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Review of the Joint Global Health Trials funding scheme

Impact Case Studies

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Summary of JGHT impact case studies – Case number links to relevant case study

Case	Grant	Call	Publication of underpinning research
JGHT-funded trials with evidence of policy influence			
Case study 1	G1100682/1, Thuy Le	Call 1	Le T et al (2017) A Trial of Itraconazole or Amphotericin B for HIV-Associated Talaromycosis. N Engl J Med 376:2329-2340
Case study 2	G1100684/1, Jeremy Day	Call 1	Beardsley J et al (2016) Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis, N Engl J Med 374: 542-554
Case study 3 Case study 4	G1100693/1 Diana Gibb (2 case studies)	Call 1	Hakim J et al (2017) Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa. N Engl J Med 377:233-245 Mallewa J et al (2018) Effect of ready-to-use supplementary food on mortality in severely immunocompromised HIV-infected individuals in Africa initiating antiretroviral therapy (REALITY): an open-label, parallel-group, randomised controlled trial. The Lancet HIV 5: PE231-E240 Kityo C et al (2018) Raltegravir-intensified initial antiretroviral therapy in advanced HIV disease in Africa: A randomised controlled trial. PLoS Med 15: e1002706
Case study 5	MR/K007211/1 Gail Davey	Call 2	Negussie H et al. (2018) Lymphoedema management to prevent acute dermatolymphangioadenitis in podoconiosis in northern Ethiopia (GoLBeT): a pragmatic randomised controlled trial. Lancet Glob Health 6:e795–e803
Case study 6	MR/L004321/1 Karen Devries*	Call 3	Devries K et al (2015) The Good School Toolkit for reducing physical violence from school staff to primary school students: a cluster-randomised controlled trial in Uganda. The Lancet Global Health 3: PE378-E386
Case study 7	MR/L004437/1 M Rowland	Call 3	Protopopoff et al (2018) Effectiveness of a long-lasting piperonyl butoxide-treated insecticidal net and indoor residual spray interventions, separately and together, against malaria transmitted by pyrethroid-resistant mosquitoes: a cluster, randomised controlled, two-by-two factorial design trial. The Lancet 391: P1577-1588
Case study 8	MR/M007413/1 David Meya	Call 4	Bahr, NC et al (2018) Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study. Lancet Infect Dis 18: 68–75
Case study 9	MR/N00597X/1 Rachel Pullan	Call 5	Pullan RL et al (2019) Effects, equity, and cost of school-based and community-wide treatment strategies for soil-transmitted helminths in Kenya: a cluster-randomised controlled trial. The Lancet 393: 2039–50
JGHT awards with potential for policy influence, PIs actively engaged			
Case study 10	G1100677/1 P Phillips-Howard	Call 1 / 5	Phillips-Howard P et al (2016) Menstrual cups and sanitary pads to reduce school attrition, and sexually transmitted and reproductive tract infections: a cluster randomised controlled feasibility study in rural Western Kenya. BMJ Open 6:e013229
Case study 11	G1100654/1 Feiko Ter Kuile	Call 1	Ahmed R et al (2019) Efficacy and safety of intermittent preventive treatment and intermittent screening and treatment versus single screening and treatment with dihydroartemisinin–piperaquine for the control of malaria in pregnancy in Indonesia: a cluster-randomised, open-label, superiority trial. Lancet Infect Dis. S1473-3099(19)30156-2
JGHT awards, main trial findings not yet published			
Case study 12	MR/K007467/1 Carlton Evans	Call 2	Community randomised evaluation of socioeconomic intervention to prevent TB – *Research ongoing*
Case study 13	MR/N006178/1, Tazeen Jafar	Call 3/5	Integrated Primary Care Strategies to Reduce High Blood Pressure-A Cluster Randomized Trial in Rural Pakistan and Sri Lanka - *Publication expected mid-Nov 2019*
Case study 14	MR/L004356/1 Angela Crook	Call 3	Papineni, P., Phillips, P., Lu, Q. et al. (2016). TRUNCATE-TB: an innovative trial design for drug-sensitive tuberculosis. International Journal of Infectious Diseases, 45: 404
Development awards with evidence of outcomes			
Case study 15	MR/M022161/1 Xiaolin Wei	Call 5	Feasibility study - Antibiotic prescribing
Case study 16	MR/P020844/1 Rosa Hoekstra	Call 7	Tekola, B. et al (2019) Adapting and pre-testing the World Health Organization's Caregiver Skills Training programme for autism and other developmental disorders in a very low-resource setting: Findings from Ethiopia. Autism: https://doi.org/10.1177/1362361319848532

*Based on desk research only. For all other case studies, PIs were consulted directly and given the opportunity to verify the accuracy of the final case study.

Case study 1

A Randomised, Open-Label, Comparative Study of Itraconazole vs. Amphotericin B for the Induction Therapy of Penicilliosis (G1100682, Call 1)

Funding period: 01/08/2011 - 31/03/2017	Funding amount: £1,540,178
Lead PI: Dr Thuy Le	Lead institution: Oxford University Clinical Research Unit (OUCRU) Viet Nam

Summary

- The 'Itraconazole versus Amphotericin B for Penicilliosis' (IVAP) trial was the first trial to compare the relative effectiveness of two treatments, amphotericin B and itraconazole, for talaromycosis, a common fungal infection among HIV-positive persons endemic to southeast Asia. The trial was conducted at five major referral hospitals in Viet Nam, and was led by Dr Thuy Le, Oxford University Clinical Research Unit (OUCRU), Ho Chi Minh City, Viet Nam.
- Before the trial, international guidelines recommended treatment with amphotericin B but were based on poor evidence. The trial showed that amphotericin was more effective than itraconazole, providing robust evidence to underpin the treatment recommendations. The trial's findings were taken up into national guidelines in Viet Nam, and also described in WHO guidelines.
- The trial led to health impacts by changing treatment of talaromycosis patients in Viet Nam, where amphotericin B is now provided to all patients, compared to only 30% of patients before the trial. This has cut the death rate in half, saving the lives of around 35 individuals every year.
- Locating the trial within the Vietnamese health system was crucial in enabling changes in policy and practice.

Background

Talaromycosis (formerly Penicilliosis) is a common infection among HIV-positive persons in south and southeast Asia, caused by the fungus Talaromyces marneffei. Where endemic, the disease is a major cause of HIV-related opportunistic infections and deaths (second only to tuberculosis and cryptococcal infection), and is responsible for 4–11% of HIV-related hospital admissions in Viet Nam[1]. While the widespread introduction of antiretroviral therapy has led to a decrease in the number of talaromycosis cases, the incidence remains high in people who are unaware of their HIV infection and those who are not on HIV therapy or are failing HIV therapy. Talaromycosis is also increasingly diagnosed among patients who are not infected with HIV but have other immunodeficiency conditions.

At the time of the trial's inception, international guidelines[2], endorsed by the United States CDC, NIH and the Infectious Disease Society of America, recommended initiating treatment of talaromycosis with the drug amphotericin B for 2 weeks, followed by treatment with another drug, itraconazole, for at least 6 months until the immune system improves on HIV therapy[3]. However, this guideline was based on data from a single non-comparative study[4]. Countries in southeast Asia, such as Viet Nam, did not have national guidelines for treatment of talaromycosis, and the choice of treatment was based on preference

[1] Limper AH et al (2017) Fungal infections in HIV/AIDS. The Lancet Infectious Diseases 17: e334–e343

[2] U.S. Department of Health and Human Services (2013) Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV - Talaromycosis (Formerly Penicilliosis)

[3] Kaplan J et al (2009) Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 58(RR-4): 1–207

[4] Sirisanthana, T. *et al.* (1998) Amphotericin B and Itraconazole for Treatment of Disseminated Penicillium marneffei Infection in Human Immunodeficiency Virus-Infected Patients'. Clinical Infectious Diseases 26: 1107–1110

of local doctors, rather than evidence. Mortality rates among affected patients who received anti-fungal therapy were high, at up to 30%[5].

Many doctors in Viet Nam had avoided amphotericin B as the drug was not widely available in south and southeast Asia due to inadequate supply chains, has significant side effects (earning it the nickname 'ampho-terrible' among doctors), requires daily intravenous infusion over 6 hours, and was prohibitively expensive in LMIC settings - in 2010, a 2-week course of amphotericin B cost approximately USD$308, excluding hospitalisation and laboratory monitoring costs, compared to a GDP per capita of USD$96/month for Viet Nam[6]. Given these disadvantages, and the lack of robust evidence, treatment with itraconazole only was more commonly provided in south and southeast Asia, e.g. to 70% of patients in Viet Nam[7]. Itraconazole is widely available, cheap (at USD$2 per day in 2010), well-tolerated, and can be given by mouth.

