohort study conducted among HIV-infected clinic attendees in South Africa. Using an algorithm that identifies those who are ‘high priority’ for immediate investigation with Xpert MTB/RIF, and allows watchful waiting for those assessed as lower priority, the study aims to compare outcomes and costs using the study algorithm with modelled outcomes and

The XTEND study will provide data to allow estimates of effectiveness, cost and cost-effectiveness of implementation of Xpert MTB/RIF in the context of the South Africa national roll-out, and it will guide the development of further work to test how Xpert MTB/RIF can best be used within the health system to improve patient outcomes and TB control.

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TuBerculosis

In intervention clinics, consenting adults attendees with CD4 count ≤ 150 cells/μL. and recruiting HIV-infected adult clinic health clinics as the unit of randomisation, conducted in South Africa, with primary TB Fast Track is a pragmatic cluster RCT, Description based on South African guidelines. managed according to standard practice this to 6-month mortality among adults treatment, then ART; and (iii) to compare at high risk of TB and ensure they start TB algorithm; (ii) to rapidly identify individuals using a point-of-care technology-based antiretroviral therapy (ART) and managed CD4 counts ≤ 150 cells/μL presenting for mortality among adults with HIV and The study aims (i) to estimate 6-month Objective Location: South Africa Funding: Joint Global Health Trials (MRC, Wellcome Trust and DfID) External investigators/collaborators: Salome Charalambous (joint-PI), Gavin Churchyard, Mpho Tlai (Aurum Institute, SA), Suzanne Johnson (Foundation for Professional Development, SA), Chris Hoffmann, Susan Dorman (Johns Hopkins University, USA) TEG investigator: Katherine Fielding (Co-PI) Other LSHTM investigators: Alison Grant (joint-PI), Anna Vassall (Co-PI) Other LSHTM investigator: Alison Elliott External investigators/collaborators: Jerrold J. Ellner (Co-PI), Edward C. Jones-Lopez (Boston University, USA), Scott Dryden-Peterson (Brigham and Women’s Hospital, Boston, USA), Nancy Reilly (Columbia University Medical Center, USA), Moses Joloba, Harriet Menyha (Joint Clinical Research Centre, Kampala, Uganda), Irene Ayakaka, Bruce Kirenga, Christopher Muchwa, Roy D. Mugerwa (Co-PI), Alphonse Okwera (Makerere University, Uganda), Soyeon Kim (New Jersey Medical School, USA), Kathleen D. Eisenach (University of Arkansas, USA), Kevin P. Fennelly (University of Florida, USA) Funding: Wellcome Trust, NIH and American Society for Tropical Medicine and Research Location: Uganda Objective To investigate the variability of infectious costs assuming testing according to the WHO-recommended strategy. Two further strategies for investigation of adults with HIV who are suspected of having TB, but whose first Xpert MTB/RIF test is negative, are also compared. The study results are expected later in 2015 and will complement the results of the XTEND study.

**TB Fast Track: a cluster RCT to guide TB care among HIV-infected adults in South Africa**

TEG investigator: Katherine Fielding (Co-PI)

Other LSHTM investigators: Alison Grant (joint-PI), Anna Vassall (Co-PI)

External investigators/collaborators: Salome Charalambous (joint-PI), Gavin Churchyard, Mpho Tlai (Aurum Institute, SA), Suzanne Johnson (Foundation for Professional Development, SA), Chris Hoffmann, Susan Dorman (Johns Hopkins University, USA)

Funding: Joint Global Health Trials (MRC, Wellcome Trust and DfID)

Location: South Africa

**Objective**
The study aims (i) to estimate 6-month mortality among adults with HIV and CD4 counts ≤150 cells/μL presenting for antiretroviral therapy (ART) and managed using a point-of-care technology-based algorithm; (ii) to rapidly identify individuals at high risk of TB and ensure they start TB treatment, then ART; and (iii) to compare this to 6-month mortality among adults managed according to standard practice based on South African guidelines.

**Description**
TB Fast Track is a pragmatic cluster RCT, conducted in South Africa, with primary health clinics as the unit of randomisation, and recruiting HIV-infected adult clinic attendees with CD4 count ≤150 cells/μL. In intervention clinics, consenting adults will be assessed based on TB symptoms, urine lipoarabinomannan antigen testing, haemoglobin concentration and BMI; based on these assessments, they will be classified as high, medium or low probability for TB. Those with high probability will start TB treatment immediately, followed by ART after 2 weeks. Those with medium probability of TB will follow the South African guidelines and will be reviewed after 1 week, to be recategorised as low or high risk of TB. Those categorised as low probability of TB will start ART as soon as possible. Clinics randomised to the control arm will receive standard of care. The primary outcome is all-cause mortality at 6 months; the cost-effectiveness of this management strategy will also be explored.

**MERGE: a cluster RCT of integrated HIV/TB care in South Africa**

TEG investigator: Katherine Fielding (Co-PI)

Other LSHTM investigators: Alison Grant (Co-PI), Anna Vassall (Co-PI)

External investigators/collaborators: Tendesayi Kufa (PI), Salome Charalambous (Co-PI), Gavin Churchyard (Co-PI) (Aurum Institute, SA)

Funding: CDC

Location: South Africa

**Objective**
To evaluate the impact of implementing an optimised TB/HIV integration model on morbidity, mortality and retention in care among newly diagnosed HIV-infected patients with TB and newly diagnosed HIV-infected patients attending primary care clinics in South Africa.

**Description**
This is a cluster RCT conducted in primary care clinics in Ekurhuleni North subdistrict, South Africa, and aims to compare an optimised TB/HIV integration intervention with standard of care. The 18 clinics are randomly assigned to intervention or standard of care arms after which they will be monitored for progress in implementing interventions as assigned. Outcomes will be measured in patients with newly diagnosed TB and with newly diagnosed HIV attending clinics for care. The incremental cost per disability-adjusted life-year averted of optimised TB/HIV intervention at the intervention site compared with the control site, and the average provider and patient costs per episode of care at the intervention and control clinics, will also be measured.

**Investigation of potential nosocomial transmission of TB in TB wards of Mulago Hospital, Kampala, Uganda**

TEG investigator: Peter Smith (Co-PI)

Other LSHTM investigator: Alison Elliott

External investigators/collaborators: Jerrold J. Ellner (Co-PI), Edward C. Jones-Lopez (Boston University, USA), Scott Dryden-Peterson (Brigham and Women’s Hospital, Boston, USA), Nancy Reilly (Columbia University Medical Center, USA), Moses Joloba, Harriet Menyha (Joint Clinical Research Centre, Kampala, Uganda), Irene Ayakaka, Bruce Kirenga, Christopher Muchwa, Roy D. Mugerwa (Co-PI), Alphonse Okwera (Makerere University, Uganda), Soyeon Kim (New Jersey Medical School, USA), Kathleen D. Eisenach (University of Arkansas, USA), Kevin P. Fennelly (University of Florida, USA)

Funding: Wellcome Trust, NIH and American Society for Tropical Medicine and Research

Location: Uganda

**Objective**
To investigate the variability of infectious
aerosols produced during coughing by patients with pulmonary TB, the feasibility of collecting cough aerosols and the risk factors for infectious aerosol production by patients with pulmonary TB in a resource-limited setting.

**Description**

Subjects with suspected TB were enrolled in Kampala, Uganda. Cough aerosol cultures, as well as clinical, radiographic and microbiological data, were collected. A subset of 38 subjects was studied on 2 to 3 consecutive days to assess reproducibility. *M. tuberculosis* was cultured from cough aerosols of 28 of 101 subjects with culture-confirmed TB, with a median aerosol 16 cfu (range, 1-701) in 10 minutes of coughing. Positive aerosol cultures were associated with a salivary/mucosalivary (compared with purulent/mucopurulent) appearance of sputum and lower number of days to positive in liquid culture (per 1 day decrease; odds ratio, 1.17; 95% CI, 1.07-1.33). The within-test and interday test reproducibility were high.

**Collecting cough aerosols from patients as a way of detecting infectiousness is feasible and reproducible in this resource-limited setting.**

**Reference:** 168

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**Community-wide TB case finding and a cluster RCT of promotion of HIV testing and prevention of HIV-related TB in Malawi: ‘Hit TB hard’**

**TEG investigators:** Richard Hayes, Emily Webb, Barbara Willey

**Other LSHTM investigators:** Liz Corbett (PI), Neil French

**External investigators/collaborators:** Grace Chitsika, Catherine Mwapasa (Blantyre District Health Office, Malawi), Gavin Churchyard (Durban University and Aurum Health Research, South Africa), Tony Harries (International Union Against TB and Lung Disease), Richard Chaisson (Johns Hopkins University, USA), Bertie Squire, Gillian Mann (Liverpool School of Tropical Medicine, UK), Geoffrey Chipungu, Nicola Desmond, Rob Heyderman, (Malawi-Liverpool-Wellcome Clinical Research Programme, Malawi), Frank Chimbwandira, Andrew Dimba, Simon Makombe, James Mpunga, (MoH, National TB Programme & HIV Unit, Malawi), Haileyesus Getahun (WHO, Geneva)

**Funding:** Wellcome Trust

**Location:** Malawi

**Objective**

To investigate the hypothesis that either TB case finding alone or TB case finding combined with intensified prevention of HIV-related TB can meet the urgent need for high-impact strategies capable of reducing TB incidence rates substantially in an urban area with high HIV prevalence in Malawi.

**Description**

This project consists of a cluster RCT of intensified HIV/TB prevention linking home-based HIV testing, including the option of self-testing, with HIV care. The trial is nested within a wider TB case-finding intervention area, where all residents will be receiving community-wide active TB case finding for undiagnosed smear-positive TB through mobile microscopy clinic visits every 6 months and extended monitoring and evaluation. The background active case-finding intervention commenced in April 2011 and the cluster RCT commenced in February 2012. The primary outcome measure for the trial is case notification rate of bacteriologically confirmed TB in adult cluster residents, and it will be evaluated at the end of the intervention period in late 2015. The study results meet a recent call by WHO for more research on acceptability and uptake of community-based universal access to HIV testing and counselling.

**The Hit TB Hard campaign aims to achieve a 30-50% decline in TB case notification rates within 4 years.**

**Reference:** 56
Neglected tropical, non-communicable and other diseases

The Group continues a major focus on neglected tropical diseases, with ongoing research projects on trachoma, visceral leishmaniasis, helminth infections and epilepsy. Several important trials were completed in 2011-12, including innovative trials of the management of trachomatous trichiasis in Ethiopia, and completion of a 5-year follow-up of the Entebbe Mother and Baby Study, which showed that there was little effect of helminth infections and their treatments on incidence of infectious diseases and eczema.

We are expanding our research into chronic diseases and mental health research. These conditions are responsible for an increasing burden of disease in Africa and other low-resource settings, and our work focuses largely on health systems research and task-shifting to lay health workers.

