Joint Global Health Trials - Call 1 Full Grant

<table>
<thead>
<tr>
<th>Project title</th>
<th>Project title details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tribendimidine for the treatment of liver fluke infection in Southeast Asia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Somphou Sayasone</td>
<td>Swiss Tropical &amp; Public Health Institute</td>
<td>G1100699/1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Co-Investigators</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Xiao-Nong Zhou National Institute of Parasitic Diseases</td>
<td>Millions of people are infected with the liver flukes Opisthorchis viverrini in Southeast Asia and Clonorchis sinensis in China. The diseases are associated with abdominal and hepato-biliar symptoms and serious manifestations such as obstructive jaundice and ascending cholangitis. Long-term consequences include the development of a fatal bile-duct cancer. Since there is currently only one drug available for the treatment of O. viverrini and C. sinensis, there is a need to develop novel trematocidal drugs.</td>
</tr>
<tr>
<td>Professor Kongsap Akkhavong National Institute of Public Health Lao</td>
<td>In a recent proof of concept trial with tribendimidine, a drug used in China for the treatment of roundworm infections, a high efficacy (based on changes in egg output after drug treatment) against infections with O. viverrini was observed. In addition, the drug was well tolerated. There is a need to follow up on these promising results. In the framework of 3 randomized trials the efficacy and safety of tribendimidine will be studied.</td>
</tr>
<tr>
<td>Dr Christoph Hatz Swiss Tropical &amp; Public Health Institute</td>
<td>First, we will study the dose-response of tribendimidine in O. viverrini patients and assess drug disposition. Second, once the ideal dose has been determined a phase 2b clinical trial will be conducted to compare the efficacies and safeties of tribendimidine with praziquantel.</td>
</tr>
<tr>
<td>Professor Jennifer Keiser Swiss Tropical &amp; Public Health Institute</td>
<td>Finally, the efficacy and safety of tribendimidine against C. sinensis infections will be studied in a proof-of-concept trial. The first two trial will be conducted in Laos, the third trial in China. In case tribendimidine has demonstrated adequate efficacy and safety in these trials we will pursue the registration of tribendimidine.</td>
</tr>
<tr>
<td>Dr Peter Odermatt Swiss Tropical &amp; Public Health Institute</td>
<td></td>
</tr>
</tbody>
</table>


**Project title**
Randomized trial of spatially targeted control to virtually eliminate malaria

**Grant holder** | **Institute** | **Grant reference**
--- | --- | ---
Dr Badara Cisse | Cheikh Anta Diop University of Dakar | G1100694/1

**Co-Investigators**
- Dr Jean Louis Ndiaye
  Cheikh Anta Diop University of Dakar
- Professor Ousmane Faye
  Cheikh Anta Diop University of Dakar
- Ms Catherine Pitt
  London Sch of Hygiene and Trop Medicine
- Professor Paul Milligan
  London Sch of Hygiene and Trop Medicine
- Mr El Hadj Konko Cire Ba Servier International Research Institute

**Summary**
There has recently been a sharp decline in the incidence of malaria in several parts of Africa, due to the strengthening of control measures, most importantly the large-scale distribution of free and highly subsidized insecticide-treated bednets, raising the prospect that malaria could be eliminated. But despite scaling-up of control, transmission persists in foci which provide a continuing source of infection. Additional strategies are needed to eliminate these foci, this is important because a resurgence of malaria in populations whose acquired immunity has lapsed could have a devastating impact.

The aim of this study is to find out whether we can virtually eliminate malaria in a population by delivering intensified control in villages with persistent transmission. The trial, which will take place in central Senegal, will run over two years. Each year we will select villages to be targeted, on the basis of malaria cases reported in the previous year, and we will operate intensified malaria control in these villages, attacking the vector population with indoor residual spraying with a highly effective residual insecticide, and treating infected persons with effective antimalarial drugs to remove the reservoir of infection.

The hope is that by targeting the places which favour transmission, there will be reduction in the prevalence of malaria infection not only in areas which are targeted but also in the surrounding villages that are not targeted. Spraying is done just before the rainy season begins, coating the places where the first mosquitoes to emerge will rest, to kill them before they can transmit infection. Chemotherapy will be done once early in September, to clear the reservoir of infection in humans before the height of the transmission season, and again in October to clear any persisting or new infections.

We will use a combination of two drugs, an artemisinin to quickly clear malaria infection, and piperaquine, which provides prophylaxis for about a month. Treatment of carriers is known to be an essential component of elimination programmes but it is an open question whether it is better to administer antimalarial drugs to all members of the community or screen and treat only those who are positive. The trial will use both approaches to see which is most effective and practical. It is hoped that the findings of this study will contribute to the elimination of malaria in areas where until recently it was the major cause of child deaths.
### Joint Global Health Trials - Call 1 Full Grant

**Project title**
Reduction of Early mortality in HIV-infected African adults and children starting antiretroviral therapy: REALITY trial

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Diana Gibb</td>
<td>Medical Research Council</td>
<td>G1100693/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

<table>
<thead>
<tr>
<th>Co-Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Martin Buxton, Brunel University London</td>
</tr>
<tr>
<td>Dr Joep van Oosterhout, Dignitas International</td>
</tr>
<tr>
<td>Professor Kathryn Maitland, Imperial College London</td>
</tr>
<tr>
<td>Dr Cissy Kityo, Joint Clinical Research Centre, Kampala</td>
</tr>
<tr>
<td>Professor Peter Mugyenyi, Joint Clinical Research Centre, Kampala</td>
</tr>
<tr>
<td>Dr Victor Musiime, Joint Clinical Research Centre, Kampala</td>
</tr>
<tr>
<td>Professor Mary Mwangome, KEMRI (Kenya Medical Research Institute)</td>
</tr>
<tr>
<td>Dr Jane Edith Mallewa, Malawi Liverpool Wellcome Trust</td>
</tr>
<tr>
<td>Professor Ann Walker, University College London</td>
</tr>
<tr>
<td>Dr Margaret Jean Thomason, University College London</td>
</tr>
<tr>
<td>Dr Martina Penazzato, University College London</td>
</tr>
<tr>
<td>Dr Bernadette O’Hare, University of Malawi</td>
</tr>
<tr>
<td>Professor Catherine Molyneux, University of Oxford</td>
</tr>
<tr>
<td>Professor James Berkley, University of Oxford</td>
</tr>
<tr>
<td>Mr Paul Revill, University of York</td>
</tr>
<tr>
<td>Professor James Hakim, University of Zimbabwe</td>
</tr>
<tr>
<td>Professor Kusum Nathoo, University of Zimbabwe</td>
</tr>
</tbody>
</table>

**Summary**

The risk of dying AFTER starting treatment with antiretrovirals (ARVs) is about 7 times higher among HIV-infected adults and children in Africa than in developed countries, particularly if immunity is poor (low CD4 cell counts), because such people often harbour infections like tuberculosis and bacterial infections which show themselves when ARVs are started and immunity improves.

The question about how to reduce high early death rates when people start ARVs has been identified by doctors and the African HIV community as being very important. In the REALITY trial, we will test 3 different ways to reduce high early death rates in 1200 adults and 600 children aged 5-12 years starting ARVs with CD4 cell counts less than 100 from 4 African countries (Uganda, Kenya, Zimbabwe, Malawi). Each approach will be compared with a standard approach (like doing 3 trials in one) and we will also be able to see if all approaches can provide additional benefits if used together in a package.

The questions are whether any of the following reduce the risk of early death after starting ARVs: (1) using stronger ARVs (4 instead of 3 ARVs) for the first 3 months; (2) giving preventative treatment (prophylaxis) against life-threatening infections (e.g., tuberculosis, bacterial infections, cryptococcal meningitis) for 3 months after starting ARVs; (3) giving extra food to everyone (not just those with malnutrition) for 3 months; this might also help people take their ARVs as we know many get very hungry after starting ARVs.

Adults and children over 5 years will be invited to join REALITY, and if they consent, at the time of starting ARVs, they will be given either the new approach or standard of care for each of the 3 questions. This will be done at random, like tossing a coin, but by a computer. All participants will be followed for at least one year to see how well they do, as well as to find out how acceptable these extra approaches are and whether there are any side effects.

We will also measure whether these new approaches are cost effective to be rolled out in Africa. Adults and children are treated together in ARV clinics across Africa and have similar HIV progression and early death rates on ARVs: including adults and children aged over 5 years in the same integrated research study will provide the most relevant answers to improve the care of future patients.
TB fast track: effect of a point-of-care TB test-and-treat algorithm on early mortality in people with HIV accessing ART

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Alison Grant</td>
<td>London Sch of Hygiene and Trop Medicine</td>
<td>G1100689/1</td>
</tr>
</tbody>
</table>

Co-Investigators

Ms Suzanne Johnson
Foundation for Professional Development

Dr Susan Dorman
Johns Hopkins Medicine (JHM)

Dr Anna Vassall
London Sch of Hygiene and Trop Medicine

Professor Katherine Fielding
London Sch of Hygiene and Trop Medicine

Dr Christopher Hoffmann
The Aurum Institute

Professor Gavin Churchyard
The Aurum Institute

Professor Salome Charalambous
The Aurum Institute

Dr Kerrigan McCarthy
University of the Witwatersrand

Summary

Treatment for HIV (antiretroviral therapy, or ART), has greatly reduced death rates among people with HIV worldwide. However in low-resource settings, death rates continue to be high even for people taking ART, particularly in the first few months on treatment. Tuberculosis (TB) is the most important cause of these early deaths, and people who are due to start ART are recommended to be screened for TB first.

However, TB is hard to diagnose because the tests which are most widely available do not work well for people with HIV. As a result, people with HIV may have to go through lots of tests for TB, which delays the start of TB treatment; it also delays the start of ART. Both of these delays increase the risk that the patient dies. We propose a study to try to reduce this high death rate.

In 20 primary care clinics in South Africa, we will enrol people with advanced HIV who have come to start ART to our study. In 10 of the clinics (intervention), selected at random, we will use simple, inexpensive tests (a new urine test for TB, weight and height, and a blood test for anaemia) which can be done on site with immediate results, to identify those patients who are at highest risk of having TB, and of dying early.

People who are high risk will start TB treatment straight away, then ART as soon as possible afterwards; people who are low TB risk will start ART straight away. People with medium TB risk will be given antibiotics while a chest X-ray and sputum (spit) test for TB are done, and will come back after a week to decide if they should start TB treatment followed by ART, or just start ART.

At the other 10 (control) clinics, patients will be looked after in the normal way, following national guidelines. We will follow all patients up for 6 months. We will compare the death rate at 6 months in the 10 intervention clinics, using our new approach, to death rates in the 10 control clinics, using the routine approach. If our new approach reduces the death rate, clinics throughout low resource settings could use this low-cost strategy to save lives among people with HIV.
**Project title**

Induction of labour in pre-eclamptic women: a randomised trial comparing balloon catheter with oral misoprostol.

**Grant holder**

Professor Andrew Weeks

**Institute**

University of Liverpool

**Grant reference**

G1100686/1

---

**Co-Investigators**

- Dr Shuchita Mundle
  - Government Medical College Nagpur
- Dr Beverly Winikoff
  - Gynuity Health Projects
- Ms Hillary Bracken
  - Gynuity Health Projects
- Dr Eric Faragher
  - Liverpool School of Tropical Medicine
- Dr Alan Haycox
  - University of Liverpool
- Professor Zarko Alfirevic
  - University of Liverpool

---

**Summary**

High blood pressure in pregnancy (or preeclampsia) is a major cause of death worldwide, killing up to 80,000 pregnant women annually. For women with preeclampsia currently available therapies improve the outcome of the illness, but the final cure only comes with delivery of the baby. Prompt delivery, preferably by the vaginal route rather than by caesarean section, is therefore vital to achieve good maternal and neonatal outcomes.

There are various methods available to start the woman's labour, and it is crucial that the method used is both effective and safe for mother and baby. This is especially important in low resource settings where the underlying illness is often severe and there are few facilities for monitoring the mother and baby.

The World Health Organisation currently recommends two low cost options ? oral misoprostol (OM) tablets and transcervical Foley catheterisation (TFC). Whilst in the former method a tablet is swallowed every two hours, in the latter a thin rubber (?Foley?) catheter is threaded through the neck of the womb and held in place with a small inflated balloon at its tip. Although OM has been widely studied, it is infrequently used in India. Furthermore, there is comparatively little research on the TFC and the two methods have never been directly compared despite their great promise. Current evidence suggests that OM may be faster but sometimes ?overcontract? the uterus, whilst TFC may be slower but safer.

We propose a study to be conducted in two large government hospitals in Nagpur, India. 800 women with preeclampsia will be randomly allocated to use OM (25mcg tablets 2hrly) or TFC (size 18F with a 50ml balloon for 12 hours) for their induction. The main outcome is the attainment of vaginal delivery within 24 hours, and a variety of other measures of maternal and neonatal morbidity including cost effectiveness will also be collected. Currently 15% of mothers with preeclampsia suffer stillbirths in this setting ? this trial will also examine whether the use of the balloon catheter can reduce this. Recruitment rates in a recent study of preeclamptic women using the same team and site demonstrate that 800 women can be recruited in 2 years.

The study will be managed on a daily basis by the successful team of Dr Mundle in GMC Nagpur and Gynuity Health Projects, one of the most successful low-resource setting clinical trial specialists in the world.
**Joint Global Health Trials - Call 1 Full Grant**

**Project title**
A clinical trial of dexamethasone to reduce mortality in cryptococcal meningitis

<table>
<thead>
<tr>
<th><strong>Grant holder</strong></th>
<th><strong>Institute</strong></th>
<th><strong>Grant reference</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Jeremy Day</td>
<td>University of Oxford</td>
<td>G1100684/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**
- Dr Cuong Do
  Bach Mai Hospital
- Dr Chau Tran Thi Hong
  Hospital for Tropical Diseases
- Dr Kinh Nguyen Van
  Hospital for Tropical Diseases
- Professor David Laloo
  Liverpool School of Tropical Medicine
- Dr Anatoli Kamali
  London Sch of Hygiene and Trop Medicine
- Dr Mayfong Mayxay
  Mahidol Oxford Research Unit
- Dr Wirongrong Chierakul
  Mahidol University
- Dr Halima Dawood
  National Dept of Health (South Africa)
- Professor Robert Heyderman
  University College London
- Dr Darma Imran
  University of Indonesia
- Dr Camilla Rothe
  University of Malawi
- Dr Marcel Wolbers
  University of Oxford
- Dr Hanh Doan Thi Hong
  Vietnam - Sweden Uongbi Hospital

**Summary**
Cryptococcal meningitis is a brain infection due to a yeast called Cryptococcus neoformans. It is important because it is a major cause of death in people infected with HIV.

There are over 600,000 deaths each year, and most of these occur in poorer countries in Africa and Asia. Even if patients receive treatment with antifungal drugs, the death rate remains high - about 55% of people with disease in Asia and 70% in Africa will die within 3 months of diagnosis. A combination of antifungal drugs is given to kill the yeast, but researchers have been unable to improve on the antifungal treatment combination that has been recommended for the past 10 years. This is despite extensive research.

We believe that new approaches are needed to try and improve outcome in this disease. The features of infectious diseases are the result of not only the infectious agent, but also the way our bodies respond to them. When our bodies’ immune systems fight infection, this causes inflammation which can sometimes make disease worse. When people have cryptococcal meningitis, there is inflammation and raised pressure in the brain. The inflammation can result in parts of the brain dying (a stroke).

The raised pressure leads to the brain getting squeezed (compressed) against the inside of the skull. This can impair the blood supply and can directly damage the brain tissue itself. These processes can lead to death. Steroids are drugs that can reduce inflammation, and are frequently used to lower raised pressure in brain diseases.

They have been found to be useful in other forms of meningitis, such as acute bacterial meningitis and tuberculous meningitis. These diseases share some features with cryptococcal meningitis. We want to test whether giving dexamethasone, a steroid, alongside antifungal therapy, can reduce the death rate in people with cryptococcal meningitis.

Dexamethasone is cheap, safe, and widely available, and if successful is a treatment that would be affordable and practical for the majority of patients around the world with this disease. We want to do this study in Africa and Asia, because this is where most people with cryptococcal meningitis live.
Joint Global Health Trials - Call 1 Full Grant

Project title
A Randomised, Open-Label, Comparative Study of Itraconazole vs. Amphotericin B for the Induction Therapy of Penicilliosis

Grant holder | Institute | Grant reference
---|---|---
Dr Thuy Le | University of Oxford | G1100682/1

Co-Investigators

- Dr Cuong Do
  Bach Mai Hospital

- Dr Chi H Nguyen
  Hospital for Tropical Diseases

- Dr Kinh Nguyen Van
  Hospital for Tropical Diseases

- Dr Mattias Larsson
  Karolinska Institute

- Professor Alastair Gray
  University of Oxford

- Dr Marcel Wolbers
  University of Oxford

- Professor Peter Horby
  University of Oxford

- Dr Hanh Doan Thi Hong
  Vietnam - Sweden
  Uongbi Hospital

- Professor Jeremy Farrar
  Wellcome Collection

Summary

Penicilliosis is one of the most common and life-threatening infections in people infected with Human Immunodeficiency Virus (HIV) in Asia. Despite the fast growing numbers of people infected with HIV in Asia where over one half of the world’s population lives, there has not been any clinical trials to evaluate the treatment of penicilliosis. The current international guideline recommends treatment with amphotericin B for 2 weeks followed by itraconazole for 10 weeks. This guideline is based on one observational study without a comparator group and is generally considered weak evidence in medicine. Further, amphotericin B is either unavailable or available in only selected major tertiary care centres in Asia, can only be given through a vein daily over 6 hours of infusion, has many side effects, and a 2 week treatment in Viet Nam for example would cost an average patient approximately 5 times his monthly salary.

Itraconazole, on the other hand, appears to be a good alternative drug that is widely available in local pharmacies in the provinces and district clinics, can be given by mouth, is generally well tolerated, and costs a fraction of the price of amphotericin B. Available data from Viet Nam, Thailand, Hong Kong and India suggest that itraconazole may have similar treatment efficacy compared to amphotericin B.

Therefore we will conduct a clinical trial comparing the relative effectiveness of itraconazole versus amphotericin in the treatment of penicilliosis. A total of 440 adults who are diagnosed with penicilliosis will be invited to participate in the study and will be randomly assigned to either itraconazole or amphotericin B during the first 2 week of therapy. Survival rates will be compared in the 2 treatment arms at the end of 2 weeks and in 6 months. This will be the landmark study for treatment of penicilliosis.

The results will either change or support the current national and international guidelines for treatment of penicilliosis. If the investigators are correct, that itraconazole is proven to be at least as effective as amphotericin B, but is much cheaper, better tolerated, and easier to administer, then itraconazole represents a better treatment choice for the patients with penicilliosis while saving significant costs for the patients and the health care system. If the investigators are correct, then itraconazole can be given immediately for patients in the local provincial and district clinics, ensuring earlier treatment and better outcomes for patients.
## Joint Global Health Trials - Call 1 Full Grant

### Project title
Menstrual solutions in adolescent schoolgirls in western Kenya: an acceptability, feasibility and safety study

### Grant holder | Institute | Grant reference
--- | --- | ---
Dr Penelope Anne Phillips-Howard | Liverpool School of Tropical Medicine | G1100677/1

### Co-Investigators
- Dr Jean Christophe Fotso
  African Population and Health Res Centre
- Dr Natalia Hounsome
  Bangor University
- Professor Rhiannon Edwards
  Bangor University
- Dr Frank Odhiambo
  KEMRI (Kenya Medical Research Institute)
- Dr John Vulule
  KEMRI (Kenya Medical Research Institute)
- Dr Kayla Laserson
  KEMRI (Kenya Medical Research Institute)
- Dr Linda Mason
  Liverpool John Moores University
- Professor Mark Bellis
  Liverpool John Moores University
- Dr Eric Faragher
  Liverpool School of Tropical Medicine
- Professor Feiko ter Kuile
  Liverpool School of Tropical Medicine
- Dr Shiprah Kuria
  Ministry of Public Health and Sanitation

### Summary

**Problem:** Adolescent health in low-income countries of Africa and Asia is neglected. The burden of sexual and reproductive harms in adolescent girls, and poor schooling, is now recognised to impact on girls' human rights, health, and wellbeing. Lack of menstrual management and pregnancy fear are identified as top stressors. Poverty necessitates use of rags, paper from walls or books, or foam from mattresses. These leak and irritate, reducing school engagement, and increasing sexual coercion as males consider them sexually mature, and girls seek money for pads from sex. Study: Menstrual cups (Mcups) are silicon bells which collect blood, are emptied, then reinserted. They last many years but are expensive (~£8). Schoolgirls in Nairobi and Nepal used Mcups but studies were too small to clarify impact. African researchers, ministry and stakeholder partners will join Liverpool and Bangor Universities to test if Mcups reduce leakage, sexual and reproductive harms, and improve schooling in a trial in western Kenya, where rates of harms (HIV, STIs and forced sex), and lost schooling is high. Community members, stakeholders, and teachers will advise on the trial throughout. Community and school meetings, personal and parental consent, baseline school hygiene, health (including HIV testing) and attendance surveys, and puberty education will be conducted before intervention. Of 152 selected schools (enrolling a total 7600 menstruating girls), half will be randomly classified as ?Mcups now? with the remaining ?controls? receiving ?Mcups later? at completion. Six-weekly over 24 months, research nurse teams will mentor ?Mcup now? girls on use and care, and ask all girls about symptoms of reproductive tract infections at private school locations. Laboratory confirmed infections from swabs will be treated. Girls will complete behaviour and quality of life questions on confidential computer notebooks. The study site has health and demographic surveillance, fingerprinting and GIS which links census and clinic records. Parallel school attendance and engagement surveys, menstrual diaries, and social studies will provide information on the wider impact of Mcups. After 24 months, a final HIV test, and school attendance survey will be conducted. Impact: We will examine if Mcups significantly reduced girls harms, increase schooling, and improve their quality of life. Mcup costs incurred to avert costs of harms, and benefited schooling and wellbeing will be evaluated. Results will be disseminated locally, nationally and internationally to schools, communities, stakeholders, ministries, aid agencies, researchers and international bodies. If positive, Mcup intervention policies will be developed for wide-scale implementation.
### Co-Investigators

<table>
<thead>
<tr>
<th>Co-Investigator</th>
<th>Institute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Jean Christophe Fotso</td>
<td>African Population and Health Res Centre</td>
</tr>
<tr>
<td>Dr Natalia Hounsome</td>
<td>Bangor University</td>
</tr>
<tr>
<td>Professor Rhiannon Edwards</td>
<td>Bangor University</td>
</tr>
<tr>
<td>Dr Frank Odhiambo</td>
<td>KEMRI (Kenya Medical Research Institute)</td>
</tr>
<tr>
<td>Dr John Vulule</td>
<td>KEMRI (Kenya Medical Research Institute)</td>
</tr>
<tr>
<td>Dr Kayla Laserson</td>
<td>KEMRI (Kenya Medical Research Institute)</td>
</tr>
<tr>
<td>Dr Linda Mason</td>
<td>Liverpool John Moores University</td>
</tr>
<tr>
<td>Professor Mark Bellis</td>
<td>Liverpool John Moores University</td>
</tr>
<tr>
<td>Dr Eric Faragher</td>
<td>Liverpool School of Tropical Medicine</td>
</tr>
<tr>
<td>Professor Feiko ter Kuile</td>
<td>Liverpool School of Tropical Medicine</td>
</tr>
<tr>
<td>Dr Shiprah Kuria</td>
<td>Ministry of Public Health and Sanitation</td>
</tr>
</tbody>
</table>

### Summary

Adolescent schoolgirls consider menstrual management as one of their main stressors. Menstrual difficulties result in missed schooling and drop-out, but studies on the true impact are limited, and baseline tools and data are lacking. One solution is Mooncups, silicone bell receptacles that store menstrual flow, available since the 1930s and marketed in Kenya and internationally.

We will conduct a randomized proof of concept feasibility study on menstrual solutions to quantify cultural acceptance, use, satisfaction, costs and safety of Mooncups, sanitary pads and 'usual practice' in 750 schoolgirls in 15 schools in the demographic health and surveillance site in western Kenya.

School nurse screening, self-completed menstrual calendars, behaviour surveys, water / sanitation / hygiene (WASH) evaluation in schools and homes, measures of school attrition, and laboratory checks on Staph aureus contamination, HIV, STI and reproductive tract infections will enable us to determine prevalence rates for outcome indicators, and exclude toxic shock syndrome and other safety concerns. Qualitative studies will provide contextual information to understand reasons for outcomes and behaviours.

Data will inform policy and provide baseline information and statistics for the preparation of a randomized controlled trial to examine the cost-effectiveness of menstrual solutions to reduce school attrition and improve wellbeing.
**Joint Global Health Trials - Call 1 Full Grant**

**Project title**
Intermittent screening and treatment or intermittent preventive therapy for control of malaria in pregnancy in Indonesia

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Feiko ter Kuile</td>
<td>Liverpool School of Tropical Medicine</td>
<td>G1100654/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

Dr Maria Endang Sumiwi  
Eijkman Institute for Molecular Biology

Dr Puji Asih  
Eijkman Institute for Molecular Biology

Dr Jeanne Rini  
Poespoprodjo (Indo)  
Gadjah Mada University (UGM)

Dr Eric Faragher  
Liverpool School of Tropical Medicine

Dr Eve Worrall  
Liverpool School of Tropical Medicine

Dr Jenny Hill  
Liverpool School of Tropical Medicine

Dr Rukhsana Ahmed  
Liverpool School of Tropical Medicine

Professor Jayne Webster  
London Sch of Hygiene and Trop Medicine

Dr Richard Price  
St George's University of London

Professor Din Syafruddin  
University of Hasanuddin

**Summary**

FIGHTING MALARIA IN PREGNANCY IN INDONESIA The control of malaria in pregnancy in Indonesia, where approximately 10% of pregnant women get infected with malaria, could receive a potential boost through a new study conducted by the Eijkman Institute for Molecular Biology and the Timika Research Facility in Indonesia. Together with experts from the Liverpool School of Tropical Medicine in the UK, they are going to test two new methods of preventing malaria and the harmful effects in pregnancy. When pregnant women contract malaria this can have devastating consequences for pregnancy, resulting in fever which may trigger preterm onset of labour or even pregnancy loss. It is also possible for women to be infected without showing any outward signs or symptoms, yet if these infections are undetected and left untreated, they can cause anaemia in the mother and can interfere with the growth of the fetus leading to low birth weight, which increases the risk of babies dying during infancy. The new project will provide malaria testing to women with or without the symptoms of malaria on every scheduled antenatal visit using a rapid diagnostic test (RDT).

The RDT is simple to perform, uses a single drop of blood and gives results within 15 minutes. Those women testing positive will be treated with an artemisinin combination drug called dihydroartemisinin-piperaquine (DHP), which is the treatment of choice in the 2nd and 3rd trimester of pregnancy in Indonesia. A second method called intermittent preventive treatment, which is used in most countries in Africa but not yet in Asia, will also be tested. With this method women without symptoms of malaria will be selected to receive the same drug but without prior blood testing.

Both methods will be compared with the existing policy in Indonesia, where all pregnant women are tested for malaria on the first antenatal visit only, and those with a positive result are treated with DHP. During subsequent antenatal visits, women are only tested if they have symptoms of malaria such as fever. This means that some infections will go undetected. It is anticipated that the two new methods will either detect infections much earlier than the current approach, or prevent them altogether. The findings of this study, together with an assessment of feasibility and cost effectiveness of each method, will be used to inform malaria prevention policy for pregnant women in Indonesia and other parts of South East Asia.
**Joint Global Health Trials - Call 1 Full Grant**

**Project title**
MVA85A Tuberculosis Vaccine Prime and Selective Delayed BCG Boost in Infants of HIV Infected Mothers

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Mark Hatherill</td>
<td>University of Cape Town</td>
<td>G1100570/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

- Dr Willem Hanekom
  Bill & Melinda Gates Foundation
- Professor Anneke Hesseling
  Stellenbosch University
- Professor Gerhard Walzl
  Stellenbosch University
- Dr Thomas Scriba
  University of Cape Town
- Professor Helen McShane
  University of Oxford
- Dr Hassan Mahomed
  Western Cape Government

**Summary**

BCG vaccine offers limited protection against lung TB in children. BCG vaccination is safe for most newborn babies, but may cause severe, often fatal, complications in babies with HIV infection, even with antiretroviral treatment (ART). The WHO recommends that BCG should not be given to babies known to be HIV infected. However, HIV testing is not accurate until 6 weeks of age, when BCG has already been given at birth. More than one quarter of South African babies were born to HIV infected mothers in 2009.

South Africa has the highest annual TB rate in the world and children of HIV infected mothers are at especially high risk of TB. New TB vaccines are being developed and tested ([http://www.stoptb.org/wg/new_vaccines/](http://www.stoptb.org/wg/new_vaccines/)). MVA85A is a new TB vaccine, similar to the smallpox vaccine, but with a TB protein added. MVA85A vaccine has been shown to be safe and generates an immune response against TB in children and adults, including people with HIV infection.

We have shown that if BCG vaccination is delayed for several weeks after birth, the immune response thought to be important for protection against TB is improved. Immunity is also improved if a new TB vaccine, such as MVA85A, is given several weeks after BCG. Some studies suggest that it does not matter for immunity whether BCG or the new vaccine is given first. We will test whether MVA85A vaccine can be given to babies at birth, at our experienced TB vaccine trial sites near Cape Town, South Africa, where rates of HIV infection and TB are high. This trial will test the safety and immunity of MVA85A vaccination at birth, compared to a dummy vaccination (placebo), in 340 babies of HIV infected mothers, followed up for one year. Only those babies proven not to have HIV infection would receive delayed BCG vaccine at 8 weeks of age. HIV infected babies would benefit by not receiving BCG and this is the reason for testing newborn MVA85A vaccination among infants of HIV infected mothers. If we show that newborn MVA85A vaccination has few side-effects and generates a good immune response against TB, we may proceed to test whether this new TB vaccine strategy actually prevents TB, among all infants, regardless of maternal HIV infection. These findings will be critically important for vaccine safety, and prevention of childhood TB, and may lead to key improvements in the global infant vaccination schedule.
Joint Global Health Trials - Call 2 Full Grant

Project title
An advanced cookstove intervention to prevent pneumonia in children under 5 years old in Malawi: a cluster randomised controlled trial

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Stephen Gordon</td>
<td>Liverpool School of Tropical Medicine</td>
<td>MR/K006533/1</td>
</tr>
</tbody>
</table>

Co-Investigators

Professor Moffat Nyirenda
Entebbe General Hospital

Dr Anja Terlouw
Liverpool School of Tropical Medicine

Professor Brian Faragher
Liverpool School of Tropical Medicine

Professor Kevin Mortimer
Liverpool School of Tropical Medicine

Professor Lesong Conteh
London School of Economics & Pol Sci

Professor Jonathan Grigg
Queen Mary University of London

Professor John Balmes
University of California, San Francisco

Dr Magi Matinga
University of Johannesburg

Dr Daniel Peter Pope
University of Liverpool

Dr Nigel Bruce
University of Liverpool

Summary
Malawi has one of the highest rates of death among infants and the under fives (69 and 110 per 1000 live births respectively in 2009) despite having made progress towards meeting the Millennium Development Goal of reducing child mortality.

Pneumonia is the leading cause of death and one of the commonest causes of morbidity with around 298 per 1000 children under the age of 5 diagnosed with pneumonia every year and a case fatality rate between 2.7 and 13.2 per 1000. Exposure to smoke produced when biomass fuels (animal or plant material) are burned in open fires is a major avoidable risk factor for pneumonia. In Malawi, where at least 95% of households depend on biomass as their main source of fuel, biomass smoke exposure is likely to be responsible for a substantial burden of this disease.

Effective strategies for reducing smoke exposure exist (e.g. ventilation, improved stoves, cleaner fuels, behaviour modification) but are out of reach for the majority due to a wide range of largely poverty-related factors. The Global Alliance for Clean Cookstoves was launched in 2010 to tackle this energy poverty issue through public private partnerships. A central aim of the alliance is for 100 million homes to adopt clean and efficient stoves and fuels by 2020.

However, there is very limited evidence to assess the potential benefits of such an approach. We have conducted preparatory and pilot work in sub Saharan Africa to determine which of the currently available advanced cookstoves would be most suitable for use in a trial in Malawi in terms of improvements in combustion efficiency, reduced emissions and ability to cook local dishes.

We have gone to considerable lengths to involve local communities in the development of this proposal.

We are now in a position to be able to study an efficient and locally acceptable advanced cookstove that substantially reduces smoke emissions in a trial to address three principal research questions:

1) Can an advanced cookstove intervention that substantially reduces biomass smoke exposure relative to an open fire prevent pneumonia in children under 5 years old in Malawi?
2) How affordable and cost effective is the intervention from household, healthcare system and societal perspectives?

3) What can be learned from trial participants and non-participants about adoption of the intervention that could inform effective implementation of the trial findings in the future?

High quality clinical trial evidence about the health and economic impacts seen when households adopt advanced cookstove technologies is needed to inform policy and decision makers across commercial, health, development and community sectors at local, regional and international levels.

The results of this trial will be relevant to local policy makers in Malawi who will have new efficacy, economic and qualitative data to guide decisions about funding advanced cookstove programmes for improving child health; to regional commercial, non-governmental and governmental organisations in sub Saharan Africa manufacturing and distributing advanced cookstove solutions; and to international (e.g. World Health Organisation (WHO)) decision and policy makers by contributing new evidence about the health and economic impacts of an advanced cookstove intervention of broadly generalisable relevance to areas of the world where biomass fuel use is common.

We have established local (e.g. community leaders), regional (e.g. commercial and non-governmental organisations and Malawi Ministry of Health) and international (e.g. WHO and Global Alliance for Clean Cookstoves) links that will allow us to disseminate the findings of the trial effectively at all levels to a wide range of stakeholders, policy and decision makers.
**Project title**
Primaquine's gametocytocidal efficacy in malaria asymptomatic carriers treated with dihydroartemisinin-piperaquine

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Umberto D'Alessandro</td>
<td>MRC Unit, The Gambia</td>
<td>MR/K007203/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

Dr Teun Bousema  
Catholic (Radboud) University Foundation

Professor Koen Peeters  
Institute of Tropical Medicine

Dr Alfred Ngwa  
London Sch of Hygiene and Trop Medicine

Dr Alice Eziefula  
London Sch of Hygiene and Trop Medicine

Dr Andrea Mann  
London Sch of Hygiene and Trop Medicine

Professor Chris Drakeley  
London Sch of Hygiene and Trop Medicine

Dr Davis Nwakanma  
London Sch of Hygiene and Trop Medicine

Dr Joseph Okebe  
London Sch of Hygiene and Trop Medicine

**Summary**

Malaria is a parasitic disease transmitted by mosquitoes of the species Anopheles. The parasite can be found in the human host in two forms, asexual and sexual. The latter does not cause disease but is responsible for the transmission of the infection from the human host to the vector mosquito.

Therefore, interventions reducing the transfer of parasite sexual forms, called also gametocytes, from man to mosquito may have a major impact on malaria transmission and hence on the burden of disease. The only available treatment against gametocytes is primaquine, an old drug that has not been extensively used in sub-Saharan Africa because it can cause the destruction of red blood cells in people with a genetic conditions called glucose-6-phosphate dehydrogenase deficiency, resulting sometimes in life-threatening anemia. However, the risk for anaemia is dose-dependent, i.e. the risk increases with increasing dose.

The amount of primaquine needed to eliminate gametocyte has been established in the 60s in a small number of experimentally challenged volunteers. It is unknown if lower dosages of primaquine, which are probably associated with a lower risk for anaemia, could have the same effect than the recommended one.

The use of primaquine at lower dosages would open the possibility of using it on a large scale in sub-Saharan Africa, where the prevalence of glucose-6-phosphate dehydrogenase deficiency can be as high as 15%. The general objective of this proposal is to determine the lowest possible dose of primaquine having similar activity against gametocytes than the recommended one. This will be done by carrying out a clinical trial in two rural sites in The Gambia. In the study area, the population will be screened for malaria infection.

Those positive, i.e. with a malaria infection but without symptoms, will be given an artemisinin-based combination treatment (dihydroartemisinin-piperaquine) and randomized to receive only this treatment or to have in addition the recommended or two lower dosages of primaquine. The treatment will be given over 3 days, with primaquine given, when required, in association with the last dose of dihydroartemisinin-piperaquine.
Study subject will be actively followed up for more than a month, with blood sampling at regular intervals. The blood collected will be used to determine the difference in gametocyte carriage between the different treatment groups. Gametocytes will be searched with molecular methods, which are more sensitive than microscopy.

In a subgroup of study subject we will check what is the actual difference in transmission to mosquitoes between individuals having received different treatments. We will collect a blood sample one week after the beginning of the treatment and we will feed laboratory-reared mosquitoes that will be dissected one week after, to check if they have become infected.

The results of this study will be used to determine the feasibility of deploying primaquine on a large scale in sub-Saharan Africa, where the malaria burden is the highest, and may contribute to the drive towards malaria pre-elimination/elimination in this continent.
# Joint Global Health Trials - Call 2 Full Grant

## Project title
Randomised controlled trial of podoconiosis treatment in northern Ethiopia.

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Gail Davey</td>
<td>University of Sussex</td>
<td>MR/K007211/1</td>
</tr>
</tbody>
</table>

## Co-Investigators

<table>
<thead>
<tr>
<th>Dr Fikre Gashe</th>
<th>Addis Ababa University</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Trudie Lang</td>
<td>University of Oxford</td>
</tr>
<tr>
<td>Professor Andy McKay</td>
<td>University of Sussex</td>
</tr>
<tr>
<td>Professor Melanie Newport</td>
<td>University of Sussex</td>
</tr>
</tbody>
</table>

## Summary

Podocoiosis is one of the forgotten types of leg swelling (elephantiasis) in the tropics. Unlike the other, better-known types of leg swelling, podoconiosis is not caused by any parasite, virus or bacterium, but by an abnormal reaction to minerals found in the clay soils of some tropical highland areas. Although an estimated 4 million people are affected by podoconiosis across Africa, there is no government health service provision for patients in any endemic country.

In Ethiopia, where 1 million people with podoconiosis live, non-government organizations (NGOs) have been responsible for the development of simple treatment methods using low-cost, locally accessible materials. Treatment takes the form of foot hygiene, skin care, bandaging, exercises to improve lymph drainage and use of socks and shoes. Although the NGOs consider the treatment to be effective, no formal test has yet been conducted. Our main objective is to test whether the 'standard' treatment reduces the number of times a patient experiences 'acute episodes', when the leg become hot, painful and more swollen than usual.

These episodes significantly compromise patients' ability to work or carry out normal day-to-day tasks. We will also test whether the effectiveness of 'standard' treatment can be increased by first giving daily lymph drainage massage for two weeks. We will measure the cost-effectiveness of both types of treatment in relation to the costs of living with untreated disease. The trial will be sited in northern Ethiopia, where 3% of the adult population is affected by podoconiosis.

Prior to the trial, an economic context survey will be performed to supply background information on typical work hours and settings, labour and medical costs and productivity losses related to podoconiosis. The trial will also be preceded by rapid ethical assessment to identify optimal methods of conveying information about the trial and the approaches to obtaining informed consent preferred by the community.

We have identified and located at least 2000 patients who need treatment but are not yet receiving it. We plan to randomly allocate 900 of these patients to one of three groups: either to 'standard' treatment, or to 'intensive' treatment or to delayed treatment. Provision of care will be organised through the IOCC Podoconiosis Project, which already has excellent links with the community and local government. The randomisation process, data monitoring and statistical analysis will be overseen by
experts at the Clinical Trials Facility in Kilifi, Kenya, who will make twice-yearly visits to the trial site. Data collection will be performed monthly by a team of 10 recruited specifically for the task, and independent of the community project assistants providing care.

More detailed examination will be performed at 6 months and 1 year. The Clinical Trials Facility will ensure data quality, will monitor safety reports and will supervise data analysis, building capacity within Ethiopia for future clinical trials through frequent training and monitoring visits.

The results of the trial will be disseminated through a workshop in Addis Ababa to government and non-government organizations affiliated to the Ethiopian National Podoconiosis Action Network; through peer-reviewed publications and Footwork (the new International Podoconiosis Initiative) to stakeholders in other podoconiosis-endemic countries.
Community intervention to improve growth among children under 2 in rural India

Grant holder: Professor Audrey Prost
Institute: University College London
Grant reference: MR/K007270/1

Co-Investigators
- Dr Andrew Copas
  University College London
- Professor Anthony Costello
  University College London
- Dr Jolene Skordis
  University College London

Summary
Many children in developing countries die or fail to grow to their full potential because of undernutrition. Forty percent of the world’s undernourished children live in India. There is a critical window of opportunity to prevent undernutrition and its long-term consequences by intervening to improve the health of mothers and children between conception and two years of age. For over eight years now, international agencies, scientists and activists have recommended the introduction of a new community worker focused on improving the health and nutrition of mothers in pregnancy and children under 2 in rural areas of India.

Currently there is currently is no scientifically tested, cost-effective and scalable intervention model for such a worker. In the proposed research we will test a community intervention implemented by a community worker modeled on the one proposed by the Indian government in order to understand whether it can reduce child undernutrition and how it could be scaled up.

The findings from this research will be generalisable to rural areas of India with a high prevalence of undernutrition, which is a population of over 170 million, and have relevance to other low and middle-income country settings.
**Joint Global Health Trials - Call 2 Full Grant**

**Project title**
A trial of the benefit of including azithromycin in the drug combination used for seasonal malaria chemoprevention in African children

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Brian Greenwood</td>
<td>London Sch of Hygiene and Trop Medicine</td>
<td>MR/K007319/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

- Dr Issaka ZONGO  
  Centre Muraz  
- Professor Halidou Tinto  
  Inst of Health Science Research IRSS  
- Professor Daniel Chandramohan  
  London Sch of Hygiene and Trop Medicine  
- Dr Diadier Diallo  
  London Sch of Hygiene and Trop Medicine  
- Professor Paul Milligan  
  London Sch of Hygiene and Trop Medicine  
- Professor Simon Cousens  
  London Sch of Hygiene and Trop Medicine  
- Dr Lesong Conteh  
  London School of Economics & Pol Sci  
- Professor Jean Bosco OUEDRAOGO  
  Research Institute of Health Sciences  
- Professor Abdoulaye Djimde  
  University of Bamako  
- Professor Alassane Dicko  
  University of Bamako  
- Dr Issaka Sagara  
  University of Bamako  
- Professor Ogobara Doumbo  
  University of Bamako

**Summary**

Good progress is being made in controlling malaria in Africa but success has been only partial. In some countries there has been only a modest decline in the incidence of malaria despite the widespread deployment of insecticide treated bed nets, spraying of the inside of houses with insecticide and treatment of clinical cases with highly effective drug combinations based on compounds derived from the plant Artemisia annua.

More efforts need to be made to scale up these interventions but additional control tools are needed. One potential new tool is seasonal malaria chemoprevention (SMC). SMC involves the administration of a treatment dose of an effective antimalarial drug combination to all children at risk during a period of maximum risk of infection.

This approach to malaria control is targeted specifically at areas where malaria transmission is limited by climatic factors to only a few months of the year so that drugs do not have to be given on more than three or four occasions. Areas where SMC would be an appropriate intervention include most of the Sahel and sub-Sahel (population approximately 200 million).

Studies conducted in areas of seasonal malaria transmission have shown that SMC with the combination of sulphadoxine/pyrimethamine (SP) and amodiaquine (AQ) reduced the incidence of severe and uncomplicated malaria by over 70% and probably reduced deaths. The intervention was safe, well tolerated and highly cost effective. Anti-malaria drugs were given successfully and safely by village volunteers.

A WHO Policy Advisory Committee has recently reviewed the results of trials of SMC and is likely to recommend this as a malaria control intervention for areas with highly seasonal malaria transmission. Despite the success of SMC with SP and AQ in reducing malaria, children in the trials of this intervention still suffered many episodes of infectious diseases, some severe and some fatal. It is likely that the majority of these severe illnesses were caused by bacterial infections.

Thus, it is possible that adding an antibiotic to the treatment regimen used for SMC could provide added benefit by preventing severe bacterial infections and hence reducing severe illnesses and perhaps deaths. The most suitable antibiotic to be used in this way is azithromycin (A2). A2 has been given as
mass treatment to millions of healthy children to control trachoma (a bacterial eye infection that can lead to blindness) and shown to be safe and well tolerated. Surprisingly, when AZ was deployed in a trachoma elimination programme in Ethiopia, overall child mortality fell by approximately 65%.

If AZ really does prevent deaths in young children, it is likely that it does so by preventing bacterial infections, particularly those caused by the pneumococcus, an important cause of death and severe illnesses in young African children. Thus, it is biologically plausible that adding AZ to SMC regimens might provide additional benefit.

To test this hypothesis, a trial will be conducted in approximately 16,000 children in areas of Burkina Faso and Mali where malaria transmission is highly. Children will be randomly allocated to receive SMC with SP+AQ either with or without the addition of AZ. Children will be followed carefully throughout the 2013 malaria transmission season (July-October).

All deaths or hospital admissions will be recorded and clinic attendances with a febrile illness will be noted. At the end of the transmission season, a random sample of 4,000 children will be examined and tested for malaria and anaemia.

Malaria parasites will be tested at this time for their sensitivity to SP and pneumococci, obtained from the nose, for their sensitivity to AZ. The costs of adding AZ to the SMC regimen and its acceptability will be determined. The results of this trial should establish clearly whether adding AZ to the regimen of SP+AQ used for
### Joint Global Health Trials - Call 2 Full Grant

#### Project title
Efficacy of mobile phone short message service (SMS) on malaria treatment adherence and post-treatment review

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Dejan Zurovac</td>
<td>University of Oxford</td>
<td>MR/K007351/1</td>
</tr>
</tbody>
</table>

#### Co-Investigators
- Professor Robert Snow
  ARCH - KWTRP
- Professor Catherine Goodman
  London Sch of Hygiene and Trop Medicine
- Professor Kevin Marsh
  University of Oxford

#### Summary
The project will be conducted in 3 phases at 4 sites (2 rural and 2 urban) in Western Kenya. In phase I - Pilot phase, we will collect and collate primary and secondary data on cell phone coverage and use to demonstrate the feasibility of the intervention.