No randomised controlled trials (RCTs) had been conducted to evaluate talaromycosis treatment strategies. At the time the IVAP trial was proposed, a review of evidence from observational studies did not indicate that amphotericin B was more efficacious than itraconazole[8], and laboratory studies showed that Talaromyces marneffei clinical isolates were highly susceptible to itraconazole *in vitro*[9].

The IVAP trial

The 'Itraconazole versus Amphotericin B for Penicilliosis' (IVAP) trial aimed to compare the relative effectiveness of these two strategies in the treatment of talaromycosis. It was the first randomised trial to assess treatment for talaromycosis.

The trial was designed to provide robust evidence, to inform national and international guidelines. In addition, the trial was expected to encourage more comparative effectiveness research of existing antifungal treatments of other important endemic fungal infections, none of which had been addressed adequately in RCTs.

A total of 440 HIV-infected adults diagnosed with talaromycosis by microscopy or culture were recruited. Trial participants received either itraconazole or amphotericin B during the first 2 week of therapy, and survival rates for the two treatments after 2 weeks and after 6 months were compared.

The trial was led by Dr Thuy Le, a faculty of the Oxford University Clinical Research Unit (OUCRU) in Ho Chi Minh City, Viet Nam. The trial team consisted of researchers from OUCRU, the University of Oxford, and from the five referral hospitals in Viet Nam where patients were recruited: the Hospital for Tropical Diseases, Ho Chi Minh City; the National Hospital for Tropical Diseases and Bach Mai Hospital, both in Hanoi; Viet Tiep Hospital, Hai Phong; and the Viet Nam–Sweden Uong Bi Hospital, Quang Ninh. These hospitals are located in provinces with the highest prevalence of HIV.

OUCRU played a crucial role in enabling the trial, providing expertise in trial design, conduct, and monitoring, data management, and data analyses – essential capabilities that were not present at the Vietnamese institutions.

Trial results

The IVAP trial showed that there was no difference in the number of patients dying between itraconazole and amphotericin B after 2 weeks of treatment. However, after 6 months, treatment with amphotericin

[5] Le T et al (2011) Epidemiology, seasonality, and predictors of outcome of aids-associated penicillium marneffei infection in Ho Chi Minh City, Viet Nam. Clinical Infectious Diseases 52(7): 945–952

[6] Le T et al (2017) A trial of itraconazole or amphotericin B for HIV-associated talaromycosis. N Engl J Med 376(24): 2329–2340

[7] Le T et al (2011) Epidemiology, seasonality, and predictors of outcome of aids-associated penicillium marneffei infection in Ho Chi Minh City, Viet Nam. Clinical Infectious Diseases 52(7): 945–952

[8] Ibid.

[9] Supparatpinyo K et al (1993) Response to antifungal therapy by human immunodeficiency virus-infected patients with disseminated Penicillium marneffei infections and in vitro susceptibilities of isolates from clinical specimens. Antimicrobial agents and chemotherapy 37(11): 2407–2411.

B was associated with half the number of deaths compared to itraconazole (11% versus 21%). The lower mortality in the amphotericin arm was seen after one month of therapy and was associated with lower incidence of disease relapses and complications. The investigators also found that amphotericin B decreased the number of the fungus in patients' blood four times faster than itraconazole.

Impacts

- Research impacts:

Dr Le has secured the following funding for follow-on studies as a result of the IVAP trial:

- A study to evaluate a novel diagnostic for early detection of talaromycosis, using samples collected as part of the IVAP trial to validate the technology. Early diagnosis of talaromycosis will allow patients to be pre-emptively treated before the disease fully develops. This is expected to change the treatment paradigm and will substantially reduce the high morbidity and mortality caused by this disease. This study is funded by a US NIH R01 grant of USD2.4m[10].
- A phase 2 trial of a 1 week course of treatment with a newer formulation of amphotericin B called liposomal amphotericin B (award pending). The IVAP trial data showed that fungal clearance from blood was achieved after 1 week of amphotericin B treatment in 98% of patients, indicating that a 2 week course may not be necessary. Liposomal amphotericin B has significantly fewer side effects than amphotericin B; its patent expired recently, causing its price to drop, and Gilead is interested in marketing the drug in LMICs.

- Policy impacts

The findings supported the current international treatment guideline[11], and provided robust evidence to underpin the treatment recommendations. The PI, Dr. Le, also presented the trial data to the WHO guideline committee, and the trial's findings were described in the 2017 Guidelines for management of advanced HIV disease[12] (WHO, 2017). She is currently developing talaromycosis guidelines for the US Department of Health and Human Services and the National Institute of Health and is coordinating a guideline for endemic mycoses for the European Confederation of Medical Mycology. She has become a member of multiple WHO guideline committees, including the WHO Guideline Development Groups on Management of Advanced HIV Disease in 2018, on the Diagnosis, Treatment, and Prevention of Cryptococcal Meningitis in 2018, and on the HIV Treatment Guidelines in 2018[13].

The PI also attempted to set up meetings with the regional WHO offices and governments of countries to which talaromycosis is endemic, to develop a policy statement on treatment of talaromycosis. This would have increased access and use of amphotericin B across southeast Asian countries; however, she was unable to identify adequate funding to allow her to engage in these activities.

- Health impacts

The trial has changed treatment of talaromycosis patients in Viet Nam, where amphotericin B is now provided to all patients, and is saving lives. At least 500 patients present with talaromycosis every year in the country; prior to the treatment change, 70% were treated with itraconazole, leading to 74 deaths per year (ca. 21% mortality). Amphotericin B cuts this death rate in half, saving the lives of around 35 individuals every year[14].

[10] NIH 1R01AI143409-01AI, entitled: "Making an early diagnosis of talaromycosis – a strategy to reduce morbidity and mortality in advanced HIV disease in Southeast Asia"

[11] U.S. Department of Health and Human Services (2013) Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV - Talaromycosis (Formerly Penicilliosis)

[12] WHO (2017) Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. Geneva: World Healh Organisation; July 2017

[13] Dr Thuy Le, personal communication, July 2019

[14] Dr Thuy Le, personal communication, July 2019

However, Viet Nam's reclassification as a lower middle-income country in 2013 has introduced a challenge in financing the HIV response, and international donors who have been covering the cost of treatment are shifting their official development assistance to lower income countries[15]. Viet Nam is currently transitioning to a national insurance system; this will challenge the sustainability of providing amphotericin B, as some patients will be unable to afford the required contribution to treatment costs.

Engagement with the local health system and policy makers

From the start, the IVAP trial team worked with the Ministry of Health in Viet Nam to plan the trial and secure participation of the trial sites. OUCRU had already established links with the Ministry of Health, and collaborations with two Hospitals for Tropical Diseases in Hanoi and Ho Chi Minh cities. However, additional sites were needed to recruit the required number of trial participants. As a multi-centre study, the trial team was required to work with the Ministry of Health. The PI of the trial, Dr Le, who had previously completed her D.Phil. research on talaromycosis with OUCRU, engaged with the MoH and presented the trial protocol in person in Hanoi. After several iterations, the protocol was approved, and relevant personnel at the ministry were aware and supportive of the trial. The MoH then sent a request to the directors of the five hospitals to be involved in the trials - including three hospitals OUCRU had not previously worked with. At the end of the trial, the data was presented at a meeting involving key stakeholders and all investigators (who also shared their experience of implementing the trial at the five sites). This 'country-wide' engagement paved the way for:

- uptake of the trial's findings into national guidelines: The Directors of the major HIV treatment centers play active roles in shaping national HIV guidelines. By involving these hospitals in the trial, the findings were immediately taken up at the end of the trial by the national guideline in December 2017, recommending amphotericin B for initial treatment of talaromycosis[16]. Viet Nam now has a standard of care based on robust evidence, whereas before treatment decisions were based on experience driven by perceptions.
- impact on treatment practice: The trial has made a significant impact on treatment practice in Vietnam. Doctors at the trial sites who had previously rejected amphotericin B due to concerns over its side effects gained experience and confidence in using amphotericin B and saw first-hand the success of amphotericin therapy in the context of a randomised controlled trial.