52 Neglected tropical diseases
  ▪ Design and analysis of clinical trials for the treatment of visceral leishmaniasis
  ▪ Can insecticide-treated curtains prevent transmission of dengue?
  ▪ Lake Victoria Island Intervention Study on Worms and Allergy-related Diseases (LaVIISWA)
  ▪ The Entebbe Mother and Baby Study (EMABS)
  ▪ Partnership for the Rapid Elimination of Trachoma (PRET)
  ▪ RCTs for the management of trachomatous trichiasis in Ethiopia
  ▪ Case-control study of trachomatous conjunctival scarring in Tanzania
  ▪ Controlling blinding trachoma: intervention and pathophysiology studies for scarring disease in Ethiopia and Tanzania
  ▪ The epidemiology and management of ocular surface squamous neoplasia
  ▪ Incidence and progression of posterior segment eye disease in a population-based cohort in Kenya

58 Non communicable diseases
  ▪ Improving the health system response to chronic diseases in Africa
  ▪ Understanding local determinants of cardiovascular disease and diabetes to inform novel intervention strategies
  ▪ Studies of the Epidemiology of Epilepsy in Demographic Surveillance Systems (SEEDS)
  ▪ Improving the health and well-being of Londoners: a cluster RCT (Well London)

60 Mental health
  ▪ MANAS: a cluster RCT of a lay health worker-led intervention for depressive and anxiety disorders in primary care
  ▪ PREMIUM: Program for Effective Mental health Interventions in Under-resourced health systems
  ▪ INTREPID: India, Nigeria, Trinidad: Researching Psychosis in Diverse settings
  ▪ SHARE: South Asian Hub for Advocacy, Research and Education on mental health
  ▪ COPSI: the Community care for People with Schizophrenia in India Trial
  ▪ The Friendship Bench

63 Neonatal, infant and child health
  ▪ Improving Newborn Survival In Southern Tanzania: the INSIST trial
  ▪ Simplified antibiotic regimens for the management of sepsis in young infants in first-level facilities
  ▪ Can mass media campaigns reduce child mortality?
  ▪ Delhi Infant Vitamin D Study (DIVIDS)

65 Pneumococcal disease
  ▪ Modelling serotype replacement in The Gambia
  ▪ Zinc supplementation in Gambian children with severe pneumonia
  ▪ Nonspecific effects of childhood vaccination on bacterial carriage
Blood meal, Phlebotomus papatasii (sand fly), the main vector responsible for the transmission of leishmaniasis
© Frank Collins, CDC
Design and analysis of clinical trials for the treatment of visceral leishmaniasis

TEG investigators: Tansy Edwards (PI), Neal Alexander, Peter Smith

External investigators/collaborators: Asrat Hailu (Addis Ababa University, Ethiopia), Monique Wasunna (DNDi Africa and KEMRI, Kenya), Clélia Bardonneau, Sally Ellis (DNDi, Switzerland), Joseph Olobo (Makerere University, Uganda), Eltahir Khalil, Ahmed Musa (University of Khartoum, Sudan), and investigators from the Leishmaniasis East Africa Platform (LEAP)

Funding: DNDi, European Commission (Grant EU-FP7)

Location: Ethiopia, Kenya, Sudan, Uganda

Objective
To conduct Phase II and Phase III multi-centre treatment trials for visceral leishmaniasis (VL) in East Africa, to identify safe, efficacious short-course treatments for patients with VL in East Africa, and to increase knowledge and understanding of treatment strategies for VL in East Africa.

Description
Six trials are intended.
1. Phase III trial of paramomycin (PM) monotherapy and a short-course combination treatment regimen of sodium stibogluconate (SSG) plus PM, compared with the standard treatment.
2. Phase I/III trial of single- and multi-dose AmBisome (amphotericin B) monotherapy treatment regimens, to determine the optimal single-dose treatment regimen of AmBisome.
3. Phase II trial of a combination regimen of SSG plus single-dose AmBisome, a combination regimen of miltefosine plus single-dose AmBisome and a monotherapy regimen of miltefosine.
4. Phase III trial of a short-course combination therapy for VL (AmBisome single dose in combination with either miltefosine or SSG) compared with the existing standard treatment regimen of SSG plus PM. This trial design is currently in process and will follow on from the Phase II trial (3) above.
5. Phase III trial of AmBisome monotherapy and a combination of AmBisome and miltefosine in patients co-infected with HIV and VL in Ethiopia.
6. Phase II proof of concept trial of fexinidazole in patients with VL in Sudan.

The results from Trial 1 demonstrated comparable efficacy and safety of the short-course combination therapy regimen of SSG plus PM with the 1-month monotherapy regimen of SSG.

The results of Trials 2 and 3 are due to be released in 2013. Results of Trial 3 will inform the design of Trial 4. Trials 4-6 are due to start recruitment in 2013. Trial 5 will focus specifically on patients co-infected with HIV and VL and Trial 6 will test a new chemical entity not previously used in the treatment of VL.

In 2012, a successful grant application for €3 million was made to the European Union Seventh Framework Programme to create a new consortium to create a Care Package for Treatment and Control of Visceral Leishmaniasis in East Africa (AfriCoLeish), comprising DNDi, LSHTM and the Institute of Tropical Medicine, Antwerp, Belgium. This grant will fund Trials 4 and 5 above.

Sodium stibogluconate plus paramomycin has been incorporated as the new standard treatment regimen for patients with visceral leishmaniasis in national treatment guidelines in Sudan, Kenya, Uganda and Ethiopia.

References: 211, 251, 260
Can insecticide-treated curtains prevent transmission of dengue?

**TEG investigator:** Neal Alexander

**External investigators/collaborators:**
Philip McCall (PI), Audrey Lenhart (Liverpool School of Tropical Medicine, UK), John Elder (San Diego State University, USA), Amy Morrison, Thomas Scott (University of California, Davis, USA)

**Funding:** Wellcome Trust

**Location:** Peru

**Objective**
To determine whether insecticide-treated curtains can reduce dengue transmission.

**Description**
Given the current lack of specific treatment for dengue, or a licensed vaccine, this trial aims to measure the impact of insecticide-treated curtains on the mosquitoes that transmit dengue to humans, and assess their potential by addressing whether insecticide-treated curtains can reduce dengue transmission in treated households (individual or household effect) and in treated communities (community or mass effect). It will also assess which human behavioural factors influence adoption, maintenance and dissemination of insecticide-treated curtains among householders.

An RCT is being conducted over 3 years in the dengue-endemic city of Iquitos, Peru. Efficacy of the intervention is being determined by measuring dengue antibodies in the human population and by monitoring for any reduction in the local vector mosquito population. Acceptance and sustainability of insecticide-treated curtains is being evaluated by interviews and discussions with householders in the treated communities.

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Lake Victoria Island Intervention Study on Worms and Allergy-related Diseases (LaVIISWA)

**TEG investigator:** Emily Webb

**Other LSHTM investigators:** Alison Elliott (PI; MRC/UWRI Unit, Uganda), Chris Drakeley, Neil Pearce

**External investigators/collaborators:**
Moses Muwanga (Entebbe Hospital, Uganda), Marielle Haks (Leiden University, Netherlands), Edridah Tukahebwa (MoH, Uganda), Pontiano Kaleebu, Harriet Mpamire, Margaret Nampijja (MRC/UWRI Unit, Uganda), James Kaweesa, Elly Tumushabe (Mukono District, Uganda), Barbara Nerima (Virus Research Institute, Uganda), David Dunne (University of Cambridge, UK), Giuseppe Pantaleo (University of Lausanne, Switzerland), Ian Hall, Hywel Williams (University of Nottingham, UK), Rafick Sekaly (Vaccine and Gene Therapy Institute, Port St Lucie, USA)

**Funding:** Wellcome Trust Senior Research Fellowship

**Location:** Uganda

**Objective**
To determine whether helminths have protective effects against asthma, eczema and atopy in humans and to assess the relative risks and benefits of mass anthelminthic treatment for health outcomes.

**Description**
There is evidence that helminth infections can protect against allergic disease. Our goal is to determine whether this is important in humans and, if so, to determine the implications for public health, and for development of interventions against allergic conditions.

LaVIISWA is cluster RCT to evaluate whether effective anthelminthic treatment will result in a substantially increased prevalence and incidence of allergy in Lake Victoria island communities in which helminth prevalence is still high. The study will assess the risks and benefits of intensive anthelminthic intervention in terms of anticipated increases in asthma, eczema and allergy, versus anticipated improvements in anaemia, growth, development and helminth-induced pathology, and vaccine-induced immune responses.

In August 2012, 26 fishing communities were randomised to receive either standard or intensive anthelminthic treatment over a 3-year period. The impact of the intervention on allergy-related outcomes and on anaemia, growth and development will be evaluated at the end of the intervention period, in 2016.
Neglected tropical, non-communicable and other diseases

The Entebbe Mother and Baby Study (EMABS)

**TEG investigators:** Richard Hayes, Emily Webb

**Other LSHTM investigators:** Alison Elliott (PI; MRC/UVRI Unit, Uganda)

**External investigators/collaborators:** Moses Muwanga (Co-PI; Entebbe Hospital, Uganda), Dennison Kizito, Moses Kizza, Patrice Mawa, Harriet Mpairwe, Maggie Nampijja, Juliet Ndibazza, Robert Tewyongyere (MRC/UVRI Unit, Uganda)

**Funding:** Wellcome Trust Senior Research Fellowship

**Location:** Uganda

**Objective**
To evaluate the impact of maternal helminths and their treatment, and childhood helminths and their treatment, on the response to childhood immunisations and on incidence of infection and atopic disease in children up to 5 years of age in Uganda.

**Description**
Previously we had observed associations of maternal helminths with infant responses to immunisations and with disease incidence in infancy, but there was little evidence that anthelminthic treatment during pregnancy impacted on these outcomes, or on maternal or perinatal outcomes. Results appeared to be at odds with the anticipated benefits of the advocated routine antenatal administration of anthelminthics.

A 5-year follow-up is now completed and the findings are consistent with interim findings: anthelminthic treatment with albendazole during pregnancy is associated with an increased risk of eczema in the offspring, while there were no beneficial effects of anthelminthic treatment during pregnancy on responses to immunisation or on infectious disease incidence during childhood. In addition quarterly anthelminthic treatment with albendazole during childhood was associated with increased rate of clinical malaria, although since prevalence of helminths was unexpectedly low in the cohort, this is not likely to be a direct effect of worm removal.

References: 153, 253, 280, 282

Partnership for the Rapid Elimination of Trachoma (PRET)

**TEG investigator:** Tansy Edwards

**Other LSHTM investigators:** Robin Bailey (Co-PI), David Mabey (Co-PI)

**External investigators/collaborators:** Sheila West (Co-PI; Johns Hopkins University, USA), Tom Lietman (Co-PI; University of California, San Francisco, USA)

**Funding:** Bill and Melinda Gates Foundation

**Location:** The Gambia

**Objective**
To evaluate strategies for the optimal coverage and frequency of mass treatment for trachoma in The Gambia.