We will also carry out facility based surveys to validate mobile phone ownership statistics among care givers attending health facilities for malaria and determine access, ownership and use of mobile phones. Further, we will pilot the SMS intervention, which will be one-way communication of SMS reminders on treatment adherence and post-treatment review sent to caregivers' personal mobile phones.

The development process will involve malaria epidemiologists, social scientists, mobile health programmers, as well as clinicians and patients from the study areas. Phase II will be a multi-centre randomized controlled trial (RCT).

Eligible caregivers of children < 5 years old with uncomplicated malaria will be randomly assigned (1:1) to two different arms: 1) the current standard of care based on provider counselling and health education alone, and 2) the current standard of care plus SMS reminders. Within each arm participants will be further equally randomly assigned to 3 different categories for the measurement of adherence. In the first category, 260 caregivers will be visited at home on day 1 of follow up to measure appropriate timing of the second artemether-lumefantrine (AL) dose. In category 2, 260 caregivers will be visited at home on day 2 to measure adherence of AL doses 2, 3 and 4.

While, in category 3, another 260 caregivers will be visited at home on day 3 after they have completed the full treatment course to measure adherence for the full course of AL. The 520 caregivers per arm in category 1 and 2 that will be visited before completion of the full dose will not be visited again to avoid biases in the subsequent measures of adherence.

These patients will also present the study group for the day 3 post treatment review. AL will be administered according to weight bands, directly observed for the first dose, and the remaining 5 doses self administered at home. Caregivers will receive standard instructions about how to administer AL at home, will be instructed to store used blister packs and to return for review if unwell. Eligible caregivers with mobile phones will be asked to key in a toll free number when the first
dose is administered or their number will be registered and input into the automated system.

The toll-free signal will generate a programme to randomly assign caregivers to either the intervention or control arm and to the 3 categories of home visits. In the intervention arm the signal will also generate a programme to automate SMS reminders from a central server depending on pilot investigative and development work, timed to when the next dose should be administered.

Category 1 and 2 caregivers in the intervention arm will in addition to the adherence SMS reminders also receive a morning SMS reminder for the appointment for review at the health facility on day 3. While category 3 participants (intervention and control) will be reviewed at home on day 3. During the second week post treatment, weekly SMS reminders prompting caregivers to visit the health facility if the child is unwell will be sent to participants in the intervention arm.

Finally, participants in the intervention arm will be sent a final SMS reminder for the appointment for review on day 28. The primary outcome are twofold: Adherence to a complete AL course (doses 2-6) measured in category 3 only and the proportion of patients reporting to the health facility for post treatment review and subsequent evaluation of clinical and parasitological cure at day 3 (category 1 and 2) and at day 28 (all categories). We will conduct individual patient level pooled analysis, according to CONSORT standards.
Joint Global Health Trials - Call 2 Full Grant

Project title
School-based Treatment with ACT to Reduce Transmission: Evaluation of the community impact of intermittent preventive treatment for malaria in Uganda

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Sarah Staedke</td>
<td>London Sch of Hygiene and Trop Medicine</td>
<td>MR/K00736X/1</td>
</tr>
</tbody>
</table>

Co-Investigators

Professor Steven Lindsay
Durham University

Dr Lucy Okell
Imperial College London

Dr Adoke Yeka
Infectious Diseases Res Collaboration

Dr Joaniter Nankabirwa
Infectious Diseases Res Collaboration

Dr Alice Eziefula
London Sch of Hygiene and Trop Medicine

Professor Chris Drakeley
London Sch of Hygiene and Trop Medicine

Dr Clare Chandler
London Sch of Hygiene and Trop Medicine

Dr Emily Webb
London Sch of Hygiene and Trop Medicine

Professor Moses Kamya
Makerere University

Dr Jamie Griffin
Queen Mary University of London

Dr Grant Dorsey
University of California, San Francisco

Summary

Despite global commitment to malaria control and substantial increases in funding, the burden of malaria in Africa remains high. Currently, malaria control is targeted at children under five years and pregnant women. School-aged children remain relatively uncovered leaving them at risk for illness and death, and with the potential to transmit malaria to other members of the community. Intermittent preventive treatment (IPT), administering antimalarial treatment at predefined intervals regardless of infection status, has been shown to benefit pregnant women, infants, and young children, and has become an important malaria control strategy.

Initial studies conducted in Uganda and elsewhere in Africa suggest that school-aged children also benefit from IPT, but the community benefits of IPT and impact on malaria transmission are unproven. We propose to evaluate the impact of IPT for malaria in Ugandan schoolchildren on indicators of health and malaria transmission in the community. We will select 36 primary schools in Kanungu district to participate in the study; 18 schools will be randomly assigned to receive the IPT intervention, and 18 will be assigned to standard care (no intervention).

Dihydroartemisinin-piperaquine (DP), a highly effective and long-acting, artemisinin-based combination therapy (ACT) will be provided to eligible children attending intervention schools once a term (3 times per year) for one year. In addition, all children in both the intervention and standard care schools will receive annual deworming, according to national guidelines. Outcomes will be measured using surveys of communities, schoolchildren, and mosquito vectors. Community and school surveys will be conducted at baseline and approximately two months after the third (and final) round of treatment.

The community surveys will consist of a household questionnaire and a laboratory evaluation of all household members; 180 residents from randomly selected households from each of the 36 clusters will be included. For the school surveys, 64 randomly selected children from each of the 36 schools will be included. In both community and school surveys, a finger-prick blood sample will be obtained to evaluate for malaria parasites and to measure blood counts (haemoglobin).
Mosquitos will also be collected from eight randomly selected households from each of the 36 clusters. Each house will be sampled once a month for the duration of the study. The primary outcomes for the trial will be the proportion of people that are infected with malaria parasites and the entomologic inoculation rate (estimated number of infective mosquito bites per person per year) in the community. We will also determine the proportion of schoolchildren that are infected with malaria parasites.

A qualitative study will run alongside the main trial to investigate perceptions of the IPT intervention, and the potential feasibility of integrating the intervention into health service and school systems in Uganda. Results from this work will help to inform the design of future Information, Education, and Communication programmes if the intervention was taken to scale.

We will also conduct mathematical modelling to determine the potential impact of the intervention in other epidemiological settings. Given the potential contribution by school-aged children to malaria transmission in the community, and the likelihood of operational success and sustainability of school-based interventions, the question of whether IPT targeted to schoolchildren could reduce malaria transmission at a population level is highly relevant.

This trial will address that question, and includes health service research and modelling to help guide future research and implementation of the intervention, and help shape policies in Uganda and elsewhere in Africa.
**Project title**  
Step-down affordable treatment for chronic hepatitis B infection in Africa and India  
**Acronym** - STEP-HEP

<table>
<thead>
<tr>
<th><strong>Grant holder</strong></th>
<th><strong>Institute</strong></th>
<th><strong>Grant reference</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Graham Foster</td>
<td>Queen Mary University of London</td>
<td>MR/K007394/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**  
Professor Paul Kelly  
Queen Mary University of London

**Summary**  
Chronic infection with the hepatitis B virus is common in the developing world. Without therapy a large proportion of those who are infected will develop liver disease (cirrhosis and liver cancer) that will lead to premature death.

Effective treatments for hepatitis B are available but they are too costly for wide spread use in the developing world. We plan to investigate a new approach to treating chronic hepatitis B. We will initiate therapy with an expensive, but very powerful, drug - tenofovir - and, when the hepatitis B is controlled, we will step down to a weaker, but much cheaper drug - lamivudine.

We will ensure that this approach is safe by checking that anyone who does not respond to lamivudine can be effectively treated by the re-introduction of tenofovir.

The best way to monitor treatment in people with chronic hepatitis B is to measure the amount of virus in the blood using very sophisticated, expensive test. These tests are often not available in the developing world and we will therefore determine whether or not we can use simple, cheap tests of liver inflammation to monitor patients receiving treatment for hepatitis B.
Joint Global Health Trials - Call 2 Full Grant

Project title
Effectiveness of antibiotic prophylaxis during surgical evacuation of the uterus for miscarriage management in low income countries. (AIMS Trial)

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Arri Coomarasamy</td>
<td>University of Birmingham</td>
<td>MR/K007408/1</td>
</tr>
</tbody>
</table>

Co-Investigators

Dr godfrey mbaruku
Ifakara Health Institute (IHI)

Dr Nicola Ann Desmond
Liverpool School of Tropical Medicine

Dr Javier Zamora
Ramon and Cajal University Hospital

Dr David Lissauer
University of Birmingham

Mr Lee Middleton
University of Birmingham

Professor Andrew Weeks
University of Liverpool

Dr Bonus Makanani
University of Malawi

Professor Jane Daniels
University of Nottingham

Dr Metin Gulmezoglu
World Health Organisation (WHO)

Professor Olufemi Taiwo Oladapo
World Health Organisation (WHO)

Summary

Infection following miscarriage surgery - A GLOBAL PROBLEM: Globally, 210 million women become pregnant each year, but 33 million of these pregnancies end in a miscarriage. A majority of women with a miscarriage will have surgery. In low income settings, the infection rate after miscarriage surgery has been reported to be as high as 30%. Infection after miscarriage can result in serious illness and death, as well as long term consequences including increased rates of ectopic pregnancy, infertility and persistent pain. Prophylactic antibiotics - A POTENTIAL SOLUTION: Prophylactic antibiotics, given before surgery, may improve outcomes.

However, for miscarriage surgery, current guidelines from the WHO, UK national guidelines, and national guidelines from low income countries do not recommend prophylactic antibiotics. This is because of limited evidence. We propose that prophylactic antibiotics, used at the time of surgery, may offer a solution to reducing the serious problem of infection following miscarriage. The existing evidence - A TRIAL IS NEEDED: A recent review of all the evidence concluded that "there is not enough evidence to evaluate a policy of routine antibiotic prophylaxis to women with incomplete miscarriage" and "There is a real and urgent need to find out whether antibiotics should be routinely used in cases of incomplete miscarriage.

The policy and cost implications arising from this research will be tremendous, and randomised clinical trials comparing antibiotics currently in use with no antibiotics are strongly recommended."The proposed AIMS trial: The question: Can pelvic infection after miscarriage surgery be reduced by giving antibiotics to women just before surgery? Study sites: The study will be conducted in 3 countries in Sub-Saharan Africa; Tanzania, Malawi and Uganda.

These countries have been chosen as women have the greatest problems with infection after miscarriage in low income countries and this is therefore the place where this research could have the greatest impact to improve health. What the trial involves: Women having surgery for miscarriage will be invited to participate, and if consent is given, women will be offered a single dose of antibiotics, to be taken by mouth two hours before the surgery.

We plan to recruit 2400 women in total over 2 years. The treatment given will be either antibiotics (400mg doxycycline...
and 400mg metronidazole) or a dummy pill (placebo). The women and clinician will not know if the tablet is the antibiotic or the dummy pill. By comparing the rate of infection and other problems such as death or admission to hospital during the first 2 weeks after surgery between the groups we can determine if the antibiotics are having any effect.

Any women in whom an infection is found will have appropriate treatment and also further tests to identify the cause of the infection. Clinician support for the trial: The trial is endorsed by international professional organisations and a survey of 124 practitioners from 23 low income countries overwhelmingly (87.5%) supported the need for the AIMS trial. User support and acceptability: Semi-structured interviews with gynaecology inpatients in Blantyre, Malawi and Mbale, Uganda showed there was recognition of the potential problems following miscarriage and that the proposed protocol was acceptable. Participants indicated they would be willing to participate and return for follow up assessments.

The trial has also been endorsed by the patient group the Miscarriage Association. The potential benefits of the trial: Miscarriage surgery is common, and infective complications are frequent and serious. Prophylactic antibiotics, if found effective, may offer a simple and affordable intervention which could be rapidly implemented to reduce the burden of maternal mortality and disease in low income countries. This may directly address MD
Improving the radical cure of vivax malaria: A multicentre randomised comparison of short and long course primaquine regimens

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Richard</td>
<td>University of Oxford</td>
<td>MR/K007424/1</td>
</tr>
<tr>
<td>Price</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Co-Investigators**

- Professor Sir Nicholas White
- Mahidol Oxford Research Unit
- Professor John Baird
- University of Oxford
- Dr Lorenz von Seidlein
- University of Oxford
- Professor Tran Hien
- University of Oxford
- Professor Yoel Lubell
- University of Oxford

**Summary**

Plasmodium vivax malaria is a major cause of morbidity and an important contributor to mortality in poorly resourced endemic areas in Asia, South America and Africa. The greatest burden of vivax malaria is in South and Southeast Asia, where 2.85 billion people are at risk and experience 100 to 300 million cases of vivax malaria each year. Plasmodium vivax causes repetitive febrile illness associated with worsening anaemia particularly in young children and in pregnant women. Severe anaemia and low birth weight resulting in direct and indirect mortality.

Despite the very large population affected by vivax malaria and its socioeconomic burden, it has been and continues to be a neglected disease; global malaria R&D spending on combating P. vivax amounted to just 3% of total spending on malaria between 2007-2009. Since the 1950s chloroquine has been the mainstay of treatment for acute vivax malaria. However resistance to chloroquine was first reported in Papua, Indonesia and there is now good evidence that it is prevalent across the Indonesian archipelago and has spread throughout much of the vivax endemic world.

Unlike Plasmodium falciparum, P. vivax has in addition to the blood stage a liver stage of the parasite (known as hypnozoite) capable of reawakening weeks or even months after the primary infection. The complete treatment of vivax malaria requires administration of antimalarials to eradicate both the blood and liver stages of the parasite. Primaquine remains the only drug on the market for its liver stage activity. However the efficacy of primaquine resistance is difficult to determine due to variable relapsing patterns of P. vivax and the need for prolonged follow up to capture the late relapses. The widespread use of primaquine has been severely limited because of concerns regarding both its efficacy and safety.

Primaquine causes haemolysis in patients with G6PD deficiency, an inherited disorder occurring in 5-35% of patients in endemic zones. There a few readily available, affordable and reliable diagnostic tools for the rapid testing of GPD deficiency, and thus clinicians often reluctant to prescribe a therapy that is potentially harmful with limited perceived benefit. When it is prescribed adherence to the currently recommended 14 day treatment regimen is poor.

This proposal aims to provide critical evidence on the use of primaquine, a drug which is being increasingly recognised as a
crucial tool in the global fight against malaria. We hypothesise that a shorter course high dose primaquine regimens will provide a practical approach to antirelapse therapy that is safe and effective. Our randomized placebo controlled multicentred trial will compare two different regimens of primaquine against schizontocidal treatment alone in 5 Asian countries. Trial centres will be established in South Asia (India, Pakistan and Afghanistan) where 70% of all cases occur and the interval between vivax relapses is relatively long, as well as two sites from South East Asia (Vietnam and Indonesia) where the interval between relapses is shorter and the risk of relapse greater.

The primary objective will be to compare two primaquine regimens giving the same total dose primaquine over either 7 or 14 days. Patients presenting with pure vivax malaria, meeting the inclusion criteria will be randomly assigned to receive one of the following three treatments: Option 1 - Standard blood schizontocidal therapy + 14 days of supervised primaquine (7mg/kg total dose). Option 2 - Standard blood schizontocidal therapy + 7 days of supervised primaquine (7mg/kg total dose). Option 3 - Standard schizontocidal therapy.

Treatment with primaquine will be deferred until the end of the follow up period. This is the control regimen. Following treatment, patients will be followed for 12 months to monitor the number of vivax recurrences and the level of anaemia.
Project title
Community randomised evaluation of socioeconomic intervention to prevent TB

<table>
<thead>
<tr>
<th>Co-Investigators</th>
<th>Summary</th>
</tr>
</thead>
</table>
| Professor James Lewis  
Cardiff University                                       | BACKGROUND. TB kills 1.5 million people each year, more than            |
| Dr Robert Gilman  
Johns Hopkins University                                    | any other single infection. There is an urgent need to evaluate        |
| Dr Delia Boccia  
London Sch of Hygiene and Trop Medicine                     | the impact of new interventions to strengthen TB control.              |
| Dr Marco Tovar  
Peruvian University Cayetano Heredia                           | Poverty is increasing globally in cities and urban areas, and is        |
|                                                          | associated with factors that increase TB risk including crowding       |
|                                                          | and malnutrition. Conversely, TB worsens poverty by increasing         |
|                                                          | expenses and reducing income. In addition, those with TB and           |
|                                                          | their families may experience stigma.                                   |

Poor people have more TB and greater TB-related needs but they tend to have least access to TB care. This mismatch between need for and access to TB care undermines TB control and worsens poverty. OBJECTIVE. We will evaluate the impact of socioeconomic interventions for reducing poverty, improving access to TB care and consequently reducing the risk of future TB. SETTING. 24 peri-urban shantytowns in Northern Lima, Peru near the site of our TB control research since 2001. Peru has an acclaimed TB control programme but its levels of TB disease remain high and its rates of multidrug-resistant TB (MDR-TB) have doubled over the last decade to the highest levels in the Americas. The high TB and increasing MDR-TB rates are concentrated in "hotspots" such as poor peri-urban shantytowns surrounding Lima. It is these "hotspots" where we will work. RELATED WORK. Since 2007, our on going pilot project has been "Innovative Socio-economic Interventions Against TB (ISIAT)" which involves developing and implementing socioeconomic interventions to fight poverty and increase equitable access to TB care.

Early analysis of the pilot ISIAT project showed promising results with the interventions described below increasing the number of people to a) complete TB treatment b) complete preventive therapy to prevent them getting TB c) be tested for TB and d) be tested for HIV. These results were published in 2011. The improvement in awareness, prevention and treatment of TB that our work and subsequent article showed has attracted the attention of funding bodies, like the World Bank and The Bill and Melinda Gates Foundation, and policymakers such as the World Health Organisation (WHO) and its Stop-TB department.

Our on going relationship and involvement of these organizations and the published results of the pilot ISIAT project are encouraging for future work. The proposed project will rigorously assess the impact of these interventions not just on poverty and access to TB care but also on actual TB control.

INTERVENTIONS AND STUDY DESIGN. The interventions will be...
inexpensive, involving a team of experts from different fields working with all TB-affected families. They will utilize household visit and fortnightly community meetings to implement an integrated program of social support for enhancing equitable access to TB-related healthcare and economic support to help people to afford TB care and to help them to become less poor.

We will include in the study all members of a household with a new diagnosis of TB, as assessed by the Peruvian national TB program, without age limit, who provides informed written consent. TB-affected households in 12 intervention communities will be offered the socioeconomic intervention for 6-months whilst the TB patient is receiving TB treatment. TB-affected households in 12 other control communities will be offered no intervention (standard of TB care). We will then re-visit those households 2 years after recruitment to assess what happened to the people with TB and those people in the household exposed to TB, and if our interventions prevented TB and reduced poverty.

BENEFITS: These socio-economic 'structural' interventions will be assessed for their capacity to reduce poverty-related TB risk factors, improve access to TB care and for reducing TB treatment failure, recurrence and transmission. This has potential importance for focusing poverty reduc
## Joint Global Health Trials - Call 2 Full Grant

**Project title**
A cluster randomized controlled trial of a STEPped CARE intervention for depression in primary care

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Oyewusi Gureje</td>
<td>University of Ibadan</td>
<td>MR/K00753X/1</td>
</tr>
</tbody>
</table>

### Co-Investigators

- **Professor Ricardo Araya**  
  King's College London

- **Dr Benjamin Olley**  
  University of Ibadan

- **Dr Bibilola Oladeji**  
  University of Ibadan

- **Ms Lola Kola**  
  University of Ibadan

- **Dr Oyindamola Yusuf**  
  University of Ibadan

- **Professor Alan Montgomery**  
  University of Nottingham

- **Dr Daniel Chisholm**  
  World Health Organisation (WHO)

### Summary

There is now considerable evidence in support of a stepped care approach to expanding mental health service. In this model, non-physician primary care providers deliver the bulk of essential mental health service under the supervision and support of physicians and of more highly trained mental health specialists.

This process, commonly described as task-shifting, facilitates the delivery of needed care even in the context of extreme shortage of specialists as seen in most LMIC. The WHO recently produced a set of guidelines, the mhGAP Intervention Guide (mhGAP-IG), that incorporates evidence based interventions for a list of priority mental health conditions, including depression, to aid the recognition and management of such conditions in non-specialist settings.

It builds on the well established knowledge that primary care providers can be trained to deliver both psychological and pharmacological interventions for several mental health conditions, while more highly trained providers, including specialists, offer necessary support and supervision and address more difficult conditions. The content of what constitutes essential ingredients to scale up mental health services is therefore generally agreed upon.

However, the mode of delivery of the intervention in diverse settings still requires empirical exploration in order to determine the best fit to local health systems. Our study is designed to provide this evidence for Nigeria, the most populous nation in Africa, and also for most other countries in sub-Sahara Africa where the settings are similar.

The proposed study sets out to assess the cost-effectiveness of a management program for depression delivered mainly by non-physician primary care providers in Nigeria in which supervision and support are provided by general doctors and specialists, wherever available, with the use of modern, affordable and readily available technology.
**Joint Global Health Trials - Call 3 Full Grant**

**Project title**
MICA: randomized trial of therapy shortening for minimal TB with new WHO-recommended doses and FDC drugs in African/Indian HIV+/HIV- children

**Grant holder**
Professor Diana Gibb

**Institute**
University College London

**Grant reference**
MR/L004445/1

### Co-Investigators
- Mr Robert Aarnoutse
  Catholic (Radboud) University Foundation
- Dr Vidya Mave
  Johns Hopkins Medicine (JHM)
- Professor Janet Seeley
  London Sch of Hygiene and Trop Medicine
- Dr Chishala Chabala
  Lusaka University Teaching Hospital
- Dr Philippa Musoke
  Makerere University
- Dr Eric wobudeya
  Mulago University Teaching Hospital
- Professor Soumya Swaminathan
  Nat Inst for Research in Tuberculosis
- Professor Anneke Hesseling
  Stellenbosch University
- Dr Elisabetta Walters
  Stellenbosch University
- Professor Mark Cotton
  Stellenbosch University
- Dr Angela Crook
  University College London
- Mrs Annabelle South
  University College London
- Professor Ibrahim Abubakar
  University College London

### Summary
Tuberculosis (TB) continues to be a major health problem in many countries. Of the estimated 9 million new TB cases every year across the world, about one million (11%) are in children with the majority in Africa and South East Asia. Based largely on research conducted only in adults, standard treatment for childhood TB is given for 6 months irrespective of how severe the disease is. Children often have mild forms of TB and it is likely that they could be successfully treated for less than 6 months.

This would have major advantages for the child, their family and carers, and for over-burdened health systems, by reducing the number of clinic visits children need to make to take their drugs. Shorter treatment would be particularly advantageous for children who also have HIV and need to take seven or eight drugs at the same time, often leading to problems with drug side effects and difficulty taking all their pills at the right time. It could also reduce the cost of treating mild forms of TB in children, freeing up money to be used for treating other people and diseases.

A trial in adult patients with mild TB disease in Hong Kong showed that they did equally well if they took four or six months of treatment. However, this study has not been repeated and no trial has studied the length of treatment needed for children with mild disease, which accounts for more than half the cases of TB worldwide in children. TB is a much neglected research area in children. In this trial, children aged twelve or younger with mild forms of TB disease who are considered by a doctor to need treatment for TB will be randomised (i.e. given by chance) to receive either the standard six months treatment recommended by international guidelines (the 'control group'), or the same drug regimen but given only for four months.

We plan to use new dissolvable mini-pills containing three anti-TB drugs, at doses which have been recently recommended by the WHO. Pharmacokinetic studies (measuring levels of drug in the blood) will be performed at the start of the trial in order to confirm, as soon as possible, whether these new baby pills have the right doses of each drug, as well as whether the weight band tables suggested by the WHO, are correct (i.e. result in the right amount of drug in the blood).

We will also check drug blood levels to ensure that the TB drugs are not causing the levels of HIV drugs to be too low, as we
Dr Margaret Jean Thomason  
University College London

Dr Martina Penazzato  
University College London

Dr Patrick Phillips  
University of California, San Francisco

Dr Helen McIleron  
University of Cape Town

Mr Paul Revill  
University of York

Dr Veronica Mulenga  
University Teaching Hospital

know these medicines interact with each other. This is an important research gap identified by the WHO HIV guidelines group. We will also do some research asking healthcare workers about how they use dosing tables for children, as the current ones for anti-TB drugs are different from the ones for anti-HIV drugs.

This could help to harmonise these better, to make it easier for healthcare workers to treat children who have both HIV and TB. TB in children is most common in places where the resources available for health care are very restricted. This means the cost of different ways of treating TB is an important issue. The health economics work we are doing as part of this trial will help to show the budget impact of adopting a shorter regimen, if it is as good as the standard one, or, if it is not as good, then whether the 6 months treatment provides value for money.

A total of 1200 children will be enrolled from clinical centres in Africa and Asia. Children with TB disease that is resistant to rifampicin, children with serious forms of TB or with advanced HIV disease will be excluded from the trial. We will follow all children for at least 18 months to check how many get TB again (relapse or get infected with a new strain of TB).

The main objective of the trial is to determine whether treatment shortened to 4 months is as good as the 6 months current standard. We will also be able to analyse whether the levels of anti-TB drugs in the blood
Joint Global Health Trials - Call 3 Full Grant

Project title
Combination interventions for controlling malaria transmitted by pyrethroid resistant mosquitoes: A novel bed net with synergist and IRS formulation.

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Mark Rowland</td>
<td>London Sch of Hygiene and Trop Medicine</td>
<td>MR/L004437/1</td>
</tr>
</tbody>
</table>

Co-Investigators
Professor Franklin Weria Mosha
Kilimanjaro Christian Medical College
Professor Immo Kleinschmidt
London Sch of Hygiene and Trop Medicine
Dr William Kisinza
National Institute for Medical Research

Summary
The massive scale-up of vector control measures has led to a major reduction in malaria burden (up to 50%) in many sub-Saharan African countries. This is giving grounds for optimism that malaria will one day cease to be a major public health problem in Africa. The main malaria prevention and vector control tools are long lasting insecticidal nets (LLINs) and indoor residual spraying (IRS).

Both rely on pyrethroid insecticides either to provide a repellent barrier between humans and mosquitoes or to kill mosquitoes before they can transmit malaria. With the huge efforts being taken to provide universal coverage of LLINs to those at risk there is, unfortunately, enormous selection pressure on mosquitoes to develop resistance to pyrethroids. Resistance is now occurring in many places and some forms appear to be so strong that vector mosquitoes survive contact and continue to transmit malaria.

WHO and manufacturing industry are responding by developing new types of LLIN that, in some cases, incorporate a chemical synergist that knocks out the resistance mechanism so the LLIN continues to protect. Other manufacturers are responding by producing long-lasting non-pyrethroid insecticides that can be sprayed on walls and provide control for almost a year. By combining the two tools it is hoped that malaria shall continue to be controlled to ever decreasing levels, pyrethroid resistant mosquitoes shall continue to be killed, and further selection of pyrethroid resistance shall be prevented.

Both products have undergone Phase II trials and both are approved by WHO for human use. There is great urgency to deploy this new generation of tools before pyrethroid resistance grows much worse, sets back control, or undermines our confidence to eliminate malaria, but first the tools need to be properly trialled. LSHTM together with its African partner institutions, KCMC and NIMR, have a long history of conducting mosquito vector and malaria control trials in Tanzania and have recently undertaken a cluster randomised trial in the Great Lakes border region (between Uganda and Rwanda) which showed that pyrethroid resistance is now commonplace and malaria transmission remains high despite several years of attempted control with pyrethroid IRS.
We therefore propose to conduct a four-arm CRT in 48 villages in the Lakes region comparing a) current practice of universal coverage of LLINs, b) full coverage of the novel LLIN plus synergist, c) the long lasting IRS, d) the novel LLIN plus the long lasting IRS. The trial will provide epidemiological, entomological, economic and social evidence of impact, as we shall be measuring the reductions in malaria prevalence and malaria transmission rates EIR, and changes in the frequency of resistance, mosquito species ratios and economic cost effectiveness.

The proposed trial will demonstrate whether the novel LLIN and long lasting IRS formulation will be more effective for controlling An.gambiae s.s. and reducing malaria prevalence than current practice with the conventional LLIN. There is great interest in conducting this trial. Alternative vector control products are limited and most new insecticides are not suitable for use on LLINs or as IRS. The main international funders of malaria control, the Global Fund and President's Malaria Initiative, are both supporting malaria control in the region. Both recognise the need to introduce new and better tools but neither has the mandate nor expertise to conduct malaria control trials. Both agencies would use the findings of this trial to make operational decisions on future strategy.

Because epidemiological effectiveness and cost effectiveness of the two interventions will be evaluated alone and together this will facilitate future allocation of malaria control resources according to situation. It would not tie us down to using these two interventions in the future; rathe
### Joint Global Health Trials - Call 3 Full Grant

#### Project title
A case for free supply of antiepileptic drugs in resource-poor regions: 3-year cost effectiveness analysis of morbidity, mortality and quality of life

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Hector Garcia</td>
<td>Peruvian University Cayetano Heredia</td>
<td>MR/L004410/1</td>
</tr>
</tbody>
</table>

#### Co-Investigators
- Dr Luz Maria Moyano  
  Hospital Jose Alfredo Mendoza Olavarria
- Professor Liam Smeeth  
  London Sch of Hygiene and Trop Medicine
- Dr Javier Bustos  
  Peruvian University Cayetano Heredia
- Mrs MARIA CARDENAS  
  Peruvian University Cayetano Heredia
- Dr Victor Sal y Rosas  
  Peruvian University Cayetano Heredia
- Dr Viterbo Ayvar Polo  
  Peruvian University Cayetano Heredia
- Professor Simon Shorvon  
  University College London

#### Summary
People with epilepsy suffer from lack of treatment. Free drug treatment will improve many lives at very low cost for governments. This trial will demonstrate the cost benefit of such a policy and change the lives of thousands of people and their families.
**Project title**  
MICA: Children's Oxygen Administration Strategies Trial

**Grant holder**  
Professor Kathryn Maitland

**Institute**  
Imperial College London

**Grant reference**  
MR/L004364/1

---

**Co-Investigators**

- Dr Isabelle Defourney  
  ALIMA
- Mr Thierry Allafort-Duverger  
  ALIMA
- Dr Patricia Njuguna  
  ARCH - KWTRP
- Professor Peter Olupot-Olupot  
  Busitema University
- Professor Andrew Bush  
  Imperial College London
- Professor Thomas Williams  
  Imperial College London
- Dr David Harrison  
  Intensive Care Nat Audit & Res Centre
- Professor Kathy Rowan  
  Intensive Care Nat Audit & Res Centre
- Dr Sarah Kiguli  
  Makerere University
- Dr Charles Engoru  
  Soroti Regional Referral Hospital
- Professor Nicole Anne Margaret Blackwell  
  University of Queensland

**Summary**

The Children's Oxygen Administration Strategies Trial (COAST) is a multicentre randomised controlled trial aimed at identifying which children admitted to hospital with suspected pneumonia with a low level of oxygen in their blood (called hypoxia) would benefit from oxygen and whether oxygen is best delivered by low flow (routine care) or by high flow.

Although oxygen is a basic element of hospital care, there are no relevant studies to guide which level of oxygen saturation should be targeted for its use and what is the best method of how to administer it (low flow or high flow) to improve outcome. In practice, many children in low-income countries do not receive oxygen, despite being recommended, owing to the lack of its availability due to the high cost, or supplies that are unpredictable (erratic delivery of cylinders or electricity to power oxygen concentrators) resulting in a mismatch between supply and demand. We will enrol 4200 African children, aged 2 months to 12 years, at admission to hospital with respiratory distress complicated by low oxygen levels (defined as a blood oxygen saturation, SaO2 level below 92%) over 30 months in 4 hospitals in 2 countries (Uganda and Niger) and follow the children up over a period of 28 days.

COAST trial will evaluate two related components of management. 1/ Who to give oxygen too? Children who are admitted to hospital in Africa with hypoxia have a poorer inhospital outcome than children with normal oxygen levels. For children with hypoxia (oxygen saturations between 80% and 92%) between 9-10% will die in hospital, similarly 26-30% will die if they have severe hypoxia (oxygen saturations <80%). COAST will examine whether or not oxygen improves outcome in hypoxia and the best threshold for giving oxygen in children without severe hypoxia (oxygen saturations 80% - 92%).

Children with severe hypoxia (SaO2 <80%) will all receive oxygen as we are unsure about the benefits of oxygen in this group. For the children with SaO2 between 80 and 92% we are not certain which is the best level to provide oxygen and whether this will result in a better outcome - so half of the children will receive oxygen the other half will not receive oxygen. 2.

How best to give oxygen? We will compare whether giving oxygen through a tube with two small prongs into the nose low flow (standard of care) to high flow in all children receiving oxygen. High flow oxygen provides extra pressure to the airways to prevent them from collapsing after every expiratory breath.
High flow is safe and well tolerated in children and babies - as it helps reduce effort of breathing in critically sick children, which is substantial when lungs are congested with infection, that often leads to respiratory exhaustion and ultimately respiratory failure in the children who cannot access mechanical ventilation (the majority of hospitals in Africa).

The major aim (or outcome) is to reduce shorter-term mortality at 48-hours (primary endpoint) and longer-term morbidity and mortality to 28 days. A trial demonstrating that oxygen is an important life saving treatment will provide important new evidence for which level of oxygen saturation to target oxygen therapy that is both clinically beneficial and cost-effective for health services.

This would lead to substantial refinements to treatment recommendations and can be used to put pressure on health services for wider implementation - allowing policymakers to make decisions on how best to allocate scarce health resources.
Joint Global Health Trials - Call 3 Full Grant

**Project title**
Two-month Regimens Using Novel Combinations to Augment Treatment Effectiveness for drug-sensitive Tuberculosis: the "TRUNCATE-TB" trial

**Grant holder**
Dr Angela Crook

**Institute**
University College London

**Grant reference**
MR/L004356/1

---

**Co-Investigators**

- **Professor liang li**
  Chinese Centre for Disease Control (CDC)

- **Professor Yin Bun Cheung**
  Duke-NUS Medical School

- **Professor Richard Coker**
  London Sch of Hygiene and Trop Medicine

- **Dr Vincent Balanag**
  Lung Center of the Philippines

- **Professor Soumya Swaminathan**
  Nat Inst for Research in Tuberculosis

- **Dr Chester Drum**
  National University of Singapore

- **Dr Lawrence Lee**
  National University of Singapore

- **Professor Nicholas Paton**
  National University of Singapore

- **Dr Sabai Phyu**
  National University of Singapore

- **Dr Jubert Benedicto**
  Philippine Tuberculosis Society, Inc.

- **Dr Hong Gao**
  Singapore Clinical Research Institute

- **Professor Andrew Nunn**
  University College London

- **Professor Ibrahim Abubakar**
  University College

---

**Summary**

TB incidence rates are falling only very slowly in many high burden countries that have healthcare systems for TB that are overstretched and experiencing large funding gaps.

Current tools and systems are clearly not able to solve the problem in the near future and alternatives must be explored - as a matter of urgency - that allow healthcare systems to use resources more effectively and economically to treat and cure more patients with drug-sensitive disease. Multi-drug-resistant (MDR)-TB is also an increasing problem, and a further advantage of improving treatment for drug-sensitive TB may be that it reduces the drive towards generating new cases of MDR-TB.

We propose a new strategic approach: instead of the current standard of care of 6 months treatment for drug-sensitive TB, we propose an approach that focuses resources on optimizing individual treatment for just 2 months, then stopping and following patients in order to re-treat the small proportion of those who relapse subsequently (which is expected to be with drug-sensitive organisms). In addition to saving programme resources, stopping after 2 months may reduce the drug pressure for generating MDR-TB as patients not taking medication cannot breed drug resistance. If relapse rates are relatively low, it is possible that such a strategy could be highly cost effective.

With recent advances in TB drug development, it is now likely that we can find one or more 2-month combination regimens with low rate of relapse that can be used in such a strategy. Previous trials show that, even with standard drugs, rates of relapse with shorter course TB treatment are low (usually below 10%). With the new drugs that have new mechanisms of action, it is likely that 2-month treatment combinations can be constructed that will have very low rates of relapse - this has already been shown in a mouse model of TB.

The only way to test which of the many promising regimens may achieve good cure rate of TB with just 2 months of treatment is to do human trials in which treatment is stopped at this time point and patients are followed for relapse. The Two-month Regimens Using Novel Combinations to Augment Treatment Effectiveness for drug-sensitive TB (TRUNCATE-TB) trial is a randomized open label, multi-arm multi-stage, parallel group trial in which we will compare four novel strategies - each using a different initial 2 month treatment combination including one...
TRUNCATE TB will recruit 1300 patients with confirmed drug-sensitive pulmonary TB and allocate them at random to receive one of the novel 2 month treatment combinations or 6 months standard-of-care treatment. All patients will be followed for 2 years to detect exacerbation of symptoms and be evaluated for relapse.

Information on clinical outcomes, microbiological clearance of TB, adverse events, quality of life and healthcare utilisation and costs will be collected. Treatments will be compared for their overall outcome (what proportion of people still have TB in their sputum at 2 years after study entry).

If the strategies are equivalent on this outcome then the various advantages and disadvantages of the strategies can be compared including safety, patient acceptability and quality of life, resource use and costs, and drug resistance. We will also look for markers of response that could permit refinements of the strategy (e.g. by identifying groups of patients, if any, in whom 2 months’ treatment can be reliably predicted to be inadequate).

The trial will be conducted at approximately 12 large TB treatment centres within an Asian TB trials network. This trial addresses a question of high relevance to real-world TB programme settings. It has the potential to
**Project title**

From malaria control to sustainable elimination: Cluster randomised trial comparing targeted versus generalised vector control in South Africa

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Immo Kleinschmidt</td>
<td>London Sch of Hygiene and Trop Medicine</td>
<td>MR/L00433X/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

- Professor Chris Drakeley  
  London Sch of Hygiene and Trop Medicine
- Professor Paul Milligan  
  London Sch of Hygiene and Trop Medicine
- Professor Rajendra Maharaj  
  South African Medical Research Council

**Summary**

Countries that have reduced malaria incidence to low levels face major challenges when trying to eliminate the disease altogether. In trying to reduce transmission further, considerable resources are required for disease prevention through mosquito vector control, for example by indoor residual spraying (IRS) of all houses.

Such mass prevention efforts can lead to reduced compliance in communities and control programs who no longer perceive a risk of malaria, and waning political and donor commitment when the disease burden is low, thereby endangering the sustainability of the elimination effort. Evidence based methods of scaling back blanket IRS have to be developed which ensure that populations are not put at risk when IRS is no longer routinely applied. In this study, targeted focal IRS in response to new cases being reported will be compared with generalised annual IRS of all houses, to determine whether it is as effective, less costly, more acceptable, results in higher coverage and compliance and increased malaria prevention seeking behaviour. A pre-condition for this approach, is a reliable rapid malaria case surveillance system, based on definitive diagnosis of suspected cases.

This trial will be carried out in South Africa, which has practised blanket IRS for many decades, where case incidence in many districts is now low enough to be considered pre-elimination, and where a high quality case reporting system is well established. Spray localities will be grouped into clusters of 5,000 to 10,000 persons which will be randomly allocated to either targeted IRS, or to blanket routine IRS. Targeted neighbourhood IRS will be triggered in response to two or more local cases occurring within 4 weeks of each other and residing within 0.5km from one another.

Spraying and community awareness activities will be carried out in a radius of 0.5km from each case house. It is postulated that focal spraying will lead to higher quality of IRS application because it can be better supervised and will be seen as protection against real risk of infection due to the occurrence of recent local cases; that it will be more acceptable to householders and hence lead to better co-operation with access to premises and hence higher spray coverage; and that householders will exercise better compliance with not repainting, washing or re-plastering of walls after spraying.
As a result we expect that incidence of cases will be no higher in targeted IRS areas than in those receiving mass IRS and that targeted spraying will be more economical and hence more sustainable. The study will measure malaria case incidence, householder acceptability and compliance, spray coverage, and economic costs of the interventions as outcome indicators.

There is some evidence from other countries that in very low transmission settings, incident malaria cases occur in hotspots that are stable over time. If such hotspots can be accurately located, they can be singled out for focal interventions such as targeted IRS at the beginning of each season. To investigate whether such hotspots of local transmission exist in South Africa, it is proposed that filter paper blood spots are collected in communities where targeted IRS is carried out, to be tested for the presence of antibody sero-positivity to malarial antigens.

The sero-prevalence of 'outbreak' communities will be compared with sero-prevalence of randomly selected communities in which no recent cases have occurred. This comparison will determine whether neighbourhoods with recent cases have historically been exposed to malaria parasites, and are therefore likely to be hotspots of transmission. The existence of such hotspots would strengthen the case for targeted control efforts. For countries that have set elimination of malaria as a policy objective this study will provide evidence upon which sustainable policy decisions abou
Joint Global Health Trials - Call 3 Full Grant

Project title
The Good Schools Study: A cluster randomised controlled trial of an intervention to prevent violence against children in Ugandan primary schools

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Karen Devries</td>
<td>London Sch of Hygiene and Trop Medicine</td>
<td>MR/L004321/1</td>
</tr>
</tbody>
</table>

Co-Investigators
Professor Charlotte Watts
London Sch of Hygiene and Trop Medicine

Professor Diana Elbourne
London Sch of Hygiene and Trop Medicine

Dr Elizabeth Allen
London Sch of Hygiene and Trop Medicine

Dr Eddy Walakira
Makerere University

Professor Jenny Parkes
University College London

Summary
Violence against children in schools is common practice in many countries, and research into prevention and treatment has been outlined as a priority in the World Report on Violence against Children. In most countries, children spend more time at school than anywhere else besides their family home, and can suffer violence from teachers and other school staff, and other children.

Despite this, in most countries evidence is lacking from rigorously conducted studies on the prevalence, epidemiology and consequences of this violence. Existing studies tend to come from North America, where corporal punishment from teachers is far less common. In Uganda, no rigorous, representative prevalence data exist, but one survey indicated more than 80% of children have experienced physical punishments such as caning and slapping by teachers.

More research exists on sexual violence in schools suffered by girls in African schools, and qualitative studies indicate girls in Ugandan secondary schools experience sexual violence and harassment from teachers and fellow students but are not able to report it for fear of reprisals. The Good School Toolkit has been developed and refined for 6 years in Uganda by Raising Voices.

The Toolkit takes a systemic approach, involving an entire school in a process of change to reduce violence and improve teaching techniques. The Toolkit draws on the Transtheoretical Model and incorporates standard behaviour change techniques such as setting a goal and making an action plan, which are effective in modifying behaviour. This study aims to determine whether use of the Good School Toolkit reduces children’s experience of violence by school staff. We will also examine the effects of the Toolkit on children’s mental health, well-being, and educational outcomes.

The study will include a trial, which will be complemented by a qualitative study, a process evaluation, and an economic evaluation. We will also follow a sub-group of trial participants over time. We will conduct a cluster randomised controlled trial in 42 primary schools in Luwero District, Uganda. Half of the schools will receive the Toolkit, and the other half will be put on a waiting list to receive the Toolkit at the end of the study if it is shown to be effective. School staff, and children in Primary 5, 6...
and 7 will be surveyed (aged about 11-14 years) at the beginning and the end of the study, and schools which received the Toolkit will be compared with those which did not. A qualitative study will also be conducted to explore mechanisms by which the Toolkit might be affecting violence, mental health and educational outcomes.

In-depth work will focus on how school staff and children have experienced the Toolkit intervention, and what aspects of it may be refined to be more effective. The Toolkit is specifically designed to be implemented at very low cost, appropriate for low income settings. An economic evaluation will be performed to explore the economic and financial costs of this intervention, with the aim of informing possible scale-up of the Toolkit.

All students in Primary 5 at baseline will be followed longitudinally until follow-up, when most will be in Primary 7. This will enable exploration of trajectories of change in mental health and educational outcomes over time, and how violence experience impacts this.

We will also be able to follow school staff over time. The results from this evaluation will be used to brief policy-makers within the Ministry of Education and Sports involved in developing country-wide policy and practice around violence against children in schools.
Joint Global Health Trials - Call 3 Full Grant

**Project title**
Uptake and impact of HIV combination (HIVCOMB) interventions on HIV incidence among fishing communities in Uganda

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Anatoli Kamali</td>
<td>MRC/UVRI Uganda Research Unit on AIDS</td>
<td>MR/L004305/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

<table>
<thead>
<tr>
<th>Co-Investigator</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Anna Vassall</td>
<td>London Sch of Hygiene and Trop Medicine</td>
</tr>
<tr>
<td>Professor Helen Weiss</td>
<td>London Sch of Hygiene and Trop Medicine</td>
</tr>
<tr>
<td>Professor Janet Seeley</td>
<td>London Sch of Hygiene and Trop Medicine</td>
</tr>
<tr>
<td>Dr Rebecca Namugabwe</td>
<td>Nsubuga London Sch of Hygiene and Trop Medicine</td>
</tr>
<tr>
<td>Ms Stella Settumba</td>
<td>London Sch of Hygiene and Trop Medicine</td>
</tr>
<tr>
<td>Professor Jonathan Levin</td>
<td>University of the Witwatersrand</td>
</tr>
</tbody>
</table>

**Summary**

HIV-1 remains a major global health problem, with 2.5 million new infections in 2011, of which 70% were in sub-Saharan Africa. In countries with mature generalised epidemics, including Uganda, there are groups that are more disproportionately affected (Most-At-Risk Populations [MARPs]) such as fishing communities, with high HIV infection, and extensive sexual networks bridging into the general population.

Proven HIV prevention strategies are often not readily available to MARPs. Recent data from fishing communities in Uganda indicate that HIV infection rates in these communities are up to 5 times higher than the national average. In Uganda, approximately 10% of the population are engaged in fishing-related activities, but this group could be contributing a substantial proportion of HIV infections. Proven HIV interventions are only partially effective, and need to be combined for effective HIV control. Combination prevention programmes are rights-based, evidence-informed and community-owned programmes that incorporate a mix of effective behavioural, biomedical and structural interventions, prioritised to meet the HIV prevention needs of individuals and communities, to have the greatest sustained impact on reducing new infections.