The IVAP trial has also primed the health service for further research. The trial was implemented at local sites; this has built local capacity for clinical research. Specifically, three of the five hospitals that participated in the study are now able to diagnose talaromycosis by microscopy and culture (previously, diagnosis was made only on clinical grounds). All five trial hospitals were trained in Good Clinical Practice and have improved their capacity to conduct international-standard clinical trials. Participation in the IVAP trial and co-authorship of the trial publication have also produced a sense of ownership and pride that Viet Nam conducted the first-ever RCT addressing a disease endemic to the country. Current discussions about a follow-on study investigating a shorter treatment course indicate that these hospitals are keen to continue to participate in clinical research. As a result of the relationships and capacity built during the IVAP trial, OUCRU has continued collaborating with some of the trial hospitals in other research projects, e.g. as part of a current grant between OUCRU, Vietnam Ministry of Health, several Vietnamese hospitals, and Duke University addressing antimicrobial resistance and stewardship.

[15] Safarnejad A et al (2017) Criteria for prioritization of HIV programs in Viet Nam: a discrete choice experiment. BMC health services research. BioMed Central 17(1): 719

[16] Vietnam Ministry of Health Hanoi (2017) 'Vietnam Guidelines for Treatment and Care of Patients with HIV/AIDS (in Vietnamese only)', p. 1 December.

Case study 2

A clinical trial of dexamethasone to reduce mortality in cryptococcal meningitis (CryptoDex) (G1100684/Call 1)

Funding period: 01/10/2011 - 31/03/2017	Award: £4,217,875
Lead PI: Professor Jeremy Day	Lead institution: Oxford University Clinical Research Unit (OUCRU), Ho Chi Minh City, Vietnam

Summary

- The Cryptodex trial determined whether addition of dexamethasone to standard treatment would improve survival among adults with HIV-associated cryptococcal meningitis. It was led by Professor Jeremy Day, Oxford University Clinical Research Unit (OUCRU), Ho Chi Minh City, Viet Nam, and involved 13 centres in 6 countries (Vietnam, Thailand, Indonesia, Laos, Uganda, and Malawi).
- The trial showed that dexamethasone is unlikely to benefit survival in patients with HIV-associated cryptococcal meningitis and its findings were taken up by WHO in the 2018 Guidelines on Cryptococcal Disease in HIV-infected adults, adolescents, and children.
- During the trial, researchers from participating centres in Africa and Asia were able to exchange experiences and share learning, e.g. on delivering interventions in relatively lower setting and approaches to patient recruitment.
- The CryptoDex trial has also helped to inform improvements in the hospital discharge protocol for patients with brain infections, and developed resources to assist patients to cope with disability and re-integrate into their communities. These resources are now being made available through an NGO, and the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam has already modified their approach to discharge planning.

The trial and impact on policy

Cryptococcal meningitis is a fungal brain infection that occurs primarily among people with advanced HIV disease. It accounts for an estimated 15% of all AIDS-related deaths globally[17], causing more than 600,000 deaths each year[18]. Drugs currently in use are more than 60 years old.

Dexamethasone is a corticosteroid that has been shown to improve outcomes in other brain infections such as tuberculous meningitis and acute bacterial meningitis, including in low income settings[19]. Pathophysiological changes associated with cryptococcal meningitis could potentially be alleviated by treatment with corticosteroids (raised intracranial pressure, vasculitis, cerebral oedema), and international guidelines recommended their use in some circumstances[20]. However, data from controlled trials were lacking at the time of the JGHT award.

The JGHT-funded CryptoDex trial aimed to determine whether addition of dexamethasone to standard treatment at the point of diagnosis would improve survival among adults with HIV-associated cryptococcal meningitis[21]. The trial had to be stopped for safety reasons after approximately half of the

[17] WHO (2016) Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children

[18] Park BJ et al (2009) Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. AIDS 23:525-530

[19] Thwaites GE et al (2004) Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med 351(17):1741-1751; Nguyen TH et al (2007) Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. N Engl J Med 357(24):2431-2440

[20] Perfect JR et al (2010) Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 50:291-322

[21] Beardsely J et al (2016) Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis. N Engl J Med 374:542-554

intended number of patients had been enrolled, because of excess rates of adverse events and slower rates of clearance of the fungal pathogen in patients receiving dexamethasone compared with those in the placebo group. The data collected up to that point showed that, while dexamethasone clearly reduced raised intracranial pressure in cryptococcal meningitis, overall is would not benefit survival in patients with HIV-associated cryptococcal meningitis.

The trial's findings were taken up by WHO in their 2018 Guidelines on Cryptococcal Disease in HIV-infected adults, adolescents, and children. The guidelines describe the CryptoDex trial and its findings in detail and based on this, advise against the routine use of adjunctive corticosteroid therapy[22]. The guideline committee had identified CryptoDex as the only trial that had investigated adjuvant corticosteroids in treating these patients and rated the certainty of the evidence it provided as 'high'.

Working across continents

The JGHT-funded trial, led by Professor Jeremy Day, OUCRU, involved 13 centres in 6 countries (Vietnam, Thailand, Indonesia, Laos, Uganda, and Malawi). The trial involved a team of Asian and African clinical researchers working across continents and cultural environments. In addition to frequent visits to sites by the central study team, researchers from all sites met together in Vietnam twice during the trial to discuss progress and share experiences in recruiting and managing patients, delivering the trial according to protocol, and identifying opportunities for sub-studies and future collaborations. Beyond information directly related to the dexamethasone trial, the teams also exchanged experiences relating to approaches to research, career development and opportunities, and patient management [23].

For example, during the meetings, investigators experienced different ways of interacting with PIs from high-income countries. African researchers were particularly relaxed and open to scientific argument and enjoyed an intellectual 'rough and tumble'. This particularly encouraged younger collaborators from Asia to have the confidence to express their views in discussions. At the same time, the African collaborators benefited from the experience of their Asian colleagues in setting up and managing relatively sophisticated interventions such as ventilation and haemofiltration, and how this can be delivered safely in lower income settings.

In direct support of the trial, the Asian collaborators learned about the African researchers' approach to patient recruitment. Collaborators from Ugandan centres in particular were very proactive during the recruitment process, with extensive community engagement including informing other hospitals about the trial to ensure that patients interested in participating had the opportunity. Profiling this proactive approach to recruitment was inspirational for the entire study team and led to improved recruitment rates following the trial meeting.

While budgetary requirements for trial team meetings from multiple LMICs (and continents) are substantial, these meetings build capacity, lay the foundations for future collaboration, and are key in developing cross-cultural teamwork and trust. This enables the delivery of high-quality evidence, relevant in a broad variety of environments, which has the validity to influence international treatment guidelines. The sites involved in the CryptoDex trial have already expressed their willingness to collaborate together in the future.

Post-trial engagement – the 'Beyond the hospital' project

Following on from the CryptoDex trial, the team expanded activity related to post-trial engagement and started working with a disability NGO in Vietnam, *Disability Research and Capacity Development* (DRD)[24]. The 'Beyond the Hospital' project was inspired by the experiences of the JGHT-funded trial

[22] WHO (2018) Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Page 21.

[23] Jeremy Day, Personal Communication, 12 June 2019

[24] https://www.drdvietnam.org/drd.html Accessed September 2019

and kicked off with funding from the award earmarked for public engagement activities as well as through a Wellcome Intermediate Clinical Fellowship, and a Wellcome Trust International Engagement Award. Additional funding was subsequently raised (USD50k).

The project aims to help patients with brain infections settle back into their communities after being discharged from hospital by learning from the different positive and negative experiences of patients following discharge from hospitals. Brain infections frequently lead to disabilities, including seizures, hearing loss, vision loss, cognitive impairment, neuromotor disability, memory and behaviour changes, and limb loss[25]. Most patients in Vietnam live in low-income settings, with little or no access to continuing rehabilitation in the community. The CryptoDex team expected that innovations to cope with disability developed by some survivors and their families would be broadly applicable to patients recovering from neurological infections.

Together with the OUCRU Public Engagement Department, CryptoDex investigators set up a team to follow up with survivors of neurological infections 'at home' following their discharge from OUCRU clinical studies. This included participants from the Cryptodex trial, and also from trials in tuberculous meningitis, viral encephalitis and acute bacterial meningitis. The aim was to understand their experience after being discharged and how they, and their families, had coped with on-going disabilities after return to their communities.