**Description**
Trachoma, an ocular infection caused by *Chlamydia trachomatis*, is the second leading infectious cause of blindness worldwide. The WHO recommends annual mass treatment for at least 3 years in communities or districts with an initial prevalence of trachoma of ≥10%. Questions remain around the time period necessary for treatment and the optimal level of treatment coverage required to reduce prevalence.

This cluster RCT aims to answer research questions relating to optimal coverage and frequency of mass treatment strategies in The Gambia, a low prevalence setting for trachoma. The primary outcomes are...
prevalence of trachoma and C. trachomatis infection. Secondary outcomes are child mortality, nutritional status and malaria morbidity. Results relating to primary outcomes of trachoma in children under-5 years of age will be available in 2013-14. Simultaneous trials with a harmonised design were conducted in Tanzania (mesoendemic) and Niger (hyperendemic).

RCTs for the management of trachomatous trichiasis in Ethiopia

**TEG investigator:** Helen Weiss

**Other LSHTM investigators:** Matthew Burton (PI), Robin Bailey, Clare Gilbert, David Mabey, Saul Rajak

**External investigators/collaborators:** Teshome Gebre (Carter Center Ethiopia), Paul Emerson (Carter Center, USA), Peng Tee Khaw (Institute of Ophthalmology, UK), Amir Bedri (Trachoma Initiative, Ethiopia)

**Funding:** Wellcome Trust, Band Aid Foundation

**Objective:** Ethiopia

**Description**

Recurrence of C. trachomatis infection of the eye surface (conjunctiva) from childhood triggers an inflammatory scarring process that causes in-rolling of the eyelids (trichiasis) and corneal opacification in later life. Success of control measures is limited; inflammation persists in children despite antibiotic treatment for chlamydia infection, and trichiasis frequently returns after surgery.

We collaborated on two companion RCTs for the management of trichiasis in Ethiopia. In the first, we evaluated methods of treatment for mild trichiasis by individually randomising 1300 individuals to immediate surgery or epilation (plucking lashes) for management of minor trichiasis. This was a non-inferiority trial and showed that epilation had a comparable effect to surgery on treatment failure (defined as ≥5 lashes touching the eye), visual acuity and corneal outcomes.

The second trial was a RCT of 1300 individuals with major trichiasis to test the hypothesis that the supportive presence of an absorbable vicryl suture for a longer period would produce more stable wound healing, leading to a better outcome. There was no evidence that use of absorbable polyglactin-910 sutures rather than silk sutures was associated with a lower prevalence of trichiasis recurrence at 1 year after surgery. However, from a programme perspective, polyglactin-910 offers the major advantage that patients do not have to be seen soon after surgery for suture removal.

**References:** 199, 267-270

For minor trichiasis, surgery should be performed whenever possible, but epilation should be used for treatment of patients without access to, or declining, surgery.

Case-control study of trachomatous conjunctival scarring in Tanzania

**TEG investigator:** Helen Weiss

**Other LSHTM investigators:** Matthew Burton (PI), Robin Bailey, Victor Hu, David Mabey

**External investigators/collaborators:** Paul Courtright, William Makupa, Patrick Massae (Kilimanjaro Centre for Community Ophthalmology, Tanzania)

**Funding:** Wellcome Trust

**Location:** Tanzania

**Objective**

To characterise the tissue and cellular changes found in trachomatous scarring and inflammation using in vivo confocal microscopy.

<table>
<thead>
<tr>
<th>Time since randomisation (months)</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
</tr>
<tr>
<td>0</td>
<td>650</td>
</tr>
<tr>
<td>6</td>
<td>641</td>
</tr>
<tr>
<td>12</td>
<td>630</td>
</tr>
<tr>
<td>18</td>
<td>620</td>
</tr>
<tr>
<td>24</td>
<td>606</td>
</tr>
</tbody>
</table>

RCTs for the management of trachomatous trichiasis study: Epilation vs surgery. Kaplan-Meier plot showing the cumulative proportion without failure in an RCT of 1300 people with minor trachomatous trichiasis; definition of failure was the presence of ≥5 lashes touching the eye at any time during follow-up (With permission from Rajak et al., 2011. PLoS Med [270])
A case-control study compared 363 people with trachomatous scarring (without trichiasis) with an equal number of healthy controls from Tanzania. All participants underwent clinical examination, and a swab was taken from the inferior conjunctival fornix. Bacterial isolates were found more frequently in cases compared with controls, after adjusting for age and other potential confounding variables. Scarring was associated with both the presence of commensal organisms (odds ratio (OR), 1.46; 95% CI, 1.01-2.09) and with the presence of pathogenic organisms (OR, 4.08; 95% CI, 1.59-10.45). There was an increasing prevalence of all bacterial isolates with increasing severity of scarring. Further, participants with clinical scarring had an increased number of inflammatory cells, consistent with the immunopathologic nature of the disease.

References: 197, 198, 200, 225

Controlling blinding trachoma: intervention and pathophysiology studies for scarring disease in Ethiopia and Tanzania

TEG investigator: Helen Weiss

Other LSHTM investigators: Matthew Burton (PI), Robin Bailey, David Mabey

External investigators/collaborators: Teshome Gebre (Carter Center Ethiopia), Paul Emerson (Carter Center, US), Peng Tee Khaw (Institute of Ophthalmology, UK), Amir Bedri (International Trachoma Initiative, Ethiopia)

Funding: Wellcome Trust

Location: Ethiopia, Tanzania

Objective
To elucidate the pathophysiological basis of blinding trachoma and to evaluate interventions to improve trichiasis surgery for this disease.

Description
Many different surgical procedures have been used to correct trachomatous trichiasis, suggesting no ideal solution exists. Surgery generally involves incision through the scarred eyelid, outward rotation and suturing of the distal segment. Randomised trials have found that, of the operations compared, the bilamellar tarsal rotation procedure (BLTR) has the lowest recurrence rate (20% at 1 year), leading the WHO to recommended this procedure. The commonest alternative is the posterior lamellar tarsal rotation (PLTR). In Ethiopia both procedures are used extensively and are recognised by the WHO as acceptable operations. However, PLTR was not included in the earlier comparative trials with BLTR. An RCT will examine whether the BLTR is superior to PLTR for treatment of trachomatous trichiasis. An RCT will also examine whether postoperative oral doxycycline can reduce recurrent trichiasis by inhibiting postoperative scarring processes. Further studies will aim to elucidate the immuno-fibrogenic basis of progressive scarring trachoma and to identify the immuno-fibrogenic determinants of recurrent trichiasis during wound healing following surgery.

Funding: Wellcome Trust

Epidemiology and management of ocular surface squamous neoplasia

TEG investigator: Helen Weiss

Other LSHTM investigators: Matthew Burton (PI), Stephen Gichuhi

External investigators/collaborators: Christine Mwangi (Center for Public Health Research, KEMRI, Kenya), Shin-ichi Ohnuma, Mandeep Sagoo (Institute of Ophthalmology, UK), Walter Jaoko (Kenya Aids Vaccine Initiative, University of Nairobi), F.S. Rana (MP Shah Hospital, Nairobi), Joy Kabiru (PCEA Kikuyu Hospital Eye Unit, Kenya)

Funding: British Council for the Prevention of Blindness
Incidence and progression of posterior segment eye disease in a population-based cohort in Kenya

TEG investigator: Helen Weiss

Other LSHTM investigators: Andrew Bastauwrous (PI), Matthew Burton, Hannah Kuper

External investigators/collaborators: Amos Kibata (Eye and Laser Centre, Nairobi), Michael Gichangi (MoH, Nairobi), Alan Bird, Irene Leung, Tunde Peto (Moorfields Eye Hospital, UK), John Murima, Elkana Onsomu, Benedict Osore (Rift Valley, Kenya)

Funding: MRC, Fight for Sight, International Glaucoma Association and British Council for the Prevention of Blindness

Location: Kenya

Objective
To assess the 5-year incidence and progression of diabetic retinopathy, age-related macular degeneration and glaucoma in a Kenyan population aged ≥50 years.

Description
Africa carries the greatest burden of blindness worldwide, most of which is preventable or treatable. There is increasing evidence that diseases affecting the back of the eye are a major problem in Africa. These conditions include glaucoma, diabetic retinopathy and macular degeneration. However, there is very little reliable information on how many people are affected or how fast these diseases progress.

These questions will be investigated in Kenya. In 2007-8, 4381 people aged 50 were randomly selected across a district and underwent detailed eye examinations. These participants will be retraced for re-examination of their eyes at 5 years after their first examination.

This will allow an estimation of how many new cases arise, risk factors for key ‘back-of-the-eye’ diseases, and the rate of progression among people affected at baseline.

The information will help to inform and guide prevention of blindness programmes in Africa, by identifying how many new cases are expected to occur each year, who is at risk of these conditions and who is most vulnerable to experiencing the adverse consequences of their eye disease.
Non communicable diseases

Improving the health system response to chronic diseases in Africa

TEG investigators: Heiner Grosskurth (PI), Fiona Ewings (both MITu/NIMR, Tanzania), Kathy Baisley, Richard Hayes (Co-PI)

Other LSHTM investigators: Saidi Kapiga (Co-PI; MITu/NIMR, Tanzania), Liam Smeeth, Sedona Sweeney, Anna Vassall

External investigators/collaborators: Bazil Baltazar, Soori Nnko, Simon Sichalwe (MITu/NIMR, Tanzania), Samuel Biraro (Co-PI), Dominic Bukenya, Peter Hughes, David Katende, Paula Munderi (Co-PI), Gertrude Mutonyi, Janet Seeley (MRC/UVRi Unit, Uganda)

Funding: MRC
Location: Tanzania, Uganda

Objective
To improve the provision of healthcare for chronic diseases in northern Tanzania and southwest Uganda.

Description
The aim of this 4-year interdisciplinary programme of research is initially to assess the burden of HIV infection and selected non-communicable diseases (such as hypertension, cardiac failure, diabetes, chronic obstructive pulmonary disease, asthma and epilepsy) and the adequacy of their current management in the primary care sector, and then if necessary, to improve services to cope more effectively with this burden.

Key components of the programme include (i) collection of data required for health planning; (ii) design and implementation of an affordable intervention to improve the primary care system; (iii) evaluation of the intervention; and (iv) activities helping to translate the results of the programme into policy. The intervention focuses on the improvement of health systems and recognises the needs that care for HIV and chronic non-communicable diseases have in common. The effectiveness of the intervention will be evaluated at the level of health facilities, using an RCT design and a set of substudies to explore its cost-effectiveness, possible adverse effects and effects on community perceptions of chronic diseases and care-seeking behaviour.