We propose a trial on the effectiveness of implementing combination prevention in fishing communities in Uganda, to generate data that will complement that from other ongoing trials taking place elsewhere in Africa in general populations. The social context of MARPs is different from general populations and designing and evaluating an appropriate combination HIV prevention package in these core groups is critical to reduce HIV rates not only in these populations but also in the wider general population.

The trial will use a stepped-wedge cluster randomised design, in which each cluster (community) will receive the intervention in a phased manner during follow-up. This ensures that all communities will receive the intervention during the trial, whilst minimising logistical difficulties in implementing the intervention in several clusters simultaneously. Twelve fishing communities will be randomised into 4 equally-sized groups, and the time at which each group first receives the intervention is randomised. The study will take 60 months, with the first 3 communities receiving the intervention from month 18.
onwards, and the last 3 communities receiving the intervention from month 42 onwards.

During the baseline phase before the intervention is introduced, a census will be undertaken in each community from which a simple random sample of 240 adults (aged 18 years or old) will be recruited in each community and their HIV status determined. The incidence of HIV among participants who were HIV seronegative during the baseline survey will be determined during follow-up surveys. This is the primary outcome. Secondary outcomes include the impact on community viral load, behaviour changes, the level of uptake of the intervention, and the cost and cost-effectiveness of the intervention. Given the burden of HIV, the "standard of care" package consisting of condom distribution, HIV risk counselling and testing (through routine government health units), and selected structural interventions targeting stigma and discrimination, harmful cultural norms and practices will be provided to all communities throughout the trial. We will select the most effective interventions, which, applied together, are most likely to have synergy and impact highly on HIV transmission.

We will consider only "real life" evidence-based interventions that are affordable and scale-able within African prevention, care and support programmes. The trial results will increase understanding of the implementation, uptake and impact of combination HIV prevention on HIV incidence among MARPS, and will aid policy makers in deciding on practical m
Joint Global Health Trials - Call 3 Full Grant

Project title
A double blind randomized community-based trial of amoxicillin versus placebo for non-severe pneumonia in children aged 2-59 months in Pakistan

Grant holder | Institute | Grant reference
--- | --- | ---
Dr Fyezah Jehan | The Aga Khan University, Pakistan | MR/L004283/1

Co-Investigators
Dr Nick Brown
Salisbury NHS Foundation Trust

Dr Muhammad Nisar
The Aga Khan University, Pakistan

Dr Syed Asad Ali
The Aga Khan University, Pakistan

Summary
Pneumonia is a major cause of illness and death in children in low-income countries. With a view to decreasing death from pneumonia, the World Health Organization and UNICEF developed the the Integrated Management of Childhood Illness (IMCI) algorithm which simplifies management of common childhood illnesses such as pneumonia and diarrhoea into different levels of severity for determining the most appropriate case management by primary healthcare providers.

Many pneumonia cases are categorized as non-severe pneumonia (defined as fast breathing above the specified age cut-off for respiratory rates). As there is incomplete information regarding the cause of this type of "pneumonia" from primary care settings, treatment guidelines by WHO are dictated by culture information from hospital pneumonia cases which are different in severity and cause. Current WHO guidelines advocate the use of oral antibiotics for non-severe pneumonia.

However, it is postulated that most non severe pneumonia not requiring hospitalization is of viral aetiology, thus does not require antibiotic treatment. The cost of antibiotic treatment for all children with pneumonia is high; an estimated US$ 200 million in South Asia & sub Saharan Africa alone. Since more than 60% of pneumonia is classified as non-severe, this puts a strain on already under-sourced programmes in low-income countries. Giving antibiotics where they confer no benefit also puts the child at risk of side effects and increases the risk of antimicrobial resistance in the community. This uncertainty forms the basis of the proposed study.

We propose to show in a clinical trial that the outcome of children diagnosed with WHO defined non severe pneumonia is similar regardless of whether they receive antibiotics or not. This study will be conducted in five primary health care centres located in low income communities of Karachi, Pakistan, with extensive trial experience. Children identified to have fast breathing without any danger signs will be randomized to receive either three days of the WHO recommended oral antibiotic (Amoxicillin 45mg/kg/day divided twice daily) or matching placebo (a drug that will taste and look like the amoxicillin but will not have an active ingredient) by a study physician working at the primary health centre. The assignment of the antibiotic amoxicillin or placebo to a child will be done using a computer generated randomization list in a manner that
at the end of the trial, there are equal numbers of children in both arms of the trial. Based on the statistical calculations for sample size, we will need to assign 521 children to receive amoxicillin and the same number of children to receive placebo.

All children will receive the antibiotic or placebo under supervision of the primary health care physician in the morning. Evening doses will be delivered by locally hired Community Health Workers (CHWs) visiting the children at their home. All children will be assessed again on day 3 by a study physician to see if the child's presenting sign of high respiratory rate has resolved or not.

All children with persistently high respiratory rate and/or development of a new clinical sign indicating illness progression will be labelled a treatment failure. There will invariably be some children with treatment failure in both the treatment arms; we hypothesize that there will be equal number of treatment failures in both the groups i.e. around 7%.

If we are able to show with the help of this trial that there is no added advantage of prescribing antibiotics to children with non-severe pneumonia we will develop an evidence base to revise the current WHO guidelines and thus reduce the financial burden on an already resource constrained health system and also decrease out of pocket expenses for families. In the long term this will have implications for decreasing global antimicrobial resis
**Project title**
Integrated Primary Care Strategies to Reduce High Blood Pressure - A Cluster Randomized Trial in Rural Pakistan and Sri Lanka

<table>
<thead>
<tr>
<th>Co-Investigators</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Benjamin Haaland</td>
<td>Cardiovascular disease (CVD) has become the leading cause of mortality worldwide, accounting for 30% of deaths even in low- and middle-income countries (LMICs). In South Asia, high rates of CVD are observed at a younger age than in other countries, causing a greater loss of productive life years with severe economic consequences. High blood pressure (BP) confers the greatest attributable risk to death and disease associated with CVD.</td>
</tr>
<tr>
<td>Dr Eric Andrew Finkelstein</td>
<td>Our Wellcome Trust funded Control of Blood Pressure and Risk Attenuation (COBRA) trial (2004 to 2007) in Karachi, Pakistan, suggested the combined strategy of family based home health education (HHE) delivered by trained community health workers (CHW) plus care of patients by trained private general practitioners (GP) to optimally manage hypertension had the most marked beneficial impact on BP compared to usual care, or single interventions. However, the COBRA intervention was designed for an urban South Asian setting, where private GPs cater to over 75% of the patients seeking care.</td>
</tr>
<tr>
<td>Professor Truls Ostbye</td>
<td>Therefore, the trial did not use the public health infrastructure per se, nor did it evaluate whether mid-level providers (MLP) can deliver first steps of hypertension care including prescribing first and second line anti-hypertensive medications. Most of South Asia is still rural (64% Pakistan, 85% Sri Lanka) where prevalence of hypertension is high and healthcare infrastructure and provider characteristics are very different compared to the urban setting. About 40-50% patients in rural Pakistan and Sri Lanka seek care (including prescription medications) from MLPs (visiting nurse, dispenser, assistant medical officer) at the government community clinics. Thus whether hypertension management by this cadre of MLPs is effective, especially when rolled out using government healthcare infrastructure is not known.</td>
</tr>
<tr>
<td>Professor Shah Ebrahim</td>
<td>Our proposed study is designed to answer this question in rural Pakistan and Sri Lanka. We propose a cluster RCT in 30 rural communities in Pakistan and Sri Lanka including 2500 individuals with hypertension with 2 year follow-up to evaluate the effectiveness of &quot;triple approach&quot; of combining intervention by 1) HHE plus 2) trained government primary health center MLP plus 3) trained private practitioners or &quot;dual approach&quot; of combining intervention of 1 and 2 only compared to no intervention (or usual care) on lowering blood pressure, and to</td>
</tr>
<tr>
<td>Duke-NUS Medical School</td>
<td></td>
</tr>
<tr>
<td>Duke-NUS Medical School</td>
<td></td>
</tr>
<tr>
<td>Professor Truls Ostbye</td>
<td></td>
</tr>
<tr>
<td>Duke-NUS Medical School</td>
<td></td>
</tr>
<tr>
<td>Professor Shah Ebrahim</td>
<td></td>
</tr>
<tr>
<td>London Sch of Hygiene and Trop Medicine</td>
<td></td>
</tr>
<tr>
<td>Dr Aamir Hameed</td>
<td></td>
</tr>
<tr>
<td>The Aga Khan University, Pakistan</td>
<td></td>
</tr>
<tr>
<td>Professor Ananda Rajitha</td>
<td></td>
</tr>
<tr>
<td>Wickremasinghe</td>
<td></td>
</tr>
<tr>
<td>University of Kelaniya</td>
<td></td>
</tr>
<tr>
<td>Professor Asita de Silva</td>
<td></td>
</tr>
<tr>
<td>University of Kelaniya</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Tazeen Jafar</td>
<td>National University of Singapore</td>
<td>MR/L004224/1</td>
</tr>
</tbody>
</table>
determine whether these approaches are incrementally cost-effective.

The delivery of care by the various public providers and the private sector is now recommended by the World Health Organization in several communicable disease control programs, such as Directly Observed Treatment (DOTS) for tuberculosis and management of malaria. However, evidence on the effectiveness of using the same platform for chronic non-communicable disease management is rather scarce.

Moreover, wider discussion among the relevant stakeholders in South Asia to refine and implement the proposed activities would be beneficial, and would increase the likelihood of up-scaling the cost-effective strategies which could also be extended to other chronic diseases (and even infectious diseases) in an integrated manner that is potentially sustainable and applicable in rural settings across many Asian countries with similar ethnic populations and healthcare infrastructure.

Comparing and contrasting the experiences from Sri Lanka and Pakistan should also provide valuable lessons not only for these two countries but also for other countries in the region and beyond.
Joint Global Health Trials - Call 4 Development Grant

Preventing for a clinical trial of interventions to maintain normal vaginal microbiota for preventing adverse reproductive health outcomes in Africa

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Janneke van de Wijgert</td>
<td>University of Liverpool</td>
<td>MR/M017443/1</td>
</tr>
</tbody>
</table>

Co-Investigators

Summary

Human body surfaces are covered by bacteria called the human microbiota. This microbial community is believed to contain at least 10 times the number of cells and 100 times the number of genes in the human body. Considerable progress has been made in characterising the human microbiota in recent years. Researchers have discovered that these microbial communities are needed for proper functioning of the human body, for example to digest complex carbohydrates in the gut and to prevent pathogen invasion.

At the same time, imbalances of the normal microbiota have been shown to be associated with a number of diseases. The human vagina also contains bacterial communities of mostly lactobacilli that are thought to protect women and their foetuses from pathogen invasion. When these bacterial communities are imbalanced, pathogens may enter the uterus, placenta, membranes surrounding the foetus, or abdominal cavity, causing pelvic inflammatory disease, miscarriages, preterm births, or maternal or neonatal sepsis.

These imbalances have also been associated with increased transmission of HIV and other sexually transmitted infections (STIs) between sexual partners and mother-child pairs. Some of the imbalances have been diagnosed in the past (using symptoms reported by the patient and microscopy of vaginal fluid) as bacterial vaginosis (BV). Unfortunately, BV has been notoriously difficult to treat, and even when treated successfully, recurrence rates are high. Because researchers have not been able to prevent BV recurrences during pregnancy, they have also not been able to prevent subsequent poor pregnancy outcomes. In this development grant, we will develop interventions to maintain normal vaginal microbiota after initially having cured BV.

The study participants will be Rwandan women who are at high risk of HIV and other STIs but who are not pregnant. We will ask one group of 15 women to use a vaginal gel (0.75% metronidazole gel) twice per week for 2 months, a second group of 15 women to use a vaginal probiotic tablet called Gynoflor thrice weekly for 2 months, and a third group of 15 women to use a vaginal probiotic capsule called Ecologic Femi thrice weekly for 2 months. Both probiotics contain 'healthy' bacteria called lactobacilli, and Gyneflor also contains a very low dose of oestradiol. A further group of 15 women will form the control group. All women in all groups will receive safer sex and family...
planning counselling as well as individualised counselling on how to integrate the study interventions into their usual vaginal hygiene practices. At the end of the project, we will evaluate whether we were able to maintain healthy vaginal microbiota during the 2-month intervention period as well as the 4 months after cessation of the interventions.

We will also evaluate the acceptability and feasibility of these interventions. A novel aspect of this trial is that we will not only use standard methods to evaluate the vaginal microbiota (i.e. reporting of symptoms and microscopy of vaginal fluid) but also new molecular methods based on the sequencing of bacterial genes. This allows for a holistic and in-depth characterisation of microbial communities. The results of this trial will be used to plan a larger randomized controlled clinical trial of the most promising intervention(s).
Project title
Policy and peer mentor intervention programs on cardiovascular disease at worksites in 3 South Asian countries.

Grant holder | Institute | Grant reference
--- | --- | ---
Professor Denis Xavier | CBCI Society for Medical Education | MR/M019624/1

Co-Investigators

Dr Deepak Kamath
CBCI Society for Medical Education

Dr Dewan Alam
ICDDRB

Dr Muhammad Ashique Haider Chowdhury
ICDDRB

Mr Shyfuddin Ahmed
ICDDRB

Dr Godwin Roger Constantine
Medical Research Institute Sri Lanka

Dr Alben Sigamani
Narayana Health

Dr Padmini Devi
St. John’s Medical College

Dr Prasad Katulanda
University of Colombo

Dr RANIL JAYAWARDENA
University of Colombo

Summary
We propose a feasibility study and a survey conducted at 6 sites - 2 in India, 2 in Sri Lanka, and 2 in Bangladesh. 1. The feasibility study will be conducted to understand the feasibility of peer-mentored interventions at the operational, research and policy levels to improve CVD health.

At the operational level, we will identify 6 worksites in Bangladesh (2), India (2) and Sri Lanka (2), obtain acceptance from the management, identify the appropriate personnel as peers to carry out interventions and identify areas at worksites to implement interventions (café, physical exercise, stress reduction, tobacco environment). At research level, we will choose the best methods to identify individuals at risk for interventions, measure risk factor levels, identify & train the peer mentors, design the most appropriate interventions, determine the training goals for the peer mentors, select the training methods, and develop the intervention tools.

At policy level, we will, in discussion with the worksite management and the concerned State Government departments (health and labour departments) determine the need, methods and outcomes of the interventions. This strategy ensures that we have useful insights on the interventions as well as the agreement and investment of key stakeholders in relevant departments.

A qualitative study will be conducted to understand the priorities for policy level changes to improve the CVD environment at worksites in each country, at the Central and Regional levels; to understand the common barriers for an optimal CVD environment at worksites; and to understand the most acceptable peer mentor-based interventions for employees to improve CVD health. We will survey at least three levels of management staff per site on the CVD environment at the workplace. Specifically this will include tobacco policy, food at workplace, opportunities for physical activity, medical care if any provided at worksites, policy on chronic care for employees, barriers for optimal care and possible interventions to improve CV health.

We will survey 5 management staff at each level or 15 per worksite for a total of 120 at 8 sites. We will conduct focussed group discussions and in-depth interviews among management staff and employees to better understand policy issues, barriers
for CVD care and acceptable interventions to improve CV health. If peer mentor mediated interventions prove to be effective in reducing cardiovascular risk factors, such interventions could be scaled up globally.

As adults can spend upto 60% of their time at workplaces, interventions such as these could prove to be effective in reducing cardiovascular risks and reap rich dividends by reducing cardiovascular deaths, thus helping to achieve World Hearth Federation’s goal of 25 by 25.
### Project title

Is Lactoferrin more effective than inorganic iron in treating iron def anaemia in non-pregnant and if effective in pregnant women? 2 randomised trials

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Tanvir Mahmudul Huda</td>
<td>ICDDR Bangladesh (ICDDRB)</td>
<td>MR/M026469/1</td>
</tr>
</tbody>
</table>

### Co-Investigators

<table>
<thead>
<tr>
<th>Dr Shams Arifeen</th>
<th>ICDDR Bangladesh (ICDDRB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Michael Dibley</td>
<td>University of Sydney</td>
</tr>
<tr>
<td>Professor William Tarnow-Mordi</td>
<td>University of Sydney</td>
</tr>
</tbody>
</table>

### Summary

Oral bovine lactoferrin is a novel, unconventional way to prevent low birthweight, preterm birth & neonatal deaths associated with maternal iron deficiency in low income settings. Each year about 20 million low birthweight babies are born worldwide.

Low birthweight is caused by either preterm delivery (babies born earlier than expected) or fetal growth retardation. In countries where perinatal health services are limited, low birthweight and preterm birth are a major cause of neonatal deaths. Low birthweight babies are 20 or more times likely to die than heavier babies, with much of this mortality burden due to preterm birth.

The current paradigm of using iron supplements (and folic acid) targeted at pregnant women often fails, in part because of the side effects, which are a strong barrier to use of the supplements early in pregnancy, a period of vulnerability for iron deficient women and their fetus and future newborn. And also because maternal inflammation and micronutrient deficiencies block effective utilization of iron. Our approach will provide a product that will efficiently deliver iron and that can be taken early in pregnancy during a critical intervention window, which offers the potential to prevent neonatal deaths.
Joint Global Health Trials - Call 4 Full Grant

**Project title**
A phase III cluster randomised placebo-controlled trial to assess the efficacy of preventive therapy in child and adolescent contacts of MDR-TB

**Grant holder** | **Institute** | **Grant reference**
--- | --- | ---
Professor Anneke Hesseling | Stellenbosch University | MR/M007340/1

**Co-Investigators**
Dr Soyeon Kim
Harvard School of Public Health

Dr James Seddon
Imperial College London

Dr David Dowdy
Johns Hopkins Bloomberg School of PH

Dr Anthony Garcia-Prats
Stellenbosch University

Dr Graeme Hoddinott
Stellenbosch University

Professor Hendrik Simon Schaaf
Stellenbosch University

Professor Mark Cotton
Stellenbosch University

Dr Sharon Nachman
Stony Brook University

Dr Lee Fairlie
Wits Health Consortium (Pty) Ltd

Dr Neil Martinson
Wits Health Consortium (Pty) Ltd

**Summary**

Context of research: To become sick with tuberculosis (TB), someone must first be exposed to someone who is coughing, become infected and then develop the disease. People with HIV and young children are more likely to develop TB disease once they are infected. One way to prevent TB is to find the people who live in a home with someone who has TB, check them and treat those with TB infection. This will prevent them from getting sick with TB disease.

Many studies have shown that a drug called isoniazid (INH) reduces the risk of developing TB when given after being coughed on, so World Health Organization (WHO) advises giving INH to HIV-infected people and children under age 6 for six months when they have contact with someone with TB. Right now it is unclear what medicine we should give a child who has been exposed to someone with multidrug-resistant (MDR)-TB, when the germ is resistant to the most commonly used TB medicines, like INH. MDR-TB is becoming more common.

The WHO estimated that there were more than half a million cases worldwide in 2012. Worldwide, it is estimated that at least a million children are exposed to MDR-TB every year. With new tests to diagnose TB quickly that can also detect resistance to the common TB medicines, the number of adults who are diagnosed with MDR-TB cases is increasing.

In turn, the number of children exposed to MDR-TB is also increasing. Treating children who become sick with MDR-TB takes a long time (usually 18 months), usually needs a hospital stay, has medicines that may have many side effects, and is expensive. For these reasons, preventing MDR-TB in children is therefore very important.

Until now, there have been no big and well designed studies to help us decide if using medicine to prevent a child with contact with someone with MDR-TB from becoming sick works. A few studies where doctors treated patients who have been in contact with MDR-TB have been done, but, each of them had problems.

We think medicine to prevent MDR-TB might work, but a better type of study, a randomised control trial, needs to be done to prove that it works before we can be sure. Aims and objectives: We want to do a study in South Africa that looks at people living in the homes of someone with MDR TB disease. We will use a
drug that doctors already use to treat MDR-TB called levofloxacin (LFX). We will test whether this medicine, given every day for 6 months, can prevent children from getting TB and/or dying. We will include children who live with someone with MDR-TB in the study.

Children who get the medicine will be compared to those who get a sugar pill or placebo. This sugar pill looks like LFX but has no active medicine. Children will be followed for 24 months to make sure they do not get TB or have any side effects. We will also check if the medicine was easy to take, if it was safe, or if the TB became resistant to the LFX. We will also check how expensive it is to give this kind of medicine in the way that we think it should be given. Some children and their families will be asked to talk about their experience of the study and the medicine with the clinic staff.

Potential applications and benefits: Until doctors learn what treatments work for preventing MDR-TB in children, it will hard to tell families what to do. If the medicine we are testing works to prevent MDR-TB, and is safe, and acceptable to families, we will be able to tell other doctors how to decrease MDR-TB all over the world. TB programmes will also benefit from this research because fewer children will get a disease which is costly to treat. Most importantly, if this medicine works, this study could greatly benefit children exposed to MDR-TB.
First Line Antimicrobials in Complicated Severe Acute Malnutrition (FLACSAM)

Co-Investigators

Ms Nicola Lord  
London Sch of Hygiene and Trop Medicine

Dr Ulla Griffiths  
London Sch of Hygiene and Trop Medicine

Dr Joseph Frank Standing  
University College London

Summary

Severe acute malnutrition (SAM) causes 1 million deaths in children annually by making children susceptible to common infections. The World Health Organisation (WHO) recommends that children with SAM should receive antibiotics together with nutritional rehabilitation. Children with SAM and complications including signs of infection or severe metabolic disturbance are referred for hospital admission.

However, most admissions with SAM present directly to hospital because of severe illness, and their SAM is only detected during clinical assessment. At the four hospital sites for the proposed trial, between 15% and 18% of paediatric admissions between the ages of 2 and 59 months have SAM. In sub-Saharan Africa, up to 30% of children admitted to hospital with complicated SAM die, usually from severe infection. Mortality is highest amongst those who also have HIV infection.

There are reports that bacteria isolated from children with SAM, when tested in the laboratory, are often not susceptible to the recommended first-line antibiotics. In Kenya we have conducted long term surveillance of bacterial infections. Amongst children with SAM, non-susceptibility has risen: in the last 5 years, more than one third of bacteria isolated at admission to hospital are non-susceptible to the recommended antibiotics.

Because children with SAM are vulnerable to infection, this to result in death rather than simply a prolonged hospital stay. An alternative antibiotic, ceftriaxone, is cheaper the currently recommended combination and only has to be given once a day instead of four times. Much less resistance to ceftriaxone is reported. Ceftriaxone would be used as first line treatment if such a child were admitted to hospital in the UK. At first sight, it seems that ceftriaxone would be a more appropriate antibiotic, and it could reduce deaths.

However, a significant concern is that ceftriaxone is known to rapidly induce resistance to multiple classes of antibiotics. This could mean that subsequent infections could be harder, and more expensive, to treat. Furthermore, studies have not shown a clear relationship between laboratory susceptibility testing and actual outcomes. In determining policy for empiric antimicrobials for this vulnerable population, potential benefits of reduced mortality, quicker recovery and reduced costs must be weighed against potential risks of infections that are difficult and expensive to treat.
There is currently no evidence to inform this decision. A second question in the antibiotic treatment of SAM is the value of metronidazole. Current WHO guidelines suggest that metronidazole may be optionally used although it has never been tested in a clinical trial.

It is effective against bacteria that cause abnormal overgrowth in the small bowel, and against gut parasites such as Giardia. These conditions are common amongst children with SAM and may cause malabsorption of nutrients and diarrhoea. Treating them improve nutritional recovery. Results of small studies suggest this may be the case. However, metronidazole can cause nausea, vomiting and other toxicities which could impede nutritional recovery.

We propose an efficiently designed trial to test both ceftriaxone and of metronidazole against standard care for the outcomes of mortality and nutritional recovery. First we will determine the optimal dosing for the drugs in malnourished children. We will carefully investigate children for infections and the antibiotic susceptibility of bacteria isolated determined. An economic analysis will measure the cost-benefit ratio of each strategy and overall costs of treatment for SAM. The trial will be run at 2 rural and 2 urban hospitals in Kenya.

The results are expected to have direct impact on antibiotic policy for the management of SAM in hospitals in Africa and will provide unique information that will contribute to global effo
### Joint Global Health Trials - Call 4 Full Grant

#### Project title

**Rapid Urine-Based Screening for Tuberculosis to Reduce AIDS-Related Mortality in Hospitalized Patients in Africa (STAMP) Trial**

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Katherine Fielding</td>
<td>London Sch of Hygiene and Trop Medicine</td>
<td>MR/M007375/1</td>
</tr>
</tbody>
</table>

#### Summary

Sub-Saharan Africa bears the brunt of the global HIV/AIDS epidemic, with 23.5 million people living with HIV and 1.2 million deaths in 2012. Tuberculosis (TB) is the leading cause of AIDS-related illness and deaths worldwide and 75% of this disease burden is in sub-Saharan Africa. Studies from across the continent have shown that 30%-67% of HIV-infected adult hospital in-patients who die have evidence of TB at post-mortem.

Much of this disease is neither clinically suspected nor diagnosed before death. This indicates abject failure of current approaches to diagnosis, which is the key problem addressed by this trial. The very large number of HIV-TB deaths means that Africa is not on track to meet the WHO TB control targets linked to the 2015 MDGs. This has therefore become a high-level strategic priority, with calls for action from WHO, UNAIDS, STOP-TB, PEPFAR and other agencies. We believe that recent advances in TB diagnosis can be harnessed to address this challenge in a fundamentally new way.

Background studies conducted by the PI in South Africa found that the burden of confirmed TB among unselected HIV-infected patients needing hospital admission was extremely high (32.6%). Symptoms were so poorly predictive for screening, however, that in day-to-day clinical practice, much of this disease remains 'under the radar' and undetected. We propose that, regardless of symptoms, all such patients should be investigated for TB on admission. In these studies the diagnostic yield using the traditional approach of sputum-based testing was, however, very limited as fewer than half of the patients could produce sputum samples and much disease involved organs other than the lungs. In contrast, urine samples could be obtained from almost all patients and the yield of diagnoses from testing these with rapid diagnostics was far greater than that obtained from sputum.

Urine was first tested using a simple 30-minute strip-test which is commercially available (Determine TB-LAM). Urine was also concentrated by simple centrifugation and tested using the new WHO-approved rapid Xpert MTB/RIF assay (Xpert). Compared to Xpert testing of sputum alone, addition of this urine-based testing strategy to the initial screen increased the early diagnostic yield of TB 3.0-fold - an extraordinary improvement. Some recent studies have reported that implementation of new
TB diagnostics with superior sensitivity did not improve patient outcomes. Thus, since use of new, costly tests might divert limited resources from other important healthcare needs, it is imperative that the impact, cost and cost-effectiveness of new diagnostic strategies such as this one are assessed in trials.

This randomised controlled trial will enrol adult HIV-infected medical inpatients admitted to two regional referral hospitals in South Africa and Malawi. On admission, patients will be randomised to one of two TB screening strategies (1,300 patients in each arm), comparing TB diagnosis by Xpert testing of sputum (standard arm) with an intervention arm in which urine will in addition be screened with a combination of the two urine-based diagnostic tests. The care of patients provided by the routine medical team will not be otherwise altered. The main study outcome will show whether additional urine-based screening results in greater survival due to improved yield and speed of TB diagnosis.

To more fully assess the overall impact on patients and the efficiency of the healthcare received, a range of additional outcomes will be assessed. These include the total yield of TB diagnoses; times to diagnosis; the proportions starting TB treatment, other antibiotics and antiretrovirals; the length of hospital stay and the need for readmission. Implementation of this intervention will be further justified by comprehensive cost-effectiveness and budgetary impact analyses. If impact is demons
**Joint Global Health Trials - Call 4 Full Grant**

**Project title**
Can improved housing provide additional protection against clinical malaria over current best practice?
A household-randomised controlled trial

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Steven Lindsay</td>
<td>Durham University</td>
<td>MR/M007383/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

- Dr Margaret Pinder
  Durham University

- Professor Umberto D’Alessandro
  London Sch of Hygiene and Trop Medicine

- Dr Lesong Conteh
  London School of Economics & Pol Sci

- Mr Balla Kandeh
  National Malaria Control Programme

- Mr Jakob Knudsen
  University of Copenhagen

- Dr Caroline Jones
  University of Oxford

**Summary**

Malaria remains one of the greatest threats to global public health, with 207 million cases of falciparum malaria and 627,000 deaths occurring in 2012, with over 80% of deaths occurring in Africa. More than 80% of malaria is transmitted indoors at night, so the number of malaria mosquitoes which enter a house is critical for getting the disease - with people living in 'leaky' houses being at most risk.

We have shown that closing the eaves (the gap between the top of the wall and the roof) and screening a house can reduce dramatically the number of malaria vectors entering a house. Here we propose to find out whether we can protect children against malaria by modifying half the study houses so that they (1) have a metal roof, (2) closed eaves, (3) screened doors and windows and (4) screened-air bricks which allow the warm air to rise out of the house, but not let any mosquitoes indoors.

The other study houses will be left with thatched roofs and open eaves and the children in these houses will serve as a comparison group. Over the past thirty years a silent revolution in house design has been happening across Africa.

The traditional thatched-roofed houses are being replaced steadily by metal-roofed houses as the continent develops. We hope to ride this wave of cultural change and further improve the design of houses to make them healthier to live in. Improved housing has the potential to improve the lives of millions of people across sub-Saharan Africa.
**Project title**  
REDEEM trial: The effect of individual and mixed REwards in DiabEtEs Management, a randomised controlled trial

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Jaime Miranda</td>
<td>Peruvian University Cayetano</td>
<td>MR/M007405/1</td>
</tr>
<tr>
<td></td>
<td>Heredia</td>
<td></td>
</tr>
</tbody>
</table>

**Co-Investigators**

Dr Katherine Sacksteder  
Johns Hopkins Bloomberg School of PH

Professor Antonio Trujillo  
Johns Hopkins University

Dr Antonio Bernabe-Ortiz  
Peruvian University Cayetano Heredia

Mr Francisco Diez Canseco  
Peruvian University Cayetano Heredia

**Summary**

Studies in developed countries have demonstrated benefits to preventive care (diet modifications, exercise) among patients with diabetes. Despite this knowledge, patients often don't manage their diabetes properly. In a study that we conducted in Lima, 71% of subjects with diabetes were aware of their disease, 40% were receiving treatment, and only 7% had achieved therapeutic goals. In Latin America, diabetes has a great impact on the health system due to high costs of disease control (US$10.7 billion) and indirect costs (US$54.5 billion) related to loss of productivity, disability, and premature death.

Payment for achieving therapeutic goals, or "rewards," have been tested as a way to improve health. Several studies have shown the promise of this approach in encouraging and maintaining weight loss, which is an important way to control diabetes. One study found that paying people to lose weight led to significantly greater weight loss. In another study in which the payments were linked to the success of multiple members of a group achieving their weight loss goals, the participants not only lost more weight, but also maintained the weight loss.

These results are intriguing, and suggest that the study of rewards in self-management of diabetes requires further research. The approach of paying people to achieve health-related goals has also worked in developing countries. For example, Juntos is a program in Peru that pays pregnant women and mothers to utilize certain health services. On study found that Juntos increased the probability that children in households met their weight-height goals. In addition, families that were part of Juntos were more likely to seek professional health assistance in case of any disease, and the pregnant women were more likely to have their delivery attended by a skilled professional.

This type of program takes advantage of the strong family structures in Latin America, and brings an element of group responsibility to the improvement of health. The individual responsible for fulfilling the requirements is not only encouraged to be responsible because of an individual reward, but to improve the situation of the family.

This highlights the potential to use responsibility to others to design more effective policies. In this project, our goal is to determine the effectiveness of two different economic reward...
programs in promoting preventive behaviors and improving the health of individuals with Type II diabetes in Peru. In addition to rewarding patients for their improved health outcomes, we will go one step further and evaluate a cash incentive for a family or friend supporter, an approach we believe has great potential and may be more effective. In our study, we will enroll diabetes patients and randomly assign them to one of three groups. In one group, patients will receive cash rewards if they achieve certain goals related to management of their diabetes. In a second group, patients and a family or friend supporter will both receive a cash reward if the patient achieves their diabetes management goals.

This will allow us to test whether or not the element of responsibility to others improves the ability of the patient to achieve their goals. Finally, a third group will not receive any cash reward. This is the "control" group to which the other groups will be compared to measure success of our approaches. We expect that after nine months of rewards, patients will effectively improve the preventive behaviors. Six months later, we will also assess if these improvements have been maintained without the cash reward. If our study is successful, it could be a way to encourage people with diabetes to better manage their disease.

While there are costs associated with this approach, it could save money in the long run by reducing the complications of diabetes that occur when people don't manage their
**Project title**

Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis.

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr David Meya</td>
<td>Makerere University</td>
<td>MR/M007413/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

- Dr Conrad Muzoora
  Mbarara University of Sci and Tech
- Dr Kabanda Taseera
  Mbarara University of Sci and Tech
- Dr Emili Letang
  Swiss Tropical & Public Health Institute
- Dr David Boulware
  University of Minnesota
- Dr Joshua Rhein
  University of Minnesota

**Summary**

Cryptococcal meningitis (CM) is a major causative agent of fungal meningitis worldwide. In sub-Saharan Africa, cryptococcal meningitis is the most common cause of meningitis in adults and causes 20-25% of AIDS-related mortality. The excessive early mortality from cryptococcosis is in large part due to the high cost, toxicity, and relatively limited repertoire of available anti-fungals, which have changed little in the last 30 years.

For these reasons, the identification of new anti-fungals effective for the treatment of fungal meningitis must be a high priority. One problem with many current anti-fungal drugs is that they penetrate poorly into the brain. This is a particularly difficult problem in treating fungal meningitis, which is an infection around the brain. New research suggests that sertraline, one of the most widely prescribed antidepressants in the world, has anti-fungal activity against Cryptococcus. The findings are the result of investigations testing sertraline against Cryptococcus neoformans in culture, in a mouse model of infection, and in studies of its mechanism of action which appear to be inhibiting protein synthesis in the Cryptococcus yeast.

Sertraline is known to be well-tolerated and is effective as an antidepressant. Preliminary investigations of sertraline in a mouse model of systemic cryptococcal infection revealed that it combats infection with efficacy similar to fluconazole, an oral anti-fungal drug used commonly for fungal disease since 1990.

Most importantly, the combination of sertraline and fluconazole was found to work better than either drug alone. Sertraline is concentrated in the brain (average of 22-fold over blood levels), and thus may be an ideal oral medicine to add to standard therapy for cryptococcal meningitis. Despite these promising initial studies, no studies have been conducted in actual humans. This study seeks to help answer these questions. The research team, based in Uganda, plans to determine whether the addition of sertraline to standard therapy for CM will result in more rapid clearance of the fungal infection. This project will have two phases.

An initial pharmacokinetic dose finding and safety study was conducted Aug 2013-Feb 2014 which has informed the sertraline dosing choices, confirmed the general tolerability, and provided preliminary data that the rate of clearance of yeasts from the cerebrospinal fluid (termed early fungicidal activity) is
approximately 25% faster over the first two weeks than current standard therapy. This proposal is for support of a multisite, Phase III study to determine whether sertraline improves survival in comparison to placebo. All research participants will receive standard anti-fungal therapy of amphotericin + fluconazole as induction therapy.

The implications of this research are clear. Since strong safety data already exists, investigation into the use of sertraline as anti-fungal is greatly accelerated. If sertraline proves to be effective in treatment of Cryptococcus in humans, it would be immediately available for use, essentially creating a shortcut from bench to bedside.

This would result in huge cost savings compared to bringing an entirely new drug to the market. Sertraline could have the potential to revolutionize cryptococcal care in Sub-Saharan Africa as it is an existing low cost, generic medicine made by >=25 manufacturers worldwide.
## Joint Global Health Trials - Call 4 Full Grant

### Project title

**Postpartum Adherence Clubs for Antiretroviral Therapy: a randomised controlled trial**

### Grant holder | Institute | Grant reference
---|---|---
Professor Landon Myer | University of Cape Town | MR/M007464/1

### Co-Investigators

<table>
<thead>
<tr>
<th>Name</th>
<th>Institute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Linda-Gail Bekker</td>
<td>Desmond Tutu HIV Foundation</td>
</tr>
<tr>
<td>Ms Anna Grimsrud</td>
<td>University of Cape Town</td>
</tr>
<tr>
<td>Dr Christopher Colvin</td>
<td>University of Cape Town</td>
</tr>
<tr>
<td>Dr Edina Sinanovic</td>
<td>University of Cape Town</td>
</tr>
<tr>
<td>Dr Francesca Little</td>
<td>University of Cape Town</td>
</tr>
</tbody>
</table>

### Summary

Over the past 20 years there have been major advances in preventing the mother-to-child-transmission (PMTCT) of HIV, and interventions based on this knowledge have resulted in transmission rates <1% in the United Kingdom and Europe, attributable largely to widespread use of combination antiretroviral therapy (ART) in pregnancy.

The remarkable effectiveness of these interventions has led many to suggest that the global elimination of paediatric HIV infection may be possible. Towards this, there is particular excitement regarding universal initiation of lifelong ART for all HIV-infected pregnant women following the World Health Organisation’s "Option B+" approach, and this strategy has been implemented in many parts of Africa, including the Western Cape Province of South Africa (SA) from July 2013.

But despite considerable optimism, more than 300 000 new paediatric HIV infections occur each year around the globe; almost 10% of these are in SA alone. In turn there is growing recognition that the "Option B+" approach must be accompanied by effective and efficient models of care for delivering ART to unprecedented numbers of HIV-infected pregnant women. For women starting lifelong ART in pregnancy, there is particular concern about the postpartum period (for the purposes of this proposal, this is from delivery until 24 months postpartum) as a time when HIV-infected women are at a very high risk of not taking their medications (non-adherence) and/or dropping out of care altogether (non-retention).

Over the last few years there has been growing evidence that the postpartum period is a difficult time for women on ART, but there are few interventions that aim to support HIV-infected women during this time. One of the few interventions for this purpose is the ‘Adherence Club’ model. In South Africa and most parts of Africa, HIV-infected patients (including pregnant and postpartum women) attend primary care clinics where doctors and nurses focus on the clinical care of individual patients. In contrast to this, the Adherence Club model is operated by community health workers (lay people without clinical training) working from community venues that are located closer to peoples’ homes.

There is preliminary evidence that the Adherence Club model could lead to better clinical outcomes than standard clinical services, but the observational studies used to generate this
evidence have significant methodological flaws. To help generate robust evidence about the Adherence Club model for managing HIV-infected women on ART during the postpartum period, we plan to enroll 388 HIV-infected pregnant women on ART immediately after delivery.

These women will be allocated at random to either attend routine primary health care clinics for their ART during the postpartum period, or to attend an Adherence Club. Women will be followed up by a study measurement team (that operates separately from either of the clinical services) at regular intervals through 24 months postpartum. This measurement team will check the HIV viral loads and administer questionnaires to women who are participating. The primary focus of the study is the retention of women in care, and their adherence to ART, during the 24-month period.

There are secondary outcomes related to the acceptability of the Adherence Club model, and also the cost-effectiveness of the model, compared to standard primary care services as the control condition.
Joint Global Health Trials - Call 4 Full Grant

Project title
A trial of low-cost, technology-assisted, integrated care delivery programme to prevent serious cardiovascular events in disadvantaged populations.

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Kazem Rahimi</td>
<td>University of Oxford</td>
<td>MR/M007510/1</td>
</tr>
</tbody>
</table>

Co-Investigators

Professor Anushka Patel
The George Institute for Global Health

Dr Praveen Devarsetty
The George Institute for Global Health

Professor Stephen Jan
The George Institute for Global Health

Dr Gholamreza Salimi-khorshidi
University of Oxford

Professor Mark Woodward
University of Oxford

Professor Stephen MacMahon
University of Oxford

Dr Farshad Farzadfar
University of Tehran

Miss Mahboubeh Parsaeian
University of Tehran

Professor Reza Malekzadeh
University of Tehran

Summary
Cardiovascular diseases (CVD) have become a major cause of disease burden in low- and middle-income countries (LMIC). More worryingly, within these countries, those in the lower socioeconomic classes are less likely to be utilising evidence-based therapies and they tend to be disproportionately affected by CVD. There are several barriers to more widespread and equitable implementation of evidence-based care and these barriers can be found at different levels of the healthcare systems.

It has been suggested that innovative solutions that incorporate the whole care delivery system and use new digital technologies that assist with high-quality delivery of recurrent tasks may be more successful in increasing the capacity of rural healthcare systems in the delivery of effective and affordable medical care for disadvantaged populations than the prevailing doctor and hospital-centred models of care.

In this large-scale collaborative project between the George Institute for Global Health, the Non-Communicable Disease Research Center at the University of Tehran and several other partners, we will implement and evaluate the effectiveness and cost-effectiveness of a multifaceted intervention that targets at least three components of the health system (health workforce, health information and communication, medical technologies). After adaptation of this previously tested intervention into the existing rural healthcare system in Iran, we will conduct a large-scale cluster randomised study of 306 rural communities to rigorously measure the effect of the intervention on clinically important cardiovascular outcomes.

number of enabling features of the Iranian healthcare system allow implementation and reliable evaluation of such disruptive solutions today at lower trial costs but with the potential of transforming CVD management worldwide. These include: a well-functioning and large network of community health workers in Iran who have prescribing authority for essential drugs and who have sufficient time to help with rapid screening and recruitment of patients into the trial; reliable access to affordable drugs at the intervention sites only with only a low risk of treatment contamination; a validated cause-specific national death register, well-established hospitalisations records, and free village landline telephones for efficient patient follow-up with almost no attrition; reliable communication infrastructure such as mobile networks for remote and near real-time study site monitoring; and government policies which
stress the need for extending the role of community health workers in better and affordable management of non-communicable diseases for disadvantaged populations.

After about 5 years, we expect the outcome of the study, which includes process and economic evaluation, to lead to the formulation of locally relevant policy recommendations with the potential to positively impact on the healthcare of millions in Iran on a daily basis, with wider applicability for other LMICs.

The research team in this collaboration provides broad skills and a unique and substantial track record in rigorous large-scale clinical trials, statistics, engineering and computer programming, qualitative methods and health economics that are required for effective and efficient implementation of the research programme.
**Joint Global Health Trials - Call 4 Full Grant**

**Project title**
A randomised controlled trial to evaluate the effect of maternal or neonatal pneumococcal conjugate vaccination on pneumococcal carriage in early life

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Ed Clarke</td>
<td>MRC Unit, The Gambia</td>
<td>MR/M007529/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**
- Professor Koen Peeters  
  Institute of Tropical Medicine
- Professor Beate Kampmann  
  London Sch of Hygiene and Trop Medicine
- Dr David Jeffries  
  London Sch of Hygiene and Trop Medicine
- Professor Martin Antonio  
  London Sch of Hygiene and Trop Medicine
- Professor David Goldblatt  
  University College London

**Summary**
The last decade has witnessed significant reductions in the number of children dying before they reach their fifth birthday (under-five mortality) across the world. Despite this, we fall far short of Millennium Development Goal 4 which called for a two-third reduction in under-five mortality between 1990 and 2015. Overall, 70 percent of under-five mortality (5.4 million deaths, 2010) occurs in those under the age of one and forty percent occurs in the first month of life.

Nearly half of all deaths occur in sub-Saharan Africa, with countries in West Africa, including The Gambia, having the highest mortality rates anywhere in the world. Consequently, new interventions to reduce mortality in early infancy in this setting have tremendous potential for life-saving impact.

Streptococcus pneumoniae (or pneumococcus) is a leading cause of childhood mortality worldwide. Recent estimates suggest the bacteria are responsible for around 11 percent of deaths in children under five, with over half of these deaths occurring in Africa. Infants in this setting become rapidly 'colonised' with bacteria in the back of the nose.

For example, in The Gambia, over 80 percent of infants will be carrying the bacteria by two months of age. Carriage is an immediate and necessary precursor to disease. Reflecting these high carriage rates, a recent systematic review confirmed that pneumococcus is the leading cause of life-threatening infections, both sepsis and meningitis, in infants up to three months of age in sub-Saharan Africa.

The burden of pneumonia related mortality is similarly extremely high in the same group. The currently available pneumococcal-conjugate vaccines (PCV) are recommended by the WHO according to a three dose six, 10 and 14 week schedule. As a result, infants are not protected against pneumococcus until 16 to 18 weeks of age, or later if the vaccines are delayed, by which point a significant burden of pneumococcal related mortality has already occurred.

Therefore, the objective of this trial is to explore alternative schedules for PCV administration to prevent pneumococcal disease in this critical window of susceptibility. Two intervention arms will be compared to a control arm in which infants will receive PCV according to a standard three dose schedule. In the maternal intervention arm, expectant mothers...
will be given a dose of PCV in the third trimester of pregnancy. This aims to boost the mother’s pneumococcal antibody levels with the expectation that these will be transferred to the infant across the placenta and in breast milk, thus protecting the infant from birth.

In the neonatal intervention arm, a dose of the vaccine will be administered to newborns on the first day of life with the aim of generating a protective immune response in the newborn as early as possible. The rate at which the infants acquire pneumococcal carriage in the back of the nose will be compared between the two intervention arms and the control arm. Given the link between carriage and disease, the rate of carriage acquisition is becoming an established ‘surrogate’ for disease in pneumococcal vaccine trials, substantially reducing the size and complexity of the trials required. Antibody levels and other measures of pneumococcal immunity will also be measured and important safety data will be collected throughout.

Given the sensitivity of vaccination in both expectant mothers and newborns the trial will also examine the acceptability of these interventions with the aim of identifying any barriers to implementation.

The WHO already recommends PCV vaccination and the vaccines are provided to eligible countries through funding provided by the GAVI Alliance. Consequently, a policy change influenced by the results of this trial could be rapidly implemented without major barriers. Given the burden of disease in infancy, if proven, the impa
## Joint Global Health Trials - Call 4 Full Grant

### Project title

The "Irie Classrooms Toolbox": a cluster randomised trial of a universal violence prevention programme in Jamaican preschools.