As a result of insights gathered in the project, the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam have modified their approach to discharge planning; other hospitals may follow suit. The developed resources are being made available through the disability NGO *Disability Research and Capacity Development* (DRD)[26]. Patients and their families are now provided with information before discharge and are given resource packs to help them deal with disability when returning to the community. The material covers aspects such as how to manage pressure sores and emotional changes patients may experience; further support is offered through narratives of how other patients and their families have coped, and a directory of services in Southern Vietnam for patients requiring post-discharge support. The information is presented in Vietnamese in easily accessible leaflets and animated films.

[25] https://www.who.int/emergencies/diseases/meningitis/en/ Accessed September 2019

[26] https://www.drdvietnam.org/drd.html Accessed September 2019

Case study 3

Reduction of EArly mortaLITY in HIV-infected African adults and children starting antiretroviral therapy: REALITY trial (G1100693/Call 1)

Funding period: Oct 2012 - Mar 2018	Funding amount: £3,986,746
Lead PI: Prof Diana Gibb	Lead institution: University College London / MRC Clinical Trials Unit

Summary

- The REALITY trial aimed to address the question of how to reduce the high early death rates when HIV-infected individuals with low immunity start antiretroviral therapy (ART). The trial tested three different approaches, at trial centres in Zimbabwe, Uganda, Malawi, and Kenya. It was led by UCL / MRC CTU.
- The trial showed that taking a package of antimicrobial drugs at the same time as starting ART reduced the rate of death by 3.3%, from 12.2% to 8.9%, i.e. saving 3 lives for every 1000 patients treated.
- The antimicrobial prophylaxis package was taken up into WHO guidelines as an option - but currently not as a first line treatment recommendation. Work to address concerns about antimicrobial resistance and cost-effectiveness of the intervention is ongoing, and is expected to inform the next WHO guideline update.
- The trial also showed that giving extra food to those starting on ART, or adding an integrase inhibitor (a new type of antiretroviral drug) to ART did not have an effect on mortality. However, the latter provided important evidence that integrase inhibitors are safe to use, lending more confidence to the WHO recommendation of an integrase inhibitor as the preferred treatment.

Background

In sub-Saharan Africa, 20%–25% of people starting antiretroviral therapy (ART) have poor immunity levels (low CD4 cell counts as a result of advanced HIV infection), and approximately 10% of these individuals die within 3 months of starting ART[27].

A number of factors contribute to this high death rate. People living with HIV in LMICs often harbour infections, like tuberculosis (TB) or other bacterial and fungal infections, which show themselves when their immunity improves when the level of HIV is reduced after starting ART. This can trigger a condition called immune reconstitution inflammatory syndrome (IRIS), an exaggerated inflammatory reaction to an infection. Another factor contributing to mortality is malnutrition: The risk of death of patients starting ART increases markedly with decreasing CD4 counts as well as decreasing body-mass index (BMI, the weight in kilograms divided by the square of the height in meters)[28]. These data suggest that additional interventions may reduce mortality by preventing infection and improving nutritional status. In sub-Saharan Africa, nutritional supplements are increasingly being given within HIV programmes. However, while lipid-based supplementary foods have been highlighted as a key potential

[27] The IeDEA and ART Cohort Collaborations (2014). Immunodeficiency at the start of combination antiretroviral therapy in low, middle-, and high-income countries. J Acquir Immune Defic Syndr 65(1):e8-16; Boulle A et al. (2014). Mortality in patients with HIV-1 infection starting antiretroviral therapy in South Africa, Europe, or North America: a collaborative analysis of prospective studies. PLoS Med 11(9):e1001718.

[28] Walker AS et al (2012). Mortality in the year following anti-retroviral therapy initiation in HIV-infected adults and children in Uganda and Zimbabwe. Clin Infect Dis 55:1707-18; Zachariah R et al (2006) Risk factors for high early mortality in patients on antiretroviral treatment in a rural district of Malawi. AIDS 20: 2355

intervention to reduce mortality in severely immunocompromised HIV-infected individuals, evidence on the effectiveness of this approach is contradictory and limited[29].

Given the high mortality rate, there is an urgent need to identify effective interventions to offer to HIV positive persons with low immunity starting on ART.

The JGHT award

The Reduction of EArly mortaLITY (REALITY) trial aimed to address the question of how to reduce the high early death rates when HIV-infected individuals with low immunity start ART. The trial investigated whether three different approaches for the first three months of ART would reduce high early death rates compared to the standard WHO-recommended ART approach:

1. Strengthening preventative treatment (prophylaxis) against TB and other bacterial, fungal and parasitic infections for three months, to reduce the level of infection and potential IRIS events
2. Increasing the potency of ART by adding the integrase inhibitor raltegravir (i.e. giving four drugs from three classes, rather than standard three from two classes). Intensifying standard triple-drug ART with the integrase inhibitor, raltegravir, should reduce HIV viral load faster and hence may reduce early mortality, although this strategy could also risk more IRIS events.
3. Giving extra food to all presenting with HIV (not just those with diagnosed malnutrition); this might also help people take their medication as we know many people get very hungry after starting these drugs.

In addition, the study included a number of sub-studies:

- A cost-effectiveness analysis, should one or more of the three approaches prove to be effective, estimating their relative costs and health gains if rolled out in Africa. This allows interventions with high potential for health improvement and comparatively low resource requirements to be prioritised.
- A social science study, to capture views of trial participants on receiving large numbers of pills, which may make them feel ill, and their motivations for, or reasons for not starting and adhering to, ART
- Collection of data on adherence and acceptability of a new co-formulated pill (Q-TIB) (see Q-TIB Case study)

The REALITY trial recruited 1805 HIV-infected adults and children over 5 years of age from Zimbabwe, Uganda, Malawi, and Kenya with low immunity (CD4 count lower than 100 cells/μL) who had not previously received ART. It compared the three approaches described above with the standard approach, in an open-label, randomised 2x2x2 factorial trial design. This design enabled the team to run one large trial to investigate three different interventions at the same time, which is more efficient than running three separate trials[30]. In addition, if there are interactions between the interventions on treatment outcomes (meaning the effect of one intervention depends on whether or not one of the other interventions is given), the trial design allows these to be identified and their relative contributions to be explored. The REALITY trial was among a small number of trials to show that a 2x2x2 factorial design could be implemented well, even in low resource settings and centres with very limited experience of conducting trials.

The trial was coordinated by Professor Diana Gibb, UCL / MRC CTU, with extensive experience in setting up and coordinating large global trials and cohorts, including in East Africa, mainly addressing questions in paediatric HIV infection[31]. Collaborating institutions in the UK were UCL's Division of Infection and Immunity, Institute of Child Health (Prof Nigel Klein), and LSHTM (Prof Janet Seeley).

[29] Tang AM et al (2015) Nutrition assessment, counseling, and support interventions to improve health-related outcomes in people living with HIV/AIDS: a systematic review of the literature. JAIDS 68 Suppl 3: S340-9

[30] Baker TB et al (2017) Implementing Clinical Research Using Factorial Designs: A Primer. Behav Ther. 48(4): 567–580

[31] https://www.ctu.mrc.ac.uk/about-us/senior-staff/diana-gibb/ Accessed 24 Aug 2019

The health economics work was carried out by researchers the Centre of Health Economics at the University of York.

The trial took place at eight sites: four sites in Uganda, two in Kenya, one in Malawi and one in Zimbabwe[32]. The PI of the trial had not previously worked with the partners in Malawi and one of the centres in Kenya. As a result of this new collaboration, the KEMRI WTRP in Kilifi are continuing to work with the group at the University of Zimbabwe and a group at Queen Mary University, London, on the analysis of samples taken during the trial (funded by a separate MRC grant, MR/P022251/1, £825,996[33]).

Professor Gibb served on a number of guideline committees, including the WHO Guideline Development Group for managing advanced HIV disease and rapid initiation of ART[34], and is a member of the expert group that provides advice to the WHO HIV department on clinical issues relating to paediatric HIV[35].

Outcomes and impacts

The REALITY trial showed that all three interventions tested had some effects - but only the enhanced prophylaxis led to a decrease in deaths and HIV-related illness. Nevertheless, all three have had an impact, or the potential to impact, current policy, WHO guidelines and practice.