Understanding local determinants of cardiovascular disease and diabetes to inform novel intervention strategies

TEG investigator: Shabbar Jaffar (Co-PI)

Other LSHTM investigators: Alemayehu Amblebir, Moffat Nyirenda (Co-PI)

External investigators/collaborators: Ndolwe Kayuni, Crispin Musicha, Jayani Pathirana, Amos Phiri, Terence Tafata (Malawi Epidemiology and Intervention Research Unit)

Funding: Wellcome Trust
Location: Malawi

Objectives
Reliable data on non-communicable diseases in Africa are lacking. We plan to examine the burden of non-communicable diseases and their risk factors in a large study in urban and rural Malawi. The research will inform health planning and build a platform for innovative intervention studies on the prevention and control of non-communicable diseases.

Description
About 50,000 adults over 18 years of age will be studied in Lilongwe Area 25 and in our health demographic surveillance site in Karonga district. We aim to determine (i) the burden of hypertension, diabetes and hyperlipidaemia; (ii) the prevalence of known risk factors – smoking, obesity, physical inactivity, alcohol, salt and saturated fat intake; (iii) whether HIV infection or its therapy is associated with increased risk of non-communicable diseases; and (iv) the barriers to accessing and remaining in care for people with non-communicable diseases. The study will screen for complications of hypertension and diabetes, such as peripheral neuropathy, retinopathy and kidney disease. It will also determine the effects of rural-urban migration.

Studies of the Epidemiology of Epilepsy in Demographic Surveillance Systems (SEEDS)

TEG investigators: Christian Bottomley, Immo Kleinschmidt, Paul Milligan

External investigators/collaborators: Charles Newton (PI), Edward Chengo, Gathoni Kamuyu, Anthony Ngugi, Rachel
Odhiambo (KEMRI, Kenya), Honorati Masanja (Ifakara Health Institute, Tanzania), Kenneth Ae-Ngibise, Seth Owusu-Agyei (Kintampo Health Research Centre, Ghana), Angelina Kakooza-Mwesige (Makerere University, Uganda), Josemir Sander (UCL, UK), Ryan Wagner (University of the Witwatersrand, SA)

**Funding:** Wellcome Trust

**Location:** Sub-Saharan Africa

**Objective:** To use demographic surveillance sites to identify cases of epilepsy at five sites in sub-Saharan Africa.

**Description**
The burden of epilepsy in Africa is thought to be high but there are few reliable estimates of prevalence. In the SEEDS study, three-stage surveys were conducted in five African countries to determine the prevalence of epilepsy at these sites. The sites were chosen to be typical of sub-Saharan Africa in terms of the parasites found there. The cases of epilepsy identified through the prevalence survey were used in a case-control study to explore the causes of epilepsy in Africa; it has been hypothesised that parasitic infection might be a significant cause of epilepsy in the region, and preliminary data appear to confirm this. Additional studies have been conducted at one of the sites (Kilifi, Kenya) to estimate the incidence of epilepsy and mortality among people with epilepsy. Results will be published in 2013.

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**Improving the health and well-being of Londoners: a cluster RCT (Well London)**

**TEG investigators:** Christian Bottomley, Richard Hayes

**Other LSHTM investigator:** Karen Lock, Mark Petticrew

**External investigators/collaborators:** Adrian Renton (PI), Derek Moore, Gemma Phillips, Elena Schmidt, Patrick Tobi, Paul Watts, Ge Yu (University of East London, UK), Rebecca Lynch (UCL, UK), Angela Clow, Alizon Draper (University of Westminster UK)

**Funding:** Big Lottery via Wellcome Trust

**Location:** London

**Objective**
To evaluate the impact of community-level interventions to improve the health and well-being of people living in some of the most deprived communities of London.

**Description**
Public health policies have repeatedly emphasised the need for preventive interventions that focus on increasing healthy eating and physical activity to reduce chronic disease incidence. In this cluster RCT, the interventions were targeted at increasing physical activity, improving mental health and developing healthy eating. The primary outcomes are levels of healthy physical activity, healthy eating and mental health and well-being, and will be compared in 20 intervention and 20 matched control communities in London. Results at baseline showed that randomisation of social interventions was acceptable and feasible. The intervention and control arms were balanced with respect to baseline measures of the primary outcomes and key sociodemographic characteristics. The matched design improved the statistical efficiency of the study amongst adults but less so amongst adolescents.

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**The Well London programme used community engagement, complemented by changes to the physical and social neighbourhood environment, to improve physical activity levels, healthy eating and mental well-being in the most deprived communities in London.**

Reference: 265
Mental health

MANAS: a cluster RCT of a lay health worker-led intervention for depressive and anxiety disorders in primary care

TEG investigator: Helen Weiss
Other LSHTM investigators: Vikram Patel (PI), Mary De Silva, Betty Kirkwood

External investigators/collaborators:
Helena Verdeli (Columbia University, USA), Gregory Simon (Group Health Cooperative, Seattle, USA), Christine Butterff, Rebecca Hock (Johns Hopkins University, USA), Sudipto Chatterjee, Neerja Chowdhary, Smita Naik, Sulochana Pednakar (Sangath, Goa), Michael King (UCL, UK), Ricardo Araya (University of Bristol, UK)

Funding: Wellcome Trust
Location: India

Objective
The MANAS trial tested the effectiveness and cost-effectiveness of a lay health counsellor-led intervention in improving outcomes among people with common mental disorders (CMDs; depression and anxiety).

Description
Depression and anxiety are the most common psychiatric conditions encountered in primary healthcare. The MANAS study is a cluster RCT of a stepped care intervention for CMDs delivered by lay health workers. A total of 24 primary healthcare facilities (12 public, 12 private) in Goa, India, were randomised to receive enhanced usual care (control) or a stepped care intervention led by lay health counsellors. A total of 2796 participants were recruited and followed for up to 12 months. Outcomes included prevalence of CMDs, symptom severity, suicidal behaviour and disability levels. In public healthcare facilities, the intervention was consistently associated with strong beneficial effects over the 12 months on all outcomes, including a 30% decrease in prevalence of CMD among those with baseline ICD-10 diagnosis, and a similar effect among those with depression at baseline. Time costs were also significantly lower in the intervention arm, whereas health systems costs were similar. In contrast, there was little evidence of an impact of the intervention on any outcome among participants attending private facilities.

Reference: 264

PREMIUM: Program for Effective Mental health Interventions in Under-resourced health systems

TEG investigator: Helen Weiss
Other LSHTM investigators: Vikram Patel (PI), Betty Kirkwood, Jim McCambridge, Abhijit Nadkarni

External investigators/collaborators:
Martin Knapp (Institute of Psychiatry, KCL, UK), Chris Fairburn (Oxford University, UK), Neerja Chowdhary (Sangath, Goa), Michael King (UCL, UK), Ricardo Araya (University of Bristol, UK)

Funding: Wellcome Trust
Location: Goa, India

Objective
To develop and evaluate culturally appropriate psychological treatments for depression and harmful drinking that can be delivered by non-specialist health workers in low-resource settings.

Description
Depression and harmful drinking are important public health problems worldwide, with high prevalence, high levels of disability and potentially fatal consequences through suicide, road traffic accidents or health complications such as liver cirrhosis. Psychological treatments have been effective in developed country settings, but the vast majority of people in low- and middle-income countries do not have...
access to these psychological treatments.

PREMIUM is being implemented in three phases: (i) development of psychological treatment in a systematic process including reviewing the existing knowledge, consultation with experts and persons affected by the two disorders, and pilot studies in primary healthcare; (ii) RCTs with primary healthcare attenders in Goa, India, to evaluate the impact of the treatments for depressive disorders and harmful drinking on health and socioeconomic outcomes at 3 and 12 months; and (iii) dissemination and planning for scale up of the treatments through public health systems.

The RCTs will begin enrolment in 2013, with results due in late 2015.

**INTREPID: India, Nigeria, Trinidad – Researching Psychosis In Diverse settings**

**TEG investigator:** Karim Anaya-Izquierdo, Helen Weiss

**Other LSHTM investigators:** Alex Cohen, Vikram Patel

**External investigators/collaborators:**
- Craig Morgan (PI), Robin Murray (Institute of Psychiatry, KCL, UK), Rangaswamy Thara (Schizophrenia Research Foundation, India), Oye Gureje (University of Ibadan, Nigeria), Gerard Hutchinson (University of the West Indies, Trinidad)

**Funding:** Wellcome Trust

**Location:** India, Nigeria, Trinidad

**Objective**
To address methodological challenges in (i) identifying and recruiting incident cases of psychosis in diverse settings, and (ii) following participants over time with minimal attrition.

**Description**
Few studies of the nature, onset and outcome of schizophrenia and other psychoses have been carried out in low- and middle-income countries. The exceptions, the WHO multi-country studies conducted in the 1960-80s, raised a number of important questions about the determinants of cross-cultural variations in the incidence and outcome of schizophrenia that have not been pursued subsequently in rigorous and comparable cross-country studies.

These questions are being addressed in a programme of research in three diverse settings: Ibadan (Nigeria), Chennai (India) and Trinidad and Tobago.

There are, however, a number of methodological challenges inherent in studying psychosis across diverse settings, with a consequent need to conduct substantial pilot work. A 3-year pilot study will test strategies to (i) identify and recruit incident cases of psychosis and representative controls (ii) follow individuals over time while minimising attrition; and (iii) establish a core set of cross-culturally valid instruments and procedures to collate data on psychopathology, social and biological exposures, and outcome.

**SHARE: South Asian Hub for Advocacy, Research and Education on mental health**

**TEG investigator:** Helen Weiss

**Other LSHTM investigators:** Mary De Silva, Daniela Fuhr, Vikram Patel (Co-PI)

**External investigators/collaborators:**
- Fareed Minhas (Benazir Bhutto Hospital, Pakistan), Martin Prince, Graham Thomicroft (Institute of Psychiatry, KCL, UK), Shakthivel Selvaraj, Rahul Shidhaye (PH Foundation of India), Neerja Chowdhary, Neha Singh (Sangath, Goa, India), Atif Rahman (Co-PI; University of Liverpool, UK)

**Funding:** US National Institute of Mental Health

**Location:** India, Pakistan

**Objective**
SHARE is a five-year programme (2011-16) which aims to reduce the mental health treatment gap in South Asia by generating evidence, building capacity and fostering the uptake of research into policy and practice.

**Description**
There is an urgent need for effective and sustainable community-based approaches to reduce the burden of depression in mothers in South Asia. SHARE will develop and evaluate a sustainable approach for the delivery of a brief psychological treatment by peer counsellors, the Thinking Health Programme, to reduce the burden of depression in mothers in...
Pakistan and India. In Goa, India, the study will be an individually randomised trial in which women with perinatal depression are recruited in their third trimester of pregnancy and the intervention delivered until the end of the 4th postnatal month. The primary outcome is maternal depression 6 months after delivery. In Pakistan, the trial will be cluster randomised and delivered by village-based female health workers.