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Helen Baker-Henningham</td>
<td>Bangor University</td>
<td>MR/M007553/1</td>
</tr>
</tbody>
</table>

### Co-Investigators

- Dr Harold Alderman
  CGIAR Consult Group Int Agricultural Res
- Dr Marcos Vera-Hernández
  University College London
- Professor Susan Walker
  University of the West Indies

### Summary

Violence is a leading worldwide public health problem with a very high prevalence in Jamaica. Interventions in early childhood are an important component in the primary prevention of violence.

Training young children's caregivers in behavioural strategies to reduce child aggression and promote child social skills can 1) prevent the early development of antisocial behaviour in children and 2) reduce violence against children by caregivers. Corporal punishment is widely used in schools across Jamaica despite efforts by the Ministry of Education to eliminate it. Although banned by law in early childhood institutions, corporal punishment is still common in Jamaican preschools.

The prevalence of conduct problems in young Jamaican children has not been accurately determined but estimates suggest it is between 12%-21%. Preschool teachers report child behaviour problems as a major concern and feel ill equipped to deal with them. We have shown that teachers trained to use evidence-based child behaviour management strategies provide a more emotionally supportive classroom environment and use less corporal punishment.

This translates to improvements in class-wide child behaviour; reductions in high-risk children's conduct problems and increases in their social skills at school and at home. Through several years working with preschool teachers in Jamaica, we have developed an intervention that involves guiding teachers in the use of a "toolbox" of key behaviour management strategies that are relevant, easy to use, effective and flexible.

The intervention is delivered through participatory and practical methods and has been specifically designed to be scalable, low cost and suitable for use in low resource settings with teachers with limited formal teacher training. We now plan to evaluate this intervention in 76 preschools (228 classrooms) to determine if benefits are obtained when the training is disseminated on a large scale.

The preschools will be randomly assigned to a group in which all teachers receive the intervention in year 1 (38 preschools, 114 classrooms) and a second group that will receive the intervention a year later (38 preschools, 114 classrooms). The intervention will involve 5 full-day workshops, monthly in-class
support and weekly text messages over the course of a school year. We will evaluate the effect of the intervention on class-wide measures of child aggression and teachers' use of corporal punishment and verbal abuse. We will also evaluate whether the intervention benefits the quality of the classroom environment, class-wide measures of children's prosocial behaviour, teachers' mental health and children's self-regulation, mental health and attendance.

We will examine issues surrounding implementation of the intervention including measuring the degree to which teachers adopt the strategies in the classroom, factors affecting teachers' uptake of the intervention and teachers' views on the components of the toolbox and the training. This will help us to refine the toolbox to ensure its' suitability for implementation at scale. An economic evaluation will be conducted to ascertain the costs associated with delivering the intervention to teachers and the ratio of costs to the benefits obtained.

This study has the potential to make an enormous public health impact in Jamaica with benefits to reduced aggression and improved child mental health at the population level. We have close links with the government agencies and training institutions responsible for early childhood education in Jamaica and are confident that, if this study shows positive results, the intervention will be integrated into on-going teacher training initiatives.

Furthermore, the intervention would be suitable for use at the preschool and early primary school level in other low and middle-income countries with potential to be an important component
Joint Global Health Trials - Call 4 Full Grant

**Project title**
The CRASH-3 Trial: Tranexamic acid for the treatment of significant traumatic brain injury.

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Ian Roberts</td>
<td>London Sch of Hygiene and Trop Medicine</td>
<td>MR/M009211/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**
- Professor Tim Harris
  Barts Health NHS Trust
- Professor Haleema Shakur-Still
  London Sch of Hygiene and Trop Medicine
- Ms Katharine Ker
  London Sch of Hygiene and Trop Medicine
- Professor RIZWANA CHAUDHRI
  Rawalpindi Medical College
  Pakistan
- Professor Rashid Jooma
  The Aga Khan University, Pakistan
- Professor Antonio Belli
  University Hospitals Birmingham
- Dr Adeniran Olubukola Fawole
  University of Ibadan
- Professor Matthew Shokunbi
  University of Ibadan

**Summary**
There are more deaths each year from injuries than from HIV, TB and malaria combined. Worldwide, about ten million people are killed or hospitalised because of a head injury every year. Most head injuries are caused by road traffic crashes, and because car use is increasing, the number of people suffering a head injury is increasing. Amongst those who survive a head injury, many are left severely disabled for the rest of their lives. For example, there is a high likelihood that Michael Schumacher will be permanently disabled as a result of his recent head injury. Most victims of head injury are young adults living in low and middle income countries.

Because many of the victims are also breadwinners for their families, head injuries can also result in loss of income which, along with medical costs, can increase household debt and lead to a fall in living standards for the whole family. When the head is injured there is often bleeding inside the brain, which can continue for some time and worsen after hospital admission. This bleeding increases pressure inside the skull causing further damage to the brain, which can be fatal or result in serious disability for the patient.

We think that we can prevent some of these deaths and disability by reducing the amount of bleeding in the brain after head injury. Tranexamic acid is a cheap drug that reduces bleeding in other conditions. A large trial in accident victims (other than those with head injury) found that it reduces the chances of bleeding to death.

If this drug also works in patients with head injury and bleeding into the brain, this would be important to know because it could save lives at a very low cost. We have already done two preparatory studies to see if tranexamic acid can help people who have bleeding inside the brain because of a head injury. Together, the results of the studies suggest that tranexamic acid should reduce the amount of bleeding inside the brain and could reduce their chances of dying or being disabled. However, because these studies were small, we are not very certain about the accuracy of their results.

Also, they were not designed to find out whether tranexamic acid reduces disability. Because doctors are still unsure about whether tranexamic acid works, it is not given to patients with traumatic brain injury. But if a new clinical trial showed that it worked, this would change very quickly. We want to find out if
tranexamic acid saves lives and reduces disability in people with traumatic brain injury. We plan to study 10,000 patients with traumatic brain injury in countries throughout the world. We will give half of them tranexamic acid and the other half a dummy medicine called a placebo. To make sure that the two groups are the same apart from tranexamic acid, we will decide who gets tranexamic acid and who gets placebo using the modern equivalent of the toss of a coin (this is called randomisation).

Everyone will of course get all the treatments that doctors usually give to traumatically brain injured patients. At the end of the trial we will see if giving tranexamic acid on top of all the usual treatments improves survival and other patient outcomes. The study will be carried out by a team of researchers with lots of experience in doing clinical trials. In fact, it will be the same team that did the successful study of tranexamic acid in accident victims.

The trial will cost several million pounds but if it shows (as we hope it will) that tranexamic acid works, we will have a very cheap way of reducing the number of people who die and are disabled after a head injury. The start up phase of trial is underway and over a thousand patients have been recruited. The trial procedures work well. This application is for funds to continue recruitment to 10,000 patients.
Joint Global Health Trials - Call 5 Development Grant

**Project title**
Pilot study: a cluster randomised trial of the provision of alcohol handgel to postpartum mothers to prevent neonatal infective morbidity in the home

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Andrew Weeks</td>
<td>University of Liverpool</td>
<td>MR/M017990/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

- Professor Brian Faragher
  - Liverpool School of Tropical Medicine
- Dr Antioneta Medina-Lara
  - University of Exeter
- Professor Enitan Carroll
  - University of Liverpool
- Dr Melissa Gladstone
  - University of Liverpool

**Summary**

The research question is "Is the provision of alcohol hand gel to pregnant women in rural Uganda a clinically and cost-effective way of preventing early infant infections?". To provide context to this question across the globe, there are an estimated 3 million neonatal deaths annually.

In Uganda, with over 1.5 million live births annually, 142,000 newborn infants die every year before reaching their fifth year with 33% of these in the neonatal period. This places Uganda 153rd out of 163 countries in the global rank for frequency of neonatal deaths. Most newborn infections and deaths occur in the community, and are frequently unreported to the health sector. For example, preliminary findings from the Iganga/Mayuge Demographic Surveillance Site showed that 60% of all deaths occur outside a health facility setting and go unreported.

African community studies suggest an infection rate of around 30%. In terms of infection prevention hand washing with soap even when washed with unclean water results in a large reduction in hand contamination. A recent systematic review concluded that there was a lack quality evidence for the effect of clean birth and postnatal newborn care practices on neonatal mortality.

However, the need for clean birth and postnatal care is widely accepted. A Delphi expert consensus process judged that clean birth practices at home with no skilled attendant could reduce neonatal sepsis deaths by 15% and tetanus deaths by 30%. The panel judged that postnatal newborn care practices could prevent 40% of neonatal sepsis deaths, but that more research is needed particularly on the content and quality of care during the early postnatal period. A research priority-setting exercise by World Health Organisation (WHO) on the reduction of newborn infection deaths found that the top ranked question was 'what is the feasibility, effectiveness, and cost of different approaches to promote the home care practices especially hand washing of caregivers?'

Despite this being 4 years ago, there are no registered studies addressing the use of alcohol hand gels for mothers in the neonatal period, and local experts know of no similar study. The importance of hand-washing in preventing infective deaths has led WHO to develop guidelines for hand hygiene both within health care settings and in the community and integrate hand
hygiene into neonatal community care programmes. For hand hygiene, the current recommended practice at the household level is handwashing with soap. However, studies show widespread non-adherence to the household guidelines, often due to a lack of water.

An alternative option could therefore be alcohol based hand gel. This is cheap ($0.6 for 60mls) and active against a broad range of Gram-positive and Gram-negative aerobic bacteria, including staphylococci, streptococci, and enteric Gram-negative bacteria. Although alcohol-based hand rubs effectively prevent acute diarrhoeal diseases.
Children Learning About Second-hand Smoke (CLASS II): A pilot cluster randomised controlled trial

**Grant holder**: Professor Kamran Siddiqi

**Institute**: University of York

**Grant reference**: MR/M020533/1

---

**Co-Investigators**

Dr Rumana Huque
ARK Foundation

Professor SHAH MONIR HOSSAIN
ARK Foundation

Professor Aziz Sheikh
University of Edinburgh

Dr Omara Dogar
University of York

Mr Steve Parrott
University of York

Dr Catherine Jackson
Valid Research Ltd

---

**Summary**

Breathing in other people’s smoke is called passive smoking; also sometimes referred to as involuntary or second-hand smoking (SHS). Second-hand smoke contains 4000 chemicals, 70 of which can cause cancer. SHS is particularly harmful to children’s health and can lead to chest and ear infections, tuberculosis, meningitis and asthma. It is also associated with lung cancer and heart disease.

Globally, 40% of children are exposed to SHS. Many countries have introduced bans on smoking in enclosed public spaces, which has significantly reduced adults’ exposure to SHS. However, for the majority of children, cars and homes remain the most likely places for them to breathe in SHS. The only possible way to protect children from SHS is to make cars and homes completely smoke free. For the last three years, we have been working with teachers, children and their parents in primary schools in Dhaka, Bangladesh to develop and test an intervention called, ‘Smoke Free Homes’. It consists of six teaching lessons delivered by schoolteachers, four fun activities and one educational take home resource. Teaching lessons help to increase pupils’ knowledge about the harms caused by breathing in other people’s smoke.

Fun activities include storytelling, role-playing, quizzes and games. These activities help to motivate children to act and feel confident in talking to adults to persuade them not to smoke inside homes. The take-home resource helps children to show what they have learned in school and to negotiate with their families to "sign-up" to a voluntary contract to make their homes smoke-free. The results of this work show that it is possible to encourage children to discuss with their families ways of restricting smoking inside their homes.

Inspired by what we found, we now wish to plan for a large study where we randomly select half of the schools to either have ‘Smoke Free Homes’ and half not to have it (but to receive it at the end of the study). We wish to examine how effective ‘Smoke Free Homes’ is in reducing children’s exposure to SHS. We are also interested to see if the intervention improves their lung health, general quality of life, school attendance and school performance.

We would also like to examine if it helps in changing their attitude towards smoking and makes it less likely for them to take up smoking in future. To provide accurate answers to these important questions, we will need to recruit many schools and
possibly thousands of children. We will also need to use objective measurements including testing children’s saliva for cotinine - a chemical derivative of nicotine found in those who are exposed to SHS. Other measures will include breathing tests to assess children’s lung capacities and volumes, questionnaires and diaries to be kept by children to record their symptoms such as cough, wheeze and scales to measure school performance and attitudes to smoking.

Before carrying out this large study, we plan to conduct a pilot study. This pilot study will simulate the large study but will be conducted on a smaller scale. The information obtained from the pilot study will help us to carefully plan for the large study and help us to test our assumptions. These include the number of schools and children to be recruited, feasibility and acceptability of the specified measurements and resource requirement for scaling up the intervention.

We are proposing to conduct this pilot study in Dhaka Division, Bangladesh. We will recruit a total of 12 primary schools and 360, year 5 (10-12 years old) children. We will undertake all the measurements as described above using internationally agreed standards and measures. Once measurements have been taken, half of the schools will be randomly chosen to receive 'Smoke Free Homes' while the other half will not receive the intervention until the end. We will repeat the assessments at two, six and twelve months after the intervention. Findings will help us to plan for the large study.
Joint Global Health Trials - Call 5 Development Grant

**Project title**
Exploring the feasibility of school based interventions to reduce sugar sweetened beverage consumption in India

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Manu Mathur</td>
<td>Public Health Foundation of India (PHFI)</td>
<td>MR/M021467/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

Mr Mathew Sunil George  
Public Health Foundation of India (PHFI)

Dr Monika Arora  
Public Health Foundation of India (PHFI)

Professor Nora Groce  
University College London

Professor Richard Watt  
University College London

**Summary**

The increased consumption of Sugar and Sweetened Beverages (SSBs) is one of the most important reasons for obesity and overweight, dental caries and Type II diabetes. The consumption of SSBs is rapidly increasing among children and adolescents especially in developing countries.

This is an important public health issue as majority of the population in developing countries is very young. Governmental bodies around the world are taking increasing action to address the availability of soft drinks in schools through increased taxation on soft drinks or banning their sale in schools.

However, the evidence around effects of restricting availability or increasing taxes on SSBs on their consumption and health is still unclear and emerging, it is likely that these actions are being driven by the belief that high-calorie, nutrient-poor drinks no longer have a place in schools, and, moreover, that schools are an appropriate starting point to reduce total consumption of SSBs among youth.

In the absence of robust evidence, an intervention cannot be delivered to test the effectiveness of various fiscal policies in reducing SSB consumption among youth. This study will test the acceptability and feasibility of a fiscal intervention delivered through schools to reduce SSB consumption among children and adolescents.
## Joint Global Health Trials - Call 5 Development Grant

### Project title
Development of Tobacco Control Trial among Migrant Workers in Guangzhou, China

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Li Ling</td>
<td>Sun Yat-Sen University</td>
<td>MR/M021513/1</td>
</tr>
</tbody>
</table>

### Co-Investigators
- Professor Xiaolin Wei
  China Global Health Research & Dev
- Dr Guanyang Zou
  Guangzhou University of Chinese Medicine
- Dr QUAN GAN
  International Union Against Tuberculosis
- Dr Wen Chen
  Sun Yat-Sen University

### Summary
It has been widely accepted that cigarette has tremendous impact on human health. Effective tobacco control effects can help prevent kinds of diseases and social-economic disasters which may happen on smokers of non-smokers exposed to secondhand smoke.

In China, internal rural-to-urban migrant (mostly migrant workers) makes a large proportion of the whole population, accounting for about 0.24 billion in 2012. This migrant workers population has a serious situation of tobacco exposure. We first propose to design a package tailoring the WHO 5A’s model into 5A’s group consulting intervention package through literature review, in-depth interview and focus group discussion.

The 5A’s group consulting package intervention would include:
1. Factsheets detailing key information on smoking, SHS.
2. Guidelines for group guiders on how to deliver the 5A’s group consulting (activities for different audiences: smokers, non-smokers exposed to SHS).
3. A leaflet that contains the key facts about smoking and SHS that can be disseminated to migrant workers after consulting. Based on the package design, we aim to recruit 8 factories (clusters) and all the migrant workers working in these factories from industrial zone of Guangzhou, China.

The clusters will be randomized to the intervention and control group in a 1:1 ratio. Clusters allocated to the intervention arm will be offered the 5A’s group consulting package. The clusters in the control arm will not be offered the package until the completion of the study. All the migrant workers who work in each factory and provides informed consent will be recruited. Factories will complete a factory survey of basic factory information, all participants will complete a questionnaire (about the status of tobacco exposure, knowledge and attitude of tobacco, and demographic information), and a non-smoking individual will provide a salvia sample which will be tested for cotinine.

All these participant outcomes (questionnaire and salvia cotinine) will be measured before and after the 3-month intervention in both arms of the trial. In addition, a purposive sample of participants will be invited for interviews to investigate the facilitators and barriers for integrating 5A’s group consulting package into workplace settings and how these can be enhanced or addressed at the end of this trial.
### Project title

A development study to examine feasibility and acceptability of pulmonary rehabilitation in Uganda for adults with chronic respiratory disease

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Rupert Jones</td>
<td>University of Plymouth</td>
<td>MR/M021734/1</td>
</tr>
</tbody>
</table>

### Co-Investigators

- Professor Sally Singh  
  University of Leicester
- Professor Adrian Taylor  
  University of Plymouth
- Mr Andy Barton  
  University of Plymouth
- Ms Jillian Pooler  
  University of Plymouth
- Professor Michael Hyland  
  University of Plymouth

### Summary

Arising from respiratory infections such as TB and HIV, tobacco smoking and nutritional impairment, chronic lung disease (CLD) affects around one in five adults in Africa, and is a major threat to health. Patients with breathlessness related to CLD create large but silent burden of human suffering, damage to the economy through lost productivity and disability, and direct health service costs with frequent and prolonged hospital admissions.

People with CLD are prone to breathlessness, inactivity, de-conditioning, declining health status and prognosis. CLDs are disproportionately prevalent in deprived populations and many sufferers can neither afford the drugs nor transport to medical clinics. While non-communicable diseases are now recognised as a major public health problem in Africa, CLDs are neglected as a health priority.

While medication may improve lung function and symptoms they do not change prognosis or rate of decline in lung function or health status. However these important systemic effects of CLDs are amenable to treatment with pulmonary rehabilitation (PR) which is a programme of exercise, and education and self management. There is strong evidence that PR improves health status, exercise capacity, social functioning and is recommended in international guidelines.

PR involves existing local resources such as nurses, doctors, physiotherapists and clinic staff. PR allows patients to help each other and themselves, without major capital outlay or equipment. PR offers a major and radical new approach to CLDs, an important neglected group for whom no effective therapy is available. A literature review found no evidence of pulmonary rehabilitation being used in Sub Saharan Africa.

In a pilot PR study we set up and ran a programme in Mulago Hospital, Kampala. A multidisciplinary team of doctors, nurses, physiotherapist and others have run 2 groups with 23 patients with chronic lung damage secondary to pulmonary TB. Results confirm that the programme is feasible and acceptable to patients and to the hospital staff at all levels.

Major improvements were seen in exercise capacity and health status. In many patients the experience was life changing, allowing severely incapacitated patients who were entirely dependent on others to now function normally in work and...
social activities. The patients in this pilot so far have been post tuberculosis patients, but we are now able to include patients with other CLDs.

The objective of this application is to develop PR to a point where it may be deployed widely in East Africa and assessed in a large trial. The main research questions are:  - What is the optimal design of the PR programme?  - What are the patient recruitment and retention strategies?  - What are the optimal assessment strategies and outcome measures?  - How can the training and roll-out be best achieved? The study has quantitative and qualitative elements.

We will continue the pilot PR programme at Mulago hospital for 3 more cohorts, totalling 30-40 people. Quantitative data will be recorded on recruitment, uptake and completion of PR. We will assess a range of measures including exercise capacity and quality of life, satisfaction, and evaluation of chest pains. In the qualitative study, detailed interviews will be held with 25 participants who have completed the programme and 5 interviews will be conducted with people who did not take part or complete PR, focusing on barriers to attending or completing PR.

A focus group and up to 5 in depth interviews with stakeholders will explore practical issues of running and extending PR in Africa. Thematic analysis will be performed by Ugandan researchers in local languages initially with further framework analysis in collaboration with the UK team. To inform the development of a full grant application we will host a meeting of all stakeholders to disseminate the findings of this work and develop the strategy for rolling out PR in East Africa.
A feasibility and pilot study of the effects of Rojiroti microfinance on the health and nutrition of children under five in Bihar, northern India

**Grant holder**  
Professor Alan Smyth  
**Institute**  
University of Nottingham  
**Grant reference**  
MR/M021904/1

<table>
<thead>
<tr>
<th>Co-Investigators</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr Sunil Choudhary</td>
<td>Every year, 2.2 million children die of malnutrition. Many more</td>
</tr>
<tr>
<td>Cen for Promoting Sustainable Livelihood</td>
<td>have their life chances restricted because of the effects of</td>
</tr>
<tr>
<td>Dr Gil Yaron</td>
<td>malnutrition on their health and intellect. Different programmes</td>
</tr>
<tr>
<td>GY Associates Ltd</td>
<td>have been tried to combat malnutrition in children. These</td>
</tr>
<tr>
<td>Professor Stephen Allen</td>
<td>include distributing food directly; giving children micronutrients</td>
</tr>
<tr>
<td>Liverpool School of Tropical Medicine</td>
<td>(eg vitamins and zinc); employing community workers to give</td>
</tr>
<tr>
<td>Dr Ranjeet Sinha</td>
<td>nutritional advice; and health interventions which protect</td>
</tr>
<tr>
<td>Patna Medical College</td>
<td>children against the consequences of malnutrition (eg</td>
</tr>
<tr>
<td>Dr Rashmi Singh</td>
<td>immunisation against measles).</td>
</tr>
<tr>
<td>Patna Medical College</td>
<td>Research by bodies such as the World Health Organisation (WHO) has</td>
</tr>
<tr>
<td>Dr Andrew Fogarty</td>
<td>shown that these strategies can lead to better nourished children.</td>
</tr>
<tr>
<td>University of Nottingham</td>
<td>However, when these approaches are used</td>
</tr>
<tr>
<td>Dr Lisa Szatkowski</td>
<td>in a large scale (eg a whole country) they sometimes fail to reach</td>
</tr>
<tr>
<td>University of Nottingham</td>
<td>those most in need (those living in extreme poverty). To help</td>
</tr>
<tr>
<td>Professor Rachel Elliott</td>
<td>the greatest number of children, we must choose approaches</td>
</tr>
<tr>
<td>University of Nottingham</td>
<td>which are cost effective and which can be sustained in the long term.</td>
</tr>
<tr>
<td>Dr Shalini Ojha</td>
<td>We are a group of community workers, scientists, economists and doctors.</td>
</tr>
<tr>
<td>University of Nottingham</td>
<td>Our partners are the Centre for Promoting Sustainable Livelihood (CPSL)</td>
</tr>
<tr>
<td></td>
<td>- which is a non-governmental organisation in India: a UK charity</td>
</tr>
<tr>
<td></td>
<td>(Rojiroti UK); Patna Medical College India; and two UK academic partners</td>
</tr>
<tr>
<td></td>
<td>(the University of Nottingham and the Liverpool School of Tropical</td>
</tr>
<tr>
<td></td>
<td>Medicine).</td>
</tr>
<tr>
<td>Our team have experience of helping very poor people in rural areas of</td>
<td></td>
</tr>
<tr>
<td>Our community workers encourage people in poor hamlets or &quot;tolas&quot; in</td>
<td></td>
</tr>
<tr>
<td>northern India to form self help groups (SHGs). Most SHGs are formed by</td>
<td></td>
</tr>
<tr>
<td>women. They are asked to save a little money regularly, initially Rs2.5 (3</td>
<td></td>
</tr>
<tr>
<td>pence) per week. If they save regularly, their savings entitle</td>
<td></td>
</tr>
<tr>
<td>them to a loan. These loans start small - Rs50 (50 pence). Women in the</td>
<td></td>
</tr>
<tr>
<td>group can receive external loans (from CPSL) of Rs500 (£5) after 3 months</td>
<td></td>
</tr>
<tr>
<td>and Rs3,000 (£30) after 6 months (if credit is good).</td>
<td></td>
</tr>
<tr>
<td>Loans may be used for emergencies (eg medical expenses); to allow women</td>
<td></td>
</tr>
<tr>
<td>access existing government support schemes (eg money to travel to subsidised</td>
<td></td>
</tr>
<tr>
<td>food shops); or to invest in livestock or agricultural equipment. Using</td>
<td></td>
</tr>
<tr>
<td>these loans helps women avoid local money lenders (who charge much higher</td>
<td></td>
</tr>
<tr>
<td>interest) and avoid emergency sales of their property (at knock down prices).</td>
<td></td>
</tr>
<tr>
<td>We call this programme Rojiroti (which translates as &quot;Livelihood&quot;). We</td>
<td></td>
</tr>
<tr>
<td>want to see if we can test whether Rojiroti improves children's health,</td>
<td></td>
</tr>
</tbody>
</table>
| using a test called a "cluster
randomised controlled trial’. We don’t yet have all the information we need to design such a trial so we will first do a feasibility and pilot study. We will start by checking the feasibility of things like consent, weighing and measuring children, collecting data accurately and keeping track of participants in the trial. We will run a small version of the trial (called a pilot study) so that we have some preliminary data on children’s nutrition.

We think a key measure of the effectiveness of Rojiroti will be the children’s weight corrected for height. This is called the weight for height Z score (WHZ). However, we will also record other measures of nutrition. We need preliminary data to work out how many tolas we will need for the definitive trial to test the effect (if any) of Rojiroti on children’s nutrition. In our pilot study, half the tolas will get Rojiroti immediately and half will get it after 18 months. Which group gets Rojiroti immediately will be decided at random. We will weigh and measure children at the beginning and again after 18 months. We will compare the two groups to see if Rojiroti makes a difference to children’s nutrition.

We do not expect to be able to show a difference in our pilot study. However, once we have done the pilot study, we will know how many tolas we would need for a full trial which would answer the question. This means we can work out how many staff we will need and what the trial will cost. We can then make a funding application which will have all the necessary details.
Joint Global Health Trials - Call 5 Development Grant

**Project title**
Pakistan Prevention Programme for Gestational Diabetes Mellitus (PPP-GDM): a feasibility study

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Paramjit Gill</td>
<td>University of Birmingham</td>
<td>MR/M022048/1</td>
</tr>
</tbody>
</table>

Co-Investigators
- Dr Shereen Bhutta
  Jinnah Postgraduate Medical Center
- Dr Asad Khan
  The Aga Khan University, Pakistan
- Dr Haider Naqvi
  The Aga Khan University, Pakistan
- Dr Rahat Qureshi
  The Aga Khan University, Pakistan
- Dr Romaina Iqbal
  The Aga Khan University, Pakistan
- Dr Sana sheikh
  The Aga Khan University, Pakistan
- Ms Shaneela Khowaja
  The Aga Khan University, Pakistan
- Mrs Andrea Roalfe
  University of Birmingham
- Professor Arri Coomarasamy
  University of Birmingham
- Professor G Neil Thomas
  University of Birmingham
- Mrs Maria Penaloza-Ramos
  University of Birmingham
- Professor Sheila
  Margaret Greenfield
  University of Birmingham
- Professor Tracy Roberts
  University of Birmingham

**Summary**

Type 2 diabetes (T2DM) and gestational diabetes mellitus (GDM) are escalating problems worldwide. Depending on the population studied, 1-14% of all pregnancies are complicated by GDM. In Pakistan, we estimate prevalence of GDM is 8% and this has huge financial costs to health care. Further, pregnancies complicated by GDM have increased incidence of fetal, maternal, and childhood long term complications. Therefore, there is an urgent need to implement a coordinated approach to prevent T2DM. It is established that lifestyle modification with weight loss/moderate exercise can reduce T2DM by up to 58% in high risk people. Our research question for the future full randomized trial is 'in women with gestational diabetes mellitus, is a lifestyle intervention programme focusing on physical activity and weight maintenance feasible in a developing country to decrease the risk of diabetes? To inform the design of a larger full trial, we will first undertake a feasibility study to test whether the components of the main study can all work together.

Specifically, it is focused on the processes of the main study to ensure the integrity of the study protocol including: - recruitment to study - willingness of participants to be randomised - randomisation process - consent for blood tests - refinement and delivery of the intervention - acceptability and adherence to the intervention - follow-up assessments. Achievement of these components will be analysed to inform decisions about progression and the experience accumulated will assist in the refinement of the design of the full trial. In addition, we will estimate the mean and standard deviation of the primary outcome to confirm the trial sample size calculations.

Many benefits will arise from this development grant proposal:
1. Academic beneficiaries through publication in peer reviewed journals and presentations at national and international conferences.
2. As there is little research on this topic in low- and middle-income countries (LMICs), we will develop and pilot a novel intervention that will subsequently be tested in a larger trial. This then has potential to be scaled-up in other LMICs.
3. Reducing and/or slowing the rise in diabetes in LMICs is a challenge for all and our developmental proposal will be of interest and use to clinicians and researchers in Pakistan as well.
as globally.

4. The close collaboration between researchers based at the University of Birmingham, UK and Agha Khan University in Pakistan will further enhanced this international collaboration.

5. This will then lead to increasing research capacity both in the UK and Pakistan.

6. We will also generate data in this feasibility and subsequent full trial which will be available for other researchers - though the data collected from the follow-on trial is more likely to be a richer database of qualitative and quantitative material.

7. Prevention of diabetes in women with GDM once the intervention is scale up and fully implemented in Pakistan.

8. Policy makers in Pakistan will have a robust, evidence-based intervention as part of their health plan.
**Joint Global Health Trials - Call 5 Development Grant**

**Project title**
Develop an interventional study on reducing antibiotic over-prescribing among children with URIs in rural Guangxi, China

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Xiaolin Wei</td>
<td>Shandong University</td>
<td>MR/M022161/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**
- Dr Jun Zeng
  Guangxi Zhuang Autonomous Region CDC
- Dr Mei Lin
  Guangxi Zhuang Autonomous Region CDC
- Dr Guanyang Zou
  Guangzhou University of Chinese Medicine
- Dr Jia Yin
  Shandong University
- Professor Qiang Sun
  Shandong University
- Dr Yanhong (Jessika) Hu
  The University of Hong Kong
- Professor John Walley
  University of Leeds

**Summary**
Irrational use of antibiotics is a serious issue globally. It is also very common among children with acute upper respiratory tract infection (URTI). It left many children suffering from the bacterial resistance due to irrational use of antibiotics, especially in less developed rural area. Antibiotic widely abused in China, more severe in rural areas.

However, few studies focused on this area in developing countries including China. We intend to carry out a feasibility study rural Guangxi, China to explore an effective approach of reducing irrational antibiotic prescription for upper respiratory infections (URTs) among children. To define the facilitators and barriers that influence antibiotic prescribing for childhood URIs in rural Guangxi, questionnaire will be used to interview policy makers from provincial, county Bureau of Health and leaders from township hospital.

We will also interview these policy-makers, clinicians and caregivers to obtain their perspective opinions regarding rational antibiotic use. Then the theory based intervention package, which had been developed in Bangladesh and tested in Zhejiang province, will be evaluated in rural Guangxi once adapted further to be sensitive to the local context. Finally the intervention package will then be tested in 6 townships within one county. Six township hospitals will be divided into three groups.

The arm A will be only targeted clinicians, with: operational guidelines and training on rational antibiotic use, mobile message reminder from pharmacist). Group B will be involving both clinicians and caregivers, which will include: the leaflet material and video information on rational antibiotic use, workshops between parents/caregivers and the trained kindergarten volunteers.

The usual-care control group C will manage patients according to the clinicians' normal procedures without any intervention. We will carry out the intervention for 6 months and collect inpatient and outpatient prescriptions for 6 months before and after interventions. A questionnaire survey will be conducted to see the changes among clinicians, caregivers and kindergarten teachers' knowledge, attitude and practice (KAP) before and after intervention at each group.

Interview and group discussion will be used to see if this study is...
feasible and acceptable with the intervention package. Also positive and negative factors for the intervention implementation will be carried out.

We will assess effectiveness though the difference in the antibiotic prescriptions rate among all the prescriptions between before and after intervention and between intervention and control groups. Those preliminary data will help us to aid in planning a larger effectiveness study in whole Guangxi province.
Joint Global Health Trials - Call 5 Development Grant

Project title
Exploratory observational study of therapeutic feeds used to treat intestinal inflammation in Malawian children with severe acute malnutrition (SAM)

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Stephen Allen</td>
<td>Liverpool School of Tropical Medicine</td>
<td>MR/M022390/1</td>
</tr>
</tbody>
</table>

Co-Investigators
Dr Robert Bandsma
Hospital for Sick Children (SickKids)
Professor Duolao Wang
Liverpool School of Tropical Medicine
Dr Wieger Voskuijl
University of Malawi

Summary
Despite interventions to prevent malnutrition, SAM, encompassing both marasmus (severe wasting) and kwashiorkor, occurred in 19m under fives in 2011 and accounted for 7% of all under 5 deaths. Many children with SAM are managed in the community using Ready-to-Use Therapeutic Food (RUTF).

However, about 20% requires in-patient care because of inability to take adequate feeds, complications such as infection or diarrhoea or failure to improve under community management. The in-patient management of children with SAM is extremely challenging. Despite following a well-established WHO protocol, case fatality often exceeds 20% and many of the survivors die following discharge home.

Amongst long-term survivors, stunting, the recurrence of wasting and re-admission to hospital are common. It has long been recognized that children with SAM have intestinal inflammation, termed "environmental" or "tropical" enteropathy. Although of unknown cause, it is thought to result from poor sanitation increasing exposure to microbial pathogens in the gut. Studies of the small intestine have shown that the marked reduction in surface area impairs food digestion and nutrient absorption.

Also, the mucosa is "leaky" which likely allows bacteria to enter the tissues and blood stream causing sepsis and exposes the gut immune cells to microbial and food antigens resulting in persistence of the inflammation and consequent gut damage. Children who also have HIV infection may have even more severe enteropathy because HIV itself damages the intestinal mucosa.

After initial stabilisation of the child’s condition, the current management of SAM focuses on re-feeding and treating infections. The feeds used (RUTF, F100) contain micronutrients such as vitamin A and zinc that are known to be important for mucosal health. However, these feeds would not be expected to improve the intestinal inflammation and this may underlie the poor response to treatment and poor long-term outcomes in many cases.

The inflammation in the intestine in SAM is very similar to that which occurs in food intolerance and Crohn’s disease. In
contrast to SAM, the treatment of these conditions targets the gut inflammation. In children, recommended treatments are with an extensively hydrolysed or elemental formula (food intolerance) or polymeric or elemental formula (Crohn's disease).

These are complete feeds that promote healing of the intestinal mucosa and nutritional recovery and are free of significant adverse effects. In children with active Crohn's disease, about 60% achieve clinical remission and another 30% improve with these feeds. The similarity in the gut inflammation across these conditions raises the possibility that treatments that effectively reduce the gut inflammation in food intolerance and Crohn's disease may also be effective in SAM.

We aim to undertake a pilot study to see if an extensively hydrolysed, elemental and/or polymeric formula are tolerated by children with SAM and to see if they reduce the intestinal inflammation. If we find that one or more of these feeds are likely to be effective, they would need to be evaluated in a larger study. If confirmed in a larger study, our findings would establish the necessity of specifically treating the intestinal inflammation in SAM.

This could then be included in standard clinical management protocols. Researchers would be encouraged to consider how these alternative therapeutic feeds could be adapted to make them practical and cost-effective in low resource settings perhaps by using local ingredients and formulation as a paste for use at home.

Also, it would be important to explore potential alternative approaches to treating the enteropathy - possibly also including children with less severe malnutrition managed in the community.
**Joint Global Health Trials - Call 5 Full Grant**

**Project title**
A randomized controlled trial of influenza vaccine to prevent adverse vascular events.

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Mark Loeb</td>
<td>McMaster University</td>
<td>MR/N005759/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Ahmed ElSayed</td>
<td>Alzaiem Alazhari University</td>
</tr>
<tr>
<td>Professor Albertino Damasceno</td>
<td>Eduardo Mondlane University</td>
</tr>
<tr>
<td>Professor Jun Zhu</td>
<td>Fu Wai Hospital</td>
</tr>
<tr>
<td>Dr Khalid AlHabib</td>
<td>King Saud University</td>
</tr>
<tr>
<td>Dr Hisham Dokainish</td>
<td>McMaster University</td>
</tr>
<tr>
<td>Dr Janice Pogue</td>
<td>McMaster University</td>
</tr>
<tr>
<td>Dr Jean-Eric Tarride</td>
<td>McMaster University</td>
</tr>
<tr>
<td>Professor Koon Teo</td>
<td>McMaster University</td>
</tr>
<tr>
<td>Professor Salim Yusuf</td>
<td>McMaster University</td>
</tr>
<tr>
<td>Dr Mondo Charles Kiiza</td>
<td>Mulago University Teaching Hospital</td>
</tr>
<tr>
<td>Professor Khalid Yusoff</td>
<td>UCSI University</td>
</tr>
<tr>
<td>Dr Lia Palileo-Villanueva</td>
<td>University of the Philippines, Manila</td>
</tr>
</tbody>
</table>

**Summary**
Cardiovascular disease is a leading cause of death globally estimated to be responsible for approximately 17 million deaths annually. Heart disease and stroke account for nearly one third of all deaths and are a major cause of hospitalization. Patients with congestive heart failure (CHF) are at particularly high risk. Clinical trials demonstrate that nearly one third of patients with CHF will experience a myocardial infarction (MI), stroke, or hospitalization for CHF.

Observational studies have established an association between influenza infection and major adverse vascular events. It follows that vaccinating such a high risk group as patients with CHF against influenza may prevent adverse vascular events. However, these studies are subject to bias and a well designed clinical trial is needed to test the effect of influenza vaccination on preventing adverse vascular events.

The goal of this study is to assess whether inactivated influenza vaccine can reduce adverse vascular events in high risk participants. We will address the question by randomizing patients at high risk for adverse vascular events to either annual inactivated influenza vaccine or to placebo over three influenza seasons. The primary outcome is a composite of cardiovascular (CV) death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalization for CHF.

We will enroll 3,500 participants from centres in seven countries: Philippines (the lead centre), Mozambique, Sudan, Uganda, Saudi Arabia, Malaysia, China. This proposed randomized trial has important implications for the management of patients at high risk for major adverse vascular events. Although the influenza vaccine is recommended annually for groups with diabetes and cardiovascular disease in many counties, uptake of these recommendations is relatively low.

Cardiologists in most jurisdictions do not routinely recommend annual influenza vaccine for their patients as a strategy to reduce future adverse vascular events such as acute coronary syndrome or stroke. Uptake of influenza vaccine in patients with heart disease varies by country but in INTER-CHF sites (where the trial will be conducted) is 11% on average.

Rigorous demonstration of influenza vaccine leading to a reduction in major adverse vascular events would represent a landmark study. We anticipate that such a trial would influence
management decisions by physicians for patients at high risk for major vascular events. The effect size we propose testing is comparable to secondary prevention strategies available and given the fact that a vaccine is given once annually it is simple and inexpensive.

Given the large burden of disease, the possibility to reduce cardiovascular and stroke related death is a compelling argument for this trial. If influenza vaccine is shown to reduce adverse vascular events, it will represent an important change in how prevention of adverse vascular events is thought about.

The fact that our primary outcome is a composite, including various forms of vascular disease will increase generalizability. The study would be a milestone in contributing to evidence-based clinical as well public health policy.
Project title
Interrupting transmission of soil-transmitted helminths: cluster randomised trial evaluating alternative treatment strategies in Kenya

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Rachel Pullan</td>
<td>London Sch of Hygiene and Trop Medicine</td>
<td>MR/N00597X/1</td>
</tr>
</tbody>
</table>

Co-Investigators
Dr Beatrice Wasunna
KEMRI (Kenya Medical Research Institute)

Dr Charles Mwandawiro
KEMRI (Kenya Medical Research Institute)

Dr Doris NJOMO
KEMRI (Kenya Medical Research Institute)

Professor Sammy Njenga
KEMRI (Kenya Medical Research Institute)

Dr Dina Balabanova
London Sch of Hygiene and Trop Medicine

Dr Elizabeth Allen
London Sch of Hygiene and Trop Medicine

Dr Katherine Halliday
London Sch of Hygiene and Trop Medicine

Dr Ulla Griffiths
London Sch of Hygiene and Trop Medicine

Summary
Some 1.45 billion people are estimated to be infected worldwide with intestinal worms, also known as soil-transmitted helminths (STH). Chronic and intense STH infections can contribute to malnutrition and iron-deficiency anaemia, and also can adversely affect physical and mental growth in childhood. Globally, STH result in 4.98 million years lived with disability each year.

Fortunately, however, the global community is increasingly committed to tackling these infections, with many countries now successfully implementing geographically-targeted programmes that provide mass treatment to school-aged children delivered through schools. However, whilst school-based deworming has many important benefits for treated children, recent mathematical modelling suggests that treating only school-aged children will rarely stop transmission of these parasites, except in very low transmission settings, and that alternative approaches to treatment, including extending coverage and frequency of treatment, are required. To effectively deliver such expanded treatment, there is an associated need to evaluate the impact and cost-effectiveness of using community health workers to treat adult populations.

We plan to evaluate the impact of school- versus community-based treatment in reducing the transmission of STH species. A range of quantitative and qualitative assessments will evaluate the costs, cost-effectiveness, acceptability and feasibility of the different strategies and delivery systems.

The study will be conducted in two contrasting settings in Kenya - south coastal and western regions - where an estimated 20% of the population are infected with STH. In order to maximize public health relevance, the study will be nested within the ongoing national school-based deworming programme, which is currently treating 4.6 million preschool and school children annually.

The study drugs will be donated by GlaxoSmithKline and the full costs of delivery through schools and communities will be covered by the Children’s Investment Fund Foundation, with additional input from the Government of Kenya. Cofunding for some of the trial activities are already funded by the Bill & Melinda Gates Foundation. There is tremendous interest in conducting this study. The Government of Kenya, other national
governments, funders and international policy makers are seeking clear policy and technical guidance as to the optimal approach to interrupt STH transmission.

At the same time, countries are increasingly using community health workers (CHW; community members who provide basic health and medical care to their community, often on a volunteer basis) to deliver a wide range of health interventions, and there is a need to evaluate the benefits of using CHWs to deliver STH treatment.

The proposed study, the first of its kind in Africa, will address these policy information gaps. Our proposed study is demand-led at the country level, with partners in Kenya supporting delivery and committed to scaling-up the new strategy, once demonstrated to be beneficial.

Not only will the findings inform policy and practice in Kenya and other STH endemic countries, they may also lead to new WHO guidelines on the community control of STH and ultimately have demonstrable benefits for the impoverished communities affected by STH.
## Joint Global Health Trials - Call 5 Full Grant

<table>
<thead>
<tr>
<th>Project title</th>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual cups and unconditional cash transfer to reduce sexual and reproductive harm and school drop-out in adolescent schoolgirls in western Kenya</td>
<td>Dr Penelope Anne Phillips-Howard</td>
<td>Liverpool School of Tropical Medicine</td>
<td>MR/N006046/1</td>
</tr>
</tbody>
</table>

### Co-Investigators

- **Dr Clayton Onyango**  
  Centres for Diseases Control (CDC)  
- **Dr Clement Zeh**  
  Centres for Diseases Control (CDC)  
- **Dr Daniel Kwaro**  
  KEMRI (Kenya Medical Research Institute)  
- **Dr Frank Odhiambo**  
  KEMRI (Kenya Medical Research Institute)  
- **Dr John Vulule**  
  KEMRI (Kenya Medical Research Institute)  
- **Professor Duolao Wang**  
  Liverpool School of Tropical Medicine  
- **Professor Feiko ter Kuile**  
  Liverpool School of Tropical Medicine  
- **Professor Louis Niessen**  
  Liverpool School of Tropical Medicine  
- **Professor Martien Borgdorff**  
  Royal Netherlands Academy Arts Sci KNAW  
- **Ms Alie Eleveld**  
  Safe Water and AIDS Project (SWAP)  
- **Dr Emily Zielinski-Gutierrez**  
  U.S. Dept of Health & Human Services

### Summary

Girls in low-income countries leave school early due to pregnancy, illness, early marriage, and lack of money for schooling and personal needs, including for menstrual hygiene management (MHM). School drop-out places girls at greater risk of sexual and reproductive health harms such as pregnancy, increased fertility, sexually transmitted infections (STIs) including HIV, and higher mortality of their children. School drop-out also reduces economic opportunity, keeping girls’ in poverty and thereby at risk of increased morbidity and reduced quality of life. For economic, health, and social reasons, these are government ministry priorities, and interventions are needed to keep girls in school and improve their sexual and reproductive health.

The Liverpool School of Tropical Medicine, with Kenyan partners including the Ministries of Education and Health (MOE/MOH), have completed a Joint Global Health Trials-funded pilot study, examining girls’ use of menstrual cups and sanitary pads in rural primary schools in western Kenya. Pre-intervention, girls reported using rags, bedding or paper for MHM, causing discomfort, humiliating leaks and odour, reducing ability to concentrate in school, and causing them to skip school.

Girls followed up revealed pads and cups were comfortable, increased their ability to engage in class, prevented leakage, and reduced the need to have sex with boyfriends in return for money to buy pads. No health or safety issues were found. At study completion girls were checked for STIs, and school drop-out (for pregnancy, marriage or other reasons). These negative outcomes combined were halved in girls using pads or cups compared with girls in control schools. Girls using cups preferred these to pads, because pads are ten-fold more costly, cause chafing if not changed frequently, and packs have to be shared with others.

Girls did not share cups for fear of infection. We now propose to conduct a large-scale trial in the same area, in secondary schoolgirls, who are older but have increased drop-out rates (over a third higher), and a higher risk of HIV, STI, and pregnancy.

We will examine if cups enable girls to stay in school and reduce their sexual and reproductive harms; while cups will improve dignity, health and wellbeing, and confidence at school, they...
may not be sufficient to resolve all girls' unmet needs, which cause them to drop-out of school. Cash transfer (CT) is an alternate but more expensive intervention, with studies showing it reduces absenteeism, drop-out, and sexual risks. In Malawi, CT reduced schoolgirls risk of HIV and human simplex virus (HSV-2; an indicator of girls' sexual risk behaviour), and reduced pregnancy.