- Enhanced prophylaxis against infection[36]

The trial determined the effects of enhanced antimicrobial prophylaxis on mortality. Participants starting on ART simultaneously received a 'package' containing additional antimicrobials compared with standard prophylaxis. It found that enhanced prophylaxis for the first 12 weeks of ART can prevent more than 3 deaths for every 100 people starting ART with CD4 <100: The enhanced prophylaxis package reduced the rate of death by 3.3%, from 12.2% to 8.9% of participants dying after starting ART, i.e. for every 1000 individuals starting ART, an additional 33 survived. Enhanced prophylaxis also reduced the number of adverse events, including new cases of TB, cryptococcal meningitis, oral and oesophageal candidiasis, and hospitalisation. It did not affect the decrease in the level of virus, despite the pill burden, indicating that those starting ART with enhanced prophylaxis adhered to the regimen the same way as those starting standard ART.

To inform the potential for roll-out of the prophylaxis strategy, data for a cost-effectiveness analyses was collected during the trial. A 'quick' estimate was included in the main trial publication, showing that the cost of enhanced prophylaxis ranged from US$8 to US$34 per day across trial countries. At the minimum price, the cost per quality-adjusted life-year falls within recently published cost-effectiveness thresholds for even the lowest-income countries. Hence, if access at low prices can be ensured for all countries, the strategy could be adopted widely across the continent. The cost–effectiveness was assessed as being US$201 per quality-adjusted life-year and US$162 per life-year saved; again, this is likely to fall within the cost–effectiveness thresholds for most resource-limited settings[37].

[32] *Uganda*: Joint Clinical Research Centre (JCRC) Kampala (coordinating centre for Uganda), with trial sites: JCRC Fort Portal; JCRC Gulu; JCRC Mbale; JCRC Mbarara. Some of the sites had had very limited experience in conducting trials; one site (JCRC Mbarara) has since become a fully-fledged trial centre. *Zimbabwe*: University of Zimbabwe Clinical Research Centre, Harare. *Kenya*: KEMRI Wellcome Trust Research Programme, Kilifi; Moi University Clinical Research Centre, Eldoret. Malawi: Department of Medicine and Malawi-Liverpool-Wellcome Trust Clinical Research Programme, College of Medicine, Blantyre

[33] https://gtr.ukri.org/projects?ref=MR%2FP022251%2F1 Accessed 24 Aug 2019

[34] Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017. Geneva: World Health Organization. https://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/

[35] Guidelines for the Diagnosis, Prevention, and Management of Cryptococcal Disease in HIV-Infected Adults, Adolescents and Children, March 2018. Geneva: World Health Organization. https://www.who.int/hiv/pub/toolkits/cryptococcal-disease-policy/en/

[36] Hakim J et al (2017) Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa. N Engl J Med 377: 233-45

[37] Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017. Geneva: World Health Organization, p. 10

Policy impact

The trial findings of the were taken up in two WHO guidelines[38,39]. Prior to the REALITY trial, guidelines recommended testing for TB and cryptococcal meningitis (a serious fungal infection of the brain and spinal column) before the initiation of ART, and only give antibiotics where disease is present[40]. While overuse of antibiotics can lead to drug resistance, the REALITY trial showed that delaying treatment to complete tests increases the risk of death. The 2017 WHO 'late-presenters' guideline[41] still recommends screening tests before deciding on antibiotic treatment; however, based on evidence from the REALITY trial, it also notes that "for people with advanced HIV disease who are eligible to start ART on the same day as HIV diagnosis, prophylaxis medications may be started at the same time"[42]. The addition of this provision resulted from a presentation of the trial data by Prof Gibb to the guideline development group (even before the main trial paper was published)[43]. A 2018 WHO guideline for cryptococcal disease management[44] strengthened the case for prophylaxis. Referencing the REALITY trial, it emphasises the need to provide prophylaxis where cryptococcal screening is not available or where receiving the result may be delayed[45].

Next steps and further research

The 2017 WHO 'late-presenters' guideline discussed the findings of the REALITY trial in detail, and described the Guideline Development Group's concerns about the prophylaxis package tested, relating to the potential for drug resistance to emerge, and to the cost-effectiveness of prophylaxis. Additional analysis of data and samples collected during the trial are providing further evidence to address these concerns[46]. The findings are expected to feed into the next update of the guideline (likely in 2020). This may help to refine and strengthen the evidence for intervention scale-up and pave the way for inclusion in the WHO guideline as first-line treatment.

[38] Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017. Geneva: WHO

[39] Guidelines for the Diagnosis, Prevention, and Management of Cryptococcal Disease in HIV-Infected Adults, Adolescents and Children, March 2018. Geneva: World Health Organization

[40] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. June 2016. Geneva: World Health Organization. http://www.who.int/hiv/pub/arv/arv-2016/en/

[41] Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017. Geneva: World Health Organization.

[42] Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017. Geneva: World Health Organization, p. 10

[43] Prof Diana Gibb, personal communication (July 2019)

[44] Guidelines for the Diagnosis, Prevention, and Management of Cryptococcal Disease in HIV-Infected Adults, Adolescents and Children, March 2018. Geneva: World Health Organization

[45] Guidelines for the Diagnosis, Prevention, and Management of Cryptococcal Disease in HIV-Infected Adults, Adolescents and Children, March 2018. Geneva: World Health Organization, p. 15

[46] 1) The group viewed the benefits of an additional broad-spectrum antibiotic (azithromycin) within a package of care to be unclear since mortality reduction could not clearly be attributed to a decline in bacterial infections (e.g. early deaths could have been a result of cryptococcal disease). The potential benefits of prophylaxis with azithromycin were considered to not outweigh concerns about the potential for antimicrobial resistance development. A current study, funded separately by the MRC and led by Prof Andrew Prendergast, Queen Mary University ('Mechanisms underlying enhanced infection prophylaxis for advanced HIV in Africa', £825,996), is using blood and stool samples collected from participants of the REALITY trial to understand which infections trial participants had, how these changed as a result of the prophylaxis package, and hence which component(s) of the package are needed and which may not have contributed to the reduction in mortality.

2) The group was concerned that routine use of fluconazole prophylaxis for cryptococcal disease would not be cost-effective and could lead to the development of fluconazole resistance. Prophylaxis with fluconazole was not included in the care package recommended by the guideline, and its use recommended only in "settings where cryptococcal screening tests are not available or results will be delayed". As the published cost-effectiveness analysis did not capture the longer-term benefits associated with reduced mortality beyond 48 weeks, the inclusion of such benefits will further increase the value-for-money of enhanced prophylaxis. The results of a full cost effectiveness analysis have been submitted for publication (currently under review[46]), investigating the different forms of management of cryptococcal disease in late presenters.

- Raltegravir-intensified ART[47]

Another strategy to decrease mortality tested in REALITY was to accelerate recovery of the immune system by reducing the patients' viral loads (level of virus) more rapidly.

The REALITY trial showed that adding the integrase inhibitor raltegravir to standard ART decreased HIV viral load indeed much faster than standard ART on its own. However, this rapid reduction in viral load did not lead to a reduction in the rate of death or development of clinical HIV events.

While the approach did not have an effect on mortality or clinical progression, the data was nevertheless important and contributed to policy decisions: It provided important evidence that raltegravir did not lead to an increase in IRIS, a side-effect that had been feared based on experiences from European cohort studies, particularly related to TB[48,49]. These adverse findings were not replicated in the REALITY trial, providing robust evidence - from a randomised controlled trial - that integrase inhibitors are safe to use. This has lent more confidence to WHO recommendation of dolutegravir, another integrase inhibitor, for use as the preferred treatment for all populations, including TB patients and those with low CD4 cell counts [50].

- Ready-to-use supplementary food[51]

Trial participants randomised to receive supplementary food had small but significantly greater increases in weight and BMI. However, this weight gain did not translate into a reduction in mortality or HIV-related illness, and they did not get stronger faster (grip strength was measured in the trial). These findings suggest that, for adults without severe malnutrition, supplementary food increases weight but does not otherwise contribute to improvement in health in addition to a healthy balanced diet for those on ART.

A change in policy to provide nutritional supplementation to all severely immunocompromised HIV-infected individuals starting ART is therefore not warranted at present. Current food assistance programmes for people with HIV can draw on this evidence to prioritise future efforts.

[47] Kityo C et al (2018) Raltegravir-intensified initial antiretroviral therapy in advanced HIV disease in Africa: A randomised controlled trial. PLoS Med 15(12): e1002706.