**COPSI: the Community care for People with Schizophrenia in India Trial**

**TEG investigator:** Helen Weiss

**Other LSHTM investigators:** Mirja Koschorke, Vikram Patel

**External investigators/collaborators:**
Graham Thornicroft (PI; KCL, UK), Mathew Varghese (NIMH and Neurosciences, Bangalore, India), Hamid Dabholkar (Parivartan, Satara, India), Madhumitha Balajui, Sudipto Chatterjee, Smita Naik (Sangath, Goa), Sujit John, Rangaswamy Thara (Schizophrenia Research Foundation, Chennai)

**Funding:** Wellcome Trust

**Location:** India

**Objective**
To compare the clinical and cost-effectiveness of two service delivery methods for people with schizophrenia and their caregivers in India.

**Description**
There are few community services for people with schizophrenia in low-income countries largely because of the shortage of mental healthcare specialists. Community-based rehabilitation, involving lay health workers, has been shown to be feasible, acceptable and more effective than routine care for people with schizophrenia in observational studies. The aim of the COPSI trial is to evaluate whether a lay health worker-led collaborative community-based care intervention, combined with usual facility-based care, is superior to usual care alone in improving outcomes for people with schizophrenia and their caregivers in India.

A total of 282 participants with a primary diagnosis of schizophrenia were recruited into this multi-centre RCT. The primary outcomes were changes in symptoms and disabilities between baseline and at 12 months measured by the Positive and Negative Syndrome Scale and the Indian Disability Evaluation and Assessment Scale, respectively. Over the 12-month follow-up, the intervention was modestly more effective than usual care, particularly in reducing disability and in improving medication adherence.

The results of the COPSI trial support the strategy of using lay or non-specialist community health workers in scaling-up services for people with schizophrenia in India and other low- and middle-income countries.

**The Friendship Bench**

**TEG investigator:** Helen Weiss

**External investigators/collaborators:**
Dixon Chibanda (PI; University of Zimbabwe), Melanie Abas (KCL, UK), Frances Cowan (UCL, UK), Ricardo Araya (University of Bristol, UK)
Funding: Grand Challenges Canada

Location: Zimbabwe

Objective To test through a cluster RCT in Harare the effectiveness of a brief psychological intervention for common mental disorders (the Friendship Bench), delivered by appropriately trained and supervised lay workers.

Description Over 30% of people utilising primary healthcare facilities in Zimbabwe suffer from common mental disorders. Faced with the high attrition of health professionals against a background of socioeconomic challenges, we have piloted a programme (the Friendship Bench) that delegates responsibilities to lower-level healthcarers, for the treatment of common mental disorders. The Friendship Bench is a task-shifted brief intervention delivered by supervised lay health workers who have received training in problem-solving therapy and behaviour activation. It consists of six structured 45-minute sessions delivered on a wooden bench within the grounds of the clinic in a discrete area. Pilot data show the Bench, which has been running since 2006, is well accepted, feasible and potentially effective.

Our primary objective is to test the effectiveness of the Bench intervention delivered by appropriately trained and supervised lay workers through a cluster RCT. A secondary objective is to carry out a cost-effectiveness analysis of the intervention, followed by a scale up to all 33 local clinics in Harare if appropriate.

Neonatal, infant and child health

Improving Newborn Survival In Southern Tanzania: the INSIST trial

TEG investigators: Joanna Schellenberg (PI), Simon Cousens

Other LSHTM investigators: Tanya Marchant, Suzanne Penfold, David Schellenberg

External investigators/collaborators: Jennie Jaribu, Fatuma Manzi, Hassan Mshinda, Donat Shamba (Ifakara Health Institute, Tanzania), Zelee Hill (KCL, UK), Marcel Tanner (Tropical and Public Health Institute, Switzerland)

Funding: Bill and Melinda Gates Foundation via Save the Children US, UNICEF Tanzania and Batchworth Trust

Location: Southern Tanzania

Objective To evaluate interventions to improve the quality of facility-based health services for mothers and newborn babies and to improve newborn care practices at home.

Description In 2009, INSIST developed a home-based counselling strategy for women in pregnancy and the early newborn period: female volunteers visit women at home three times in pregnancy and twice in the first few days of infant life. Over 800 volunteers have been recruited and trained. Every 3 months, groups of volunteers met with supervisors and district health staff for a review meeting. Half the 1,311 wards in six districts of Lindi and Mtwara Regions, Tanzania, were randomly selected to receive the intervention. In 2011, a survey of 5,000 households showed strong evidence that some behaviours had improved as a result of the intervention, including tying the cord with clean thread, delayed bathing after birth and feeding only breast milk for the first 3 days. To October 2012, 86% of women in intervention areas have been visited by a volunteer in pregnancy and 67% were visited in the early newborn period. In 2013, a large household survey, including all women of reproductive age in over 300,000 households, will enable the investigators to estimate the effect of the strategy on newborn survival.

Over 40% of under-5 deaths globally are in the first month of life, the newborn period.
Can mass media campaigns reduce child mortality?

**TEG investigator:** Simon Cousens (PI)

**LSHTM investigator:** Sophie Sarassat

**External investigators/collaborators:**
Nicolas Meda (Centre Muraz, Burkina Faso), Roy Head (Development Media International, UK)

**Funding:** Wellcome Trust Strategic Award

**Location:** Burkina Faso

**Objective**
To test whether a mass media campaign targeting the leading causes of child death can change behaviours sufficiently to result in a detectable impact on child mortality.

**Description**
A cluster RCT is being conducted in 14 locations in rural Burkina Faso to evaluate whether a comprehensive mass media campaign delivered through local community radio stations can reduce child mortality. A baseline survey was conducted in early 2012 and the intervention began in March 2012. The intervention will run for 2.5 years followed by an endline survey to measure knowledge, behaviour and child mortality.

Approximately 7 million children under 5 years die each year worldwide. Mass media campaigns are an approach that could be scaled up relatively quickly if shown to be effective.

Newborn baby having anthropometric measures taken during a post-natal check
© Dr Tanya Marchant

Delhi Infant Vitamin D Study (DIVIDS)

**TEG investigator:** Andrea Rehman

**Other LSHTM investigator:** Suzanne Filteau (Co-PI)

**External investigators/collaborators:**
Geeta Trilok-Kumar (Co-PI; Delhi University, India), Harish Chellani, M.S. Prasad (Safdarjung Hospital, India), H.P.S. Sachdev (Sitaram Bhartia Institute, India)

**Funding:** Government of India, Nutrition Third World and Sight and Life

**Location:** India

**Objective**
To evaluate whether weekly vitamin D supplementation given at RDA doses from birth to 6 months for term infants of low birthweight from low-income Indian families will reduce rates of mortality and hospital admissions.

**Description**
The RCT enrolled term infants (>37 weeks of gestation) of low birthweight (1.8-2.5 kg) born in a large government hospital catering to a low- to middle-income population in Delhi. Mothers and infants were recruited at delivery and randomised to receive 35 μg vitamin D per week, or matching placebo. Supplements were delivered by fieldworkers, blinded to the intervention arm, at weekly home visits for 6 months. A total of 2079 infants were enrolled. The primary outcome was mortality or incidence of any illness requiring admission to hospital. At 6 months, there was no effect on death plus hospitalisation or on referral to outpatient clinic for moderate morbidity. In adjusted analyses, vitamin D treatment was associated with significantly increased Z-scores at 6 months for weight.
length and arm circumference and decreased the proportion of children stunted (length-for-age Z-score, < –2) or with low arm circumference (Z-score < –2).

**A weekly dose of vitamin D improved vitamin D status and benefited the classical vitamin D function of bone growth. It did not affect resistance to infection in young breastfed infants.**

Reference: 232

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**Pneumococcal disease**

**Modelling serotype replacement in The Gambia**

**TEG investigator:** Christian Bottomley (PI)

**Other LSHTM investigator:** Brian Greenwood

**External investigators/collaborators:** Anna Roca (MRC, The Gambia), Valerie Isham (UCL, UK), Philip Hill (University of Otago, New Zealand)

**Funding:** MRC

**Location:** The Gambia

**Objective**

To test the hypothesis that zinc supplementation given to Gambian children, as an adjunct therapy in severe or very severe pneumonia, is associated with more rapid recovery.

**Description**

600 Children under 5 years of age presenting with severe or very severe pneumonia were randomised to placebo or zinc supplementation. The primary outcome was treatment failure at day 5 and day 10. To confirm that the Gambian children were zinc deficient, zinc supplementation was continued in a subgroup of 240 children for 6 months after recovery from severe or very severe pneumonia. The impact of zinc supplementation on linear growth and immune competence in this subgroup was measured. Analysis of the data is currently underway.

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**Zinc supplementation in Gambian children with severe pneumonia**

**TEG Investigators:** Christian Bottomley

**LSHTM Investigators:** Paul Snell

**External investigators/collaborators:**

Leads: Stephen Howie (Co-PI; MRC, The Gambia), Akram Zaman (Co-PI; Public Health, England)

**Funding:** MRC

**Location:** The Gambia

**Nonspecific effects of childhood vaccination on bacterial carriage**

**TEG Investigators:** Christian Bottomley

**External investigators/collaborators:**

Anna Roca (PI), Abdoulie Bojang, Umberto D’Alessandro (MRC, The Gambia)

**Funding:** MRC

**Location:** The Gambia

**Objective**

To assess the non-specific effects of childhood vaccines on bacterial carriage, a necessary step for bacterial disease which is a leading cause of mortality in Africa.

**Description**

A cohort of 149 children from rural Gambia was recruited at birth and followed for 1 year. Nasopharyngeal swabs were taken immediately after birth, every 2 weeks for the first 6 months and then every month. The presence of bacteria in the nasopharynx (Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus) was compared before and after the administration of BCG, DTP and measles vaccines. A paper is currently in preparation.
Research Methods

One of the Group’s objectives is to develop novel study designs, and statistical and epidemiological methods, to facilitate interventions against its priority diseases. In 2011-12, we published methods in three main areas.

1. Randomised trial and other study designs, including endpoint selection, with emphasis on parasitological and entomological outcomes.
2. Causal inference, which seeks to estimate the strengths of relationships based on models of dependence.
3. Survey design and behavioural measurement, motivated by studies of HIV and other STIs.