Cash amounts vary by study but the researchers recommend $5 (£3.5) a month as sufficient. Our 4.5 year trial will examine if cash, cups, or cash and cups both provided, will prevent school drop-out and improve girls' sexual and reproductive health. For statistical rigor we will recruit 4032 secondary schoolgirls in 56 schools, provide interventions and follow-up them for 2 school years (6 terms). We will evaluate the cost per outcome (school drop-out including for pregnancy, HIV and HSV-2) prevented for single and combined interventions.

The study will provide vital information on the comparative value of each intervention, how the interventions are used, any problems encountered, and their effect on girls' sexual behaviour, their wellbeing and school completion. We will seek advice from girls, schools, communities and stakeholders, working with all beneficiaries including MOE/MOH, using workshops to evaluate progress and develop materials for implementation packages.

Girls clubs will be funded to encourage peer-support and advocacy. Packages will support scale-up should the trial demonstrate cost-effective outcomes. Findings will be widely disseminated to strengthen the evidence base supporting advocacy to improve the quality and equity of girls' lives.
Joint Global Health Trials - Call 5 Full Grant

Project title
Multicenter RCT to evaluate the clinical and cost-effectiveness of a culturally adapted therapy (C-MAP) in patients with a history of self-harm

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Nusrat Husain</td>
<td>The University of Manchester</td>
<td>MR/N006062/1</td>
</tr>
</tbody>
</table>

Co-Investigators

- Professor Carolyn Chew-Graham
  Keele University
- Professor Richard Emsley
  King's College London
- Professor Imran Chaudhry
  Pakistan Institute of Living & Learning
- Professor Christopher Roberts
  The University of Manchester
- Professor Linda Davies
  The University of Manchester
- Dr Nasim Chaudhry
  The University of Manchester
- Dr Penny Bee
  The University of Manchester
- Dr Syed Mohiuddin
  University of Bristol
- Dr Khatidja Chantler
  University of Central Lancashire
- Professor Christopher Williams
  University of Glasgow

Summary

Suicide is a serious global public health issue ranked amongst the leading causes of death in many countries. The worldwide rates of suicide have increased by 60% in the last 45 years, and the 1.8% total global burden of disease attributed to suicide in 1998 is expected to increase to 2.4% by 2020.

The WHO Mental Health Action Plan 2013-2020 and all the member states have committed to work towards the global target of a 10% reduction in the suicide rate by 2020. WHO's Mental Health Gap Action Programme includes suicide as one of the priority conditions and the recent WHO report "Preventing suicide: a global imperative" calls for suicide prevention to be a high priority on the global public health agenda.

More than 800,000 people across the world die due to suicide each year and for each suicide there are more than 20 people attempting suicide. Each suicide takes the life of the individual and has a tremendous effect on friends, family and the wider community.

Up to 75% of all suicides occur in low- and middle-income countries where resources and services are limited for treatment and support for people who need. There is a clear gap in the robust evaluation of culturally appropriate suicide prevention strategies in low and middle income countries. Individuals who have a history of self-harm are at much higher risk of dying by suicide than individuals who do not have such a history.

The WHO recommends that offering them appropriate treatment should be a key component of all suicide prevention strategies. There are in excess of 100,000 acts of self-harm carried out in Pakistan annually. The aim of the proposed trial is to evaluate the clinical and cost-effectiveness of a culturally adapted psychological therapy (C-MAP) in patients with a history of self-harm.

We carried out a study in Karachi to determine the effectiveness of a 6-8 session CBT-based intervention (C-MAP) in people who had recently self-harmed. The assessments were carried out at baseline, 3 & 6 months. There was a significant reduction from baseline in suicidal ideation, severity of depression and hopelessness in the intervention group compared to the Treatment as Usual (TAU) group at each follow up assessment. The findings from this work have highlighted the applicability of
such an intervention to health services in Pakistan for patients who present after a self-harm episode.

The proposed research will be conducted in Karachi, Lahore, Rawalpindi, Quetta and Peshawar. Participants will be randomized either to the Intervention (C-MAP) or TAU. The existing culturally adapted intervention (C-MAP) includes an evaluation of the self-harm episode, crisis skills, problem solving and basic cognitive techniques to manage emotions, negative thinking and relapse prevention strategies. The intervention will be delivered in six sessions over 12 weeks.

Assessments will be conducted at baseline and at 3 months (end of intervention) 6 months and 12 months after randomisation. The outcome measures will include questionnaires to measure the repetition of self-harm, severity of suicidal ideation; depression; hopelessness; quality of life and coping resources. In addition, qualitative interviews and focus groups will provide rich information regarding the experiences of participants and therapists, which will inform the development of more effective and sensitive services for self-harm management.

TAU will be standard routine care delivered by local medical, psychiatric and primary care services according to their clinical judgement. A record will be kept of any treatment received by each participant.

This trial will provide detailed clinical and cost-effectiveness analyses for the management of self-harm which will inform future research and national clinical practice guidelines. We have established contacts with the ministry of health and once the trial is completed we will enter discussions to present the results to them and attempt to influence policy change.
Joint Global Health Trials - Call 5 Full Grant

**Project title**
A randomised, observer-blind, non-inferiority trial to evaluate alternative human papillomavirus vaccination schedules in young females in West Africa

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Ed Clarke</td>
<td>MRC Unit, The Gambia</td>
<td>MR/N006070/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

- Professor Beate Kampmann  
  London Sch of Hygiene and Trop Medicine
- Dr David Jeffries  
  London Sch of Hygiene and Trop Medicine
- Professor Heidi Larson  
  London Sch of Hygiene and Trop Medicine
- Professor Mark Jit  
  London Sch of Hygiene and Trop Medicine
- Dr Simon Beddows  
  Public Health England
- Professor Margaret Stanley  
  University of Cambridge

**Summary**

Cervical cancer is consistently associated with infection with the human papilloma virus (HPV). The cancer occurs more frequently in sub-Saharan Africa than anywhere else in the world and is the most common cause of cancer-related death in females in this setting. In addition, the burden of cervical cancer on the continent is expected to double over the next 15 years as the population gets older.

For those diagnosed with cervical cancer, the chances of survival are also much lower in this setting than in many other parts of the world. In the absence of cervical screening programmes, the diagnosis is often made late and the treatment available may also be limited. Two different HPV types, type 16 and type 18, are associated with nearly three quarters of all cervical cancer worldwide, including in sub-Saharan Africa. Vaccines are already available against both HPV types and antibodies, which are thought to be responsible for protection, can be measured with a blood test after vaccination as an indicator of the immunity the vaccine generated.

When given to adult women, 3 doses of an HPV vaccine have been shown to be extremely effective - generating high levels of antibody and providing sustained protection from HPV infection and hence cervical cancer for upwards of 10 years in studies so far. Further research has gone onto show that the level of antibody generated by the HPV vaccines in young adolescents is even higher than in adults. Indeed, in studies conducted in other parts of the world, young adolescents given just 2 doses of the vaccine have been shown to generate higher levels of antibody than those generated in adult women, even following 3 doses.

Early data are now beginning to suggest that even a single dose of an HPV vaccine may provide sufficient levels of antibody to prevent infection, and hence cervical cancer, although this needs to be further studied. Given how effective at preventing HPV infection and cervical cancer the vaccines have been shown to be in other settings, the main hurdle to overcome if much of the burden of cervical cancer across sub-Saharan Africa is to be prevented is one of programme implementation - i.e. the capacity of countries to consistently deliver the required number of vaccine doses to a high proportion of the target female population.
The WHO currently recommends that 2 doses of the vaccines are given to 9 to 13 year old girls and that a gap of at least 6 months is left between doses. However, there is no established system in place across much of sub-Saharan Africa to deliver such a programme and no easy way to reliably access adolescent females.

While school-based programmes have shown some success, many females do not complete primary education or attend school only inconsistently at this age. Consequently ensuring the reliable delivery of 2 vaccine doses is a major challenge. This trial will ask 2 main questions, both of which aim to make it easier for countries across sub-Saharan Africa and elsewhere to reliably deliver HPV vaccine programmes: 1. Are 2 or 3 HPV vaccine doses needed to provide protection or would 1 dose be enough? It would be much easier and cheaper to ensure all females get a single dose of an HPV vaccine than to ensure they all get 2 doses separated by at least 6 months. 2. Could the HPV vaccines be given to girls younger than 9 years of age? School-based programmes could be designed more flexibly to target the age of peak school attendance.

Also, the delivery of HPV vaccines through established child health programmes which continue to monitor growth and to provide vitamin and iron supplements to children until 5 or 6 years becomes possible thus impacting on cost as well as vaccine coverage. The costs of the various schedules and ways to deliver the vaccines will also be examined and vaccine acceptability in rural West Africa will also be explored to ensure the maximum future impact of the trial on public health policy.
Joint Global Health Trials - Call 5 Full Grant

Project title
Reactive household-based self-administered treatment against residual malaria transmission: a cluster randomised trial

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Umberto D’Alessandro</td>
<td>MRC Unit, The Gambia</td>
<td>MR/N006100/1</td>
</tr>
</tbody>
</table>

Co-Investigators

Professor Koen Peeters
Institute of Tropical Medicine

Dr Davis Nwakanma
London Sch of Hygiene and Trop Medicine

Dr Gian Luca Di Tanna
London Sch of Hygiene and Trop Medicine

Dr Jane Achan
London Sch of Hygiene and Trop Medicine

Dr Joseph Okebe
London Sch of Hygiene and Trop Medicine

Dr Shunmay Yeung
London Sch of Hygiene and Trop Medicine

Dr Juan Muela Ribera
Rovira i Virgili University

Dr Julie Balen
University of Sheffield

Summary

Thanks to preventive interventions such as long-lasting insecticidal bed nets and indoor residual spraying, and prompt and efficacious treatments, the malaria burden has decreased substantially over the last decade in several countries, including some in sub-Saharan Africa.

Nevertheless, current interventions are unable to interrupt transmission which is maintained by a (probably) large and hidden human reservoir of infection, meaning a proportion of individuals carrying a malaria infection without any symptom. The latter are not sick but they can still infect mosquito vectors that, once infectious, infect other individuals. Several approaches have been proposed to deal with the human reservoir of infection and include the administration of an efficacious treatment to the whole population (mass drug administration), general or targeted screening and treatment of infected individuals.

They all require major efforts by the health system, exclude the active participation of the local communities, and, for the screening and treatment approaches the field-based diagnostic tests are not sufficiently sensitive to detect all infected individuals. We propose a novel approach in which clinical malaria cases diagnosed in health facilities are considered index cases around which malaria-infected individuals are probably clustered.

Therefore, the intervention will consist in providing to malaria patients (or the parent/guardian in case of children) sufficient doses of dihydroartemisinin-piperaquine, the second line treatment in The Gambia, to systematically treat all members of the household, i.e. reactive household-based self-administered treatment (RHOST). Health staff will follow the treatment by liaising via telephone with the resident village health worker, who will check a few days after completion of the treatment course whether this has been taken at the correct dosage by all household members. The village health worker will also assess for and document any adverse events.

The intervention will be optimized by carrying out, during the first year of its implementation, formative research that will provide sufficient information to adapt RHOST to the local context and, at the same time, actively engage local communities. Formative research will (i) provide baseline data relevant to RHOST; (ii) develop and test health Information,
Education and Communication (IEC) messages and strategies for RHOST through a community-based and participatory approach; (iii) monitor and evaluate IEC messages and strategies for the continuous adaptation of RHOST to the local context. This phase will be followed by the implementation of a locally adapted RHOST and the evaluation of its impact on the human reservoir of malaria infection.

The primary outcome will be the prevalence of malaria infection determined by molecular methods in all age groups at the end of the second transmission season following the intervention. The impact on the local health system, e.g. stock and flow of antimalarial medication, impact on the activities of the health workforce, will be assessed. The economic evaluation will estimate the incremental cost and cost-effectiveness of the intervention using the trial outcome measures.

The trial will be carried out in The Gambia, in the North Bank West Region, stretching from the coast up to the town of Farafenni, as the coverage of preventive intervention is high and malaria prevalence low. In intervention villages, RHOST will be implemented while in the control villages there will be no additional intervention besides the standard control measures implemented by the National Malaria Control Program and routine clinical care provided by health facilities.

The trial will be implemented in 32 moderate sized (400- 800 persons) villages, 16 in the intervention and 16 in the control arm, which will provide sufficient power to detect a significant difference between the 2 study arms.
**Project title**
A randomized trial to evaluate the toxicity and efficacy of 1200mg and 1800mg rifampicin daily for 4 months in the treatment of pulmonary tuberculosis

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Amina Jindani</td>
<td>St George’s University of London</td>
<td>MR/N006127/1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Co-Investigators</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ms Ilona Ida Frieda Westermann de Patiño Bolivian Red Cross</td>
<td>Approximately 20 million people globally are infected with tuberculosis, and about 1.5 million people die of the disease annually, i.e. one death every 20 seconds. Currently, tuberculosis of the lungs is treated with four drugs ethambutol, isoniazid, rifampicin, and pyrazinamide daily for the first two months, followed by the two drugs isoniazid and rifampicin for the next four months. This drug combination is recommended by the World Health Organisation and is used in most countries of the world. The combination is highly effective if taken properly, but despite this about 15% patients worldwide are not cured.</td>
</tr>
<tr>
<td>Dr TEFERA AGIZEW CDC Botswana - BOTUSA</td>
<td>Factors such as patients not completing the course, missing multiple doses, or taking (or being prescribed) the wrong dose contribute to treatment failure. Although the drugs are free to patients, there is a substantial cost, in terms of time and administration, to both the patient and the treatment services. A recent study by Gospodarevskaya et al (Int J Tub Lung Dis. 18: 810-817) has found that patients have to terminate productive/economic activities and are often forced to borrow money and/or sell assets to cover cost of treatment, which can amount to more than three-quarters of patients’ income, in the last 2 months of treatment.</td>
</tr>
<tr>
<td>Professor Eduardo Ticona Dos de Mayo National Hospital</td>
<td>Reducing the duration of treatment should increase the number of people who successfully complete treatment and reduce the cost to them. A reduction could be achieved in one of two ways: using combinations of the new drugs currently under development, or by using the currently available drugs more effectively.</td>
</tr>
<tr>
<td>Dr Maryline Bonnet Epicentre</td>
<td>Given the enormous cost and long time required to develop new drugs the second option is attractive. Increasing the dose of one of the currently available drugs may allow the duration of treatment to be shortened in the very near future.</td>
</tr>
<tr>
<td>Dr Daniel Atwine Epicentre Mbarara Research Base</td>
<td>Three recently published Phase III trials (RIFAQUIN, ReMOX, OFLOTUB) have failed to demonstrate that treatment shortening can be achieved with the quinolones. hus, the rifamycins offer the best hope if higher doses can be shown to be safe. Rifampicin which is responsible for killing most tuberculosis bacteria, appears to be the best choice since increasing doses of rifampicin increases its ability to kill TB bacilli in vitro and animal studies.</td>
</tr>
<tr>
<td>Professor Katherine Fielding London Sch of Hygiene and Trop Medicine</td>
<td></td>
</tr>
<tr>
<td>Dr Adam Witney St George’s University of London</td>
<td></td>
</tr>
<tr>
<td>Professor Denis Mitchison St George’s University of London</td>
<td></td>
</tr>
<tr>
<td>Dr Jasvir Dhillon St George's University of London</td>
<td></td>
</tr>
<tr>
<td>Prof. Philip Butcher St George's University of London</td>
<td></td>
</tr>
<tr>
<td>Professor Thomas Harrison St George's University of London</td>
<td></td>
</tr>
<tr>
<td>Dr Marcos Burgos University of New Mexico</td>
<td></td>
</tr>
</tbody>
</table>
A similar result could be obtained in human tuberculosis. However, one concern would be a possible increase in unwanted serious side effects with increasing doses. Liver damage by rifampicin appears to be rare and not connected to dose size. In the RIFATOX Trial, a dose of 1200mg, in 100 patients did not increase its toxicity.

The central question this trial aims to answer is therefore: does an increase in the dosage of rifampicin allow us to shorten treatment from 6 to 4 months? We are assessing whether giving double or triple the usual dose of rifampicin (1200mg, or 1800mg rather than 600mg daily) is safe and, when given for 4 months only, will result in relapse rates similar to (or better than) those found in the standard 6 month course of treatment. Patients with newly diagnosed tuberculosis of the lung, who agree to participate and have signed a consent form, will receive either the standard 6 month treatment or a 4 month treatment containing the standard drugs but with a double or triple dose of rifampicin.

Treatment allocation will be random. The success of treatment in each method will be closely monitored both clinically and by regular microscopic examination of sputum, and the safety of the increased dose of rifampicin will be monitored clinically and with blood tests. If the trial is successful, it will lead to a shorter treatment course for pulmonary tuberculosis.

The expected consequences would be: more patients completing the course and higher rates of cure, reduction in rates of transmission of tuberculosis with fewer people becoming infected, a reduced cost of treatment for both patients and treatment facilities and, perhaps, a reduction in the emergence of bacterial drug resistance.
Joint Global Health Trials - Call 5 Full Grant

Project title
A Dose Reduction Immunobridging Study of two HPV vaccines in Tanzanian girls

Grant holder | Institute | Grant reference
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Deborah Watson-Jones</td>
<td>London Sch of Hygiene and Trop Medicine</td>
<td>MR/N006135/1</td>
</tr>
</tbody>
</table>

Co-Investigators

Dr Silvia de Sanjose
Catalan Institute of Oncology

Professor Joakim Dillner
Karolinska Institute

Ms Kathy Baisley
London Sch of Hygiene and Trop Medicine

Professor Philipp Mayaud
London Sch of Hygiene and Trop Medicine

Professor Richard John Hayes
London Sch of Hygiene and Trop Medicine

Professor Saidi Kapiga
London Sch of Hygiene and Trop Medicine

Mr John Changalucha
National Institute for Medical Research

Dr Ligia Pinto
National Institutes of Health (NIH)

Dr Wilm Quentin
Technology University of Berlin

Dr Kirstin Mitchell
University of Glasgow

Professor Charles Lacey
University of York

Summary

Cervical cancer is the commonest cancer among women aged between 15 and 44 years in Tanzania. Mortality from the disease is extremely high because screening programmes are frequently absent or limited in scale and women usually present late, leaving palliative care as the only option. HPV vaccines are most effective if provided to girls who have not yet acquired HPV infection. In Tanzania we have shown that HPV vaccine is safe, is very acceptable and can be delivered with high coverage (around 80%) but setting up and sustaining an HPV vaccination programme for young girls requires considerable investment in human and financial resources.

Despite high acceptability of the vaccine in East Africa, a number of studies have estimated that the cost of delivering HPV vaccine is considerably higher than costs for delivering traditional infant/child vaccinations, even if vaccine is subsidized by the GAVI Alliance. This is primarily because of start-up costs to establish outreach programmes and associated personnel costs with involvement of teachers and nurses who must spend significant time away from their health posts to deliver vaccine, especially if multiple doses are needed. There is global interest in simplifying delivery by reducing the number of doses of HPV vaccine.

The cost savings of offering fewer doses of HPV vaccine would be substantial and would also result in less time that health personnel are away from their stations and simplification of vaccine delivery. If a single dose could be given, this could halve the costs of vaccine delivery, making HPV vaccine more accessible to the populations that need it most. Recently, the WHO recommended that 2 doses of HPV vaccine could be given to girls aged less than 15 years, based on studies in high and upper middle income countries.

However in Africa there are high rates of infections like malaria and worms that can affect immune responses to vaccines. We need be sure that a reduction in the number of vaccine doses does not reduce the protective immune response of these vaccines. We are planning a randomised trial in healthy Tanzanian females aged 9-14 years to establish whether a single dose of HPV vaccine produces immune responses that are likely to be effective in preventing cervical cancer in Africa.

We will compare two different HPV vaccines, the bivalent (2-v) vaccine that protects against HPV 16/18 (the cause of 70% of
cancers) and a new 9-valent (9-v) vaccine that protects against 9 HPV types. Our trial will enrol and randomise 900 girls aged 9-14 years into 6 groups.

They will receive either the 2-v or the 9-v HPV vaccine, as 1, 2 or 3 doses. Girls will be followed up for 36 months after the first dose so we can measure the quality and sustainability of immune responses. We will compare the girls receiving 1 or 2 doses with those receiving 3 doses of the same vaccine, to ensure that the reduced dose regimen produces an immune response that is not inferior to the standard 3 doses.

We will also compare the immune responses in our study with results from other countries without a high prevalence of malaria and worm infections, and where the vaccine has been shown to be protective. This will give us information about whether a reduction in the number of doses is likely to be protective in Africa.

This trial will address fundamental questions about HPV vaccine dose reduction in a setting where the potential impact is greatest, and will be extremely important in informing future HPV vaccination policy.
Joint Global Health Trials - Call 5 Full Grant

**Project title**
Primary Care Strategies to Reduce High Blood Pressure: A Cluster Randomized Trial in Rural Bangladesh, Pakistan and Sri Lanka

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Tazeen Jafar</td>
<td>National University of Singapore</td>
<td>MR/N006178/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**
Dr Eric Andrew Finkelstein  
Duke-NUS Medical School  
Dr Pryseley Assam  
Duke-NUS Medical School  
Dr Dewan Alam  
ICDDRB  
Dr John Clemens  
ICDDRB  
Dr Aamir Hameed  
The Aga Khan University, Pakistan  
Dr Imtiaz Jehan  
The Aga Khan University, Pakistan  
Professor Ananda Rajitha  
Wickremasinghe University of Kelaniya  
Professor Asita de Silva  
University of Kelaniya

**Summary**
Cardiovascular diseases (CVD) have become the leading cause of mortality globally. In South Asia, high rates of CVD are observed at a younger age than in other countries causing a reduction in productive life years with severe economic consequences. High blood pressure (BP) confers the greatest attributable risk to death and disability associated with CVD.

Our Wellcome Trust funded Control of Blood Pressure and Risk Attenuation (COBRA) trial (2004 to 2007) in Karachi, Pakistan, suggested the combined strategy of family based home health education (HHE) delivered by trained community health workers (CHW) plus care of individuals by trained private general practitioners (GP) to optimally manage hypertension had the most marked beneficial impact on BP compared to usual care, or single interventions. However, the COBRA intervention was designed for an urban South Asian setting, where private GPs cater to over 75% of the patients seeking care.

Most of South Asia is still rural (73% Bangladesh, 64% Pakistan, 71% India, 85% Sri Lanka) where prevalence of hypertension is high and healthcare infrastructure and provider characteristics are very different compared to the urban setting. The COBRA trial did not evaluate effectiveness of strategies delivered using the public health infrastructure, or generalizability to the rural population in Pakistan.

It is also not clear whether any benefit would extend to rural communities in other South Asian countries. In our ongoing COBRA-BPS feasibility study in Bangladesh, Pakistan, and Sri Lanka, we modified COBRA by developing a comprehensive "multicomponent intervention (MCI)" for effective delivery of hypertension care using the rural predominantly public primary care infrastructure. We also conducted extensive stakeholder consultation and received very favourable response for a full scale trial to evaluate MCI in 3 countries.

We now propose a cluster randomised controlled trial (RCT) on 2550 adults with hypertension in 30 rural communities in Bangladesh, Pakistan and Sri Lanka, to evaluate a comprehensive MCI comprised of specifically comprised 1) home health education (HHE) by government community health workers (CHWs), 2) blood pressure (BP) monitoring and stepped-up referral to a trained general practitioner (GP) using a checklist, 3) trained public and private providers in
management of hypertension and using a checklist, 4) designated hypertension triage counter and hypertension care coordinators in government clinics, 5) a financing model to compensate for additional health services including targeted subsidies.

A total of 15 communities (5 in each country) will be randomised to MCI and 15 (5 in each country) to usual care in 3 countries. Individuals with hypertension will be followed for 2 years to assess whether MCI compared to usual care is more effective at lowering BP, and cost effective in terms of preventing CVD related disability and death. We will also interview stakeholders and conduct serial focus group discussions of patients on their experience with the strategy in relation to various components of MCI. If shown to be successful, our findings will be helpful in securing political commitment from stakeholders for up-scaling MCI strategies at the national level in these South Asian countries.

The South-South collaboration and shared experiences will be very valuable in co-ordinating a regional action plan on NCDs with a focus on hypertension as an entry point. Our trial will provide direct evidence of the value of using comparable models and platforms for non-communicable disease management which would extend to other Asian countries with similar ethnic population and healthcare infrastructure.
Joint Global Health Trials - Call 6 Development Grant

Project title
Performance of EArly Retinal Laser (PEARL)

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Nathan Congdon</td>
<td>Queen's University of Belfast</td>
<td>MR/N021037/1</td>
</tr>
</tbody>
</table>

Co-Investigators

- Professor Michael Clarke
  Queen's University of Belfast
- Professor Noemi Lois
  Queen's University of Belfast
- Professor Chenjin Jin
  Sun Yat-sen University
- Professor Yanbing Li
  Sun Yat-Sen University
- Professor Norman Waugh
  University of Warwick

Summary

Diabetes, an illness in which the body cannot manage blood sugar safely, is often thought of as a disease of wealth. In fact, over 80% of diabetes occurs in poor or middle-income countries, where rates are growing very quickly. In China, there is ten times more diabetes now than there was 30 years ago, and rates (12%) exceed the US.

Over years, diabetes damages blood vessels and vision cells in the eye, and can cause blindness. Most diabetic blindness can be prevented with laser if caught early, but only 10% of rural diabetic persons in China receive care. A major reason is that standard treatment of diabetic eye disease ("DR") calls for patients to return for examinations until their eyes reach a late stage called "PDR", which may take many years, before any treatment is given.

This can be very difficult for rural patients, who are often less educated and poorer, meaning they drop out before receiving care. We have completed a review of papers written about earlier treatment of DR, at a stage called "No PDR" or "NPDR." This review showed studies are needed to prove that this approach is safe and beneficial, but evidence suggests that early treatment could be better to preserve vision, and easier for patients who might otherwise drop out of standard care.

To fill the gap in evidence, we designed a study where patients with disease at an earlier stage ("NPDR," the Early Group) get laser treatment right away in one eye chosen by chance and the other eye only get laser if "PDR" develops later, which is the current standard.

We will compare eyes treated at NPDR and PDR stages for several outcomes important to patients: vision, developing more serious "PDR" disease, and damage to the eye from treatment. An important goal of this study is to find out if patients who get early treatment are less likely to drop out of follow-up. Since one eye of a patient can't "drop out," we will also have a second group of people who will get later treatment in both eyes only if PDR develops ("Standard Group").

We will compare the rate of dropout between the Early and Standard group. The cost of Early versus Standard treatment will also be examined. An equal number of urban and rural patients will be recruited, because our early work shows that rural patient are at special risk for dropping out, because of their lack of understanding of their disease, but we want to understand
patients from both settings.

Our study will have two main aims:

1. This kind of study, a "trial," is expensive and hard. We want to first do a small "Pilot" (100 patients each in Early and Standard groups, versus 300 in each for the main trial) to show that we can find enough patients, convince them to join the study, give them the treatment as selected by chance, follow them for 1 year and collect necessary data.

2. Care of DR in rich settings often depends on expensive tests or advanced training to define the stages ("NPDR," "PDR") and complications of treatment that require further care. Such tests and training may not be practical in poorer settings.

In our study, trained local doctors will define stages and find complications using simple, cheap examinations. We will compare their results against more expensive tests and photo grading by experts to find out how well this simpler and cheaper approach works.

Finding out if these locally appropriate ways work is very important for diabetic eye care in poorer areas, and will be an important part of our Pilot study. Our team includes Chinese and UK experts in diabetic eye care, statistics and trials such as this one.

Patients will be recruited at the First Affiliated Hospital in Guangzhou, which has one of the largest diabetic clinics in China, and treated at Zhongshan Ophthalmic Hospital (ZOC), China's largest eye hospital. The main investigator, Prof Congdon, is an eye doctor based now in the UK, who has worked in China at ZOC for many years, is fluent in Chinese, and will help to link teams.
InterTxt2Heart pilot: A trial to evaluate efficacy of text message to improve adherence to cardiovascular medications in secondary prevention.

Grant holder | Institute | Grant reference
---|---|---
Professor Pablo Perel | London Sch of Hygiene and Trop Medicine | MR/N021304/1

Co-Investigators

Professor Norma Serrano
Cardiovascular Foundation of Colombia

Professor Dorairaj Prabhakaran
Centre for Chronic Disease Control

Dr Vamadevan S Ajay
Centre for Chronic Disease Control

Dr Caroline Free
London Sch of Hygiene and Trop Medicine

Professor Peter Lamptey
London Sch of Hygiene and Trop Medicine

Professor Elizabeth Murray
University College London

Dr Juan P Casas
University College London

Professor Rob Horne
University College London

Dr Amos Laar
University of Ghana

Summary

In less developed countries cardiovascular diseases (heart diseases and stroke) have a vast deleterious impact at individual and society level. Patients with cardiovascular diseases can benefit from affordable and effective medications, but only a minority of patients takes the medications, and strategies tested in the past to improve taking of these medications have failed. Mobile phones are becoming an essential instrument in daily life of people living in less developed countries and therefore have become an ideal "instrument" to deliver interventions to change behaviours, such as taking medications.

Previous successes of studies using mobile text messages to improve adherence to HIV-medications provides a strong precedent that this success could be translated to cardiovascular diseases. However, to achieve this, it requires a carefully work on understanding the reasons why people stop taking medications that also considers the local-context. To date, there are no studies in cardiovascular disease that full fill these criteria. Our long-term aim is to conduct the largest study to evaluate if mobile text messages can be helpful to increase adherence to life-saving cardiovascular medications. As a first step (current proposal), we will be studying reasons for poor adherence to cardiovascular medications using "state of art" psychological strategies co-developed by some of the co-applicants.

Then, we will convert this knowledge, on reasons for poor adherence, into short-text messages tailor to the specific needs of patients in order to increase adherence of cardiovascular medications. In a second step (not included in this proposal) we will test under controlled experimental conditions (known as randomized trial) if mobile text messages are useful to increase adherence to cardiovascular medications that decrease blood pressure and the bad-cholesterol as well as making the blood thinner to avoid occlusion of arteries in the heart, brain and extremities. The study will take place in Colombia, Ghana, and India, representing major geographical areas with different stage of economic development and health care systems. We expect that our wide-coverage of less-developed countries will facilitate a rapid adoption of our intervention (if successful) to other less-developed countries. Our study will inform the World Health Organization initiative on uses of mobile text phone interventions to improve management of chronic conditions such as cardiovascular diseases.
**Joint Global Health Trials - Call 6 Development Grant**

**Project title**
A Pilot Study of Improving Outcomes in Teenage Pregnancy Using a Combined Tailored M-Health Program and Motivational Interviewing Intervention

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Priscilla Reddy</td>
<td>Human Sciences Research Council</td>
<td>MR/N021355/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**
- Professor Roger Vaughan
  Columbia University
- Professor Pamela Naidoo
  Human Sciences Research Council
- Miss Ronel Sewpaul
  Human Sciences Research Council
- Professor Ken Resnicow
  University of Michigan

**Summary**
Mortality among pregnant teenagers in South Africa (SA) is very high: institutional Maternal Mortality Ratio (iMMR) of 67.1 deaths per 100,000 live births in teenagers; with 71.7% of deaths resulting from four causes: hypertension (22.8%); non-pregnancy related infections (21.1%) (HIV/AIDS-related, such as TB or pneumonia); obstetric haemorrhage (14.2%); and medical and surgical disorders (13.6%).

Risk factors for these include poor antenatal clinic (ANC) attendance, lack of adherence to antiretroviral therapy, poor compliance to treatment for tuberculosis, inadequate management of preeclampsia, and slow referral of high risk pregnancies to secondary and tertiary centres.

Changing the health-related behaviour of pregnant teenagers, using an m-health intervention combined with motivational interviewing (MI), could reduce the prevalence of these risk factors and, thus reduce mortality. This pilot study will test the feasibility, user acceptability and preliminary efficacy of an enhanced version of MomConnect - an m-Health program developed by our partners, the Praekelt Foundation and the SA National Department of Health (NDOH).

The enhancements include adding tailored content to the SMS messaging platform; and an MI counselling intervention (4 sessions) delivered face to face by trained healthcare workers. The SMS messages will be tailored by age (13 - 19 years), motivational variables, appointment adherence, language and culture. Messages will be designed, pretested, and refined through formative evaluation procedures, under direction of our health communications expert.

The revised program, Teen-MomConnect, will integrate both the enhanced SMS messages and the MI counselling for each pregnant teenager. For example, the MI counsellors will have access to the survey question responses, as well as ANC appointment-keeping status obtained via the cell phone. The MI clinical behavioural counselling training and implementation will be designed by, and pilot tested with health workers, who will deliver the counselling. Starting from week 12 of their pregnancy, the teenagers will receive 4 MI sessions delivered face to face (or via cell phone) at the ANC by a healthcare worker. The study has two phases. Phase 1 aims to develop, test, refine, and then pilot the major program enhancements.
(SMS and MI) to MomConnect. Phase II is the pilot field test and its aims are: 1) to demonstrate whether pregnant teenagers can be recruited and retained in the study; 2) whether the causes of 71.7% of mortality in pregnant teenagers can be measured, 3) to establish uptake rates (both SMS use and completion of MI visit) for the enhanced Teen-MomConnect intervention; 4) evaluate if the integrated motivational behavioural face to face counselling, and the tailored health SMS intervention, impact pregnant teenagers ANC attendance (primary outcome), and the other risk factors for teenage maternal mortality.

For the Phase II field pilot study, 200 pregnant teenagers will be recruited through clinics, schools and community organisations - 100 will be randomised to the behavioural intervention of Teen-MomConnect plus MI; and 100 will be given "usual care" with MomConnect alone. The study will take 18 months to complete at a cost of £150,000. The results of the pilot will be used to design a randomised controlled trial (RCT) to test the effectiveness of the Teen-MomConnect in a fully powered cohort of pregnant teenagers.

The RCT will also include a cost effectiveness analysis. The products from this grant will include the Teen-MomConnect App and SMS messages; an MI training program for health workers; research instruments that have been designed and validated for the larger RCT; recruitment and retention protocols and a partnership between an international collaboration of scientists, Praekelt Foundation and the NDOH. This grant application has received the support...
Bridging the Mental Health Treatment Gap through Tele-psychiatry - ‘REACH’ a Formative Research Project from Goa, India.

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Richard Velleman</td>
<td>Sangath</td>
<td>MR/N021886/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

Dr Anil Rane  
Inst of Psychiatry & Human Behaviour

Dr Abhijit Nadkarni  
London Sch of Hygiene and Trop Medicine

**Summary**

India has a significant burden of mental illness with almost 70 million people having some form of mental illness. This problem is compounded by an acute shortage of trained specialist manpower to provide mental healthcare to those who require it. The existing manpower can only provide care for one third of the mental health needs.

Furthermore, 70% of this manpower is inequitably concentrated in urban areas while 70% of the Indian population lives in the villages. This mismatch is a great public health challenge and there is an urgent need to look at innovative ways to overcome this barrier to access. Affordable technology, which is easily accessible in India today, might provide the turning point in the field of mental healthcare delivery.

In this project we plan to use videoconferencing technology to provide mental healthcare for patients attending primary care clinics. We plan to discover whether such an innovation is feasible and safe to deliver, acceptable to the various stakeholders and has a positive impact on the mental health of the people. Videoconferencing facilities will be established between District Hospital and Primary Health Centres, where most patients access health care.

Patients with Depression, Alcohol use disorders and Severe mental illness will be identified by research workers, who will be offered consultations with a psychiatrist based in the District Hospital via videoconferencing. Medication and follow up services will be provided in the primary health centres.

Before-after assessment will measure change in symptoms and disability level. Since the service is delivered in the community we expect better compliance rates. In-depth interviews will be conducted with all stakeholders including service delivery agents, patients and their families to determine the acceptability of tele-psychiatry.

Demonstrating that delivering mental health care through tele-psychiatry is feasible and acceptable has significant policy implication. Tele-psychiatry can then play a transformational role in mental health delivery in low resource settings.
Joint Global Health Trials - Call 6 Development Grant

Project title
Improved Breastfeeding Support to Treat Acute Malnutrition amongst Infants under 6 months (IBAMI)

Grant holder | Institute | Grant reference
---|---|---
Dr MARTHA MWANGOME | ARCH - KWTRP | MR/N021940/1

Co-Investigators
Professor James Berkley
University of Oxford

Summary
For the first time, in 2013, the WHO guidelines for treating children with Severe Acute Malnutrition (SAM) included guidance on how to diagnose and treat SAM in infants aged below 6 months.

The treatment guidelines for infants under 6 months focused on inpatient treatment and recommended that admitted infants with SAM be supported to re-establish exclusive breastfeeding before they can be discharged. The recommendation was based mainly on programmatic reports and a few studies that had shown that lactation failure is common among infants with SAM, and that re-establishing breastfeeding among infants being treated for SAM is possible using re-lactation techniques such as supplementary suckling.

However, since none of the studies followed infants up after discharge, we still do not know i) if exclusive breastfeeding was retained after discharge; ii) if retaining exclusive breastfeeding after discharge is sufficient for nutritional recovery and iii) if additional breastfeeding support offered to mothers of discharged infants would be beneficial. The proposed study is aimed at generating important information to develop a trial to establish the effectiveness of home-based breastfeeding support to mothers of infants discharged from SAM treatment on survival and growth.

The main aim of the proposed study is to i) establish the breastfeeding retention rate among infants under 6 months discharged from SAM treatment within the current strategies that are without a specific post discharge breastfeeding support; and ii) establish whether among infants retaining exclusive breastfeeding, breastmilk alone is sufficient for nutritional recovery. This information will form the baseline data from where any success of any applied intervention will be measured.

Hence the findings from this study will strengthen the calculations of the sample size required to show an improvement in the outcomes due to an intervention. In addition, the study will provide insight on the acceptability and sustainability of using peer breastfeeding supporters commonly used to encourage breastfeeding in preterm neonates for infants with SAM. It will also provide information on the optimal trial follow-up strategy that could be applied successfully for this group of participants. Apart from providing information for trial development, the study findings will by themselves provide data to previously identified research gap. Within the 2013 updated
WHO guidelines on management of SAM in children, http://apps.who.int/iris/bitstream/10665/95584/1/9789241506328_eng.pdf (page 66) the question of how breastfeeding is most effectively established is raised.

Our study intends to optimize the WHO inpatient treatment guidelines and will in the process develop a step-by-step re-lactation protocol that would be applicable for resource poor settings. Recently, using the well developed and highly recommended Child Health and Nutrition Research Initiative (CHNRI) methodology, researchers, developmental partners and other stakeholders including UN agencies identified that research into the components of a package care for outpatient care as one of the top research priorities for infants with SAM (Angood, McGrath et al. 2015).

Findings from the proposed study will provide baseline information useful in designing and testing a package for outpatient care.
**Joint Global Health Trials - Call 6 Development Grant**

**Project title**
Parenteral interventions to support families of children with neurodisability in low resource settings

<table>
<thead>
<tr>
<th>Co-Investigators</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Catherine Kyobutungi</td>
<td>There are few services to support children with neurological disabilities and their families in resource poor settings, such as those found in sub-Saharan Africa. The parents and carers report that the two main features that impair their child's and family's quality of life are difficulties with their child's behaviour and communicating with the child.</td>
</tr>
<tr>
<td>African Population and Health Res Centre</td>
<td>Recent reviews of the literature have supported that parent interventions may be the most acceptable and feasible way to improve communication and behaviour. In particular, the Stepping Stones parenting programme, which has been developed for parents of children with disabilities was suggested as an appropriate intervention, since it does not require specialised therapists, does not involve hours of therapy and empowers the parents and carers.</td>
</tr>
<tr>
<td>Dr Amina Abubakar</td>
<td>This programme has been used in over 23 countries, shown to be effective in improving behaviour and communication in children with disabilities; but has not been tested in low-resource settings. The World Health Organization has also recognised these interventions, and promotes them through the mental health treatment gap interventions for children with developmental disorders.</td>
</tr>
<tr>
<td>University of Oxford</td>
<td>In addition the WHO has developed a a parent based intervention i.e. Parent Skills Training to improve communication and behaviour, but this intervention has not been tested in the field. The objectives of this grant are to examine the cultural acceptability and feasibility of administering two interventions i.e. Stepping Stones Programme and Patent Skills Training delivered through parents or carers to improve the communication, behaviour and quality of life of children with neurological disabilities.</td>
</tr>
<tr>
<td></td>
<td>In particular we will identify the barriers to the administration of a parent intervention. In addition we will examine the reliability, validity and responsiveness of tools to measure behaviour, communication, parenting, stress and quality of life in these settings. This data of this project will be used to develop an intervention to be tested in a randomised control trial. Testing the interventions are likely to provide some support to the children with disabilities and their families. The data will also be fed back to non-government organisations, the Ministry of Health, Education and Social Services who support children with disabilities in Kenya.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Charles Newton</td>
<td>University of Oxford</td>
<td>MR/N022157/1</td>
</tr>
</tbody>
</table>
Joint Global Health Trials - Call 6  Development Grant

**Project title**
Development grant for a multicentre, randomised trial to reduce surgical site infection following emergency gastrointestinal surgery in LMICs

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Aneel Bhangu</td>
<td>University of Birmingham</td>
<td>MR/N029984/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

- **Professor Hosni Salem**
  Cairo University

- **Dr Gustavo Alberto Recinos Lemus**
  Guatemala Institute Social Security

- **Mr Alphonse Zeta Mutabazi**
  National University of Rwanda

- **Professor Stephen Tabiri**
  University for Development Studies

- **Professor Dion Morton**
  University of Birmingham

- **Dr Dmitri Nepogodiev**
  University of Birmingham

- **Dr James Fitzgerald**
  University of Birmingham

- **Dr Laura Magill**
  University of Birmingham

- **Professor Thomas Pinkney**
  University of Birmingham

- **Mr Ewen Harrison**
  University of Edinburgh

- **Dr Adesoji Ademuyiwa**
  University of Lagos

- **Dr Andrew Kirby**
  University of Leeds

- **Dr Jen Cornick**
  University of Liverpool

- **Professor Paramjit Gill**
  University of Warwick

- **Professor Richard Lilford**
  University of Warwick

**Summary**

**THE PROBLEM:** Infections in wounds after bowel surgery are common in all countries. They have adverse effects for patients, doctors and health systems. For patients, they are painful, smelly, reduce quality of life and reduce time taken to return to normal activities. They are hard to treat and require prescriptions of long courses of antibiotics and return trips to the operating theatre, increasing antibiotic resistance and reducing future available treatments. They are extremely costly and require long lengths of stay in hospital and lots of nursing time. In low and middle-income countries, they are at least twice as common as they are in high-income countries. Rates of antibiotic resistance are also higher, meaning they are even harder to treat. Wound infections affect both adults and children and since people of working age can't return quickly to work, their families and communities are also adversely affected.

**FUTURE PROPOSED TRIAL:** We aim to perform a large, multi-country randomised controlled trial looking at two simple interventions to reduce wound infections after emergency bowel surgery. Emergency surgery is the most common, demanding and burdensome type of bowel surgery in low and middle income countries (LMICs). Since the burden of wound infections is highest in these countries compared to other places in the world, this research proposal if timely and focussed toward a clinical need in LMICs.

Wound infections are complex and testing two interventions at the same time may show even greater effect than just testing one, and it also improves value for money. The trial will be large and require around 2000 patients. **NEED FOR A DEVELOPMENT GRANT:** Before we can submit a highly competitive, world-class grant proposal, we need to perform some development work to ensure that we are prepared.

This work will develop a final, tangible plan for that application, and engage local doctors and research staff into the process. We aim to: 1. Hold on site meetings in participating countries, led by local surgeons, to engage a range of staff and shortlist interventions which could be tested in their units. 2. Deliver on-site research skills training that will increase local research capacity and leadership. 3. Perform small observational studies to ensure that sites have a strategy to follow-up patients during the main trial. 4. Hold our first face-to-face collaborator group
meeting, to develop a finalised protocol based on the selected interventions, that can be used for a main trial application. This meeting will also allow us to foster the strongest possible relationships between our new collaborative and improve team working.

NEED FOR MORE SURGICAL RESEARCH: There is a lack of surgical research across the world, partly driven by a lack of doctors regularly performing surgical research. This initial proposal will allow is to form a collaborative that could last for many decades. We predict that this network will enable us to deliver more trials into the future, of larger sizes and complexity. In the UK, we have developed hub and spoke research networks to deliver similar trials. We aim to transfer these research skills from the NHS to LMICs to help disseminate best surgical research practice widely.

This will also speed recruitment to trials and maximise generalizability. We aim that this development grant and subsequent main grant will produce a generation of surgical researchers focused on testing cost-effective interventions internationally.
**Joint Global Health Trials - Call 6 Full Grant**

**Project title**
A comparative trial of seasonal vaccination with the malaria vaccine RTS,S/AS01, seasonal malaria chemoprevention and the two interventions combined

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Brian Greenwood</td>
<td>London Sch of Hygiene and Trop Medicine</td>
<td>MR/P006876/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

- Dr Issaka ZONGO
  Centre Muraz
- Professor Halidou Tinto
  Inst of Health Science Research IRSS
- Professor Daniel Chandramohan
  London Sch of Hygiene and Trop Medicine
- Dr Irene Kuepfer
  London Sch of Hygiene and Trop Medicine
- Dr Matthew Cairns
  London Sch of Hygiene and Trop Medicine
- Professor Paul Milligan
  London Sch of Hygiene and Trop Medicine
- Mrs Silke Fernandes
  London Sch of Hygiene and Trop Medicine
- Professor Jean Bosco OUEDRAOGO
  Research Institute of Health Sciences
- Professor Abdoulaye Djimde
  University of Bamako
- Professor Alassane Dicko
  University of Bamako
- Dr Issaka Sagara
  University of Bamako
- Professor Ogobara Doumbo
  University of Bamako

**Summary**

There has been substantial progress in the control of malaria during the past decade, but it is estimated that in 2015 there were still 438,000 deaths from malaria, despite widespread deployment of insecticide treated bednets and an increase in access to diagnosis and effective treatment: new tools and approaches are needed.