[48] Wijting I et al (2017) Integrase inhibitors are an independent risk factor for IRIS: an ATHENA cohort study. Conference on Retroviruses and Opportunistic Infections; Seattle, WA, USA. Feb 13–16, 2017. Abstract 731; Dutertre M et al (2017) Initiation of antiretroviral therapy containing integrase inhibitors increases the risk of iris requiring hospitalization. J Acquir Immune Defic Syndr 76: e23–26; Psichogiou M et al (2017) Integrase strand transfer inhibitors and the emergence of immune reconstitution inflammatory syndrome (IRIS). Curr HIV Res 15: 405–10.

[49] Integrase inhibitors are a class of antiretroviral drug that lead to significantly more rapid declines in HIV viral load than all other classes, but were not yet included in standard WHO-recommended ART at the time of the trial due to lack of robust evidence of safety and effectiveness at the time, e.g. in LMIC settings). In particular, there was concern that this strategy could risk more IRIS events, as a result of 'bounce back' of the patient's immune system. This had been suggested from observational studies but there was no randomised evidence in patients with very low levels of immunity.

[50] Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017. Geneva: World Health Organization, p. 18

[51] Mallewa J et al (2018) Effect of ready-to-use supplementary food on mortality in severely immunocompromised HIV-infected individuals in Africa initiating antiretroviral therapy (REALITY): an open-label, parallel-group, randomised controlled trial. Lancet HIV 5: e231–240

Case study 4

Reduction of EArly mortaLITY in HIV-infected African adults and children starting antiretroviral therapy: REALITY trial (G1100693/Call 1)

Funding period: Oct 12 - Mar 18	Funding amount: £3,986,746
Lead PI: Prof Diana Gibb	Lead institution: University College London / MRC Clinical Trials Unit

Summary:

- WHO recommends preventative therapy against tuberculosis for people living with HIV, including the antimicrobials cotrimoxazole and isoniazid. However, access to isoniazid remained poor and few people were receiving this treatment.
- To increase access and adherence, Cipla Ltd developed a co-formulated pill, combining cotrimoxazole and isoniazid. The enhanced prophylaxis arm of the REALITY trial provided an opportunity to test Q-TIB and gather data on adherence and acceptability, to contribute to submission for WHO pre-qualification.
- In 2017, Q-TIB was included on WHO essential medicines list and its use recommended in WHO guidelines. It is now available on the market.

Background

Co-trimoxazole and isoniazid are antimicrobials shown to be effective against *Mycobacterium tuberculosis*, the causative agent of tuberculosis (TB). In 2017, 10 million people fell ill with TB, and 1.6 million died from the disease[52]. TB is responsible for more than a quarter of HIV-related deaths, and the risk of developing TB is estimated to be between 15-25 times greater in people living with HIV than among those without HIV infection[53]. TB also complicates the management of HIV.

Both co-trimoxazole and isoniazid preventative therapy are recommended by WHO for people living with HIV[54,55,56]. The aim of co-trimoxazole is to reduce morbidity and mortality, whereas use of isoniazid reduces the risk of tuberculosis. However, while the effectiveness of isoniazid was first recognised by WHO and UNAIDS more than 20 years ago[57], countries were slow to adopt the recommendation. By the end of 2009, only 85 000 people living with HIV received the drug[58]. Access to isoniazid remained poor, mainly due to the lack of availability of isoniazid as a single drug within country programmes, and also in part due to the scepticism of TB experts who voiced fears about developing drug resistance[59].

[52] WHO fact sheet: Tuberculosis (2018) https://www.who.int/en/news-room/fact-sheets/detail/tuberculosis

[53] https://www.who.int/hiv/topics/tb/en/ Accessed 24 Aug 2019

[54] WHO (2006) Guidelines on co-trimoxazole prophylaxis for HIV infections among children, adolescents and adults in resource-limited settings: recommendations for a public health approach. Geneva: World Health Organization

[55] WHO (2008) Essential prevention and care interventions for adults and adolescents living with HIV in resource-limited settings. Geneva: World Health Organization; 2008.

[56] WHO (2011) Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva, Switzerland, World Health Organization

[57] WHO (1998) Policy statement on preventive therapy against tuberculosis in people living with HIV. Geneva: World Health Organization (WHO/TB/98.255)

[58] WHO (2010) WHO Global tuberculosis control: a short update to the 2010 Report. December 2009. Geneva, Switzerland, World Health Organization

[59] Harries AD et al (2015) Benefits of combined preventive therapy with co-trimoxazole and isoniazid in adults living with HIV: time to consider a fixed-dose, single tablet coformulation. Lancet Infect Dis 15: 1492–96

By 2015, several effective ART regimens were available to patients to take as one pill once per day; however, co-trimoxazole and isoniazid preventative therapy still had to be taken as two separate pills[60]. To simplify treatment and improve adherence to the recommended preventative treatment, WHO had been exploring the possibility of a fixed-dose combination of co-trimoxazole, isoniazid, and Vitamin B6[61], e.g. the 2011 'WHO Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings' identifies a number of priority research gaps related to TB preventative treatment[62]. This included the "co-formulation as a fixed-dose combination of isoniazid and vitamin B6 with co-trimoxazole, and with antiretrovirals, and evaluation of the efficacy and effectiveness of such fixed-dose combinations". In 2014, WHO placed a co-formulation on its expression of interest list[63].

Impact of the JGHT-funded research

The Reduction of EArly mortaLITY (REALITY) trial aimed to address the question of how to reduce the high early death rates when HIV-infected individuals with low immunity start ART (see case study 0).

One arm of the trial investigated the effect of strengthening preventative treatment (prophylaxis) against infections on mortality. Patients starting on ART simultaneously received an enhanced 'package' of antimicrobials, consisting of co-trimoxazole, isoniazid, Vitamin B6, fluconazole, azithromycin, and albendazole, compared with standard prophylaxis (co-trimoxazole alone).

Professor Gibb had worked with generics manufacturer Cipla Ltd, Mumbai, India, prior to the REALITY trial. The company had developed a fixed-dose formulation of co-trimoxazole, isoniazid, and Vitamin B6 (Q-TIB), and conducted bioequivalence studies comparing this formulation with individually formulated drugs. The REALITY trial provided an opportunity to test Q-TIB and gather data on its acceptability and adherence, which contributed to data submitted to the WHO for pre-qualification (which authorises it to be procured and distributed by international funding bodies, such as the Global Fund and PEPFAR). Professor Gibb presented the results of using Q-TIB as part of the enhanced prophylaxis trial arm at the World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease in 2016[64], and engaged in regular communication with WHO to progress the pre-qualification process. In 2017, Q-TIB was included on the WHO essential medicines list[65], and its use was recommended in the WHO late-presenters guidelines[66].

Cipla Ltd brought Q-TIB to market in 2017, albeit at a relatively high price which limited access to the drug. In June 2018, Unitaid and Cipla agreed that the company will reduce the ceiling price of the medicine by more than 30% from USD3 to USD1.99 per person, per month, for all public-sector procurers in LMICs[67]. Q-TIB is currently also being used as part of routine treatment in other trials: in the EDCTP-funded CHAPAS 4 trial[68] and in a new trial funded by UNITAID and Australia's NHMRC (not yet started).

60 Ibid.

61 Isoniazid depletes Vitamin B6 levels, to be supplemented in order to reduce the risk of side-effects on the nervous system.

62 WHO (2011) Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva, Switzerland, World Health Organization

63 WHO 12th invitation to manufacturers and suppliers of medicinal products for HIV infection and related diseases, including treatment for hepatitis B and C, to submit an Expression of Interest (EOI) for product evaluation to the WHO Prequalification Team– Medicines. Geneva; World Health Organization, 2014

64 Gibb DM et al (2016) Sulfamethoxazole/trimethoprim/isoniazid/pyridoxine scored tablets are bioequivalent to individual products and are acceptable to patients with advanced HIV infection in the REALITY trial. 46th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union)

65 WHO Model List of Essential Medicines 2017, 20th list (accessed 29/07/2019). Section 6.4.2.5, page 21

66 https://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/ , p. 9: "The use of fixed-dose combinations is recommended as one way to improve adherence, and the fixed-dose combination tablet of co-trimoxazole, pyridoxine and isoniazid, as used in the REALITY trial, has recently been added to the WHO List of Essential Medicines."