68 Designs of randomised trials and other epidemiological studies
   • Selection and quantification of infection endpoints for trials of vaccines against intestinal helminths
   • Analysis of parasite and other skewed counts
   • Alternatives to randomisation in the evaluation of public health interventions: design challenges and solutions

69 Causal inference
   • Using causal diagrams to guide analysis in missing data problems
   • gformula: estimating causal effects in the presence of time-varying confounding or mediation

70 Survey design and behavioural measurement
   • How you ask really matters: randomised comparison of four sexual behaviour questionnaire delivery modes in Zimbabwean youth
   • Evaluation of respondent-driven sampling
   • Vaginal practices diary: development of a pictorial data collection tool for obtaining sensitive behavioural data
   • Considerations in the design of clinical trials to test novel entomological approaches to dengue control
   • Field Trials of Health Interventions: a Toolbox
Data from a cluster-randomised trial of insecticide-treated curtains and water container covers for dengue control in Venezuela (Kroeger et al. BMJ 2006;332:1247–1252). The image shows a choropleth map of depth: a novel measure to quantify indirect effects of the intervention in control-arm individuals. The tiles are formed using the Dirichlet tessellation of houses, and control-arm regions are delimited by double lines. Investigators: Neal Alexander, Karim Anaya-Izquierdo (TEG), Audrey Lenhart (CDC). Research methods work funded through TEG.
Selection and quantification of infection endpoints for trials of vaccines against intestinal helminths

**TEG investigators:** Neal Alexander, Bonnie Cundill, Peter Smith

**Other LSHTM investigators:** Simon Brooker (PI), Laura Rodrigues, Lorenzo Sabatelli

**External investigators/collaborators:** Jeffrey Bethony (FIOCRUZ, Brazil), David Diemert, Peter Hotez (George Washington University, USA)

**Funding:** Bill and Melinda Gates Foundation, via the Sabin Vaccine Institute

**Objective**
To estimate the likely impact of trial interventions on the force of human helminth infection, and hence statistical power, using a modelling approach.

**Description**
Motivated by the development of hookworm vaccines, this study ranks the statistical power of three measures of efficacy in clinical trials: (i) the ratio of mean parasite intensity at the end of the trial; (ii) the odds ratio of infection at the end of the trial; and (iii) the rate ratio of incidence of infection during the trial.

The measures are expressed in terms of two parameters of the negative binomial distribution (the mean, and the dispersion parameter k), which are assumed to characterise the numbers of parasites per person. Smaller values of k imply a distribution of parasites that is more clustered between people. For a given mean parasite intensity, larger values of k correspond to higher prevalence, and higher incidence rates (see the figure).

The study concluded that the end-of-trial mean parasite intensity is a suitable endpoint for later phase vaccine trials, and that mass effects of trial interventions are unlikely to appreciably reduce the force of infection in the community – and hence statistical power – unless there is a combination of high vaccine efficacy and a large proportion of the population enrolled.

Reference: 288

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Analysis of parasite and other skewed counts

**TEG investigator:** Neal Alexander (PI)

**Funding:** Bill and Melinda Gates Foundation, via the Sabin Vaccine Institute

**Objective**
To review methods for analysis of count data (0, 1, 2, 3, etc.) with a parasitological focus.

**Description**
Commonly used statistical methods for analysing count data were identified from 10 years of the journal Tropical Medicine and International Health. Of the 90 papers identified, 89 were descriptive and 60 had inferential analysis. One commonly used measure of location is the Williams mean, which is obtained by adding 1 to all the data points, taking the geometric mean, then subtracting 1 again. In the papers reviewed, it was often hard to tell whether this, or the geometric mean itself, had been used. The different measures are compared, emphasising that, depending on the objective of the study, the arithmetic mean may be a suitable measure for skewed data. For example, in lymphatic filariasis, the arithmetic mean number of infective larvae per mosquito is of interest because it is proportional to the transmission potential.

The t test and related methods were often used on untransformed data, which is likely to be invalid due to skewness (see the figure) and other considerations. Several more suitable approaches to inferential analysis are described, emphasising (i) non-parametric methods, while noting that they are not simply comparisons of medians; and (ii) generalised linear models (GLMs). GLMs compare arithmetic means (as do t tests) but the choice of a distribution family, such as the negative binomial, allows correct weighting of large values. Additional methods, such as the bootstrap, with potential for greater use are also described.

Reference: 287

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Selection and quantification of infection endpoints study: Relation between the proportion parasite-positive at the end of the trial, incidence rate and the two parameters of the negative binomial distribution. It is assumed that parasites are cleared at the start of a trial, then re-infection over time is estimated using a mathematical model (Reproduced with permission from Alexander et al., 2011 [288]; © 2013 Elsevier)
Alternatives to randomisation in the evaluation of public health interventions: design challenges and solutions

**TEG investigators:** Simon Cousens (PI), James Hargreaves, Richard Hayes, David Ross

**Other LSHTM investigators:** Chris Bonell, Betty Kirkwood, Mark Petticrew

**Objective**
To conduct a non-systematic exploratory review to describe specific scenarios in which randomised trials may not be possible and describe, exemplify and assess alternative strategies.

**Description**
There is growing interest in alternatives to randomisation in the evaluation of public health interventions. In many scenarios, barriers are surmountable and RCTs are possible. It is possible to rank alternative designs, based on internal validity considerations, but the study context will also determine which choices are preferable. Evidence from non-randomised designs is more convincing when confounders are well understood, measured and controlled for. This review concluded that non-randomised trials might provide adequate evidence to inform decisions when interventions are demonstrably feasible and acceptable, and where evidence suggests there is little potential for harm, but caution that such designs may not provide adequate evidence when intervention feasibility or acceptability is doubtful, and where existing evidence suggests benefits may be marginal and/or harms possible.

Reference: 289

Causal inference

**gformula: estimating causal effects in the presence of time-varying confounding or mediation**

**TEG investigator:** Simon Cousens (PI)

**Other LSHTM investigators:** Rhian Daniel, Bianca DeStavola

**Funding:** MRC

**Objective**
To use causal diagrams to complement and clarify some of the central issues in missing data theory.

**Description**
A key aim of medical and epidemiological research is to establish causal links between treatments, or other exposures, and outcomes. However, estimating causal effects from incomplete data requires additional and inherently untestable assumptions regarding the mechanism giving rise to the missing data. This study showed that using causal diagrams to represent these additional assumptions both complements and clarifies some of the central issues in missing data theory. It demonstrated how Pearl's theory of causal diagrams can be used to determine whether a causal effect can be estimated without bias by analysing only the subjects with complete data. When this is not possible, the modified extended diagrams introduced in the study provide an intuitive tool to help in understanding how and why a complete records analysis is biased.

Reference: 293

**Using causal diagrams to guide analysis in missing data problems**

**TEG investigator:** Simon Cousens

**Other LSHTM investigators:** Rhian Daniel (PI), Bianca DeStavola, Mike Kenward

**Funding:** MRC

**Objective**
To describe a new STATA command, gformula, which is an implementation of the g-computation procedure.
Description
In problems concerning time-varying confounding and mediation, standard regression analyses are invalid when confounders are affected by the exposure. The g-computation procedure is valid under a weaker set of assumptions that allows for confounders to be affected by past exposure. The gformula command estimates the causal effect of time-varying exposures on an outcome in the presence of time-varying confounders that are themselves also affected by the exposures. The procedure also addresses the related problem of estimating direct and indirect effects when the causal effect of the exposures on an outcome is mediated by intermediate variables and, in particular, when confounders of the mediator-outcome relationships are themselves affected by the exposures.

Reference: 292

Survey design and behavioural measurement

How you ask really matters: randomised comparison of four sexual behaviour questionnaire delivery modes in Zimbabwean youth

TEG investigator: Richard Hayes (PI), Yin Bun Cheung

Other LSHTM investigators: Sophie Pascoe

External investigators/collaborators: Lisa Langhaug (UCL, UK), Petronella Chirawu, Frances Cowan, Godfrey Woelk (University of Zimbabwe)

Funding: US National Institute of Mental Health

Objective
To compare the validity and reliability of sexual behaviour measures between four questionnaire delivery modes among rural Zimbabwean youth.

Description
A total of 1495 youth were randomised to one of four questionnaire delivery modes: self-administered questionnaire (SAQ); SAQ accompanied by an audio soundtrack (Audio-SAQ); face-to-face interview with sensitive questions placed in a confidential voting box (ICVI); and audio computer-assisted survey instrument (ACASI).

Non-response was significantly higher with SAQ and Audio-SAQ than with ICVI and ACASI (p < 0.001). After adjusting for covariates, the odds of reporting sexual activity among Audio-SAQ and ACASI users were twice as high as for SAQ users, with no evidence of reporting difference between ICVI and SAQ users.

Overall, the study found that ACASI appears to reduce bias of reported sexual behaviour and is feasible and acceptable in resource-poor settings with low computer literacy. Its increased use would likely improve the quality of questionnaire data in general and sexual behaviour data specifically.

Reference: 298
Evaluation of respondent-driven sampling

TEG investigator: Richard Hayes

Other LSHTM investigators: Richard White (PI)

External investigators/collaborators: Andrew Copas, Fatima Jichi, Pam Sonnenberg (UCL, UK), Lisa Johnston (Center for Global Health Equity, New Orleans, USA), Natasha Lunel (University of St Andrews, UK), Nicky McCreesh (University of Durham, UK), Joseph Katongoole, Dermot Maher, Matilda Ndagire Tarsh, Richard Ndungu (MRC/UVRI Unit, Uganda), Simon Frost (University of Cambridge, UK)

Funding: MRC Methodology Research Fellowship

Objective
To evaluate respondent-driven sampling in a well-connected, non-hidden population in Uganda by comparing respondent-driven sampling estimates with those from a total population survey.

Description
Total population data on age, tribe, religion, socioeconomic status, sexual activity and HIV status were available for 2402 male household-heads from an open cohort in rural Uganda. A respondent-driven sampling survey was carried out in this population, recruiting 927 household-heads.

Respondent-driven sampling produced a generally representative sample of this well-connected non-hidden population of male household-heads. However, current inference methods for respondent-driven sampling failed to reduce bias when it occurred and it is unclear whether the data required to remove bias and measure precision can be collected in a survey using this sampling method. Respondent-driven sampling should be regarded as a (potentially superior) form of the convenience-sampling method, and caution is required when interpreting findings based on this sampling method.

Reference: 299

Vaginal practices diary: development of a pictorial data collection tool for obtaining sensitive behavioural data

TEG investigators: Richard Hayes (PI), Kathy Baisley, Suzanna Francis, Heiner Grosskurth (MITu/NIMR, Tanzania)

Other LSHTM investigators: Tony Ao, Saidi Kapiga (both MITu/NIMR Tanzania), Shelley Lees

External investigators/collaborators: Andrew Bahati, Judith Vandepitte, Flavia Zalwango (MRC/UVRI Unit, Uganda)

Objective
To evaluate whether use of daily self-administered diaries may decrease bias associated with obtaining sensitive behavioral data.

A technician working on the intravaginal practices project, making preparations at a mobile clinic in Shinyanga, Tanzania © Suzanna Francis, LSHTM
behavioural data from face-to-face interviews.

**Description**

Intravaginal practices (IVP) comprise a variety of behaviours that women use to manage their health and sexual life and are highly prevalent among women at increased risk for HIV in sub-Saharan Africa. IVP data collected by face-to-face interviews (FTFI) may be subject to recall or social desirability bias. IVP data from a diary and FTFI were compared during the multi-centre Microbicide Feasibility Study in Tanzania and Uganda (p32).

In all, 200 women were recruited and given diaries to complete daily for 6 weeks. Comparison of FTFI and the vaginal practice diary suggests that recall of IVP may be improved by a daily self-administered diary, particularly for frequency of cleansing and cleansing in proximity to sexual intercourse. The vaginal practices diary can provide a more detailed understanding of IVP and aid in the interpretation of findings from FTFI.