In the African Sahel and sub-Sahel, the risk of malaria is concentrated in the few months of the rainy season, although some transmission continues during the rest of the year. The seasonality of malaria in this part of Africa has allowed the development of a control measure called seasonal malaria chemoprevention (SMC), which involves treatment of young children, regardless of whether they have any symptoms, with the antimalarials sulphadoxine-pyrimethamine (SP) and amodiaquine (AQ) at monthly intervals on four occasions during the malaria transmission season, a regimen which is very demanding on health care givers and recipient children.

The malaria vaccine RTS,S/AS01 has been in development for over 20 years. A recent trial conducted in 15,439 children showed that when three doses of the vaccine were given to children aged 5-17 months, followed by a fourth dose a year later, the vaccine provided 37% protection against clinical attacks of malaria over a period of 4 years, and a similar level of protection against severe malaria.

The vaccine caused febrile convulsions in about 1% of children and there was a small, unexplained, increase in the incidence of meningitis in vaccine recipients. These findings were reviewed by the European Medicine Agency in July 2015 and, based on the balance of benefits and risks, the Agency gave the vaccine a positive opinion. WHO has subsequently recommended that several large pilot implementation studies should be done before the vaccine is deployed more widely and that alternative approaches to its delivery should be explored.

A characteristic feature of the vaccine is that it produces high levels of protection in the first few months after vaccination but that this subsequently wanes. Vaccine efficacy of 86% (26/30 subjects protected) was obtained in a recent trial in USA military volunteers challenged shortly after three doses of vaccine had been given, the last dose at a lower concentration than usual. The aim of this study is to take advantage of the high initial
efficacy of RTS,S/AS01 to investigate its potential to provide protection to children exposed to malaria for just a few months each year.

A three arm trial is proposed which will compare (a) administration of three doses of RTS,S/AS01 to young children followed by a fourth and a fifth dose at the beginning of two subsequent malaria transmission season (b) administration of SMC with SP + AQ as recommended by WHO (c) the combination of these two interventions. The main objectives of the trial will be to determine whether RTS,S/AS01 provides a similar level of protection to that of SMC and is equally cost effective as SMC but is easier to administer and whether combination of the two interventions provides an added, cost effective benefit.

The trial will be conducted in 6,000 children (2,000 in each arm) in Hounde, Burkina Faso and Bougouni, Mali where a trial of adding the antibiotic azithromycin to the anti-malaria treatment regimen used for SMC is currently under way and due to finish at the end of 2016. The study team and many of the techniques needed for the new trial are, therefore, in place.

The main end-point of the new trial will be the incidence of episodes of clinical malaria severe enough to warrant treatment. Other end-points will be the incidence of severe malaria, hospital admissions with malaria and anaemia.

The safety of the two interventions will be monitored, with a focus on meningitis. The costs of the two approaches and of the combination will be measured and the preference of the local populations for each intervention will be determined.
Project title
Intermittent Preventive Treatment with DHA-piperaquine for malaria in pregnancy in areas with high sulphadoxine-pyrimethamine resistance in Africa

Grant holder | Institute | Grant reference
--- | --- | ---
Professor Feiko ter Kuile | Liverpool School of Tropical Medicine | MR/P006914/1

Summary
Context of the research Each year over 30 million pregnancies occur in malaria endemic areas of sub-Saharan Africa. Malaria in pregnancy (MiP) has devastating consequences for the mother and unborn child. The control of malaria in pregnancy in parts of East and southern Africa is under threat.

Pregnant women are often infected with malaria without showing any outward signs or symptoms which, if left undetected and untreated, can cause anaemia and interfere with the development of the foetus leading to loss of the pregnancy, or premature birth and low birth weight, which in turn increases the risk of early infant death. The World Health Organisation (WHO) therefore recommends a preventive strategy called 'intermittent preventive treatment in pregnancy' (IPTp) in which mothers receive a single dose of 3 tablets of medication called sulphadoxine-pyrimethamine (SP) at each scheduled antenatal visit starting in the 2nd and 3rd trimester.

However, the effectiveness of this strategy is being compromised due to high levels of resistance to SP in the malaria parasite population. The recent search for safe, effective and well-tolerated alternatives drugs has proven elusive because most of the new candidates tested were not tolerated well enough to be used for preventive purposes. Other trials evaluating test and treat strategies have also proven disappointing. All hopes are now pinned on an antimalarial called dihydroartemisinin-piperaquine (DP), which is known to be safe in the 2nd and 3rd trimester of pregnancy and highly effective for treatment of clinical malaria.

The high profile journals Lancet and the New England Journal of Medicine recently published the results of two exploratory trials, completed in 2015 (including one by this research team in Kenya). These showed that DP, when taken as IPT by pregnant women, was well tolerated and much more effective than SP in preventing malaria. However these two trials were not big enough to be able to evaluate the impact on the pregnancy outcome and the health of the newborn.

WHO reviewed the evidence in July 2015 and concluded that DP is indeed a promising alternative to SP and recommended that a larger, confirmatory, trial is needed, before it can consider whether to recommend this drug as an alternative to SP in areas of high resistance. Study aims and objectives This multi-centre
The trial will enrol about 3,000 pregnant women in six hospitals in Kenya and Malawi and compare the safety, tolerance and beneficial effects of IPTp with DP to the current strategy with sulphadoxine-pyrimethamine in reducing pregnancy loss, low birthweight, preterm birth and small-for-gestational-age babies, and early infant deaths.

The trial will include sub-studies on health economics to determine the cost of the strategy in relation to its benefits, the acceptability of the intervention among pregnant women and health providers, paying particular attention to adherence to the 3-day regimen, and the operational feasibility of implementing the intervention in the routine health system.

Potential applications and benefits After a decade of intensive multi-centre trials to find new prevention strategies for malaria in pregnancy, DP has been shortlisted as the only potential alternative to SP for IPTp, but evidence of its benefits on infant outcomes is needed. As an experienced network, specialised in malaria prevention trials in pregnancy, we are in a unique position to address these gaps in an expedited manner.

The findings of this new trial will provide the definitive evidence for whether or not this drug should be recommended to replace SP in areas with high levels of resistance by the parasite to SP. A positive result may lead to a direct policy change by the WHO in countries experiencing these levels of parasite resistance, including most countries in East and southern Africa, benefiting women at risk of malaria in these regions resulting in healthier pregnancies and healthier newborns.
Project title
High Dose AMBISOME on a Fluconazole Backbone for Cryptococcal Meningitis Induction Therapy in sub-Saharan Africa: A Randomized Controlled Trial

Grant holder | Institute | Grant reference
--- | --- | ---
Dr Joseph Jarvis | London Sch of Hygiene and Trop Medicine | MR/P006922/1

Co-Investigators
Dr Mosepele Mosepele
Botswana Harvard AIDS Initiative Partner

Professor David Laloo
Liverpool School of Tropical Medicine

Professor Duolao Wang
Liverpool School of Tropical Medicine

Professor Shabbar Jaffar
Liverpool School of Tropical Medicine

Professor David Mabey
London Sch of Hygiene and Trop Medicine

Dr Awilly chofle
National Institute for Medical Research

Mr John Changalucha
National Institute for Medical Research

Dr Sile Molloy
St George’s University of London

Professor Thomas Harrison
St George’s University of London

Professor Graeme Meintjes
University of Cape Town

Professor William Hope
University of Liverpool

Dr cecilia Kanyama
University of North Carolina Chapel Hill

Professor Mina Hosseinipour
University of North Carolina Chapel Hill

Dr Azure Makadzange
University of Zimbabwe

Professor Chiratidzo NDHLOVU
University of Zimbabwe

Summary
Cryptococcal meningitis is a leading cause of death in HIV-infected individuals in Africa. The current recommended treatment is a drug called amphotericin B deoxycholate.

Treatment with amphotericin B requires 14 days of intravenous infusions given in hospital, making it difficult and costly to administer. It also causes many side effects, including kidney failure and low blood count, making close laboratory monitoring essential. The combination of the costs associated with prolonged hospital admissions, the difficulties in administration and the need for laboratory monitoring make amphotericin B treatment difficult in much of Africa.

The only alternative currently available treatment is called fluconazole. Treatment with fluconazole is inadequate, and is associated with death rates of approximately 60%. A modified form of amphotericin B is available called liposomal amphotericin B (Ambisome).

This is considerably less toxic than standard amphotericin B, and is known to be efficacious in treatment of cryptococcal meningitis. Its use has been limited by the high cost of therapy, but recent data suggest that much shorter courses of Ambisome may be effective in the treatment of cryptococcal meningitis. Due to its lower toxicity, higher doses of Ambisome can be given safely, and it also persists for a long time in the tissues, raising the possibility of delivering highly effective induction therapy with very few (1, 2, or 3) doses.

A large reduction in the number of doses and duration of hospitalisation, together with reduced pricing of Ambisome, may result in cryptococcal meningitis treatment costs that are not more than those with 2 weeks of conventional amphotericin B, and provide a convenient, safe and efficacious alternative to conventional amphotericin B therapy.

This study aims to define the most effective and most cost-effective schedules for Ambisome use in the treatment of cryptococcal meningitis. A currently ongoing study is testing the safety and effect on rate of clearance of cryptococcal infection of one, two or three dose Ambisome treatment regimens compared to the standard 14-day course. The shortest of these Ambisome regimens that is found to be safe and effective will be utilized in this proposed large clinical trial to determine...
whether or not it is as effective as the standard 14-day amphotericin B deoxycholate treatment in terms of preventing deaths from cryptococcal meningitis.

If short-course Ambisome treatment regimens were shown to be of comparable effectiveness in the treatment of HIV-associated cryptococcal meningitis, the results of this study would lead to changes in international treatment guidelines, and provide an effective and practical treatment option for HIV-associated cryptococcal meningitis with the potential to prevent many thousands of deaths.
Joint Global Health Trials - Call 6 Full Grant

**Project title**
Pre-delivery administration of azithromycin to prevent neonatal sepsis and death: a phase III double-blind randomized clinical trial

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Anna Roca</td>
<td>MRC Unit, The Gambia</td>
<td>MR/P006949/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

- Professor Halidou Tinto
  Inst of Health Science Research
  IRSS
- Professor Koen Peeters
  Institute of Tropical Medicine
- Mr Christian Bottomley
  London Sch of Hygiene and Trop Medicine
- Dr Shunmay Yeung
  London Sch of Hygiene and Trop Medicine
- Professor Umberto D'Alessandro
  London Sch of Hygiene and Trop Medicine

**Summary**

Though maternal and neonatal health are high priority areas for international development, worldwide there are 1 million maternal and 4 million neonatal deaths every year and half of them occur in sub-Saharan Africa.

Bacterial infections, namely sepsis, are a leading cause of maternal and neonatal deaths in sub-Saharan Africa. Newborns can be infected during labour - when passing through the birth canal - and also during the first days/weeks of life, as a consequence of the close physical contact with the mother, when the latter carriers bacteria even when she does not show any symptoms. As the mother is an important source of bacterial transmission to the newborn, treating mothers with antibiotics during labour should reduce the occurrence of severe bacterial disease and mortality in the newborn.

In many high-income countries, pregnant women are screened during pregnancy for vaginal carriage of Group B Streptococcus, the bacteria responsible for the vast majority of neonatal sepsis in the developed world. If women are carriers, they are treated with intravenous antibiotics during labour to reduce transmission and subsequent risk of severe disease to their offspring. Although this intervention has been successful in developed countries, infrastructure and resource limitations in regions like sub-Saharan Africa prevent both screening and use of intravenous antibiotics.

Also, in sub-Saharan Africa several bacterial pathogens are responsible for neonatal sepsis and antibiotics, to be effective, would need to cover a wide range of bacteria. We propose to conduct a large trial in The Gambia and Burkina Faso to determine if a single dose of an oral antibiotic given to women during labour decreases newborn mortality. The trial will also assess whether giving the antibiotic reduces hospitalisations in mothers and their newborns during the first few weeks after birth.

We will use an antibiotic (azithromycin) that has already been used to eliminate other diseases in sub-Saharan Africa, such as trachoma (the most important cause of blindness caused by infection), and has the potential to eliminate most of the bacteria commonly causing severe disease in the region. An advantage of using this antibiotic in sub-Saharan Africa is that it can be stored at room temperature without the need of a fridge. Importantly, since this antibiotic is not widely used in clinical
care in sub-Saharan Africa, any temporary increase in resistance, as a result of using the antibiotic, will have small impact on clinical care. We have generated robust preliminary data on the effect of the intervention in a smaller trial conducted in The Gambia (829 women recruited).

We found that, babies born to mothers who had taken this antibiotic during labour were less likely to carry bacteria that can cause severe disease. Furthermore, these babies were also less likely to have bacterial skin and umbilical infections, both of which are common among newborns in sub-Saharan Africa. And in mothers who had taken azithromycin, fevers and mastitis (both common after giving birth) were less frequent. The preliminary data confirm our hypothesis that azithromycin can be used to reduce bacterial transmission but it was too small to assess the effect of the antibiotic on mortality and hospitalizations.

If we find that azithromycin prevents severe bacterial infections in mothers and newborns, then it could be an effective intervention since it is cheap and simple to administer.
**Joint Global Health Trials - Call 6 Full Grant**

**Project title**
RCT to evaluate an intervention for depressed HIV-positive women in the perinatal period, to enhance child development and reduce maternal depression

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Alan Stein</td>
<td>University of Oxford</td>
<td>MR/P006965/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

- Dr Abraham Jacobus Herbst  
  Africa Health Research Institute
- Professor Deenan Pillay  
  Africa Health Research Institute
- Professor Aisha Yousafzai  
  Harvard School of Public Health
- Dr Chris Desmond  
  Human Sciences Research Council
- Dr Tamsen Rochat  
  Human Sciences Research Council
- Dr Melanie Abas  
  King’s College London
- Ms Pollyanna Hardy  
  University of Birmingham
- Professor Michelle Craske  
  University of California Los Angeles
- Dr Ruth Margaret Bland  
  University of Glasgow
- Professor Edmund Juszczak  
  University of Oxford
- Professor Linda Richter  
  University of the Witwatersrand

**Summary**

The majority of people living with HIV in the world live in sub-Saharan Africa (SSA), with women of child-bearing age carrying the greatest burden. Up to 35% of women attending antenatal clinics in some parts of South Africa are HIV-positive. Many receive their diagnosis during pregnancy when they are screened for HIV. Depression afflicts many HIV-positive women during pregnancy; over 40% score above the threshold for depression on screening questionnaires, and approximately 23% fulfil diagnostic criteria. Depression is associated with reduced adherence to ART, as well as low clinic attendance, suicidal thoughts, and low rates of exclusive breastfeeding.

Moreover, perinatal depression has negative effects on parenting and early child development. Children born to depressed mothers are at increased risk of compromised cognitive development, behaviour and growth, especially when faced with socio-economic disadvantage and lack of support. There is also emerging evidence from a separate body of literature that HIV is associated with negative effects on caregiving and children’s outcomes (the vast majority of these children are HIV-negative).

Improving the wellbeing of mothers and infants requires effective treatment of perinatal depression, ensuring adherence to ART, as well as enhancing key parenting skills. In particular, depressed mothers often need help to sensitively respond to and care for their infants in order to mitigate the negative effects of depression on parenting.

Our aim is to conduct a cluster RCT to test an integrated home-based intervention programme that jointly treats depression and enhances parenting. The intervention, delivered during pregnancy and the postnatal period, comprises a combination of behavioural activation (BA) therapy to treat the symptoms of depression and a parenting programme to improve maternal responsiveness to infants (CCD).

BA is a structured therapeutic approach that focuses on increasing behaviours that are rewarding, improving mood and quality of life, and reducing behaviours that maintain or worsen depression such as passivity or avoidance and rumination. It has been shown to be as effective as CBT. This focus on behaviour rather than beliefs makes BA culturally acceptable. Another advantage of BA is that it does not require extensive training for
delivery or complex skills from the therapist; thus lay counsellors can deliver this treatment. CCD, developed by WHO/UNICEF, has been shown to improve parenting and promote early child development in LMIC when integrated in existing health services.

We have augmented CCD to focus particularly on parenting skills in early infant learning and attention, especially contingent responsiveness and the provision of early stimulation opportunities. The control treatment will be enhanced treatment as usual, comprising standard care with an additional in-person therapy session during pregnancy, two follow-up phone calls, and a parenting booklet in the postnatal period. The RCT will comprise 48 clusters (24 per arm) with 11 mothers (and infants) per cluster. This includes an additional 25% to take account of attrition, for a total of 528 mothers and infants. Women who meet criteria (i.e. have depression during pregnancy and are HIV-positive) will be recruited between 20 and 32 weeks of pregnancy and followed until the child is aged 2 years.

The main aims of the trial are to test whether the intervention:
1. Improves child cognitive development at 2 years of age
2. Reduces maternal depression during pregnancy and the postnatal period
3. Increases maternal adherence to ART
4. Increases rates of exclusive breastfeeding
5. Improves maternal contingent responsiveness to infant cues and quality of cognitive and emotional stimulation
6. Improves child growth, behaviour, and language development, and reduces gastro-intestinal infections
## Joint Global Health Trials - Call 6 Full Grant

### Project title
Assessing the safety of low dose primaquine in Plasmodium falciparum infected African children with glucose 6 phosphate dehydrogenase deficiency.

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Nicholas Day</td>
<td>University of Oxford</td>
<td>MR/P006973/1</td>
</tr>
</tbody>
</table>

### Co-Investigators

- Professor Peter Olupot-Olupot
  - Busitema University
- Professor Kathryn Maitland
  - Imperial College London
- Professor Thomas Williams
  - Imperial College London
- Professor Sir Nicholas White
  - Mahidol Oxford Research Unit
- Dr Charles Engoru
  - Soroti Regional Referral Hospital
- Professor Adrianus Dondorp
  - University of Oxford
- Dr Caterina Fanello
  - University of Oxford
- Professor Joel Tarning
  - University of Oxford
- Dr Marie Onyamboko
  - University of Oxford
- Dr Walter Taylor
  - University of Oxford

### Summary
Malaria remains a major problem in tropical countries, especially in Africa. Insecticide treated bednets and new powerful antimalarial drugs have led to a reduction in the number of malaria deaths. However, malaria control remains poor in many areas, and if we are to eliminate and eventually eradicate the disease from the world we will require the use of all the tools at our disposal. One potentially very valuable tool, currently underused, is the antimalarial drug primaquine, which is uniquely able to kill the mature male and female sexual forms of the malaria parasite. Research has shown that primaquine greatly reduces the malaria offspring in the mosquito and thus effectively reduces transmission of the disease. So, primaquine looks to be a good ‘transmission blocker’ and, if used widely in patients, may reduce malaria transmission and contribute to the elimination of malaria in a community.

Unfortunately primaquine has one major disadvantage. It can damage the red blood cells and cause anaemia in individuals who carry a very common genetic abnormality deficiency of an enzyme called glucose-6-phosphate dehydrogenase, G6PD for short. This deficiency is much more common in men because of the way it is inherited. This is called haemolysis. This is a real downside of primaquine, though this problem has mainly been seen when primaquine is given in high doses for many days. However, for its ‘transmission blocking’ effects on the malaria parasite only a single, low dose of primaquine is thought to be required. This is considered by most experts to be too little primaquine to cause a major problem with haemolysis. Despite this many malaria control programmes are unwilling to use primaquine because they consider it too dangerous.

You can test for G6PD deficiency but this requires test kits and staff to administer them. Many countries cannot afford to test millions of malaria patients before giving primaquine. In 2012 the World Health Organization (WHO) concluded on the basis of the available evidence and expert opinion that single low dose primaquine was safe to use even in malaria patients with G6PD deficiency. However, the WHO also called for more research. Four years later virtually no one is using low dose primaquine because that research has not been done. If we can show beyond doubt that low dose primaquine is safe in G6PD deficient children with malaria, malaria programmes would feel much happier giving it and we could then go to the drug companies and ask them to make primaquine that is suitable for children.
To see if single low dose primaquine is as safe as experts think we plan to study over 1,500 children with malaria attending outpatients in two hospitals in Uganda and one in the Democratic Republic of the Congo. Using a simple test for G6PD deficiency we will find 750 children with malaria who have G6PD deficiency, and 750 who have normal G6PD levels. Within these two groups we will, on a random basis, give half of the patients normal antimalarial treatment and the other half normal antimalarial treatment PLUS single low dose primaquine.

We will then watch the children very carefully to see whether giving primaquine causes more anaemia than not giving primaquine, and whether this occurs particularly in the G6PD deficient group. We need to have comparison groups of children who do not receive primaquine and some children who do not have G6PD deficiency as malaria itself causes haemolysis, as can G6PD deficiency in some circumstances even without primaquine treat. Our aim is to unpick the effects of G6PD deficiency, malaria, and primaquine administration to really be sure whether in all circumstances giving low dose primaquine is safe.

If this research shows that giving single low dose primaquine is safe, this will enable WHO and national governments to recommend safe treatment regimens that will both cure the patient and also prevent transmission of malaria to other children.
Co-Investigators

Dr Belen Torondel Lopez
London Sch of Hygiene and Trop Medicine

Professor Christopher Bonell
London Sch of Hygiene and Trop Medicine

Professor Janet Seeley
London Sch of Hygiene and Trop Medicine

Dr Suzanna Francis
London Sch of Hygiene and Trop Medicine

Dr David Ross
World Health Organisation (WHO)

Summary

In many resource-poor settings, girls lack adequate knowledge, facilities and materials to manage their menstruation. Challenges girls face include: feelings of embarrassment, fear of leaking menstrual blood or of teasing from boys due to a lack of privacy at school.

Many girls do not have access to adequate materials (pads, tampons or cups) to manage their menstruation. These factors can lead girls to be absent from school during menstruation. We recently completed an MRC-funded study (MENISCUS-1) among girls aged 14-17 years old in peri-urban Wakiso District in Uganda. This was a series of small sub-studies to understand perceptions about menstruation, to estimate the association with school absenteeism, and to develop an intervention package designed to improve school attendance and performance, knowledge and attitudes towards MHM, and prevalence of the reproductive tract infection bacterial vaginosis.

The study showed that menstruation is a key reason for school absenteeism, along with poverty. In a sub-study in which girls were asked to complete a daily diary recording school attendance and menstrual cycles, girls reported missing school on 1 in 4 schooldays when they were menstruating compared with 1 in 14 days when not menstruating.

We tested the components of a possible MHM intervention, each in a small number of girls. In the current study (MENISCUS-2), we plan to pilot test the interventions together as a package, delivered to all girls (about 150 per school) in one school year (S2) in two schools in Wakiso District.

The intervention components are: - Training of teachers to improve delivery of the Government guidelines for puberty education. - A drama skit to address issues around menstruation while engaging parents, boys and teachers. - Provision of a menstrual cup kit: Our implementing partner, WoMena, will train selected teachers and older girls to teach girls how to use a menstrual cup (the Ruby Cup) and a re-usable sanitary pad (AfriPad), both provided in a bag with a mirror, sterilisation/storage container and soap. The cup is reusable for 10 years, holds twice the volume of most pads, and can be used for up to 12 hours (i.e. girls do not usually need to empty it at school) so it should help girls manage periods whilst at school. - Supply painkillers for period pain (delivered using a voucher
Simple improvements to school water and sanitation facilities including locks on the toilet doors, provision of toilet paper, and a soap dispenser for hand-washing.

The primary outcome of MENISCUs-2 is to evaluate the intervention package works sufficiently well to enable a trial to be justified. We will decide this based on how well the intervention package is delivered (e.g. of analgesics delivered). The criteria for progression is that the education session and drama skit were delivered, the majority of girls using the Ruby Cup or re-usable pads provided at endline, and accessing painkillers as needed, and soap and toilet paper available in schools for the majority of the time.

We will also estimate the number of girls who progress to the next school year in order to know the likely loss to follow-up within a future trial. The criteria for progression to a trial will be a retention rate of 80% to allow for an acceptable loss to follow-up in the future trial. We will also estimate the likely intervention effect size.

Finally, we will estimate the cost of the intervention delivery, and cost of monitoring trial outcomes. As part of the study, we also piloted a football-based intervention in Uganda to promote safe male circumcision for HIV prevention, which we have previously used in Zimbabwe. This worked well after modifications, and we will deliver this intervention in the future trial alongside the MHM intervention, but are not including this component in this study as it was fully tested previous
**Joint Global Health Trials - Call 7 Development Grant**

**Project title**
Alcohol use disorders-Mobile based Brief Intervention Treatment (AMBIT): Technological innovation to bridge the treatment gap for hazardous drinking.

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Abhijit Nadkarni</td>
<td>Sangath</td>
<td>MR/P020348/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**
Professor Richard Velleman
Sangath

**Summary**
The World Health Organization (WHO) defines three levels of problematic alcohol consumption, namely hazardous drinking (HD) (which puts a person at risk of developing health/social problems), harmful drinking (where health/social problems are already occurring), and alcohol dependence (where serious problems have already occurred). Although HD and harmful drinking affects a larger proportion of the population (and causes many more problems) than alcohol dependence (the 'prevention paradox'), in India health policy focuses mainly on institutional delivery of care for alcohol dependence. Extensive evidence globally demonstrates the effectiveness of Brief Interventions (BIs) in reducing drinking in HD.

However, in India, the major barriers to providing such evidence-based psychosocial treatments are the lack/inequitable distribution of trained healthcare professionals and concerns about the cultural generalisability of psychosocial interventions developed in the West. One innovation to overcome the human resource barrier is to use mobile phone technology like SMS (Short Messaging Service) and interactive voice response (IVR) to deliver BIs to large numbers of HDs, quickly and at low cost, as demonstrated in interventions for smoking cessation. Furthermore, a growing body of evidence demonstrates that following a systematic methodology to culturally adapt psychosocial interventions increases acceptability by recipients and delivery agents, and feasibility of delivery. The overall objective of AMBIT is to develop a contextually appropriate BI for HD that can be delivered using mobile phone technology to overcome barriers to access in low resource settings.

The specific aims of AMBIT are to 1) Develop a BI package delivered using mobile phone technology, in partnership with our technology partner; 2) Examine if it is acceptable/feasible to deliver such an intervention in an Indian setting; 3) Conduct preliminary testing to see if the intervention helps in reducing drinking; and 4) Fine-tune procedures for the definitive testing of the effectiveness of the intervention. The aims of the programme will be achieved through a range of processes including identification of the existing evidence; development of the intervention in partnership with our technology partner and utilising feedback from a range of individuals and groups including Hazardous Drinkers; refinement of the intervention; and testing of its preliminary impact. The output of this treatment development process would be a contextually...
acceptable and feasible mobile-technology-delivered BI package which can then be tested in a larger trial. To summarise, we want to help hazardous drinkers to reduce levels of harm caused to them, their families and society in general, by transforming a way of helping (BIs) which has in the past been delivered face-to-face by healthcare workers into a much more accessible and widely available form, by using mobile phones (widely owned across India and other LMICs) and SMSs (widely used across India and other LMICs).

HD is a big and growing problem, both in itself, and also because many people with HD will go on to develop even more problematic versions of AUD. If successfully developed and found to be cost-effective, our intervention can reach millions of people across the world (as mobile phone use has increased exponentially even across the developing world) and could be a real game changer in the field of public health.
Joint Global Health Trials - Call 7 Development Grant

**Project title**
Intravenous fluid for adults with sepsis in sub-Saharan Africa: developing the design of an randomised controlled trial

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Jamie Rylance</td>
<td>Liverpool School of Tropical Medicine</td>
<td>MR/P020577/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

Dr Tim Baker
Karolinska Institute

Dr Joseph Lewis
Liverpool School of Tropical Medicine

Professor Stephen Gordon
Liverpool School of Tropical Medicine

Dr Grace Wit Katha
Ministry of Health Malawi

Professor Danny McAuley
Queen's University of Belfast

Dr Stephen Aston
Royal Liverpool University Hospitals NHS

Dr PATRICK KAMALO
University of Malawi

**Summary**

Severe infections are a major global health problem, and are the leading cause of admission to hospital. The sources of infections are variable, but are commonly the lungs (pneumonia) and the gut (gastroenteritis). The body’s usual protective responses should contain and destroy the bacteria or microbes causing infection. However, these responses can often become damaging: this is sepsis, and it is life threatening. During sepsis, a complex mix of abnormalities cause problems throughout the body, including with the immune system, breathing, blood circulation and kidneys.

The flow of blood through vital organs can be compromised, causing further organ failure. Many patients die in the first few hours, before antibiotics have a chance to work. Improving early supportive care of patients with sepsis has been associated with significant improvements in patients' survival, but it is not certain which interventions work. Much focus has been on early aggressive treatment with intravenous fluids, in order to raise low blood pressure and to improve blood supply to vital organs.

However, fluids can cause "waterlogging" of the lungs (pulmonary oedema), of the kidneys (worsening kidney function), and other organs. This is particularly damaging where there are no intensive care facilities to "rescue" the patient. A large, well conducted trial in in sub-Saharan Africa showed that intravenous fluid given quickly for sepsis caused children to die.

We do not know if the same could be expected in adults: current clinical guidelines for adults emphasise quick fluid "boluses" to try to bring blood pressure back to normal. * What this development proposal would lead to We believe that a randomised controlled trial of intravenous fluids in adults should answer the question: "In sub-Saharan Africa, which is the better treatment for sepsis: 1) quick, larger volume fluids given to try bring blood pressure back to normal or; 2) slower fluid given to prevent dehydration, but not designed to "correct" blood pressure.

* Objectives Before this type of trial could start, we have to define carefully who should be enrolled, how many patients we could expect, and how they should be monitored during treatment. This development grant proposal will examine each of these areas, by systematically reviewing existing knowledge, and by collecting data from a representative sub-Saharan
African hospital (Blantyre, Malawi).
* Why the trial is needed now and why in Malawi? New guidelines for the diagnosis and management of sepsis have been published using data from US hospitals and Intensive Care Units. These used no data from Low Income settings, yet are promoted as internationally useful. Their generalisability to sub-Saharan Africa is poor, and the region must develop and act on clinical evidence which is relevant to areas with younger patient groups, high rates of HIV, and low healthcare spending. *

Stakeholders

Acute infection is a national research priority, and we will ensure that the Malawi Ministry of Health and the College of Medicine (University) have input into the design and chosen outcomes. We will also engage the public and clinical stakeholders to ensure that the trial will be acceptable and appropriate to the healthcare setting.

We will build on expertise in Applied Health Research (CAHRD network), develop South-South collaborative networks, and enhance North-South support in trials design (Co-I: DM).
**Joint Global Health Trials - Call 7 Development Grant**

**Project title**

WHO’s Parent Skills Training for developmental disorders: Piloting task-shifting to non-specialists in Ethiopia

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Rosa Hoekstra</td>
<td>King’s College London</td>
<td>MR/P020844/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

- Dr Abebaw Fekadu Wassie  
  Addis Ababa University
- Dr Fikirte Girma Bayouh  
  Addis Ababa University
- Dr Charlotte Hanlon  
  King’s College London
- Dr Chiara Servili  
  World Health Organisation (WHO)

**Summary**

Developmental disorders including intellectual disability and autism are common worldwide and have a large impact on the lives of the individuals concerned and their families. Providing adequate support for children with developmental disorders is a major challenge, especially for low- and middle-income countries, where health service facilities and trained personnel are lacking.

In Ethiopia this lack is particularly pronounced: there are only two specialist child psychiatrists; services for children with developmental disorders are restricted to the country’s capital Addis Ababa and inaccessible to the majority (85%) of the population living in rural areas. Most children with developmental disorders in Ethiopia receive little or no formal help and have no access to interventions.

To address this gap the World Health Organization has developed a low-cost, scalable Parent Skills Training (PST) for caregivers of children with developmental disorders. The PST consists of nine weekly PST group sessions and three individual home visits, and teaches caregivers strategies to support their child’s learning and to address challenging behaviours. Our research team is currently conducting a pre-pilot to test how the PST programme can best be adapted for use in the Ethiopian context.

This pre-pilot is facilitated in a clinical setting by mental health specialists to allow for expert response in case any challenges emerge. However, the PST programme is ultimately designed to be delivered by non-specialists, so that the programme can be provided at a low cost to large groups of families. Before the PST can be implemented it is necessary to assess whether it is feasible to train non-specialists to successfully deliver the PST programme, and whether this non-specialist facilitated programme is acceptable to caregivers and addresses their needs.

Moreover, before the impact of the PST can be fully evaluated (in a randomised controlled trial, RCT) we need to know whether the measures proposed to assess the impact of the programme are reliable and appropriate for use in the Ethiopian setting. In this proposal funding is requested to allow for 40 caregivers of a child with a developmental disorder to take part in the programme as delivered by non-specialists. Detailed feedback will be asked from caregivers, non-specialist PST...
facilitators and their supervisors to assess the programme’s feasibility and acceptability. The potential impact of the programme will be assessed by comparing this group of caregivers and their children with a group of 40 caregivers and children who have not yet enrolled in the programme. Furthermore data will be collected on the PST’s proposed outcome measures from 300 children (150 with developmental disorders, 150 with other problems) who attend two child mental health clinics in Addis Ababa.

Based on the children's scores on these measures we will be able to determine whether the scales assess what we intend to measure (i.e. the validity of the measures) and whether the scales assess these characteristics consistently (i.e. the reliability of the measures). This study will generate evidence on how to best adapt and implement a scalable and sustainable training programme for caregivers of children with developmental disorders in a context of high need and extremely limited provision. Implementing the programme in such a setting will not be without challenges; this study will provide crucial insights in these obstacles and how to best overcome them.

The findings of this study are likely to apply to other low-income settings too, especially to other sub-Saharan African countries. Our proposed project can inform future implementation of the PST programme in these settings.
Joint Global Health Trials - Call 7 Development Grant

Project title
Exploratory randomised trial of face to face and mobile phone counselling against usual care for tobacco cessation in Indian primary care

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Irwin Nazareth</td>
<td>University College London</td>
<td>MR/P021166/1</td>
</tr>
</tbody>
</table>

Co-Investigators
Dr Rajmohan Panda
Public Health Foundation of India (PHFI)
Ms Rachael Hunter
University College London
Professor Rumana Omar
University College London

Summary
Smoked and smokeless tobacco use is a major cause of heart disease, cancer and lung diseases and it is one of the leading causes of ill health and death in India. Services that promote stopping the use of tobacco is best delivered best in Indian primary care since it is the first point of public access to the health care system.

Over a third of people attending primary care in Rajasthan use smoked or smokeless tobacco and the cost to the state of Rajasthan (where this development work will be conducted) attributed to this behaviour is estimated at 1160 crores (i.e. £1.3 billion) rupees. There is hence an urgent need to improve the evidence to reduce the use of tobacco amongst people seen in Indian primary care. The evidence from high income countries suggest that treatments delivered by health professionals, counsellor and through the mobile phones can be effective. The co-PI in the UK (Irwin Nazareth) has already worked on two major RCTs on smoking cessation in UK primary care and the co-PI in India (Rajmohan Panda) has developed tobacco cessation interventions in India that use online and face to face interventions for delivery in primary care clinics.

Some of his early work suggests that Indian primary care physicians do not have the time to offer tobacco cessation counselling session and hence this should be delivered by dedicated counsellors as is done in the UK. Mobile phone interventions are widely used for healthcare in the developed world and research in the field of smoking cessation suggest that they can increase the chance of quitting tobacco by 25-50%. Even though the WHO has advocated the use of such interventions in low and middle income countries (LMIC), to date there have been no evaluations of its effectiveness.

There is hence, an urgent need to test the use of mobile phone call and messages for tobacco cessation in Indian primary care. Our overarching aim is to conduct a randomised trial designed to evaluate the effectiveness as measured by tobacco cessation and overall cost value of a face-to-face counselling intervention coupled with a mobile phone call and messaging intervention delivered to smoking and smokeless tobacco users visiting Indian primary care clinics in addition to routine care provided by the primary care professional.

In order to do this we need to do early development work that finalises the intervention and tests whether it is acceptable and
feasible to test it in a small randomised trial. In this development grant we will initially finalise the development of the two components of a complex intervention which are a single 10 minute face to face counselling session delivered by a tobacco cessation counsellor and a mobile phone intervention that offers regular calls and messages every three weeks over six month.

The first component has already been developed by the Indian co-PI (RP) and the mobile phone component will be developed as a part of this study. The details of how these treatments are delivered within the trial will be written into a study manual that will be used by the professionals involved. This will then lead to the testing of the intervention within a small feasibility trial in which people will be randomly given either the intervention or usual care. We will assess how many tobacco users in the study centres who are asked to take part in the study agree to be randomised.

We will also assess how many of them will then agree to be followed up at six months so as to allow us to assess the outcome of these treatments. We will recruit 250 users from 10 primary care clinics in the state of Rajasthan, India. Successful development of the intervention, adequate recruitment to the trial and follow up at six months will be the main success measures of this development grant. This will then allow us to apply to the MRC and any other relevant funders for the next stage of this research which will be the conduct of a full randomised trial.
Feasibility and pilot study of a complex community intervention to improve rural adolescent health

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Shane Norris</td>
<td>University of the Witwatersrand</td>
<td>MR/P021174/1</td>
</tr>
</tbody>
</table>

Co-Investigators

- Professor Tobias Chirwa
  Private Address
- Professor David Dunger
  University of Cambridge
- Professor Ian Wilkinson
  University of Cambridge
- Professor Ken Ong
  University of Cambridge
- Professor Audrey Pettifor
  University of North Carolina Chapel Hill
- Professor Mary Barker
  University of Southampton
- Professor John Pettifor
  University of the Witwatersrand
- Professor Kathleen Kahn
  University of the Witwatersrand
- Dr Lumbwe Chola
  University of the Witwatersrand
- Professor Stephen Tollman
  University of the Witwatersrand
- Professor Lisa Miclesfield
  Wits Health Consortium (Pty) Ltd

Summary

Throughout the world the numbers of people with non-communicable (NCDs) diseases, like type 2 diabetes and high blood pressure, are increasing. The risk of developing diabetes is associated with being poorly nourished as a child and then becoming obese later in life, being inactive, having a poor quality diet, as well as with genetic inheritance and poor growth in the womb.

Low- and middle-income countries, like South Africa, have particularly fast-growing numbers of people with NCDs and have health systems already struggling to manage the burden of infectious diseases. We have shown that in rural South Africa a third of girls have growth faltering at one year of age, and a third of adolescents and young women are overweight or obese by 20 years of age.

Five percent of 7 to 15 year olds already show early warning signs for the development of diabetes. To combat the problem of an increasing prevalence of NCDs, it has been suggested that improving adolescent nutritional status may be a successful strategy, and that developing and evaluating pre-pregnancy interventions that promote healthy behaviours in poor communities where childbearing tends to start at a younger age, may be part of the solution.

Sub-Saharan Africa is the only region worldwide where the number of adolescents is predicted to grow, but it also has the worst adolescent health profile. To date, we are still unclear about how best to intervene to improve nutritional status in adolescents in low- or middle-income countries. Our extensive research over the last five years, has informed the development of an intervention targeting adolescent girls and boys.

It will employ trained adolescent-focused community health workers (AHWs) to work with adolescents to address both underweight and obesity by: (i) promoting healthy behaviours and increasing their use of adolescent health services; (ii) encouraging better caregiver and friend support and increasing opportunities in the community to become more healthy; and (iii) supporting adolescent girls who become pregnant to use antenatal health services earlier in their pregnancies and more frequently. This intervention aims to identify and reduce NCD risk in adolescents, and increase their use of health services through supporting behaviour change. AHWs will be trained in ‘Healthy Conversation Skills’, a set of skills to support behaviour...
change specifically developed and tested for use with socioeconomically disadvantaged women to improve their confidence that they can achieve their health goals. AHWs will use these skills as the basis for their work in rural SA villages over two years, building relationships with adolescents and their families to encourage social support for healthier adolescent lifestyles.

The intervention is flexible in its approach and will focus on the most relevant area of difficulty for each participant. AHWs will also involve their adolescent peer group in the village to promote health literacy. Health literacy will both increase adolescent access to health information and develop their ability to use this information effectively. AHWs will mobilise village community leaders to create greater opportunities to promote and support healthier lifestyles. Adolescents who become pregnant will be further supported by AHWs to access and regularly attend antenatal services, facilitate caregiver involvement, and reinforce optimal individual health (including weight gain) during pregnancy.

Through these interventions we aim to reduce the incidence of low of high birthweight in the infants, as these have been associated with diabetes risk in later life. The proposed development grant will enable us to complete a feasibility and pilot study in two villages to provide critical data to inform both the design and implementation of the trial.
**Joint Global Health Trials - Call 7 Development Grant**

**Project title**
Pharmacokinetics of azithromycin in severe malaria bacterial co-infection in African children

<table>
<thead>
<tr>
<th><strong>Grant holder</strong></th>
<th><strong>Institute</strong></th>
<th><strong>Grant reference</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Kathryn Maitland</td>
<td>Imperial College London</td>
<td>MR/P021492/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

Professor Peter Olupot-Olupot  
Busitema University

Professor David Burger  
Catholic (Radboud) University Foundation

Dr Rob ter Heine  
Catholic (Radboud) University Foundation

Professor Ann Walker  
University College London

Professor Diana Gibb  
University College London

**Summary**

Severe malaria killed an estimated 475,000 African children in 2013. Fast-acting effective antimalarial drugs are now used in most hospitals, but a large number of children still die (~1 in every 10). To reduce this number, we need to find better ways to manage these sick children.

Some children with severe malaria infection also have a higher chance of also having infections caused by bacteria at the same time. These bacterial infections increase the risk of children with severe malaria dying in hospital even more (to ~1 in 4 chance). Around one-third of all severe malaria deaths in African children are thought to be due to these bacterial infections. The problem is that most African hospitals are not able to grow the bacteria from blood to work out which children really have these bacterial infections.

So there are two options: no one gets antibiotics, or everyone gets antibiotics. The problem with giving all these children antibiotics is that most of them don’t need them, and using antibiotics for all children can increase the risk of resistance in the community (meaning antibiotics stop working for people who really need them). There is no agreement on which antibiotics, at what dose or for how long, they should be used in children with severe malaria. The main bacteria responsible for these infections come from the gut, because the gut becomes 'leaky' in severe malaria so these bugs can cross over into the blood. These bacteria are frequently resistant to, or are not treated by, currently recommended and commonly available antimicrobials.

What is needed now is to examine one of the antibiotics that can be given by mouth which has the potential to treat most common causes of infections and to find out what is the correct dose to give (to treat infections) in order to progress to the next step which will be a larger trial comparing different types of antibiotics to improve both short term and longer term outcomes.

We plan to examine 3 doses (10, 15 and 20mg/kg) of an oral antibiotic called azithromycin given for 5 days to find the optimal dose for curing infection in 105 Uganda children hospitalized with severe malaria that have the greatest risk of bacterial co-infection. We have chosen azithromycin because it is not used commonly to treat other infections, so using it in many children with severe malaria should not stop it working for these other conditions. Previous studies have also suggested...
that azithromycin could help the body fight infections and maybe helpful itself against malaria. To find out which is the right dose we will measure the levels of azithromycin in samples sent to a specialist laboratory in Nijmegen and pharmacological data will be compared to the clinical and infection (microbiological) outcomes of the children in the study in order for us to select the optimal and safest dose for future clinical trials.

We also want to find out whether we can identify children with severe malaria who are at risk or bacterial infection and those who are not so antibiotics could be targeted in future. We will also recruit a small number of children (n=50) hospitalised with non-severe malaria to examine whether special blood tests that could be done at the patient's bedside in combination with clinical signs could predict which children with severe malaria really have bacterial infections as well as malaria and so need antibiotics. We want to do this so that we can target antibiotics better in future to children who really need them, and reduce the total amount of antibiotics we use.

This is to stop the spread of antibiotic resistance. Using cheap tests like this would help resource-limited hospitals across many parts of Africa where microbiological services to grow bacteria are poorly developed or non-existent.
# Joint Global Health Trials - Call 7 Development Grant

## Project title
Healthier lifestyles through a peer-education and peer-support system: a school-based pilot project in adolescents in Ho Chi Minh City, Vietnam

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Dame Hong Kim Tang</td>
<td>Pham Ngoc Thach University of Medicine</td>
<td>MR/R004587/1</td>
</tr>
</tbody>
</table>

## Co-Investigators

- Dr Doan Trang Nguyen Hoang
  Pham Ngoc Thach University of Medicine
- Mr Ngoc Minh Nguyen
  Pham Ngoc Thach University of Medicine
- Dr Ashraful Alam
  University of Sydney
- Professor Michael Dibley
  University of Sydney

## Summary

Plain summary: Overweight and obesity in junior high school students have been rising sharply over the recent years in Ho Chi Minh City. The obese state is dangerous as it makes the children more prone to a series of diseases including heart and blood problem, diabetes and even some types of cancer. Recent studies found that low physical activity and quite high consumption of fast food and soft drinks were among the main causes. The research team has planned for a program to tackle this problem at junior high schools around the city.

The program consists of four weekly education sessions of why and how to choose food & drinks healthily and also how to be more physically active. Additionally, the program includes a school and online support system to help maintain the effort of the students.

Both of the education sessions and the support system are run by the star students (peer leaders) to take advantage of the influence between the children themselves. This first small-scale project is for the purpose of checking the acceptance of the students, their teachers and their family members and the possibility of success in school settings for the future larger program in Ho Chi Minh City.

This purpose is achieved through the results of interviews and group discussions with the students, the peer leaders, the teachers and the parents.
## Joint Global Health Trials - Call 7 Full Grant

### Project title
Effectiveness of bi-treated long lasting insecticidal nets and deployment strategy for control of malaria transmitted by pyrethroid resistant vectors

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Natacha Protopopoff</td>
<td>London Sch of Hygiene and Trop Medicine</td>
<td>MR/R006040/1</td>
</tr>
</tbody>
</table>

### Co-Investigators

- **Professor Franklin Weria Mosha**  
  Kilimanjaro Christian Medical College  
- **Professor Mark Rowland**  
  London Sch of Hygiene and Trop Medicine  
- **Dr Alphaxard Manjurano**  
  National Institute for Medical Research  
- **Dr Manisha Kulkarni**  
  University of Ottawa

### Summary

The massive scale up of long-lasting insecticidal nets (LN) from 2% in 2000 to 55% in 2015 has made the major contribution to the decline of malaria in Africa. LN effectiveness is entirely dependent on the pyrethroids, and with high LN coverage resistance has increased in distribution and strength. Leading LN brands are giving less protection than before and in North West Tanzania are failing to control malaria despite high coverage and usage rates. This problem was anticipated, and WHO has long encouraged industry to develop new types of 'combination' LN treated with new chemical compounds to overcome resistance and restore effectiveness.