67 https://www.who.int/hiv/mediacentre/news/unitaid-price-cut-oi/en/ Accessed 24 Aug 2019

68 Children with HIV in Africa – pharmacokinetics and acceptability of simple second-line antiretroviral regimens ISRCTN22964075

Case study 5

Randomised controlled trial of podoconiosis treatment in northern Ethiopia (GoLBeT) (MR_K007211_1/Call 2)

Funding period: 01/02/2013 - 30/05/2017	Funding amount: £777,890
Lead PI: Prof Gail Davey	Lead institution: Brighton and Sussex Medical School, University of Sussex

Summary

- Podoconiosis is a form of lymphoedema (leg swelling) in people who walk barefoot on volcanic soil in highland tropical areas. The GoLBet trial was the first trial to measure the effects of a simple foot care package on ADLA, the most severe consequence of podoconiosis, an acute inflammation of skin, tissue, lymphatics, and lymph nodes. The trial was led by Prof Gail Davey, University of Sussex, and conducted in rural communities in the East Gojjam Zone, Ethiopia.
- The trial showed that the simple, inexpensive care package was effective in reducing the frequency and duration of ADLA. The package is now set to be incorporated into the next 5-year Ethiopian Neglected Tropical Diseases masterplan (2020-2025).
- So far, an estimated 100,000 podoconiosis patients have been trained to self-treat with the foot care package in Ethiopia, including through a financial commitment by the Ethiopian government for training in 2018. In addition, the University of Sussex working with NGOs trained 200 health professionals in endemic areas.
- The GoLBeT team have also started working in neighbouring countries, e.g. in Rwanda, where the foot hygiene package will be referenced in the national Strategic Plan for 2020-2025, and in Uganda and Cameroon where approx. 40 health professionals where trained.
- A Rapid Ethical Assessment ahead of the trial was important to lay the groundwork for the trial. Gathering local knowledge through community consultation facilitated patient recruitment and enabled the trial team to effectively address challenges encountered during the trial.

Background

Podoconiosis is a form of lymphoedema (leg swelling) in people who walk barefoot on volcanic soil in highland tropical areas. The disease results in oedematous feet and legs and subsequently progresses to elephantiasis. It is unusual, in being an entirely preventable non-communicable disease (and has been eradicated from Scotland, France, and the Canary Islands since footwear became routine)[69]. Although podoconiosis is rarely a direct cause of mortality, it greatly reduces productivity, leading to significant stigma from the community and health professionals, and a low quality of life.

Podoconiosis affects an estimated 4 million subsistence farmers globally[70]. Most of the highly-affected countries are in the African region, with prevalence particularly high in Cameroon, Ethiopia and Uganda[71]. In Ethiopia, the national average prevalence is estimated to be 4.0%[72]; another study reported

[69] Price EW (1990) Podoconiosis: non-filarial elephantiasis. Oxford Medical Publications, Oxford

[70] Davey G et al (2007) Podoconiosis: a tropical model for gene-environment interactions?. Trans R Soc Trop Med Hyg 101:91–6; Tekola AF et al (2012) HLA class II locus and susceptibility to podoconiosis. N Engl J Med 366:1200–8

[71] Deribe K et al (2018) Global epidemiology of podoconiosis: A systematic review. PLoS Negl Trop Dis 12: e0006324 and references within

[72] Deribe K et al (2015) Epidemiology and individual, household and geographical risk factors of podoconiosis in Ethiopia: results from the first nationwide mapping. Am J Trop Med Hyg. 92:148–589

1.6 million people living with podoconiosis in Ethiopia with 35 million people at risk of the disease in the country[73].

Among the most severe clinical consequences of lymphoedema are episodes of acute dermatolymphangioadenitis (ADLA). These are characterised by malaise, fever, chills, diffuse inflammation, swelling of the limbs, lymphangitis, adenitis and, eventually, skin peeling. They occur frequently (reports vary from five to 23 episodes per year), and lead to an average 4.4 days off work per episode – hence contributing substantially to the disability and social effects associated with podoconiosis[74].

In 2011, podoconiosis was recognised by WHO as a neglected condition, but did not appear on the 2018 list of WHO neglected tropical diseases (NTDs). With low knowledge and awareness of the disease, and very few research groups investigating the issue, health interventions addressing podoconiosis are often grouped alongside lymphatic filariasis (LF) programmes, the 'better-known' elephantiasis caused by parasitic worms[75]. However, recent mapping efforts have shown that these diseases are frequently found in different regions of countries, or different countries altogether[76]. Diagnosis and provision of health interventions for people with podoconiosis hence requires a separate programme from LF.

The JGHT award

The JGHT-funded trial (GoLBeT - the Gojjam Lymphoedema Best Practice Trial) was the first randomised controlled trial to measure the effects of a lymphoedema management package on the most important consequence of podoconiosis, ADLA. The trial enrolled just under 700 patients from the East Gojjam Zone in Ethiopia and tested whether a simple foot care package, comprising information about foot hygiene, skin care, bandaging, exercises to improve lymph drainage, and use of socks and shoes, was effective in reducing the number of ADLA attacks suffered by patients with podoconiosis lymphoedema.

At the time of the JGHT award, only one small uncontrolled study on the management of podoconiosis lymphoedema had been conducted, showing positive effects of a foot care package which patients can administer themselves[77]. This package was being offered to people with podoconiosis through small non-government organisations in some areas of the three most heavily affected regions in Ethiopia. Before including a recommendation for this type of morbidity management in a national guideline and in the national NTD masterplan, the Ethiopian Ministry of Health asked for robust evidence from a larger trial. GoLBeT was set up to provide such evidence. The trial team's involvement was based on a long-standing engagement with the NTD department of the Ministry of Health since its inception in 2008/2009, and regular communication with policy makers continued throughout the trial.

The GoLBeT team was led by Professor Gail Davey, Brighton and Sussex Medical School, University of Sussex and included researchers from the University of Sussex, Oxford University, and the University of Addis Ababa in Ethiopia. The latter not only provided input to the scientific design but also aided the implementation of the trial, e.g. by navigating the local bureaucracy. The Kenya Medical Research

[73] Deribe K et al (2015) Mapping and modelling the geographical distribution and environmental limits of podoconiosis in Ethiopia. PLoS Negl Trop Dis 9:e0003946; Deribe K et al (2017) Estimating the number of cases of podoconiosis in Ethiopia using geostatistical methods. Wellcome Open Res 2

[74] Bekele K et al (2016) Burden assessment of podoconiosis in Wayu Tuka Woreda, east Wollega zone, western Ethiopia: a community-based cross-sectional study. BMJ Open 6: e012308; Molla YB et al (2012) Patients' perceptions of podoconiosis causes, prevention and consequences in east and west Gojam, northern Ethiopia. BMC Public Health 12: 828

[75] Marks M & Mitja O (2019) Prevalence surveys for podoconiosis and other neglected skin diseases: time for an integrated approach. The Lancet Global Health 7: PE554-E555

[76] Deribe K et al (2017) Mapping the geographical distribution of podoconiosis in Cameroon using parasitological, serological, and clinical evidence to exclude other causes of lymphedema. Plos Negl Trop Dis. 12: e0006126; Deribe K et al (2019) Geographical distribution and prevalence of podoconiosis in Rwanda: a cross-sectional country-wide survey. Lancet Glob Health 7: e671–e680

[77] Sikorski C et al (2010) Effectiveness of a simple lymphoedema treatment regimen in podoconiosis management in southern Ethiopia: one year follow-up. PLoS Negl Trop Dis 4: e902; Brooks J et al (2017) A randomised controlled trial to evaluate the effect of a new skin care regimen on skin barrier function in those with podoconiosis in Ethiopia. Br J Dermatol 177: 1422–31.

Institute-Wellcome Trust Research Programme (KWTRP) in Kilifi, Kenya, provided data management, statistical support, and independent monitoring for the trial (as there was not yet sufficient capacity in Ethiopia to cover these roles in-country). An NGO active in the trial region provided the financial infrastructure and housed the trial office at their headquarters in the district capital Debre Markos.

Trial results and impacts

GoLBeT showed that the simple, inexpensive package of lymphoedema self-care was effective in reducing the frequency and duration of ADLA[78].