Reference: 295

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**Considerations in the design of clinical trials to test novel entomological approaches to dengue control**

**TEG investigator:** Immo Kleinschmidt

**External investigators/collaborators:**
- Christl Donnelly (ICL, UK), Cameron Simmons (PI; Oxford University Research Unit, Vietnam), Marcel Wolbers (University of Oxford, UK)

**Objective**

To review the design and statistical considerations relevant to the conduct of clinical trials of novel interventions for dengue, and the practical challenges posed by the epidemiology of dengue in endemic settings.

**Description**

There are no licensed vaccines for prevention of dengue, and the public health response in endemic countries relies mostly on combating the principal mosquito vector, *Aedes aegypti*, via insecticides and breeding site removal. While the review focused on *Wolbachia*-infected *Aedes. aegypti*, it is also relevant to other vector control interventions.

Parallel cluster RCTs are the design of choice for testing novel entomological methods of dengue control. Under realistic assumptions, this design requires a substantially lower sample size than a stepped-wedge design, for example a minimum sample size of 20 clusters (10 per study arm) with each cluster providing 100 person-years of follow-up per year and a follow-up duration of 3 years.

Although careful planning and substantial funding are required to run such a trial, the benefits of having a robust evidence base from which to promote programme roll-out and/or further optimisation of the strategy should prove invaluable.

Reference: 303

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**Field Trials of Health Interventions: a Toolbox**

**TEG investigators:** Peter Smith (PI), David Ross

**External investigators/collaborators:**
- Richard Morrow (Johns Hopkins Bloomberg School of Public Health, USA)

**Funding:** WHO Tropical Disease Research

**Description**

A team of over 40 intervention trial experts from developed and developing countries is working on the production of a third edition of *Field Trials of Health Interventions: a Toolbox*. The book provides practical guidance on the design, conduct and reporting of field trials in developing countries, including the types of technical and practical information that are rarely given in any detail in published papers. Earlier editions of the book have been extensively used by those conducting trials, but it is now undergoing a substantial revision because of the many developments in technology and trial governance that have taken place over the last decade, which have changed the ways in which trials are conducted. It is expected that the third edition will be published in 2013.
A community health worker waits for the results of a rapid diagnostic malaria test on a seven month-old baby girl during a home visit to the Ghanian village of Takoradi © LSHTM
Malaria


115. Napierala Mavedzenge, S.M., A.M. Doyle, and


Tuberculosis


Strengthening research capacity

The long-term sustainability of epidemiological research in Africa and other resource-poor settings depends on developing a cadre of scientists from those settings with epidemiological and statistical skills. As part of its remit to strengthen such capacity, TEG undertook a number of capacity building initiatives in 2011-12, including:

• training three medical statisticians under the TEG Training Fellowship Programme in Medical Statistics (p89);
• providing close support and guidance to locally employed statisticians and epidemiologists at the MRC research units, MITu/NIMR, and other collaborating centres in Africa, and teaching on statistical and epidemiological courses at these centres;
• developing the specialist Clinical Trials Data Centre at DNDi Africa in Nairobi, providing capacity building in data management, statistical design and statistical analysis of clinical trials;
• supervising 11 doctoral students from Africa in 2011-12;
• teaching a short course on the design and conduct of clinical trials to medical students of the Graduate School of Xinjiang Medical University, Urumqi, as part of a collaboration established via the British Council’s Development Partnerships in Higher Education (DelPHE) scheme; and
• provided funding for the purchase of financial software and books for the on-site library (through the biomarkers study, based in MITu/NIMR; p32), along with training for the laboratory management system (LIMS) and training of technicians in the use of quantitative real-time polymerase chain reaction and microbiology techniques.

TB research capacity development case studies

Many TB drugs are currently in development, and complex trials of these new drugs need to be conducted quickly and efficiently. This requires local institutions and organisations to have sufficient capacity and expertise in place to execute large, complex trials.

The OFLOTUB project

The OFLOTUB trial (a multi-centre, RCT of gatifloxacin-containing, short-course regimen for the treatment of pulmonary TB; p45) is developing local capacity and expertise through the establishment or provision of:

• two haematological laboratories within the National Reference Laboratory of the TB programme, one in Benin and one in Guinea;
• three data management departments within the national TB programmes running in Benin, Senegal and Guinea;
• regular local training on Good Clinical Practice and Good Laboratory Practice, targeted at teams working across nine clinical centres in Benin, Guinea, Kenya, Senegal and South Africa;
• sponsorship of an MSc in epidemiology, in Guinea; and
• freezers (-80°C) to institutions in Benin, Guinea and Senegal, thus facilitating the conduct of pharmacokinetic studies, along with provision of relevant training to enable researchers to work on US Food and Drug Administration, and European Medicines Agency approved/registered trials.

The OFLOTUB study has also raised the profile of the national TB programme as a location for the conduct of international clinical trials in compliance with Good Clinical Practice.

The RAFA project

This project builds on the developments of OFLOTUB, assessing the efficacy of three treatment strategies in TB/HIV patients. It has:

• trained on-site monitors and project managers locally in Senegal;
• provided staff with London-based mentors;
• developed the expertise of data managers in Benin, Guinea and Senegal through the provision of mentoring and short courses (at LSHTM);
• enabled solar panels to be installed in clinical centres in Guinea, providing a constant uninterrupted supply of electricity;
• equipped a centre in Guinea with a CD4 cell count machine, and centres in Benin and Guinea with an Xpert/MTB-RIF machine; and
• supported five MSc and two PhD students from Africa in 2011-12.

Plans are currently under way to send the data managers to a data management centre in Luxembourg to gain practical experience which they can then apply in the local setting.
MRC Tropical Epidemiology Group Fellowship Scheme

About the scheme

The fellowship scheme is pivotal to the Group’s capacity development strategy. It provides 2 years of training in Medical Statistics to students from sub-Saharan Africa. Successful fellows have a background in statistics and previous experience in medical research. In recent years, competition for the fellowships has been strong, with around 50-100 applicants each year. Fellows study for an MSc in Medical Statistics at LSHTM and, after completing this, spend a year on a professional placement at an African research institution.

At LSHTM, fellows are tutored by a member of TEG, who also supervises their summer project. Chosen by the fellow, these projects often provide an introduction to the research topic to be pursued further during the placement year. During the placement year, the fellow is exposed to different aspects of research including study design, data management, analysis and reporting of findings. They are guided by local statisticians and researchers as well as relevant TEG members.

To date, seven fellows have completed the 2-year programme and all have continued to work in medical research following on from their fellowship award:

- Nuredin Ibrahim Mohammed is currently studying for a doctoral degree, and Sylvia Kiwuwa Muyingo successfully completed her PhD in June 2012 and is now working as a statistician at the MRC/UVRI Unit, Uganda. Tim Awine is working as a medical statistician in Northern Ghana.
- Nakua Emmanuel Kwelu is a lecturer based in Ghana and plans to start a doctoral degree in September 2013 and Phellister Nakamya is a researcher in Uganda.
- Evans Muchiri is currently working with Wits Reproductive & HIV Institute in South Africa, and James Jafali has now finished his TEG placement and is working as a statistician at MRC, The Gambia.

Thus far, four fellows have had placements with MRC, The Gambia. The other 3 placements have been with MRC/UVRI Unit, Uganda, the Aurum Institute, South Africa, and KEMRI, Kenya.

The current Fellow, Ivan Kasamba, completed his MSc in September 2012 and is currently on placement at MITU/NIMR, Tanzania.

SEVEN FELLOWS have completed the 2-year programme

Fellows during the period 2011-12

<table>
<thead>
<tr>
<th>Evans Muchiri, Kenyan</th>
<th>James Jafali, Malawian</th>
<th>Ivan Kasamba, Ugandan</th>
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</thead>
<tbody>
<tr>
<td>Evans completed his MSc in Medical Statistics in 2010 and now works at the Wits Reproductive Health &amp; HIV Institute in South Africa.</td>
<td>James completed his MSc in Medical Statistics in 2011 and is now a statistician at MRC, The Gambia.</td>
<td>Ivan completed his MSc in Medical Statistics in 2012, and is currently on placement at MITU, Tanzania.</td>
</tr>
</tbody>
</table>
# PhD/DrPH students 2011-12

Studies completed in 2011-12

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<th>PhD Student</th>
<th>Supervisor</th>
<th>Dissertation title</th>
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<tr>
<td>Erin Anastasi (DrPH)</td>
<td>Sian Floyd</td>
<td>Between women's use of antenatal care and skilled birth attendance? A case study in Northern Uganda</td>
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<tr>
<td>Samuel Biraro</td>
<td>Helen Weiss</td>
<td>Herpes Simplex Virus type-2: Epidemiological trends and relation with trends in HIV incidence and HIV transmission in south-western Uganda</td>
</tr>
<tr>
<td>Salome Charalambous</td>
<td>Katherine Fielding</td>
<td>A study to determine site-level factors which may determine clinical outcomes on antiretroviral therapy (ART) in patients attending primary health clinics in South Africa.</td>
</tr>
<tr>
<td>Laura Ferguson</td>
<td>David Ross</td>
<td>Linking women who test HIV-positive in pregnancy-related services to HIV care and treatment services in Kenya: missed opportunities</td>
</tr>
<tr>
<td>Suzanna Francis</td>
<td>Richard Hayes</td>
<td>Are intravaginal practices a risk factor for HIV acquisition: An in-depth exploration of highly prevalent behaviours among women at high risk of HIV infection in Tanzania and Uganda (Awarded Cicely Williams Prize)</td>
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<tr>
<td>Peter Horby</td>
<td>Neal Alexander</td>
<td>Avian, inter-pandemic, and pandemic influenza in Vietnam</td>
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<tr>
<td>Anatoli Kamali</td>
<td>Richard Hayes</td>
<td>Research on the epidemiology and prevention of HIV in rural South West Uganda, 1989-2010 (City University, London)</td>
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<tr>
<td>Susan Mavedzenge-Napierala</td>
<td>Helen Weiss</td>
<td>The epidemiology of Mycoplasma genitalium and HIV infection</td>
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<tr>
<td>Joshua Mendelsohn</td>
<td>David Ross</td>
<td>Is forced displacement a barrier to acceptable treatment outcomes among refugees on antiretroviral therapy? A field study in Malaysia and Kenya</td>
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<tr>
<td>Anthony Ngugi</td>
<td>Immo Kleinschmidt</td>
<td>Prevalence, incidence and mortality of epilepsy in four health and demographic surveillance sites in Sub-Saharan Africa</td>
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<tr>
<td>Anita Rames</td>
<td>Neal Alexander</td>
<td>The role of residential proximity to public and private water sources in lymphatic filariasis</td>
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<tr>
<td>Michael Wallace</td>
<td>Simon Cousens</td>
<td>Facilitating correction for classical covariate measurement error</td>
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</table>