The strongest resistance is mediated by cytochrome P450s, enzymes that metabolise the pyrethroid to inactive compounds. One solution is the synergist PBO which inhibits the P450 system in insects. LN products combining pyrethroid and PBO are available but due to limited evidence of additional impact against malaria these nets have not been widely deployed. This situation is changing as we showed in a randomised controlled trial in Tanzania that LN with PBO (Olyset Plus) was able to control malaria transmission where standard LN failed due to resistance.

Presently there are two types of PBO-LN available that differ in distribution of PBO on the net and it is not clear how they would compare making it difficult for malaria control agencies to make an informed choice. 'Mosaic LN' restrict the PBO to the roof panel where mosquitoes may first contact the net due to convection of CO2 from the sleeper inside. Others like Olyset Plus have all panels treated with PBO. Bi-treated nets incorporating new types of insecticide have also become available. A leading product mixes pyrethroid with an insect growth regulator pyriproxifen (PPF) that sterilises mosquitoes that contact the net. Another type mixes pyrethroid with the pyrrole chlorfenapyr (CFP), whose unique mode of action is unlikely to confer cross resistance with other public health insecticides.

LSHTM has helped develop both types of mixture LN and has evaluated them entomologically in laboratory and experimental huts. With its in depth knowledge LSHTM is in a unique position to continue evaluation at community level for malaria control. Earlier experience provides insight on how to measure the characteristics of these unusual compounds on nets when used.
by communities. It is important to monitor effectiveness over 3 years lifespan because effectiveness is likely to change over time. It is important to decide how, where and when the main categories of bi-treated LN should be deployed to maximize effectiveness and resistance management potential. Insecticide combinations, as with drug combinations in the example of antimalarial therapy, are considered the best way to reduce selection pressure for resistance but the LN may differ in this capability.

To address these issues we propose a four-arm randomized non-inferiority trial in 56 villages comparing the two PBO-LN types 1/ reference PBO-LN (Olyset Plus) and 2/ mosaic PBO-LN (PermaNet 3.0), and the two mixture-LN 3/ PPF-LN (Olyset Duo) and 4/ CFP-LN (Interceptor G2). The trial will demonstrate whether the mixture PPF-LN and CFP-LN provide similar or greater protection against malaria transmission than the reference PBO-LN. It will show whether mosaic PBO-LN provides equivalent protection to the reference PBO-LN. It will show whether bi-treated LN will reduce or prevent the selection of resistance. Health economic analysis will define which interventions are cost effective.

The trial findings will guide national malaria control and international agencies (Global Fund, President's Malaria Initiative, WHO) on malaria control strategy, effectiveness of different types of bi-treated LN, cost effectiveness and deployment options to maximize impact against resistance.
Joint Global Health Trials - Call 7 Full Grant

Project title
Mass drug administration of ivermectin and dihydroartemisinin-piperaquine as an additional intervention for malaria elimination

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Umberto D'Alessandro</td>
<td>MRC Unit, The Gambia</td>
<td>MR/R006075/1</td>
</tr>
</tbody>
</table>

Co-Investigators

Dr Guido Bastiaens
Catholic (Radboud) University Foundation

Dr Rob Baltussen
Catholic (Radboud) University Foundation

Dr Teun Bousema
Catholic (Radboud) University Foundation

Professor Steven Lindsay
Durham University

Dr Hannah Slater
Imperial College London

Professor Koen Peeters
Institute of Tropical Medicine

Professor Chris Drakeley
London Sch of Hygiene and Trop Medicine

Dr Davis Nwakanma
London Sch of Hygiene and Trop Medicine

Dr Jane Achan
London Sch of Hygiene and Trop Medicine

Dr John Bradley
London Sch of Hygiene and Trop Medicine

Dr Muna Affara
London Sch of Hygiene and Trop Medicine

Mr Balla Kandeh
National Malaria Control Programme

Dr Juan Muela Ribera
Rovira i Virgili University

Summary

Since 2000, there has been a substantial decrease of the malaria burden in sub-Saharan Africa due to the scale up of vector control interventions such as long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS), and better case management with artemisinin-based combination therapy (ACT).

Though some African countries such as The Gambia and Senegal have achieved excellent coverage of standard control interventions, malaria transmission has not been interrupted. This is probably due to two major factors, namely (i) the large and hidden human reservoir of infection, meaning individuals without any symptom but infected with malaria and thus able to infect the mosquito vector, and (ii) vector-related factors, e.g. vector behaviour and insecticide resistance, allowing vectors to escape standard control interventions such as LLIN and IRS. These two factors maintaining transmission require additional interventions specifically targeting them.

Mass Drug Administration (MDA) consists in administering at regular intervals a full antimalarial treatment to the whole population. This intervention has been identified as a potential tool to further reduce transmission where coverage of vector control activities is already high as it would clear malaria infection from asymptomatic carriers and thus reduce the human reservoir of infection. An ACT administered to the whole population should decrease the number of malaria-infected individuals and thus may have an effect on transmission. Ivermectin (IVM) is a mosquitocidal agent that is safe for humans but toxic to Anopheles mosquitoes when feeding on individuals recently treated with it. Combining an ACT with an IVM may have a synergistic effect because the former would reduce the human reservoir of infection while the latter would kill mosquitoes that have escaped standard vector control interventions.

In addition, combining an ACT with IVM would also reduce the minimal coverage required by MDA to have an effect on transmission. Transmission models suggest that adding IVM to a MDA intervention may interrupt transmission where standard MDA would be insufficient. However, this has never been rigorously evaluated in a well-designed cluster-randomized trial. This community-based, cluster-randomized trial will be carried out in the Upper River Region of The Gambia. Thirty two villages (clusters) at least 3-4km apart and with 200-600 inhabitants will
be randomized to either the intervention or the control arm. MDA with IVM and dihydroartemisinin-piperaquine (DP) will be implemented in 16 intervention villages and any other human settlement in the buffer zone around intervention villages (2km). MDA will consist of 3-monthly rounds per year during the malaria transmission season for two years.

Malaria prevalence at the peak of each transmission season and the mosquito population age structure will be compared between intervention and control arms. We will also collect qualitative social science data on coverage, potential bottlenecks for the intervention, adherence and acceptability; a health economics study will determine the cost of the intervention in relation to malaria infections and malaria patients prevented.
Supportive care and antibiotics for severe pneumonia among hospitalized children: A pragmatic randomised controlled trial

**Grant holder**
Dr Ambrose Agweyu

**Institute**
University of Oxford

**Grant reference**
MR/R006083/1

**Co-Investigators**
Dr Elizabeth Allen
London Sch of Hygiene and Trop Medicine

Miss Emma Beaumont
London Sch of Hygiene and Trop Medicine

Ms Joanna Sturgess
London Sch of Hygiene and Trop Medicine

Professor Mike English
University of Oxford

**Summary**

Pneumonia, an infection of the lungs, is the leading cause of deaths among young children. The World Health Organization (WHO) have developed recommendations for the diagnosis and treatment of pneumonia in low and middle income countries using simple clinical features and low cost, widely available antibiotics. The recommend treatment for children at the highest risk of death (severe pneumonia) is injectable benzylpenicillin or ampicillin and gentamicin.

Following the introduction of vaccines against the main causes of pneumonia to national immunization programmes in many low-income countries, there has been growing debate over the appropriateness of the currently recommended treatments. Many clinicians already believe that the recommended treatment is ineffective and frequently opt to use other antibiotics such as amoxicillin-clavulanic acid and ceftriaxone instead.

The first key question in this study seeks to compare two antibiotics against the current recommended treatment. We will investigate is whether either (i) intravenous amoxicillin-clavulanic acid or (ii) ceftriaxone is superior to benzylpenicillin plus gentamicin (standard care) for the treatment of children admitted to hospital with severe pneumonia. Some authorities advise against feeding through a tube inserted into the stomach through the nose in severely ill children.

The main reason for this is the potential for compromising the ability to breath in a patient already experiencing difficulty breathing and an increased risk of choking on feeds given through the tube. However, the alternative, providing fluids through an intravenous drip requires careful monitoring by a nurse to ensure the fluid is given at a safe rate over the desired duration. This a common challenge in many low resource settings where a limited number of nursing staff are required to attend to several duties. Fluids provided through a drip are also lack the necessary nutrients to match the increased demands of the body during a serious illness.

The second key question for this study is therefore whether feeding through a tube inserted into the stomach through the nose is superior to providing fluids through an intravenous drip for the management of children with severe pneumonia. We will recruit 4392 children at 12 hospitals in Kenya. Children who meet the criteria for recruitment will be allocated to the study.
treatment groups through a balanced process pre-determined process that ensures each participant has a fair chance of receiving any given study treatments. Each of the two questions will be studied in the same set of patients. Thus, a child recruited in the study will receive any one of the three antibiotic treatments and either of the two fluid treatments. For each of the study questions, we will compare the percentage of children who die within the first five day of recruitment in the alternative treatment groups.

We will also compare the length of hospitalisation, and the percentage of children who die within 30 days of recruitment in the alternative treatment groups. Chest X-rays and blood samples will be collected in a smaller group of patients to examine possible explanations for differences in responses to the treatments. Finally, we will compare the costs of receiving the alternative study treatments against the outcomes we observe among children assigned to the respective study groups and explore the social perceptions of caregivers and health workers towards the treatments.
Joint Global Health Trials - Call 7 Full Grant

<table>
<thead>
<tr>
<th>Project title</th>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short enhanced anti-tuberculosis and anti-thrombosis treatment for children with tuberculous meningitis</td>
<td>Professor Diana Gibb</td>
<td>University College London</td>
<td>MR/R006113/1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Co-Investigators</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Peter Olupot-Olupot, Busitema University</td>
<td>Children who come into contact with an adult who has tuberculosis (TB) are at a high risk of getting TB themselves. Globally, nearly a million children get TB each year. As well as being at high risk of getting TB, young children are especially prone to getting severe TB, which affects the brain. This is called TB meningitis (or TBM).</td>
</tr>
<tr>
<td>Dr James Seddon, Imperial College London</td>
<td>About one in five children who get TBM die of the disease. Of the children who survive, half will have some kind of disability. As well as this tragedy for the child, there is a large personal and financial cost to families who look after these children, often for many years. Health systems and societies are also affected. The World Health Organization currently advises 12 months of treatment for children with TBM. They recommend that children with other sorts of TB have 6 months of treatment. This advice is not based on good quality evidence.</td>
</tr>
<tr>
<td>Dr Kelly Dooley, Johns Hopkins Medicine (JHM)</td>
<td>Experts have been calling for a study to be done to try to find out if it is safe and effective to treat children with TBM for six months. Halving the treatment time would probably have large benefits for families and health systems.</td>
</tr>
<tr>
<td>Dr Chishala Chabala, Lusaka University Teaching Hospital</td>
<td>Researchers in South Africa have investigated treating children for six months, by giving them slightly different drugs and at higher doses. This means higher drug concentrations are achieved in the brain. The outcomes for these children seem at least as good as the outcomes in other places where 12 months of treatment are given.</td>
</tr>
<tr>
<td>Dr Mwate Mwambazi, Ministry of Health of Republic of Zambia</td>
<td>However, we cannot be sure if it is safe and effective because it has never been tested in a randomised trial. The drug aspirin has been used for many years for fever and pain. It is also known to make the blood clot less readily. It is used widely as a treatment for adults who have had heart attacks or strokes to prevent blood clots. Much of the damage in children with TBM is caused by stroke. Aspirin (in addition to TBM treatment) may help to reduce this damage.</td>
</tr>
<tr>
<td>Dr Eric wobudeya, Mulago University Teaching Hospital</td>
<td>Two studies have looked at this issue in children. One study showed that aspirin was beneficial and one showed that it was not. Both studies were quite small and doctors remain unsure whether to use aspirin. We plan to carry out a randomised trial to answer two questions. 1) Is it safe and effective to treat children with TBM for 6 months as opposed to 12 months? We plan to see if children treated for 6 months have outcomes that</td>
</tr>
<tr>
<td>Dr Mary Kaluma Nyathi, National Univ of Sci &amp; Tech (Zimbabwe)</td>
<td></td>
</tr>
<tr>
<td>Dr Angela Crook, University College London</td>
<td></td>
</tr>
<tr>
<td>Dr Anna Turkova, University College London</td>
<td></td>
</tr>
<tr>
<td>Dr Margaret Jean Thomason, University College London</td>
<td></td>
</tr>
<tr>
<td>Professor Guy Thwaites, University of Oxford</td>
<td></td>
</tr>
<tr>
<td>Dr Hilda Angela Mujuru, University of Zimbabwe</td>
<td></td>
</tr>
</tbody>
</table>
are as good as children treated for 12 months. The children treated for 12 months will receive the currently advised treatment.

The children treated for 6 months will receive higher dosages of the drugs and one drug that is different. 2) Does aspirin reduce the risk of disability in children with TBM? We plan to give half the children aspirin and the other half a placebo (sugar pill) so that neither they nor the study team knows which child is receiving which treatment. We will monitor all children for side effects. We will also investigate whether these two approaches are acceptable to families and what the financial implications are for both families and for health systems.

We will need about 400 children in the trial to answer these questions. We will carry out the trial in Uganda, Vietnam, Zambia and Zimbabwe. By doing the trial in many different places, we can be confident that any results that we find will be relevant for children all over the world.

If either shortening treatment or adding aspirin is safe and effective, the results of this trial could improve how doctors treat children with TBM across the world.
## Joint Global Health Trials - Call 7 Full Grant

### Project title

Will the ongoing use of a two-dose, rather than three-dose schedule of pneumococcal conjugate vaccine, have similar impact in rural Gambia?

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Grant Mackenzie</td>
<td>MRC Unit, The Gambia</td>
<td>MR/R006121/1</td>
</tr>
</tbody>
</table>

### Co-Investigators

- Professor Brian Greenwood  
  London Sch of Hygiene and Trop Medicine
- Dr M. Jahangir Hossain  
  London Sch of Hygiene and Trop Medicine
- Dr Ousman Secka  
  London Sch of Hygiene and Trop Medicine
- Dr Stefan Flasche  
  London Sch of Hygiene and Trop Medicine
- Dr Syed Mohd Akramuz Zaman  
  London Sch of Hygiene and Trop Medicine
- Professor Umberto D’Alessandro  
  London Sch of Hygiene and Trop Medicine
- Dr Cattram Nguyen  
  Murdoch Childrens Research Institute
- Professor Edward Mulholland  
  Murdoch Childrens Research Institute
- Dr Arto Palmu  
  National Inst for Health and Welfare THL
- Dr Jukka Jokinen  
  National Inst for Health and Welfare THL
- Dr Deborah Atherly  
  PATH
- Dr Jason Hinds  
  St George’s University of London

### Summary

Many countries have introduced pneumococcal conjugate vaccines (PCV) using three or four dose schedules with substantial reductions of invasive pneumococcal disease (IPD) and pneumonia. Herd protection effects have prevented more cases than the direct effects in vaccinated children.

Many African and Asian countries have now introduced PCV using the standard schedule of three doses in early infancy (3+0 schedule). Data from South Africa and Kenya suggest that direct and herd protection effects of PCV are substantial. In The Gambia, we have observed a 90% reduction in IPD due to vaccine serotypes (VT) following the introduction of PCV. Global control of pneumococcal disease however, is hampered by the cost of PCV. Low-income countries receive subsidised vaccine through the GAVI Alliance.

However, when countries' per capita income exceeds the World Bank 'low-income' threshold, they 'graduate' from GAVI support and co-payments increase substantially. GAVI will spend 2.8 billion USD on PCV in the next 5 years, which represents approximately half of its vaccine budget. Cost has prevented most middle-income countries from introducing PCV. To be effective, a two-dose schedule of PCV must provide adequate direct protection in infancy and maintain the low transmission of VT pneumococci in the community that is critical to sustain herd protection.

In fact, as immunisation programmes mature the role of herd protection becomes predominant over that of direct protection. Thus, we propose to test a vaccine schedule that includes a booster dose at 9 months of age, which when compared to schedules without a booster dose, has been associated with greater antibody levels at ages 1-4 years and greater protection against pneumococcal carriage at ages 1-2 years.

We hypothesise that the first dose in the new schedule (at age 6 weeks) will provide protection against a low risk of VT disease from 2-9 months of age in our setting. We hypothesise that the booster dose at age 9 months will provide superior direct and herd protection effects from 1-3 years of age compared to the 3+0 schedule. This trial will compare two- versus three-dose schedules of PCV delivered according to government immunisation clinics which serve subpopulations in discrete geographic areas.
We plan to deliver two-dose (doses at age 6 weeks and 9 months, '1+1') or three-dose (doses at age 6, 10, 14 weeks, '3+0') schedules to infants resident in the trial area over a period of 4 years. The immunisation programme will administer vaccines at 68 immunisation clinics serving separate catchment populations (clusters). The immunisation clinic catchment population will be randomised to either trial group (1+1 or 3+0). Safety monitoring by surveillance for IPD, pneumonia and mortality in the 1-59 month age group will be conducted throughout the trial.

After allowing time for the potentially different effects of the two schedules to develop, the study endpoints will be measured during the 4th year of the trial. The primary endpoint will be nasopharyngeal carriage of VT pneumococci in children aged 1-59 months with clinical pneumonia. The secondary endpoint will be VT carriage in infants aged 6-12 weeks presenting for their 1st dose of PCV. The analysis will test whether the difference in VT carriage between the two groups is less than a pre-set threshold.

Mathematical modelling will explore the role of the booster dose and the coverage needed to induce herd protection. Modelling inputs will include trial data and data from surveys of pneumococcal carriage and interpersonal contact patterns in the community. We will conduct a cost-effectiveness analysis of the 1+1 versus 3+0 schedule. Finally, working with WHO we will conduct a multi-country investigation of factors that will influence the implementation of 1+1 schedule.
**Joint Global Health Trials - Call 7 Full Grant**

**Project title**
A non-inferiority trial to assess the safety and immunogenicity of yellow fever vaccine dose sparing strategies for campaign and programmatic use

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Ed Clarke</td>
<td>MRC Unit, The Gambia</td>
<td>MR/R006148/1</td>
</tr>
</tbody>
</table>

**Summary**
Yellow fever is a viral infection which is transmitted from person to person by mosquitoes. The virus is found in a total of 44 countries across sub-Saharan Africa and South America and most recent estimates suggest that it now causes more than one-million infections each year including 180,000 severe cases and 78,000 deaths in Africa alone. These infections continue to occur despite the availability of a safe and highly effective vaccine which confers lifelong protection against disease after only a single injection.

In 2016, the worst epidemic (disease outbreak) of yellow fever in 30 years occurred in Central Africa. Cases due to international travel, also occurred in China sparking fears of uncontrolled disease spread in Asia. The epidemic occurred on the background of progressive increases in yellow fever disease over the past two decades and drove the publication of a new 'Global Strategy to Eliminate Yellow Fever Epidemics' by the World Health Organisation (WHO) in late 2016. This document highlighted the emerging global threat posed by the yellow fever and the major role played by shortages of the yellow fever vaccine in the current disease resurgence. Nearly half of the 34 countries which have introduced the vaccine into their routine immunization schedule for infants ran out of vaccine between 2013 and 2015 with many countries receiving only 50% of the number of doses of the vaccine they needed.

These shortages got worse during the recent epidemic when, faced with the possibility of running out of vaccine completely, the WHO took the decision to recommend that ‘fractional’ doses of the vaccine should be used in the emergency vaccination campaigns being used to control the outbreak. In this way, one fifth (0.1mL) of the normal dose (0.5mL) is given to each person meaning that five times as many people can be vaccinated. There are no studies to see how good fractional doses of the yellow fever vaccine are in babies and children and no studies of have tested fractional doses of the vaccine in sub-Saharan Africa. This is why this study is important.

The mains questions we want to ask in 9 to 12 month old Gambian infants are: 1. Does giving a fractional dose of a yellow fever vaccine to an infant given them as much protection from yellow fever infection as giving them a full dose of the vaccine? 2. Is there a difference in the amount of protection from yellow fever generated when a fractional dose is given subcutaneously (under the skin - the normal way yellow fever vaccines are

**Co-Investigators**
- Professor Bali Pulendran
  Emory University
- Dr David Jeffries
  London Sch of Hygiene and Trop Medicine
- Mr Darin Zehrung
  PATH
- Professor Matthias Niedrig
  Robert Koch Institute
given) or intradermally (into the skin). Is there any difference in the safety of a fractional dose of the vaccine depending on whether it is given subcutaneously or intradermally? The results of the study will give the WHO expert committee on vaccination policy important information.

It will help them to decide if fractional rather than full doses of the yellow fever vaccine can be recommended for future emergency vaccination campaigns including infants and children. It will also help them to decide if fractional rather than full doses can be given to infants as part of their routine scheduled vaccinations or in preventative campaigns. It is hoped that the results of the study will help to stop yellow fever epidemics across sub-Saharan Africa in the future.

Co-Investigators

Professor Vikram Patel
Harvard Medical School

Professor Richard Emsley
King's College London

Dr Gauri Divan
Sangath

Professor Linda Davies
The University of Manchester

Grant holder

Professor Jonathan Green
The University of Manchester

Grant reference

MR/R006164/1

Summary

Eighty percent of the world's children with Autism Spectrum Disorders (ASD) live in low resource settings. Recent evidence from high-income countries supports the effectiveness of targeted parent-mediated interventions for the early treatment of children with ASD.

Interventions that are delivered through parents have the additional advantages of improving parental knowledge and morale, potentially promoting the social empowerment of mothers, generalising into improvements in the family environment for the child and thus potentially conferring long-term impacts on the social context, the child's environment and functional outcomes. The Pre-school Autism Communication Therapy (PACT) trial conducted in the UK is the largest yet trial of this kind. It is targeted at getting parents to recognize their child's social communication difficulties and create an environment which gives the child a space and time to communicate at their own pace.

This intervention uses video feedback techniques to work with parents to enhance their understanding and responsiveness to the atypical communications of young children with autism. The trial showed that children with ASD who received this treatment benefited from the enriched communication environment that their parents were able to create; this in turn had a positive impact on the social interactions the children initiated. More importantly these changes, in the parent child interaction and independent communication from the child, were sustained in a follow up study after six years which demonstrated a decrease in autism symptoms in children who received the intervention.

The intervention has now been successfully adapted for use in South Asia, including relevant cultural adaptation to enhance parental acceptability, developing a supervision and training cascade to allow the intervention to be delivered by community based non-specialist workers, and delivery of the intervention at home. The resulting Parent mediated intervention for Autism Spectrum Disorders in South Asia (PASS) was subsequently evaluated in a pilot trial which demonstrated its acceptability, feasibility and efficacy.

Subsequently, the team in India have developed and piloted a complementary comorbidity package creating a comprehensive intervention for children with ASD in the 2-9 year age group (PASS Plus). Evaluation methods have also been adapted and
tested in both of these pilot studies. Most children with ASD in India and other low resource settings do not receive evidence based care which the proposal investigators have shown can reduce the symptoms of ASD and is feasible and acceptable for delivery in the proposed study setting. The proposed trial will build on this pilot work already carried out in India, and will carry out the largest, definitive, trial of the intervention, involving 240 participants recruited through two tertiary government hospitals in the capital city of New Delhi, which cater to an urban poor population.

The intervention will be delivered through existing health system frontline workers. The trial will evaluate the effectiveness and cost effectiveness of the intervention on symptoms of ASD and parent-child interaction as well as more general impacts on child functioning, parental well-being and social empowerment.

COMPASS will be the largest trial of its kind for ASD in any low resource setting and the evidence generated will have an impact not only health policy and practice in India, home to over 5 million children with ASD, but also other low resource settings in the region.
A randomized trial comparing oral misoprostol alone with oral misoprostol followed by oxytocin in women induced for hypertension of pregnancy

**Grant holder**  Professor Andrew Weeks  
**Institute**  University of Liverpool  
**Grant reference**  MR/R006180/1

**Co-Investigators**
- Dr Shuchita Mundle  
  Government Medical College  
  Nagpur  
- Dr Beverly Winikoff  
  Gynuity Health Projects  
- Ms Hillary Bracken  
  Gynuity Health Projects  
- Professor Brian Faragher  
  Liverpool School of Tropical Medicine  
- Mr Simon Leigh  
  Nexus Clinical Analytics Ltd  
- Dr Mark Turner  
  University of Liverpool  
- Professor Zarko Alfirevic  
  University of Liverpool

**Summary**
Every year around 30 000 women die from high blood pressure in pregnancy (pre-eclampsia). In South Asia alone it is responsible for 10 000 deaths annually. Many of these deaths are preventable with timely delivery of the baby, which is the only curative treatment. Vaginal delivery is safer than caesarean section (CS) but labour induction in preeclampsia presents additional challenges. It is more difficult as mothers are often preterm and in their first pregnancies, and more dangerous as babies can be growth restricted.

Induction of labour occurs in two stages; softening and opening of the neck of the womb (cervical ripening) followed by stimulation of contractions (augmentation). Our previous study established low dose oral misoprostol (LDOM) as the optimal method for cervical ripening in the low and middle-income country (LMIC) setting, and this is now strongly recommended by the World Health Organization. Standard practice in these settings is cervical ripening with LDOM followed by augmentation using intravenous oxytocin through a gravity drip infusion (M/Ox).

However, gravity drip infusions have a high potential for human error and equipment faults, so constant monitoring and accurate titration of oxytocin are essential. Excessive contractions put mothers and babies at risk; whereas inadequate contractions lead to a failed induction. Both these mechanisms could explain the high CS rate (41%) seen in our previous labour induction study 'INFORM' in India. There is an urgent need to establish a safe and effective induction method that does not rely on oxytocin for augmentation.

Avoiding oxytocin and continuing LDOM into labour for augmentation, could have numerous clinical and logistic benefits:  
- A cold-chain is not required for LDOM as it is heat stable (unlike oxytocin).  
- The lack of an intravenous infusion means that women will be free to mobilise in labour.  
- LDOM does not need to be actively monitored or titrated against contractions. It is therefore less work-intensive than an oxytocin infusion, giving health practitioners more time to care for other aspects of the women's labour.  
- The simplicity of the protocol may allow task-shifting.  
- In the absence of close monitoring, an unattended patient on oxytocin could receive hours of inappropriate stimulation. In contrast, LDOM does not need constant monitoring, the stimulation will cease unless there is drug administration every 2 hours.
will be significant health system savings by negating the need for IV infusion pumps and continuous presence of a health practitioner.

A misoprostol-only induction protocol has been successfully used in three randomized trials in South Africa. The trial participants that received a misoprostol-only (M/M) protocol required 40% less CSs compared with those using a standard (M/Ox) protocol (15 vs 26%). Despite promise, these rates cannot be directly compared as they occurred in different trials. Indeed, no published study has ever directly compared the two protocols.

We propose a randomized superiority trial in three large government hospitals in Nagpur, India. 1000 pregnant women with hypertensive disease will be randomly allocated to use the conventional (M/Ox) protocol or the misoprostol only (M/M) protocol. The primary objective is to investigate whether a misoprostol only labour induction (M/M) protocol, compared to the standard protocol (M/Ox), can reduce the rate of CS in women undergoing labour induction for pre-eclampsia in low-income settings. We also propose a qualitative study, a situational analysis and an economic evaluation to be conducted alongside the trial. The objectives of these studies are: to explore care providers' perspectives on the potential advantages, barriers and risks of each protocol; understand current knowledge, attitudes and practices concerning induction of labour; and compare the cost-effectiveness of the protocols.
### Joint Global Health Trials - Call 7 Full Grant

#### Project title
Cluster randomised controlled trial (RCT) for late life depression in socioeconomically deprived areas of São Paulo, Brazil (PROACTIVE)

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Ricardo Araya</td>
<td>King’s College London</td>
<td>MR/R006229/1</td>
</tr>
</tbody>
</table>

#### Co-Investigators
- Professor Timothy James Peters  
  University of Bristol
- Professor William Hollingworth  
  University of Bristol

#### Summary
Depression in later life is common, costly, and can have devastating consequences for those affected, their relatives, and society. Notwithstanding this, it usually goes unrecognised and untreated, especially in low-middle income countries. The Brazilian population is ageing rapidly, with already 20 million people aged 60 or more.

The Brazilian health care system, especially the mental health sector, is poorly prepared to meet this challenge. There is an urgent need to develop cost-effective depression treatment programmes for older people living in low- and middle-income countries. The Brazilian primary care system is an excellent setting to introduce and evaluate an intervention to reach a large proportion of this neglected part of the population. The intervention proposed (PROACTIVE) aims to overcome barriers for treating old people with depression, such as patients' social isolation and difficulties in accessing services, lack of skilled and supported staff to deliver effective interventions, and poor coordination and accountability among staff caring for elderly people.

PROACTIVE will be a two-arm cluster randomised controlled trial aiming to compare the effectiveness and cost-effectiveness of adding to usual care a psychosocial, community-based intervention mostly delivered at home by Community Health Workers employed by the existing primary care system. The intervention will be compared with an 'enhanced' usual care in reducing depressive illness and improving functioning among adults 60 years or older from poor socioeconomic backgrounds in São Paulo, Brazil.

Primary Care Family Health Units will be randomised to one of these two treatment groups. All or a random sample of the Family Health Teams within a Unit, depending on size of the Unit, will be invited to participate. PROACTIVE consists of 8 to 11 home sessions, depending on severity of depression, delivered over 17 weeks. The initial phase is given to all participants and comprises three sessions covering psycho-education and learning simple coping strategies to improve mood.

The Second Phase is based on behaviour activation and relapse prevention strategies; the number of sessions depends on the severity of symptoms. Community Health Workers will be equipped with tablet computers to assist with the delivery and accountability of the intervention and to receive further training.
and supervision. Those participants who do not improve with the intervention, in relation to specified clinical algorithms, will be discussed in supervision and regular team meetings and, if needed, other clinical decisions will be adopted. The control group will receive 'enhanced' usual care in so far as improved identification and periodic assessments of high-risk cases treated as per a 'high-risk' protocol. The primary outcome measure of PROACTIVE is the 9-item Patient Health Questionnaire (PHQ-9).

We will compare the recovery of cases (PHQ-9<10) across arms at 8 and 12 months after entering the trial, using an intention-to-treat analysis. Several secondary outcomes will be also measured including quality of life and levels of functioning. Direct and indirect costs in both arms will be measured to undertake a cost-effectiveness analysis. We anticipate recruiting a total of 1,440 participants registered in 20 FHUs (clusters), yielding 86.5% power for a 15 percentage point difference (25% to 40%) in recovery at 8 months. We have developed and successfully tested the feasibility and acceptability of the proposed intervention in primary care in São Paulo (RCUK/FAPESP). This project has the potential for a timely and major impact on the wellbeing of depressed older adults, further reducing dependency on specialised mental health resources already under strain in Brazil and most LMIC.

The Brazilian primary care model is being replicated in several other LMIC, contributing to increase the port
Joint Global Health Trials - Call 8 Development Grant

Project title
Yoga programme for type-2 diabetes prevention (YOGA-DP) among high-risk people in India: intervention development and feasibility study

Grant holder | Institute | Grant reference
--- | --- | ---
Dr Kaushik Chattopadhyay | University of Nottingham | MR/R018278/1

Co-Investigators

- Professor Nikhil Tandon
  All India Inst of Medical Sciences
  Delhi
- Professor Dorairaj Prabhakaran
  Centre for Chronic Disease Control
- Professor David Ross Harper
  Chatham House
- Professor Sanjay Kinra
  London Sch of Hygiene and Trop Medicine
- Professor Mark Hamer
  Loughborough University
- Professor Tess Harris
  St George's University of London
- Dr NK Manjunath
  S-VYASA University
- Professor Sheila Margaret Greenfield
  University of Birmingham
- Professor Sarah Lewis
  University of Nottingham

Summary

Diabetes (type-2) is a complex metabolic disorder with significant health, social and economic consequences. India has the world's second largest diabetic population. Another huge population in India is at high-risk of developing diabetes, i.e., their blood sugar levels are higher than normal but lower than the established threshold for diabetes itself. They are more likely to develop diabetes and its complications than people with normal blood sugar levels. Physical activity reduces blood sugar levels. However, physical activity levels are lower among Indians, especially among women and older people. Contemporary physical activities have some limitations, which includes their poor acceptability.

Yoga, a mind-body discipline that originated in the Indian subcontinent, has some advantages over contemporary physical activities and can meet the aim of the recommended physical activity for diabetes prevention among high-risk people in India (target users). The main aim is to establish whether or not a yoga programme can prevent diabetes among high-risk people in India. This will be tested in a future main study. Before this, we will develop the programme content and will check with our study participants if the future main study can be conducted. This early phase study will be carried out in New Delhi, India - a huge population in New Delhi is at high-risk of developing diabetes. Qualified yoga practitioners will provide group yoga sessions, for 75 minutes, twice a week for six months at local community centres.

The development of the programme content will include several steps, such as a systematic review of scientific literature to generate a list of yogic practices that are recommended for managing diabetes. Subsequently, at least 40 experts (yoga and exercise professionals) will validate each of these yogic practices. Based on this, the programme will be drafted and pre-tested among 20-30 target users, recruited using a multipronged approach (i.e., from the community as well as public and private healthcare providers). Yoga practitioners will provide the programme to them, followed by qualitative interviews to improve the programme.

Once the programme details are finalised, a study will be conducted among at least 64 target users, to check if the future main study can be conducted. They will be randomly allocated either to the yoga programme group or the control group. The control group participants will receive enhanced standard care,
i.e., a leaflet and a group session on routine physical activity advice. The multipronged approach will be used to recruit them. Quantitative data (numerical) will be collected and analysed on study-specific issues, such as a quantity which is needed to estimate study size of the future main study, recruitment and follow-up of participants, and attendance of yoga programme group participants in the yoga programme.

Qualitative interviews will take place with 20-30 participants to explore how they have found participating in the study and any particular issues experienced. Those who decline to participate in the study will be interviewed to explore the reasons behind.

If the feasibility of undertaking the future main study is promising, the main study will be conducted. If the yoga programme is found to be effective, it will be a low-cost local solution to prevent diabetes among high-risk people in India and to become healthier overall. The future clinical, personal and economic burden of diabetes on patients and their families will be prevented. The benefits of preventing diabetes may extend to the prevention of its complications.

They will be provided with more evidence-based choices to meet the recommended physical activity for diabetes prevention. The programme will simultaneously empower participants to manage their health.
**Project title**

A pilot assessment of miltefosine's efficacy and tolerability for treating cutaneous Leishmania tropica in Afghanistan

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Walter Taylor</td>
<td>University of Oxford</td>
<td>MR/R018391/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

- Professor Bilal Ahmad Rahimi  
  Kandahar University
- Professor Joel Tarning  
  University of Oxford
- Dr Mavuto Mukaka  
  University of Oxford

**Summary**

Cutaneous leishmaniasis (CL) is a skin disease that has been around since biblical times. The disease is caused by the leishmaniasis parasite, which is transmitted by sand flies between humans or between small animals or dogs to humans. Historically, CL is divided into Old and New World leishmaniasis (OW or NWCL). OWCL stretches from the Mediterranean Sea, across the Middle East and Caucasus region, to western India. There are also affected areas in east and west Africa. NWCL is found in Mexico, central and most countries in South America (except Chile, Argentina and Uruguay).

The World Health Organization (WHO) estimates that the number of CL cases per year in the world is 600-900,000 with 90% occurring in seven countries: Afghanistan, Algeria, Brazil, Iran, Peru, Saudi Arabia, and Syria. CL thrives where there is poverty, war and large population displacements. This is particularly the case in Syria and Afghanistan. CL results in ulcers, nodules, and dry scaling of the skin especially on the face which patients find upsetting. NWCL may also invade the mouth, nose and throat leading to a more unsightly and severe disease. This form is rare in OWCL but has been reported in Syrian refugees because they have not been able to receive early treatment. Treatment for CL is limited to toxic drugs because there is little interest by drug companies and governments to conduct research.

This is why leishmaniasis is a WHO-designated neglected tropical disease. We plan to conduct a small pilot study to see if a drug called miltefosine is effective in OWCL in Afghanistan. Miltefosine is effective for treating visceral leishmaniasis (leishmaniasis affecting our internal organs) and some types of NWCL. It can be given by mouth, a big advantage over currently used treatments, but over 28 days which may be a challenge for patients. In Afghanistan, CL is caused by the Leishmania tropica species which is transmitted between humans. This explains the high number of cases in Afghanistan and Syria and why the WHO recommends treatment.

Sodium stibogluconate (SSB) is the only drug available for treating CL in Afghanistan. It has to be given over 20 days by injection into the skin, vein or muscle which is painful and distressing, especially for small children who make up about 25% of cases. SSB is toxic and may affect the liver, kidneys, pancreas, blood, and heart. As a result, some patients have to stop it early. Better alternatives are needed. Our pilot study will
give miltefosine and SSB, using recommended doses, and follow patients for six months to see if their skin is cured; a long follow up is needed because CL can return even though the skin appears healed.

We will also measure miltefosine levels in the blood and the leishmania parasites in the skin over time and examine the relationship between the two. This has never been done before for L. tropica. We will also ask patients about their knowledge of CL, how it affects their life, and how much they are willing to pay for a treatment that they prefer to SSB.

If our study shows miltefosine has promise, we will apply for more money to do a large study comparing 14 and 28 days of miltefosine with SSB. A large study will give us confidence in the results. We are willing to accept a lower miltefosine cure rate (e.g. 5-10%) over SSB if it is more popular with patients. If 14 days of miltefosine is also very effective, this would be a big plus because miltefosine is expensive; the WHO price is about 70 and 100 pounds for children and adults, respectively.

Having an effective and popular oral treatment, especially over 14 days, would be so much more convenient for clinics and patients and will improve access to treatment for many people with OWCL.
**Joint Global Health Trials - Call 8 Development Grant**

**Project title**
Development and evaluation of an integrated early childhood development and violence prevention teacher-training intervention in Jamaican preschools

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Helen Baker-Henningham</td>
<td>Bangor University</td>
<td>MR/R018421/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**
- Dr Marcos Vera-Hernández
  University College London
- Professor Susan Walker
  University of the West Indies

**Summary**

The 'Irie Classroom Toolbox' is a universal violence prevention programme, developed for use in low and middle-income countries (LMIC), which involves training preschool teachers in classroom behaviour management and in how to promote young children’s social-emotional competence. We recently conducted a study in Jamaica in which 76 preschools were randomly assigned to either receive training in the 'Irie Classroom Toolbox' (38 schools, 115 teachers) or to receive the training at a later date (38 schools, 114 teachers).

We found that teachers trained in the 'Irie Classroom Toolbox' used 67% less violence against children (including physical punishment, verbal abuse and intimidation) than teachers who did not receive the training. Furthermore, the training led to significant improvements to the emotional and organisational climate of the classroom, and to observations of children's class-wide prosocial skills. A random sample of children was evaluated (n=865) and benefits of intervention were found for children's inhibitory control and for the proportion of children with clinical level behaviour difficulties.

Although significant benefits were also found to the instructional support offered by intervention teachers; the scores for both intervention and control teachers were low (<2 on a 7-point scale); indicating that cognitive and language stimulation was inadequate.

To maximise the effectiveness of the 'Irie Classroom Toolbox' to promote children’s development across the cognitive and language domains in addition to the social and emotional domains, teachers need additional training. In this study, we plan to evaluate a module on instructional support which will include include i) how to promote children’s higher order thinking and cognition, ii) how to provide feedback to expand child learning and understanding and iii) how to facilitate children’s language development. 20 preschools who been trained in the 'Irie Classroom Toolbox' will be randomly assigned to a group in which teachers receive training in instructional support (10 schools, 30 classrooms) or a second group that will receive no additional training (10 schools, 30 classrooms). A random sample of 5 children per class will also be evaluated (300 children; 150 in each group).
The intervention involves 2 full-day training workshops and 4 in-class support sessions (once a month for four months). We will evaluate the effect of the intervention on teachers' use of the instructional strategies during teaching and learning activities. We will also evaluate the selected children's school readiness and language skills. To monitor that this additional training does not reduce teachers' behaviour management skills, we will measure teachers' use of violence against children and child behaviour difficulties in both groups. We will document factors relating to the implementation of the intervention on an ongoing basis including teachers' engagement with the material, their strengths and needs in implementing the strategies and barriers and enablers to implementation. Through this study we will investigate the acceptability, feasibility and effectiveness of the intervention and we will use the data to develop intervention manuals that are suitable for national dissemination including materials for teachers (e.g. activity guides) and materials for trainers (e.g. training manuals). The enhanced 'Irie Classroom Toolbox' produced through this study will be a teacher-training programme to i) prevent violence against children by teachers, ii) prevent the early development of antisocial behaviour and iii) promote children's social, emotional cognitive and language skills in early childhood classrooms. The intervention will be suitable for use with poorly trained teachers, working in poorly resourced settings in LMIC. The outputs of this study will make a strong contribution to th
Project title
ToQuit: Development and preliminary evaluation of a technology assisted tobacco cessation intervention in India

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Abhijit Nadkarni</td>
<td>Sangath</td>
<td>MR/R018456/1</td>
</tr>
</tbody>
</table>

Co-Investigators
Dr Pratima Murthy
NIMHANS (Mental Health & Neuroscience)

Dr BIDYUT KANTI SARKAR
Public Health Foundation of India (PHFI)

Professor Richard Velleman
Sangath

Dr Felix Naughton
University of East Anglia

Summary
Context: India is the second largest consumer and third largest producer of tobacco in the world; and has one of the highest mortality rates related to tobacco. Although there is good evidence for the effectiveness of tobacco cessation interventions they are not completely suitable for the Indian context because they focus on smoked tobacco (whereas the most commonly used tobacco in India is smokeless tobacco) and are designed to be delivered by healthcare workers (a limited resource in India).

Hence, despite the growing public health impact of tobacco use, only a very small proportion of those who want to discontinue tobacco use receive any help to quit. One way of increasing access to tobacco cessation interventions in low resource settings is to develop and scale up an effective and contextually appropriate but non-resource-intensive intervention. Our proposal is to develop and then preliminarily evaluate, a contextually appropriate intervention, that can be delivered using mobile text messaging (a cheap and easily available technological platform in India).

Thus we will overcome the human resource barriers by using mobile phone technology to deliver tobacco cessation interventions to large numbers of tobacco users, quickly and at low cost. Furthermore, we will follow a systematic methodology to culturally adapt the intervention to increase acceptability by tobacco users and the feasibility of delivery using a technology platform.

Aims/Objectives: The overall objective of ToQuit is to use evidence-based treatment development processes to develop a contextually appropriate tobacco cessation intervention that can be delivered using mobile phone technology in order to overcome barriers to access in low resource settings.

The specific aims of ToQuit are to 1) Develop a tobacco cessation intervention package, to be delivered in India using mobile phone technology; 2) Examine if it is acceptable and feasible to deliver such an intervention in an Indian setting; 3) Conduct preliminary testing to see if the intervention helps in increasing tobacco quit rates; and 4) Fine-tune procedures for the definitive testing of the effectiveness of the intervention within a feasibility RCT. These aims will be achieved through a range of processes including development of the intervention and adapting it utilising feedback from a range of individuals and
groups, including tobacco users; refinement of the intervention; and testing of its preliminary impact. The output of this treatment development process would be a contextually acceptable and feasible tobacco cessation intervention package that can be delivered through mobile phone technology; and which is ready to be tested in a larger trial. Potential applications and benefits: Tobacco use is a big and growing problem, because it leads to high levels of health problems (e.g. cancers) and deaths.

We want to help tobacco users to reduce levels of harm caused to them, by transforming a way of helping which has in the past been delivered face-to-face, only by highly trained and expensive healthcare workers, into a much more accessible and widely available form, by using mobile phones (widely owned across India and other low and middle income countries [LMIC]). If successfully developed and found to be cost-effective, our intervention can reach millions of people across LMICs and could be a real game-changer in the field of public health.
Project title
Expanding mental health counselling from primary care to reach at-risk youth (Expanding MINDS-Y).

Grant holder
Professor Bronwyn Myers

Institute
South African Medical Research Council

Grant reference
MR/R018464/1

Co-Investigators
Dr Claire van der Westhuizen
University of Cape Town

Dr Katherine Rae Sorsdahl
University of Cape Town

Dr Tracey Naledi
Western Cape Government

Summary
Ensuring youth (aged 15-24) who are at high risk for common mental disorders like depression and hazardous alcohol use have access to mental health counselling could improve their emotional well-being and prevent injuries, the acquisition of communicable diseases such as HIV, and the onset of non-communicable diseases (NCDs).

Like many low- and middle-income countries (LMICs), South Africa (SA) faces the challenge of how to reduce the high prevalence and impact of communicable diseases and NCDs, including mental disorders where limited services are available. Common mental disorders among youth are important to address to prevent these future physical health problems.

Yet, the mental health treatment gap in SA is large, particularly for youth. Failure to reach 15-24 year olds is a major service gap as this is often the age of onset for common mental disorders. Service planners recognise that they need to expand the coverage of mental health counselling to include at-risk youth. However, a lack of information about where to situate mental health counselling services, who should be delivering these services, and how to format services to ensure acceptability to and utilisation by at-risk youth has hampered the expansion of available services to this key population.

The expansion of mental health counselling to at-risk youth also has been delayed by a lack of youth-oriented counselling programmes that are acceptable to and effective for improving the mental health of at-risk youth. The goal of this study is to address this knowledge gap by providing information on youth preferences for mental health counselling services, adapting an adult-oriented programme to meet the needs of youth; and testing the feasibility of recruiting youth and initial outcomes of this adapted counselling programme on mental health outcomes.

Through this study, we hope to obtain information that can be directly useful to health planners for the design and development of youth-friendly mental health counselling services and have a feasible, youth-friendly counselling programme that shows promise for reducing both depression and hazardous alcohol use among at-risk youth.

Findings from this study are likely to be highly relevant for use in other LMICs given similarities between the burden of disease,
treatment populations, and profile of risk behaviours among youth in SA and other LMICs.