Richard Hayes with Suzanna Francis at her graduation ceremony in July 2011, LSHTM
Studies ongoing in 2011-12

<table>
<thead>
<tr>
<th>PhD Student</th>
<th>Supervisor</th>
<th>Dissertation title</th>
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<tr>
<td>Elhadji Ba</td>
<td>Paul Milligan</td>
<td>Establishing demographical surveillance system for monitoring serious adverse events</td>
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<td>and mortality in an area where seasonal IPTc is being implemented</td>
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<tr>
<td>Intira Collins</td>
<td>Shabbar Jaffar</td>
<td>Outcomes and cost-effectiveness of anti retroviral treatment in HIV-affected children</td>
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<td>Sapna Desai</td>
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<td>The effect of community health worker-led group education on women's health and</td>
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<td>utilisation of health insurance: A cluster randomised trial in Gujarat, India</td>
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<tr>
<td>Stefanie Dringus</td>
<td>David Ross</td>
<td>Sports-based HIV prevention programme</td>
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<td>Benson Droti (DrPH)</td>
<td>David Ross</td>
<td>One month versus three months of ARV refills in Uganda</td>
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<td>Joel Francis</td>
<td>Heiner Grosskurth/ Helen Weiss</td>
<td>Epidemiology of alcohol use disorders and their contribution to STIs and HIV in</td>
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<td>Stephen Gichuhi</td>
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<td>The epidemiology and management of ocular surface squamous neoplasia in Kenya</td>
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<td>Claudia Hanson</td>
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<td>The epidemiology of maternal mortality in Southern Tanzania</td>
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<td>Gregory Kabadi</td>
<td>Joanna Schellenberg</td>
<td>Towards a new method for evaluating national maternal health programmes in Tanzania:</td>
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<td>measuring implementation strength of focused antenatal care and emergency obstetric</td>
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<td>Ronnie Kasirye</td>
<td>Heiner Grosskurth/ Emily Webb</td>
<td>Whether to stop or continue cortrimoxazole in HIV affected adults on ART</td>
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<td>Zachery Kaufman</td>
<td>David Ross</td>
<td>Sport-based HIV prevention in South African schools: a cluster RCT</td>
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<td>Pierre Martel</td>
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<td>Measuring child mortality</td>
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<td>Lori Miller</td>
<td>Richard Hayes</td>
<td>Measurement of adherence in microbicides effectiveness trials</td>
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<tr>
<td>Ghina Mumtaz</td>
<td>Helen Weiss</td>
<td>The epidemiology of HIV infection among high-risk populations in the Middle East and</td>
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<td>North Africa</td>
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<tr>
<td>Pamela Muniina</td>
<td>Sian Floyd</td>
<td>The impact of adult HIV infection and mortality on household composition, family</td>
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<td>structure, and household welfare in rural south-west Uganda, 1989-2006</td>
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<td>Kalpana Sabapathy</td>
<td>Richard Hayes</td>
<td>From Testing to Treatment in PopART/HPTN 071 – Factors associated with the uptake</td>
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<td>of interventions and the impact on clinical status of patients presenting for care</td>
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<td>Kate Sabot (DrPH)</td>
<td>Joanna Schellenberg</td>
<td>Evaluating factors that determine the effectiveness of national scale-up of community</td>
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<tr>
<td>Yusuke Shimakawa</td>
<td>Christian Bottomley</td>
<td>Natural history of chronic hepatitis B infection in the Gambia, West Africa</td>
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<td>Philippa West</td>
<td>Immo Kleinschmidt</td>
<td>Investigating the complementary use of two malaria vector control methods: A cluster</td>
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<td>randomised control trial in Northwest Tanzania</td>
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## Membership of national and international committees and boards

<table>
<thead>
<tr>
<th>TEG Member</th>
<th>Committee/Board name</th>
</tr>
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</table>
| **Neal Alexander** | Chair, Data & safety monitoring board: Use of corticosteroids in pulmonary leptospirosis  
Data & safety monitoring board: REMSTART trial  
WHO Technical Advisory Group on dengue vaccines in late stage development |
| **Karim Anaya-Izquierdo** | Associate Editor, Statistical Methods & Applications, Journal of the Italian Statistical Society  
WHO Technical Advisory Group on dengue vaccines in late stage development |
| **Kathy Baisley** | Data & safety monitoring board: NUSTART trial  
Wellcome Trust Bloomsbury Centre for Clinical Tropical Medicine, Policy Group |
| **Christian Bottomley** | Associate Editor, Tropical Medicine & International Health  
Steering committee for a randomised controlled trial of habit-based advice for weight control in general practice |
| **Tansy Edwards** | Pharmacovigilance Steering Committee: Management of Visceral Leishmaniasis in the endemic regions of India  
Data & safety monitoring board: Use of Fosphenytoin for treatment of seizures in Kenya – KEMRI, Kilifi |
| **Katherine Fielding** | Data & safety monitoring board: REMoxTB  
Data & safety monitoring board: RIFACUIN  
Data & safety monitoring board: TB Vaccine RUTI |
| **Richard Hayes** | Chair, Trial Steering Committee, Uganda Mother & Baby Study  
Academy of Medical Sciences, Public Health sub-committee  
Board of Management, Mwanza Intervention Trials Unit  
Executive Committee, PEPFAR Combination Prevention Trials Group  
MRC Cross-Board Cohort Advisory Group  
MRC Infections & Immunity Board  
MRC Population Health Sciences Group  
Wellcome Trust Bloomsbury Centre for Clinical Tropical Medicine, Policy Group  
Programme Advisory Committee, INTHEC Trial  
Programme Management Board, Liaison Group & Trial Steering Committee: DFID/MRC Microbicides Development Programme  
Scientific Advisory Committee, MRC Uganda  
Scientific Programme Committee, Microbicides 2012 Conference (Sydney)  
Wellcome Trust, Expert Group on study design |
| **Shabbar Jaffar** | Chair, EDCTP Scientific Advisory Committee  
Joint Editor, Tropical Medicine and International Health  
Steering Committee: Cooking Stoves for Pneumonia (CAPS) trial in Malawi |
| **Immo Kleinschmidt** | Bioko Island Malaria Control Project: Technical Advisory Group  
Innovative Vector Control Consortium: External Scientific Advisory Committee, Liverpool School of Tropical Medicine  
Regional Scientific & Technical Advisory Committee (STAC): Sustainable alternatives to DDT & strengthening of vector control, WHO-EMRO/UNEP  
South African Malaria Elimination Committee (SAMEC)  
Steering Committee: MRC funded spraying & nets towards malaria elimination (SANTE) trial in the Gambia  
USAID’s President’s Malaria Initiative’s Impact Evaluation: Technical Advisory Group  
WHO appointed member of DDT expert group under the Stockholm Convention on Persistent Organic Pollutants |
<p>| <strong>James Lewis</strong> | Data &amp; safety monitoring board: Rifapentine in place of rifampicin for intensive phase treatment of smear-positive TB |</p>
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<tr>
<td>Paul Milligan</td>
<td>Joint Technical Expert Group on Phase III malaria vaccine trials, IVR, WHO Geneva</td>
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<td>Malaria Vaccine Advisory Committee, WHO Geneva</td>
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<tr>
<td>Peter Smith</td>
<td>Chair, Diagnostic Evaluation Expert Panel (DEEP) (UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases)</td>
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<td>Chair, Programme Board for Global Health and Vaccination Research (GLOBVAC) of the Research Council of Norway</td>
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<td>Chair, Scientific Review Board and Member of Governance Council of the INDEPTH Effectiveness and Safety Studies of Anti-malarials in Africa (INESS)</td>
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<td>Chair, UK Childhood Cancer Study Steering</td>
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<td>Chair, WHO Global Malaria Programme(GMP)/IVR Joint Technical Expert Group (JTEG) on malaria vaccines in pivotal phase III trials &amp; beyond</td>
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<td>Chair, WHO Malaria Policy Advisory Committee Evidence Review Group on malaria burden estimation</td>
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<td>Scientific Advisory Board of International Vaccine Institute, Seoul, Korea</td>
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<td>Scientific Advisory Board of the LeishDNAvax project (EU FP7 funded project)</td>
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<td>Chair, Scientific Advisory Committee to the MRC Laboratories in The Gambia</td>
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<td>WHO Ad Hoc Advisory Working Group on the use of A (H1N1) vaccines</td>
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<td>Andrea Rehman</td>
<td>Data &amp; safety monitoring board: Strategies to improve malaria diagnosis and use of ACTs in the home management of malaria in Uganda</td>
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<td>Emily Webb</td>
<td>Entebbe Mother &amp; Baby Study Trial Steering Committee</td>
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<td>Associate Editor, Tropical Medicine &amp; International Health</td>
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<tr>
<td>Helen Weiss</td>
<td>Associate Editor, Sexually Transmitted Infections</td>
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<td>Data &amp; safety monitoring board: ANRS 12249 treatment as prevention trial</td>
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<td>Scientific Advisory Committee, treatment as prevention trial, Swaziland, MSF</td>
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<td>Wellcome Trust Bloomsbury Centre for Clinical Tropical Medicine, Policy Group</td>
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<td>WHO Technical Advisory Group on male circumcision</td>
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Current staff members

**Neal Alexander**
Reader in Medical Statistics and Epidemiology
Malaria, Neglected Tropical Diseases, Research Methods

**Simon Cousens**
Professor of Epidemiology and Medical Statistics
Newborn and Child Health, Research Methods

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HIV, TB

**Karim Anaya-Izquierdo**
Lecturer in Medical Statistics
Research Methods

**Bonnie Cundill**
Lecturer in Medical Statistics and Epidemiology
Malaria

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HIV, TB

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Lecturer in Epidemiology and Medical Statistics
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HIV, Sexually Transmitted Infections

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HIV, Sexually Transmitted Infections

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Neglected Tropical Diseases, Research Methods

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Lecturer in Medical Statistics
Neglected Tropical Diseases

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Research Fellow in Medical Statistics and Epidemiology
Malaria

**Eleanor Estchild**
Group Administrator

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Malaria, Modelling

**Fiona Ewings**
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HIV, Non Communicable Diseases
Hannah Jeffery
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TB

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and Medical Statistics
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HIV, TB

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Malaria

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Malaria

Kalpana Sabapathy
Research Fellow in Clinical Epidemiology
HIV

Barbara Willey
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Malaria, Newborn and Child Health

Corinne Merle
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HIV, TB

Albertus Schaap
Research Fellow
HIV, TB

Joanna Schellenberg
Reader in Epidemiology and International Health
Malaria, Newborn and Child Health

Shabbar Jaffar with Sameen Shrey Jaffar

Latest additions to the TEG team, born in 2012

Emily Howcutt (Webb) with Maisie Ella Howcutt

Natasha Larke with Luca Violet and Finlay Peter Grant

We also welcome Frances Leila Bernice Hamilton
Tropical Epidemiology Group

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