The study will comprise three phases. In the first phase, we will conduct in-depth interviews with service providers, at-risk youth, and their caregivers to assess barriers to youth participation in mental health counselling and to identify youth preferences for where and how services should be delivered (Aim 1). Findings from this phase will be used to initially adapt our proposed programme to address these barriers and ensure acceptability. In Aim 2, we will demonstrate this adapted intervention in focus groups with at-risk youth in order to obtain information on how the intervention content, structure and layout should be adapted to meet the needs of youth.

In Phase 3, we will test the feasibility of recruiting at-risk youth to participate in the adapted intervention and the initial effect of the adapted intervention on depression and hazardous alcohol use. We will recruit 100 at-risk youth from impoverished community settings and we will randomize them to receive the intervention or be in a control group.

We will assess the effect of the intervention on depression and alcohol use three months after study enrolment. Once the three month assessment has been completed, participants in the control group will be offered the counselling intervention. Findings from this phase will be used to initially evaluate the feasibility and effect of the intervention (Aims 3-4).

If the outcomes are promising, findings will also be used to inform the design of a large trial to assess
## Joint Global Health Trials - Call 8 Development Grant

### Project title
Gastroenteritis: rehydration for children with severe acute malnutrition (GASTRO-SAM)

### Grant holder | Institute | Grant reference
---|---|---
Professor Kathryn Maitland | Imperial College London | MR/R018502/1

### Co-Investigators

<table>
<thead>
<tr>
<th>Professor Peter Olupot-Olupot</th>
<th>Busitema University</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Kirsty Houston</td>
<td>Imperial College London</td>
</tr>
<tr>
<td>Dr Victor Musiime</td>
<td>Joint Clinical Research Centre Kampala</td>
</tr>
<tr>
<td>Dr Sarah Kiguli</td>
<td>Makerere University</td>
</tr>
<tr>
<td>Professor Diana Gibb</td>
<td>University College London</td>
</tr>
<tr>
<td>Mrs Elizabeth George</td>
<td>University College London</td>
</tr>
</tbody>
</table>

### Summary

Children with severe acute malnutrition (SAM) who are admitted to a hospital in Africa frequently (>50%) have diarrhoea (3 watery stools/day). The outcome in such children when they managed in accordance to World Health Organization (WHO) SAM treatment guideline is very poor with over 20% dying during hospital admission.

One standard treatment of diarrhoea that causes dehydration is 'rehydration' therapy either by using a drip (intravenous) for those who have developed severe dehydration, where approximately 10% or more of the body weight has been lost from watery diarrhoea. The other treatment is oral rehydration salt (ORS) solutions which is given to those with less severe dehydration or as a follow-on rehydration treatment for children after they have received their drip (intravenous) treatment.

However, the WHO guidelines for SAM children with severe dehydration recommend restriction of intravenous therapy only to cases with late stage advanced shock (where the blood pressure is low) and focus exclusively on the use of low sodium (salt) oral rehydration solutions (ORS) for fear of causing heart failure and giving too much salt (sodium). Therefore, for children requiring ORS guidelines recommend a low sodium ORS called ReSoMal.

These guidelines are very controversial since they are based on expert opinion, and do not have the relevant clinical studies or clinical trials to back up the evidence to support these recommendations. Owing to the very poor outcomes, we therefore aim to evaluate in a clinical trial called GASTROSAM whether the usual standard treatment that is given to children who are well nourished is better and safer that the intravenous and oral rehydration recommended treatments for SAM children with diarrhoea.

We will conduct a small trial that will test whether it is safe to give intravenous rehydration for SAM children with severe dehydration of 100mls/kg (the equivalent volume to replace what has been lost) which is currently recommended for children without malnutrition. We will do this in two ways by either infusing the fluid rapidly (over 3-5 hours), or more slowly (over 8 hours) and compare this to what is currently being recommended (which largely recommends to treat this with oral rehydration salts and only to start drip treatment if shock occurs). We will also test whether the standard ORS (with a higher amount of sodium) given for children without severe
malnutrition is safer and has less harmful effects that the current ORS called ReSoMal which has a much lower sodium content and has in the past has been shown to result in children developing very low sodium levels which can cause harm.

The results of the trial will help us design a much larger trial in which we aim to compare rapid rehydration versus slower rehydration in all children who are admitted to hospital irrespective of their nutritional status (i.e. well-nourished and malnourished).

We are currently conducting another small trial called GASTRO in children with severe diarrhoea who do not have malnutrition comparing rapid (standard recommended treatment) versus slower rehydration as the outcomes even for children who are not malnourished is also very poor. The data from this trial will also help us design a future large trial.
Joint Global Health Trials - Call 8 Development Grant

Project title
MICA: A pragmatic approach to the prevention of gestational diabetes and pre-eclampsia in obese pregnant women in resource poor settings

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Jane Norman</td>
<td>University of Edinburgh</td>
<td>MR/R019142/1</td>
</tr>
</tbody>
</table>

Co-Investigators

Professor Moffat Nyirenda
Entebbe General Hospital

Professor Evarist Njelesani
Lusaka Apex Medical University College

Dr Thomas Sukwa
Lusaka University Teaching Hospital

Professor Harry Campbell
University of Edinburgh

Professor John Norrie
University of Edinburgh

Professor Liz Grant
University of Edinburgh

Professor Rebecca Reynolds
University of Edinburgh

Professor Amelia Crampin
University of Glasgow

Dr Frank Taulo
University of Malawi

Summary
Gestational diabetes (too much sugar in the blood in pregnancy) and pregnancy hypertensive disorders (high blood pressure that occurs in pregnancy, and which can lead to fits in the mother and death in the baby) cause significant maternal and neonatal mortality and morbidity in low and middle income countries and there is no systematic approach to prevention.

The estimated global prevalence of gestational diabetes is 16%, with higher rates in in South Asia and Africa [1]. Gestational diabetes increases the incidence of the adverse outcomes of caesarean section, pregnancy induced hypertensive disease, excessive birthweight, birth injury, future obesity and future diabetes: untreated, it contributes to a cycle which promotes obesity and diabetes in future generations[2]. Pregnancy hypertensive disorders account for 17.3% of maternal deaths in low socio-economic countries, and are the second commonest cause of maternal death after haemorrhage[3].

In resource rich countries, testing for gestational diabetes is undertaken in women at high risk, together with treatment of those affected and regular self-monitoring of blood sugar levels. Such an approach is inappropriate in resource poor settings due to the high cost of testing and blood sugar monitoring, and the lack of availability of blood sugar monitoring kits. However, measurement of maternal body mass index (weight and height) cheaply and effectively identifies a high-risk group for both gestational diabetes and pregnancy hypertensive disorders. Additionally, one of the treatments (metformin) for gestational diabetes is relatively cheap, widely available, and safe, regardless of blood sugar levels [4-6].

Recent in vitro and clinical data suggest that metformin might reduce the incidence and severity of pregnancy hypertensive disorders [6-8]. We propose that metformin could be a pragmatic approach to preventing gestational diabetes and pregnancy hypertensive disorders in obese pregnant women in resource poor settings. This is a feasibility study of a clinical trial to determine whether metformin is effective in preventing gestational diabetes and pregnancy hypertensive disorders in women at high risk of both conditions.

In this feasibility study, we will find out if it is possible for us to do a full trial, how big such a trial would be, and how expensive it would be. We will ask obese pregnant women in participating sites in Malawi and Zambia to take either metformin or
matching placebo tablets. We will see how many women wish to participate, how many take the treatment, and what effect the treatment has.

We will also be able to see how common gestational diabetes and pregnancy hypertensive disorders are in this population. Although this feasibility study is too small to answer the question "Is routine administration of metformin a pragmatic approach to preventing gestational diabetes and pregnancy hypertensive disorders in obese pregnant women in resource poor settings" it will facilitate a larger (and likely more expensive study) to be able to do so.

Our group of clinicians, researchers and policy makers in Malawi, Zambia and the UK has the necessary expertise to carry out both the feasibility study and a further substantive study, and we are well placed to be able to translate the results of the research into clinical practice.

## Joint Global Health Trials - Call 8  Development Grant

### Project title
The Clean Study

<table>
<thead>
<tr>
<th>Co-Investigators</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Fatuma Manzi</td>
<td>Every year, thousands of mothers and babies suffer from infections acquired during a hospital stay, sometimes from poor hygiene and sometimes with fatal consequences. This study will investigate whether training 'cleaning champions' to educate hospital cleaners in best practice methods improves environmental hygiene in maternity and newborn units in three Tanzanian hospitals.</td>
</tr>
<tr>
<td>Ifakara Health Institute (IHI)</td>
<td>It will also measure whether doing this leads to changes in the knowledge, beliefs, skills and behaviour of champions and cleaners. The lessons learnt from this study will help inform a bigger trial to investigate whether our intervention actually reduces infections in mothers and babies. Our previous research in two regions of Tanzania found most maternity beds to be contaminated, and that most cleaners had not received training in the last year.</td>
</tr>
<tr>
<td>Dr Stella Kasindi Mwita</td>
<td>In this study we will start by identifying staff (for example, nurse/midwives, ward managers, or experienced cleaners) in each hospital who can become 'cleaning champions'. Next, the champions will receive training on how to educate cleaners on the maternity and newborn units. We will adapt and use an existing training package which includes a set of lessons on best cleaning techniques (e.g. start in a clean area, and end in a dirty area; wear personal protective equipment); and also on how cleaning breaks the 'chain of transmission' of infection.</td>
</tr>
<tr>
<td>Ifakara Health Institute (IHI)</td>
<td>Practical demonstrations are included (e.g. using talcum powder to show how invisible germs are spread) which encourage active participation - an approach which is better for adult learners, especially those with lower literacy, than traditional teaching methods. The training of the cleaning champions will be undertaken by an experienced local organisation (e.g. School of Nursing at Muhimbili University of Health and Allied Sciences). However, training alone will not necessarily improve environmental hygiene, rather other improvements need to occur too (e.g. ensuring mops and disinfectant are always provided when they run out).</td>
</tr>
<tr>
<td>Mrs Giorgia Gon</td>
<td>We will use 'Quality Improvement' (QI) methods to identify these needs and to monitor performance of cleaning staff after they have been trained by their local cleaning champion. These champions will be supported in their role by regular supervisory meetings over a four-month period from the organization who trained them. To determine if there have been any positive</td>
</tr>
<tr>
<td>London Sch of Hygiene and Trop Medicine</td>
<td></td>
</tr>
<tr>
<td>Ms Loveday Anna Penn-Kekana</td>
<td></td>
</tr>
<tr>
<td>London Sch of Hygiene and Trop Medicine</td>
<td></td>
</tr>
<tr>
<td>Dr Sandra Virgo</td>
<td></td>
</tr>
<tr>
<td>London Sch of Hygiene and Trop Medicine</td>
<td></td>
</tr>
<tr>
<td>Professor Simon Cousens</td>
<td></td>
</tr>
<tr>
<td>London Sch of Hygiene and Trop Medicine</td>
<td></td>
</tr>
<tr>
<td>Dr Tanya Marchant</td>
<td></td>
</tr>
<tr>
<td>London Sch of Hygiene and Trop Medicine</td>
<td></td>
</tr>
<tr>
<td>Professor Wendy Graham</td>
<td></td>
</tr>
<tr>
<td>London Sch of Hygiene and Trop Medicine</td>
<td></td>
</tr>
<tr>
<td>Professor Stephanie Dancer</td>
<td></td>
</tr>
<tr>
<td>NHS Lanarkshire</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Co-Investigators</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Alexander Aiken</td>
<td></td>
</tr>
<tr>
<td>Institute</td>
<td>Grant reference</td>
</tr>
<tr>
<td>London Sch of Hygiene and Trop Medicine</td>
<td>MR/R019274/1</td>
</tr>
</tbody>
</table>
changes we will do assessments both before and after the training of the champions and the cleaners. This includes measuring their knowledge and beliefs using questionnaires.

We will also secretly stick fluorescent tags on relevant places, like beds, which can only be removed by thorough cleaning, and monitoring these tags will help us to know if the environment has become cleaner. This will enable us to decide upon the methods to be used in the bigger follow-on trial, which will also include measuring hygiene levels using microbiology, and measuring infections in newborns using the same clinical methods a doctor would employ, such as recording temperature and blood pressure.

We will share the findings of this preliminary research both in Tanzania and internationally, through published papers, local workshops, conference presentations and relevant websites.
<table>
<thead>
<tr>
<th>Co-Investigators</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Shevin Jacob</td>
<td>While serious mental illness (SMI) defined as schizophrenia, bipolar disorder, or psychosis is only 0.06% of global mental illness, those suffering from SMI in low income countries do not have access to reliable and well accepted community based treatment, where they could get the support and care of family and local community.</td>
</tr>
<tr>
<td>Liverpool School of Tropical Medicine</td>
<td>People with SMI in Uganda can be treated in the national mental hospital and be given medication. But once their condition has been stabilised, and they are ready to leave hospital, even if their family are prepared to have them back home, there are no government agencies to counsel, care and follow up their recovery needs. There are simply few resources available and little international attention and research has focused on this area.</td>
</tr>
<tr>
<td>Dr Noeline Nakasujja</td>
<td>Addressing this important gap is the focus of this research. The Preventing Hospital Re-admissions for People with Severe Mental Illness in East Africa (PRISM) development project has been designed in partnership with the Ugandan NGO YouBelongHOME (YBH), who have begun an innovative programme working to improve appropriate, hospital to home mental health interventions with human rights values at the core. Butabika Mental Health Hospital, Kampala, Uganda are partners in this work.</td>
</tr>
<tr>
<td>Makerere University</td>
<td>YBH is delivered by a multi-disciplinary team. Due to extremely scarce resources, sustainability can only occur by empowering families and local communities, to provide a basic level of support and care, and by re-creating the national mental hospital as short term acute care to stabilise people with severe mental illness and to return them to community care as soon as possible.</td>
</tr>
<tr>
<td>Dr Byamah Brian Mutamba</td>
<td>YBH is centred on post hospital discharge interventions to empower the family as an active agent in the returned person’s recovery, and also, to connect to family, friends and communities. Recovery is supported through discussions and dialogue with family and discharged person regarding health, housing security, family income, medication needs, knowledge of mental illness/myths, how to assist in the recovery process, reinforcing particular tribal values to give impetus to supportive behaviour, developing problem solving skills, ways to give and receive respect and recognition.</td>
</tr>
<tr>
<td>YouBelong Uganda</td>
<td></td>
</tr>
<tr>
<td>Mr David Cappo</td>
<td></td>
</tr>
<tr>
<td>YouBelong Uganda</td>
<td></td>
</tr>
</tbody>
</table>
Despite its potential, the YBH intervention lacks systematically gathered evidence for its effectiveness in East African LICs. Before conducting a larger clinical trial which aims to establish this evidence, more information is needed to determine the feasibility, acceptability, and appropriateness of the YBH intervention in settings like Uganda.

To gather this information PRISM will explore 3 areas. 1) Explore who is at risk of mental health hospital readmission in Uganda within 3 months of discharge and develop a risk score as a tool for health workers; 2) Using action research and patient and family interviews, test and refine the YBH pre- and post-discharge intervention with a sub-set of patients and families in Kampala and Wakiso districts, the principal catchment area for Butabika Hospital. What could be improved and how? 3) Undertake a feasibility assessment of community-based initiatives using qualitative data collection and a Delphi Method as a means of involving a range of people with different perspectives sharing their expertise, and coming to a consensus about best options.

There are many options (e.g. community development at village and family level; rapid or emergency response team and micro-financing initiatives, peer support workers). Which might work best and against what criteria? The research findings will inform the design of a future clinical trial which has a primary outcome to decrease readmission within three months of discharge among high-risk patients with SMI in East African countries, and better support people discharged from hospital recover at home.
HCVAVERT: designing a trial to cure hepatitis C virus (HCV) in HCV-infected pregnant women and prevent VERTical HCV transmission

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Ali Judd</td>
<td>University College London</td>
<td>MR/R019746/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

- Dr Aya Mohamed
  - Ain Shams University
- Professor Manal El-Sayed
  - Ain Shams University
- Mrs Sylvie Deuffic-Burban
  - INSERM
- Professor Yazdan Yazdanpanah
  - INSERM
- Dr Giuseppe Indolfi
  - Meyer
- Dr Marc Lallemant
  - PHPT Research Unit (HIV Prevent & Treat)
- Dr Anna Turkova
  - University College London
- Dr Claire Thorne
  - University College London
- Dr Deborah Ford
  - University College London
- Professor Diana Gibb
  - University College London
- Dr Eleni Nastouli
  - University College London
- Dr Intira Collins
  - University College London
- Dr Sarah Pett
  - University College London
- Professor A E Ades
  - University of Bristol

**Summary**

In 2015, an estimated 71 million people, or 1% of the world’s population, were living with hepatitis C, including 5 million children, most of whom were infected from their mother during pregnancy. Hepatitis B and C together caused 1.34 million deaths globally in that year alone, which is comparable to the number of people dying from tuberculosis, and higher than the number for HIV.

Until recently, treatment for hepatitis C involved patients having daily injections of medication, which made some of them feel poorly. Remarkable developments of direct acting antivirals (DAAs) have recently transformed this treatment, and patients now take pills which are safe and effective, and which cure nearly everyone. Because of this, the WHO would like to eliminate hepatitis C by 2030. However there is currently no treatment available for pregnant women with hepatitis C, and around 6 in every 100 will transmit it to their baby. Pregnancy is an important opportunity to test and diagnose hepatitis C, but it is not known whether treatment of hepatitis C during pregnancy is safe and if it can be used to stop transmission from a mother to her baby.

Testing and treatment in pregnancy is the foundation of treatment and control of transmission of infectious diseases such as HIV, syphilis and hepatitis B. In many low and middle income countries, pregnant women do not present to healthcare services until the third trimester, and drop out of care after delivery, highlighting the importance of this window of opportunity to engage in medical care. However as there is no recommended treatment for hepatitis C in pregnancy, currently those identified in pregnancy are told to delay treatment until after birth.

This means that there is still a risk that the mother will transmit the virus to the baby, and the mother’s disease may get worse during pregnancy and after birth, especially if they drop out of care. We plan to design a trial to treat pregnant women with hepatitis C, to cure them and prevent transmission to their babies. We will probably conduct this trial in Egypt and Ukraine, which both have a large number of people with hepatitis C. However before we do this, we need to find out additional background information to help us design the trial.

We would like to: (1) contact experts about blood test results that they already have from pregnant women and their babies.
which can help us understand when transmission of hepatitis C is likely to occur. We will put this information from different studies together to see if it helps us work out when we would need to treat pregnant women for hepatitis C (e.g. early pregnancy or late pregnancy) (2) do a literature review to understand which DAAs seem to be the safest to give in pregnancy, to help us choose the safest treatment for our trial (3) evaluate the benefit and cost of different ways that pregnant women could be tested for hepatitis C and treated (for example, early in pregnancy compared to later in pregnancy), to help us in terms of what we compare in our future trial (4) ask pregnant women and doctors what they think about treatment for hepatitis C in pregnancy, and assess which clinics in Egypt and Ukraine may be suitable to participate in our trial.

Answering these questions will help us design the trial, for which we will then apply for separate funding.
### Project title
Male partner-assisted contact tracing for HIV and tuberculosis in Malawi: an adaptive multi-arm multi-stage randomised trial (mPATCH-TB)

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Peter MacPherson</td>
<td>Liverpool School of Tropical Medicine</td>
<td>MR/R019762/1</td>
</tr>
</tbody>
</table>

### Co-Investigators

- Dr Eleanor MacPherson  
  Liverpool School of Tropical Medicine
- Professor Katherine Fielding  
  London Sch of Hygiene and Trop Medicine
- Professor Liz Corbett  
  London Sch of Hygiene and Trop Medicine
- Dr Hendramooorthy Maheswaran  
  University of Liverpool

### Summary

In Africa, tuberculosis and HIV (the virus that causes AIDS) are major health problems, and both affect millions of adults every year. HIV slowly weakens the immune system, and makes individuals very susceptible to developing severe tuberculosis. Although effective treatments are available for both tuberculosis and HIV, many individuals who need treatment don't receive it because they are unaware that they have the infection, or experience difficulties in accessing testing and treatment at clinics.

Whilst they are not receiving treatment, they can transmit infection to others in their household or communities, and may die of the consequences of infection. Men in Africa experience particular difficulties in accessing testing and treatment for tuberculosis and HIV. Our previous research in Africa has shown that two-times as many men than women have untreated tuberculosis in the community. Men experience substantially longer delays than women in accessing diagnosis for HIV and TB (on average up to one year longer). This is for a number of reasons including masculine care-seeking behaviour, competing demands with employment, and perceptions that health centres are unwelcoming for men.

We have additionally shown that men are responsible for up to 2/3rds of new tuberculosis infections in Africa. This means that improving timely diagnosis of TB and HIV among men could have important health benefits for men, women and children in the community by reducing infection risk. Building upon our substantial experience in undertaking HIV and tuberculosis research in sub-Saharan Africa, in this research we aim to rigorously identify strategies that could improve mens' rates of testing for tuberculosis and HIV.

Women are substantially more likely than men to attend health centres with symptoms of tuberculosis, and are therefore a key group through which male partners with undiagnosed infection can be accessed. We have previously successfully demonstrated this approach in a recent study in which pregnant women attending clinics were asked to distribute HIV self-test kits to their partners.

In the first stage of this research, we will conduct detailed interviews with men, women and health providers to identify and refine interventions that are likely to be feasible and
acceptable when delivered by women to their male partners. We will base interventions upon those that we have experience of testing through previous studies.

Types of interventions include: availability of a "male-friendly fast-track clinic"; written information and reminder phone-calls/text messages; home collection of sputum by partners; home HIV test delivery by partners; and varying levels of financial incentives. We will then conduct an innovative trial to identify which of these interventions has greatest potential to be effective, affordable and safe at increasing male partners' rates of TB and HIV testing.

We will do this by recruiting a total of 445 women attending a health centre in Blantyre with symptoms of tuberculosis. Women participants will be tested for TB and HIV, and then randomly allocated to one of the five intervention groups according to the day they attend the clinic. After 30 days, we will assess how many male partners in each group have completed screening for tuberculosis and HIV. (To ensure equity of care, all household members will be able to access screening at the clinic, however the primary focus will be on male partners because of their high risk of disease).

We will compare rates of testing between groups, and interventions that do not achieve rates of competing testing higher than the standard of care will be discarded, leaving only interventions with high potential for public health effectiveness. By the completion of the study, we will have identified 1-2 interventions that can be evaluated in a larger definitive trial that will in
Joint Global Health Trials - Call 8 Full Grant

Project title
MICA: Hydroxyurea - Pragmatic Reduction In Mortality and Economic burden (H-PRIME)

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Thomas Williams</td>
<td>Imperial College London</td>
<td>MR/S004904/1</td>
</tr>
</tbody>
</table>

Co-Investigators

Dr Djesika Amendah
African Population and Health Res Centre

Dr Mainga Hamaluba
ARCH - KWTRP

Dr Sophie Uyoga
ARCH - KWTRP

Professor Peter Olupot-Olupot
Busitema University

Dr Russell Ware
Cincinnati Children's Hospital

Professor Kathryn Maitland
Imperial College London

Mr Charles Kiyaga
Ministry of Health (Uganda)

Professor Ann Walker
University College London

Professor Diana Gibb
University College London

Mrs Elizabeth George
University College London

Summary

Sickle cell anaemia (SCA) is a common inherited condition that affects around 1% of all children born in much of sub-Saharan Africa. Without early diagnosis and appropriate treatment under-5 mortality in those affected is between 50 and 90%. As a result, through much of the continent SCA is responsible for between 5 and 16% of total under-5 mortality. These high levels of mortality could be reduced dramatically with simple treatments that include educating parents to recognise danger signs and seek emergency care, and by measures that protect against acute bacterial and malarial infections using vaccines and prophylactic antibiotic and anti-malarial drugs.

Nevertheless, without specific treatments that modify the course of the disease, many of those affected will live lives that are characterized by frequent and recurrent bouts of severe illness that include acute and chronic pain and progressive multi-organ deterioration. Unlike diseases like HIV, malaria and tuberculosis, SCA does not enjoy a high profile in the eyes of the international community and remains widely neglected by ministries of health through much of sub-Saharan Africa. Through H-PRIME, we will address three key questions in the management of children with SCA in Africa today through a single large, efficient and pragmatic clinical trial.

First, we will determine whether hydroxyurea, a common and effective treatment for SCA in resource-rich regions, could be a useful option in parts of Africa with limited access to medical care. In most countries hydroxyurea is administered and monitored in a way that will not be achievable in most of Africa and our primary question, therefore, will be whether the drug can be used safely and effectively to reduce mortality and improve the quality of life in survivors when administered pragmatically following a weight-band-based dosing strategy with minimal clinical and laboratory monitoring. Second, we will investigate whether better protection from bacterial infections in children with SCA can reduce all cause hospital admission and further reduce mortality.

The current approach to the prevention of bacterial infections is through the use of oral penicillin. However, this is only effective against a narrow range of bacterial organisms and we will therefore investigate whether the addition of a second agent, co-trimoxazole, could bring further benefits in the absence of harm. Finally, the current approach to the prevention of malaria infections relies on drugs that are associated with high levels of resistance. We will therefore investigate whether
malaria prevention with a more modern and highly effective drug - dihidroartemisinin-piperaquine - could be used as an alternative, and that this will not cause harm in terms of side effects and the development of further drug resistance.
**Joint Global Health Trials - Call 8 Full Grant**

**Project title**
Phase III, Multicentre, Randomized, Double-blind, Placebo-controlled Study to Evaluate Efficacy of Probiotic Supplementation for Prevention of Neonatal Infections

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Anju Sinha</td>
<td>Indian Council for Medical Res (ICMR)</td>
<td>MR/S004912/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

- Dr Arti Kapil
  - All India Inst of Medical Sciences Delhi
- Dr SAILAJANANDAN PARIDA
  - Asian Institute of Public Health (AIPH)
- Dr Sunil Sazawal
  - Centre for Public Health Kinetics (CPHK)
- Dr Adhisivam Bethou
  - JIPMER
- Dr Ashish Bavdekar
  - KEM Hospital Research Centre, Pune
- Professor Arvind Saili
  - Lady Hardinge Medical College
- Dr Subodh Gupta
  - Mahatma Gandhi Institute of Medical Sci
- Professor Rajni Gaind
  - Safdarjung Hosp & Vardhaman Mahavir MC
- Professor Narendra Kumar Arora
  - The INCLEN Trust International

**Summary**

Summary (layman): Neonatal infections are a major cause of sickness and death in infancy in the developing countries. Treatment with antibiotics has limitation as the bacteria have become resistant and there is dearth of new antibiotics.

At present there is lack of knowledge about how to prevent the disease. Current trial aims to find out if feeding probiotics daily for 30 days during the first month of life would prevent these infections. Remaining healthy in the first month is important as it allows the newborns to grow to become healthy adults. The study would be coordinated by three research organizations and implemented at six sites in India. 6500 Newborn infants weighing less than 2500gms would be allocated to either the probiotics or a placebo group without the study participants' or researchers’ knowledge of the group assignment.

They would be fed the assigned drug and followed up in their homes regularly upto 60 days by trained field workers (daily in the first week, biweekly during 2-4 weeks of life, and weekly during the second month) to find out if they fell sick. Sick infants would be referred/taken to study physician for examination, testing and treatment.

All study related information would be captured on Tablets/hand held devices and sent to a central location for analysis. After completion of the study the data would be analysed to see whether there were less infections/sepsis cases in the group where infants were fed with probiotics as compared to the other group. If the results favour the probiotics it could be used as a new method of preventing neonatal infections in the developing countries. This would benefit millions of newborns who are currently dying due to infections.
**Joint Global Health Trials - Call 8  Full Grant**

**Project title**
Effectiveness and safety of calcium channel blockade for organophosphorus and carbamate anticholinesterase insecticide poisoning (CCBOC study)

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Michael Eddleston</td>
<td>University of Edinburgh</td>
<td>MR/S004947/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**
- Dr Fazle Rabbi Chowdhury
  Bangabandhu Sheikh Mujib Medical Uni
- Dr Aniruddha Ghose
  Chittagong Medical College
- Professor Dr. Md. Zakir Hossain Zakir
  Dhaka Medical College
- Dr MD BARI
  Dhaka Medical College
- Dr Mohammad Amin
  Dhaka Medical College
- Professor Abul Faiz
  Mahidol Oxford Research Unit
- Professor John Norrie
  University of Edinburgh

**Summary**
Attempted suicide by drinking pesticides used in farming (called 'pesticide self-poisoning') is the second most important global means of suicide, killing over 150,000 people each year, mostly in poor rural Asian communities. The pesticide used is often stored in the home and easily available at moments of stress or anger. Importantly, survival after self-poisoning allows families, community, and medical/social services to support the person, to help them find reasons not to do it again.

Pesticides called organophosphorus (OP) and carbamate insecticides are responsible for about two thirds of these deaths across the world. They both inhibit an enzyme called acetylcholinesterase, which usually breaks down the chemical acetylcholine found in the brain and nerves. Because its breakdown is now stopped, acetylcholine accumulates and causes problems with breathing which may be severe enough to kill, even with best available treatment.

Unfortunately, no new medicine has been introduced into medical practice for 50 years, despite thousands of studies and millions of deaths. Current treatment does not always work; new treatments are urgently required. Flow of calcium salt into the nerve cells is essential for allowing nerves to work and communicate with other cells in the body. Carefully reducing this flow of calcium with medicines that partially block channels in the nerve cell - calcium channel blocking medicines [CCB] or the magnesium salt - may reduce the pesticides' effects and prevent deaths.

Eight studies of magnesium have already been done in poisoned patients; some have suggested benefit from this treatment but overall the studies have been too small and the results mixed. There is no clear information on whether these medicines work. We propose to set up a big study (or randomised controlled trial, RCT) of patients with OP or carbamate poisoning admitted to 4 large Bangladeshi hospitals where this poisoning is a major problem, killing thousands of people each year. We will recruit around 3,100 patients to the study over 3 1/2 years.

One third of the patients selected at random will receive routine treatment, while 1/3 will get additional CCB medicines and 1/3 will get the additional magnesium. The extra treatments will be given for 2 days. We will check how many patients die (currently about 11% die with normal treatment) and how many need to go to the intensive care ward for help with their breathing.
(called mechanical ventilation where a machine breathes for them) across the three groups. We will look to see whether these additional treatments reduce the number of patients dying or needing mechanical ventilation. Our group has a great deal of experience treating and studying poisoned patients, having done similar studies of pesticide poisoning in Sri Lanka and Bangladesh and led recent global improvements in treatment.

The study will provide proof about whether these relatively cheap, widely available treatments help the poisoned patients. It potentially will result in the first new treatment for these forms of poisoning for 50 years being introduced in routine hospital practice across the world. The results will be shared with the World Health Organisation and our colleagues in poison centres and hospitals across Asia. Better treatment offers the opportunity to save tens of thousands of lives amongst some of the poorest communities in rural Asia and reduce the heartbreak of suicide amongst children, families, and communities.

There will be other benefits from the study. It will set up high-quality infrastructure in Bangladesh that other doctors and researchers will be able to use to set up studies for patients with other diseases and problems. The study will offer useful experience to clinical researchers that they will be able to use for their own research. We will also work with academic laboratories to do studies that will help us better understand the effects of these poisons on human bodies.
Joint Global Health Trials - Call 8 Full Grant

Project title
High Dose Oral Rifampicin to Improve Survival from Adult TB Meningitis - [HARVEST] Trial

Grant holder | Institute | Grant reference
--- | --- | ---
Dr David Meya | Infectious Diseases Institute (IDI) | MR/S004963/1

Co-Investigators

Dr Lindsey te Brake
Catholic (Radboud) University Foundation

Professor Reinout van Crevel
Catholic (Radboud) University Foundation

Mr Robert Aarnoutse
Catholic (Radboud) University Foundation

Dr Fiona Cresswell
London Sch of Hygiene and Trop Medicine

Dr Conrad Muzoora
Mbarara University of Sci and Tech

Dr Felicia Chow
University of California, San Francisco

Dr Darma Imran
University of Indonesia

Dr Suzaan Marais
University of KwaZulu-Natal

Dr David Boulware
University of Minnesota

Dr Joshua Rhein
University of Minnesota

Dr Katherine Hullsiek
University of Minnesota

Dr Radha Rajasingham
University of Minnesota

Dr Raph Hamers
University of Oxford

Dr A. Rizal Ganiem
University of Padjadjaran

Professor Rovina Ruslami
University of Padjadjaran

Summary

Tuberculous meningitis (TBM) is the most severe form of tuberculosis (TB). TB meningitis results in death or neurological disability in >50%. The risk of death is more than 2-fold greater in HIV-infected persons. The currently recommended initial treatment regimens for TB meningitis and pulmonary TB are identical, despite that fact that rifampicin penetrates very poorly into cerebrospinal fluid (CSF).

At the typical rifampicin dose (given at 10mg/kg/day) the concentrations of rifampicin in cerebrospinal fluid (CSF) seldom achieve the levels necessary for activity against TB. In a small randomised clinical trial in Indonesia of 60 people, our team found that a higher intravenous dose of rifampicin (13mg/kg) led to a 58% reduction in the hazard of death.

A follow-up detailed exposure-response analysis revealed that as the level of rifampicin increased, survival improved. In a second phase II trial of rifampicin given orally at a dose of 30mg/kg/day, the favourable blood and CSF drug exposure and survival benefit were confirmed. Based on the exposure-response analysis we believe a >3-fold increase in rifampicin dose is needed to achieve the CSF levels that correlate with better outcomes.

This may explain why an oral rifampicin dose of 15 mg/kg evaluated in a large phase III trial in Vietnam did not show any survival benefit overall, although improved survival was seen in individuals with TB resistant to isoniazid. Data from all these international studies have recently been combined and analysed in a detailed model by our team that has led to our conviction that a flat dose of 1500mg for Asian or 1800mg for Africans will produce rifampicin exposures that correlate with improved outcomes. A phase III study is the rational next step. Based on these studies and pharmacokinetic modelling, we propose to evaluate a 3.5-fold higher oral dose of rifampicin in a double-blinded randomised phase III clinical trial in 600 adult TB meningitis patients in Indonesia, Uganda, and South Africa.

In order to simplify future implementation, we have chosen a single (flat) high rifampicin dose for all patients (1500mg in Indonesia and 1800mg in Uganda/South Africa, corresponding to ~35mg/kg), to be administered during the first 8 weeks of treatment. All patients will receive three other first-line TB drugs, standard adjuvant steroids, and anti-retroviral treatment as indicated. The primary outcome will be 6-month mortality.
Additionally, we will also evaluate the diagnostic accuracy of the new Xpert MTB/Rif Ultra for diagnosis of TB meningitis while screening patients for this trial. We expect that a high dose of rifampicin could be implemented broadly and quickly to the benefit of many TB meningitis patients, considering that the drug is widely available at low cost and its properties are known to clinicians all over the world.

To confirm this we will carefully examine the cost-effectiveness of the intervention as well as factors relating to the optimal implementation of high dose rifampicin for TB meningitis patients. We expect this trial (if successful) to change the worldwide standard of care for the treatment of TB meningitis.
**Joint Global Health Trials - Call 8 Full Grant**

<table>
<thead>
<tr>
<th>Project title</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMWaNA Operationalising kangaroo Mother care before stabilisation among low birth Weight Neonates in Africa: RCT to examine mortality impact in Uganda</td>
<td>MR/S004971/1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Joy Lawn</td>
<td>London Sch of Hygiene and Trop Medicine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Co-Investigators</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Moffat Nyirenda Entebbe General Hospital</td>
<td>Globally, there are 2.6 million neonatal deaths each year (defined as death during the first 28 days) and over 80% of these deaths occur in babies who are born small, due to being born too soon (preterm), being too small for their gestational age, or both. Preterm birth complications are the most common cause of death for children under age five worldwide, and yet there has been much slower progress in reducing these deaths compared to child deaths from malaria or HIV.</td>
</tr>
<tr>
<td>Dr Cally Tann London Sch of Hygiene and Trop Medicine</td>
<td>Three-quarters of deaths due to prematurity occur in sub-Saharan Africa and south Asia, where there is limited availability of neonatal intensive care and most hospitals lack basic equipment. In Uganda alone, an estimated 45,000 newborn deaths occur annually, at least a quarter of which are directly due to complications of prematurity. Kangaroo Mother Care (KMC) involves placing the baby skin-to-skin with a caregiver, usually the mother, promoting warmth and breastfeeding and also empowering the mother, increasing maternal confidence to improve bonding with the baby. KMC has been found to reduce deaths by 40% for newborns weighing less than 2000g, but these trials included only babies that were considered to be stable.</td>
</tr>
<tr>
<td>Ms Catherine Pitt London Sch of Hygiene and Trop Medicine</td>
<td>WHO guidelines recommend KMC for babies weighing 2000g or less at birth, starting as soon as they are 'stable,' i.e., not on any other medical treatments. However, the majority of deaths occur in babies before they have stabilised, with complications like breathing difficulties, soon after birth and in settings without neonatal intensive care. The only randomised controlled trial of KMC on survival amongst babies before stabilisation reported a 43% mortality reduction compared to standard care (incubators). Importantly, this trial excluded over half of eligible babies and had other design problems. Hence, there is currently not enough evidence to recommend KMC for small babies before stabilisation who could benefit the most.</td>
</tr>
<tr>
<td>Dr Christian Hansen London Sch of Hygiene and Trop Medicine</td>
<td>A well-designed trial is needed to assess the impact of KMC started before stabilisation on mortality compared to incubator care. The Operationalising kangaroo Mother care before stabilisation among low birth Weight Neonates in Africa (OMWaNA) trial is a partnership of the Medical Research Council Uganda, Makerere University, and the London School of Hygiene and Tropical Medicine. Omwana means 'child' in Uganda's national language. The aim of this trial is to determine the</td>
</tr>
<tr>
<td>Professor Diana Elbourne London Sch of Hygiene and Trop Medicine</td>
<td></td>
</tr>
<tr>
<td>Dr Elizabeth Allen London Sch of Hygiene and Trop Medicine</td>
<td></td>
</tr>
<tr>
<td>Professor Janet Seeley London Sch of Hygiene and Trop Medicine</td>
<td></td>
</tr>
<tr>
<td>Mr KENNETH ROGER KATUMBA London Sch of Hygiene and Trop Medicine</td>
<td></td>
</tr>
<tr>
<td>Dr Melissa Morgan London Sch of Hygiene and Trop Medicine</td>
<td></td>
</tr>
<tr>
<td>Dr Elizabeth Ekirapa Kiracho Makerere University</td>
<td></td>
</tr>
<tr>
<td>Professor Peter Waiswa Makerere University</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Peter Waiswa Makerere University</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Summary</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A well-designed trial is needed to assess the impact of KMC started before stabilisation on mortality compared to incubator care. The Operationalising kangaroo Mother care before stabilisation among low birth Weight Neonates in Africa (OMWaNA) trial is a partnership of the Medical Research Council Uganda, Makerere University, and the London School of Hygiene and Tropical Medicine. Omwana means 'child' in Uganda's national language. The aim of this trial is to determine the</td>
<td></td>
</tr>
</tbody>
</table>
impact of KMC, started before stabilisation, on mortality (at 7 and 28 days) compared to incubator care in a group of babies weighing 2000g or less.

In the trial, 2188 babies who are not yet stable will be assigned by chance to receive either KMC or incubator care. The trial will take place in four "typical" hospitals without intensive care (Jinja, Masaka, Iganga, Entebbe). Incubators are the standard method of keeping small and preterm babies warm in Ugandan hospitals, often with several newborns sharing. The trial will also compare the overall costs of KMC and incubator care, considering both costs to hospitals and costs to families. With parents and hospital staff, we will evaluate issues that support or discourage starting KMC before stabilisation.

In addition, we will measure quality of life among women caring for small babies in Uganda with a new survey tool. The Ugandan Government committed to meeting an ambitious global goal for newborn survival and has given high priority to addressing newborn deaths. The National Newborn Steering Committee has recommended increased scale-up of KMC in health facilities. Key stakeholders will be engaged throughout the trial including the Uganda Ministry of Health, Uganda Paediatric Association, UNICEF (headquarters and country), WHO, and the International KMC Network.

The findings of this trial will help inform wider use of KMC in Uganda and around the world, especially in settings where most babies die, and where neonatal intensive care is not available.
**Joint Global Health Trials - Call 8 Full Grant**

**Project title**
Effects of metronidazole plus intermittent preventive treatment of malaria in pregnancy on birth outcomes: a randomised controlled trial in Zambia

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Daniel Chandramohan</td>
<td>London Sch of Hygiene and Trop Medicine</td>
<td>MR/S004998/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**

Dr David MacIntyre  
Imperial College London

Dr Elizabeth Allen  
London Sch of Hygiene and Trop Medicine

Professor Philipp Mayaud  
London Sch of Hygiene and Trop Medicine

Dr R. Matthew Chico  
London Sch of Hygiene and Trop Medicine

Dr Suzanna Francis  
London Sch of Hygiene and Trop Medicine

Dr Mike Chaponda  
Tropical Diseases Research Centre Zambia

Dr Modest Mulenga  
Tropical Diseases Research Centre Zambia

Dr Sebastian Hachizovu  
Tropical Diseases Research Centre Zambia

Professor Nigel Klein  
University College London

Dr Antioneta Medina-Lara  
University of Exeter

Dr Enesia Chaponda  
University of Zambia

**Summary**

In areas of East and Southern Africa, malaria infection during pregnancy and curable sexually transmitted and reproductive tract infections (STIs/RTIs) are very common. About one-third of women in the sub-region are infected with malaria parasites during pregnancy, one-half of them have bacterial vaginosis (BV) and one-quarter are infected with trichomonas vaginalis (TV). All of these cause adverse birth outcomes. Malaria parasites sequester in the placenta and, therefore, taking conventional blood test may not detect the infection. Thus, the World Health Organization recommends that women who live in malaria-endemic areas receive intermittent preventive treatment (IPTp) using sulphadoxine-pyrimethamine (SP) during their second and third trimesters of pregnancy. However, malaria parasites have developed resistance against SP. An alternative to SP, dihydroartemisinin-piperaquine (DP), has been shown to clear malaria parasites from pregnant women better than SP. However, SP appears also to confer some protection against non-malaria causes of adverse birth outcomes including curable STIs/RTIs. So a switch from SP to DP might not be best. It is possible that SP or DP - if combined with treatment against BV and TV metronidazole (MTZ), a medicine that is also safe to administer in the second and third trimesters of pregnancy - may be better than providing SP, the current standard of care. To examine this, we are proposing a three-arm trial, partially placebo-controlled, that will compare SP plus MTZ placebo versus SP plus MTZ versus DP plus MTZ in a geographic area of north-east Zambia where malaria transmission is high, malaria parasite-resistance to SP is high, and the prevalence of BV and TV in pregnant women is also high.

As part of the main trial, we will also conduct a full economic evaluation of trial interventions establish costs, the incremental cost-effectiveness, and acceptability of the three study treatments using discrete choice experiments. We will ask prospective participants if they will provide vaginal swabs and stool samples which we will use to characterise the effect of treatment across trial arms on the vaginal and intestinal microbiota communities, vaginal and intestinal bacterial loads and identify potential triggers of preterm birth that are related to inflammation. Finally, we will also measure the drug sensitivity of several pathogens implicated with vaginal discharge, lower abdominal pain, or genital ulcers.
Joint Global Health Trials - Call 8 Full Grant

**Project title**
Adjunctive Ivermectin Mass Drug Administration for Malaria Elimination: A cluster randomized trial

<table>
<thead>
<tr>
<th>Grant holder</th>
<th>Institute</th>
<th>Grant reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Anna Last</td>
<td>London Sch of Hygiene and Trop Medicine</td>
<td>MR/S005013/1</td>
</tr>
</tbody>
</table>

**Co-Investigators**
- Dr Amabelia Rodrigues  
  Bandim Health Project
- Dr Hannah Slater  
  Imperial College London
- Dr Catherine Greenland  
  London Sch of Hygiene and Trop Medicine
- Ms Catherine Pitt  
  London Sch of Hygiene and Trop Medicine
- Professor Chris Drakeley  
  London Sch of Hygiene and Trop Medicine
- Professor David Mabey  
  London Sch of Hygiene and Trop Medicine
- Professor James Logan  
  London Sch of Hygiene and Trop Medicine
- Dr John Bradley  
  London Sch of Hygiene and Trop Medicine
- Dr Muna Affara  
  London Sch of Hygiene and Trop Medicine
- Professor Robin Bailey  
  London Sch of Hygiene and Trop Medicine
- Dr Thomas Ant  
  London Sch of Hygiene and Trop Medicine
- Professor Umberto D'Alessandro  
  London Sch of Hygiene and Trop Medicine
- Dr Paulo Djata  
  Ministry of Health (Guinea Bissau)
- Mr Hamadou Boiro  
  National Institute of Studies & Research

**Summary**
This trial will be the first to investigate the impact of adding ivermectin (IVM) to mass drug administration (MDA) with an efficacious antimalarial (e.g., dihydroartemisinin-piperaquine (DP)) to reduce malaria transmission in a seasonal low-transmission setting. Additive IVM MDA will be compared to DP-only MDA (with treatment daily for three days during the three months of peak malaria transmission (July-September)) in combination with standard programmatic interventions for malaria control (long-lasting insecticidal nets (LLIN) and intermittent preventative treatment in pregnancy (IPTp)) in a cluster-randomized community-based trial.

Primary outcome measures will be population-based Plasmodium falciparum (malaria infection) prevalence (estimated using ultra-sensitive PCR tests) and Anopheles gambiae (malaria vector) survival (measured using parity estimated by dissection of Anopheles ovaries). Data on MDA coverage, acceptability and feasibility of the intervention and a cost-effectiveness analysis will be included. We have established field infrastructure on the Bijagós Archipelago (including trained field entomologists and field laboratory technicians) and have detailed recent baseline data on the burden of disease caused by malaria and other neglected tropical diseases (NTDs) and vector populations on the islands.

This 'natural laboratory' island setting provides an unparalleled opportunity to understand transmission and its interruption using a combined MDA strategy through investigating the impact of imported infections (through an expanded community-based CDSAT (case detection screen and treat) intervention which we will include in both arms), using serological (immune) markers in the blood to define transmission dynamics and estimate entomological inoculation rate (EIR) and monitoring the effect of IVM MDA on confined vector populations over time.