- Impacts in Ethiopia

Evidence was presented in March 2019 to the Ethiopian Ministry of Health, to inform the next 5-year national NTD masterplan (2020-2025). The lymphoedema package assessed in GoLBeT is set to be incorporated into this plan (likely to be published in early 2020), potentially paving the way for national implementation[79]. In 2018, the Ethiopian government committed 9m Birr (approx. £300,000) in domestic budget to extend treatment to other districts by training health professionals to provide supportive supervision for self-treating patients. In addition, the University of Sussex and Footwork (a charity supporting prevention and treatment of podoconiosis founded and led by Prof Davey) secured a UK BIG Lottery award (£500,000, 2014-2017)[80], assisted by the fact that GoLBeT was underway. Working with the National Podo Action Network (NaPAN, a consortium of NGOs) and the Ethiopian government, this effort delivered care to 70,000 patients and trained 200 health professionals in endemic areas. Subsequently, Footwork has received two further grants of USD$100k each from the Izumi Foundation (2016-2018) to extend care to 8,000 more patients, and supported NaPAN to secure funding from DfID to provide lymphoedema care. In total, an estimated 100,000 podoconiosis patients have been trained to self-treat with the foot care package in Ethiopia.

- Impact beyond Ethiopia's borders

Having catalysed the first steps of government action against podoconiosis in Ethiopia, the research team more recently worked in neighbouring countries, e.g. in Rwanda[81] where the foot hygiene package trialled for lymphoedema care will be referenced in the national Strategic Plan for 2020-2024[82]. A team from Ethiopia and Footwork also travelled to Uganda and Cameroon to demonstrate the lymphoedema care package and to guide programme set-up (providing training to approx. 40 health professionals in each country)[83]. However, Uganda, Rwanda and Cameroon are yet to commit domestic budget, and so the package is reaching relatively small numbers (probably no more than 500 patients in either country) via NGOs.

Further research

GoLBeT has contributed to a scaling up of research activity in the area of podoconiosis, and led to implementation research in the area of limb care more generally:

The University of Sussex secured a grant to establish an NIHR Global Research Unit (for £5.7m, 2017-21). One of the unit's work packages, the 'Excellence in Disability Prevention Integrated across NTDs' (EnDPoINT) Consortium[84], is taking an implementation research approach to investigate how different

[78] Negussie H et al (2018) Lymphoedema management to prevent acute dermatolymphangioadenitis in podoconiosis in northern Ethiopia (GoLBeT): a pragmatic randomised controlled trial. Lancet Glob Health 6: e795–803

[79] Prof Gail Davey, personal communication (August 2019)

[80] https://www.bsms.ac.uk/research/global-health-and-infection/wellcome-trust-brighton-and-sussex-centre-for-global-health-research/current-research/podoconiosis/the-elimination-of-podoconiosis.aspx . Accessed 16 Aug 2019

[81] Deribe K et al (2019) Geographical distribution and prevalence of podoconiosis in Rwanda: a cross-sectional country-wide survey. Lancet Glob Health 7: e671–e680

[82] Unpublished; Prof Gail Davey, personal communication (August 2019)

[83] Prof Gail Davey, personal communication (August 2019)

[84] https://www.bsms.ac.uk/research/global-health-and-infection/nihr-global-health-research-unit-for-ntds/nihr-work-packages.aspx . Accessed 16 Aug 2019

foot care and well-being (psychosocial care) interventions for NTDs which cause lymphoedema (including lymphatic filariasis, podoconiosis and leprosy) can be integrated into a holistic care package and embedded into routine health care services. The research takes place in selected districts in Ethiopia and combines a team of researchers from the UK and Ethiopia (including Prof Davey and other GoLBeT team members), policy makers and practitioners. The results will further inform national policy, and will be transferrable to other countries with podoconiosis patients. In addition, the group was awarded a DfID grant, 'Improving access to integrated Morbidity management and disability' (IMPRESS), to explore stigma reduction alongside physical management of limb problem (USD193,775, 2020-21).

Preparing the ground – rapid ethical assessment to aid trial implementation

GoLBeT was conducted in the Amhara region in Northern Ethiopia, in a low resource setting. The area had not previously been involved in health-related trials, and the GoLBeT team needed to lay the groundwork for the trial to enable recruitment and inform the consent process. To this end, a rapid ethical assessment was conducted by a team comprising the (Ethiopian) trial coordinator, an anthropologist, and a public health scientist[85]. By talking to key stakeholders and conducting focus groups over a six weeks period before the intended start of the trial, to "map the ethical terrain", the team gathered important local knowledge, e.g. on how the community operates, what the community understands about research, and their views on trial characteristics, such as being assigned randomly as part of the research and the broader understanding of randomness such as in lotteries. Specific suggestions were incorporated into the preparatory phases of the trial or used during the course of the trial itself to avoid potential issues. These included:

- Randomisation and delayed treatment were explained in community meetings and with individual patients attending enrolment sessions by drawing parallels with existing local 'random methods' to decide whose turn it is to graze cattle, and comparisons of traditional and modern fertilisers used by agricultural development workers
- In one trial location, misinformation spread by a local individual alarmed patients. Acting on suggestions made during the Rapid Ethical Assessment about quashing community rumours, the trial coordinator and data manager arranged an emergency district meeting to negotiate with gatekeepers and prevent further rumours being spread.

Other activities included sensitisation meetings with local leaders or the police; explaining of detailed trial information by individuals with deep local knowledge; and incentivising participants in the 'delayed' intervention arm to continue in the trial by giving them small gifts (in this case, a small bag of coffee, which likely contributed to a high retention rate).

The trial team published their experience of the rapid ethical assessment and trial implementation in itself, to inform other investigators implementing trials in remote rural areas[86,87].

[85] Negussie H et al (2016) Preparing for and Executing a Randomised Controlled Trial of Podoconiosis Treatment in Northern Ethiopia: The Utility of Rapid Ethical Assessment. PLoS Negl Trop Dis 10: e0004531

[86] Ibid.

[87] Molla M et al (2018) Pragmatism in practice: lessons learned during screening and enrollment for a randomised controlled trial in rural northern Ethiopia. BMC Medical Research Methodology 18:26

Case study 6

The Good Schools Study: A cluster randomised controlled trial of an intervention to prevent violence against children in Ugandan primary schools (MR/L004321/1, Call 3)

Funding period: 31/12/2013 - 30/12/2015	Funding amount: £664,266
Lead PI: Karen Devries	Lead institution: London School of Hygiene and Tropical Medicine

Summary

- Physical, sexual or psychological violence is a global health problem affecting 1 billion children worldwide every year. The problem is particularly acute in Ugandan primary schools with more than 90% of children reporting some form of physical violence from school staff.
- A team led by Dr Karen Devries at the London School of Hygiene and Tropical Medicine tested The Good Schools Toolkit, a behavioural intervention developed by a Ugandan NGO Raising Voices, in primary schools in Uganda in a two-arm cluster-randomised controlled trial. A qualitative study, economic evaluation, and process evaluation were also included in the study.
- Trial results showed that the intervention was effective at reducing violence towards children by 42% in the space of 18 months. This evidence informed WHO violence prevention guidelines. Moreover, 434 of the children participating in the trial were referred to Child Protective Services. Thus, the study itself has had an impact on the health and wellbeing of children.
- The Good Schools Toolkit is now being used in Tanzania, Kenya and Rwanda in addition to Uganda. It is also being adapted for secondary schools and a randomised controlled trial of this new toolkit is planned for 2020.

Each year, 1.4 million people worldwide die as a result of violence and many more are injured or suffer from a range of physical, sexual, reproductive and mental health problems due to violence.[88] Violence also affects 1 billion children globally every year, which is over half of all children aged 2–17 years.[89] Violence towards children in Ugandan primary schools is particularly widespread, with more than 90% of children aged between 11–14 years reporting physical violence from school staff.[90] Specific behaviour change for school staff, including teachers, is needed in order to reduce violence towards children.

In 2006, the Ugandan NGO Raising Voices developed a behavioural intervention, the Good Schools Toolkit, to help change the behaviour of school staff and reduce violence towards children in schools. The intervention includes setting goals and developing action plans at the school level; training on positive discipline; behaviour-change techniques for teachers, children, administrators and parents; and the formation of child-led committees.[91]

The Toolkit was already being used in Ugandan primary schools. However, even after 6 years, its effectiveness had not yet been evaluated. Therefore, a team led by Dr Karen Devries at the London School of Hygiene and Tropical Medicine (LSHTM) decided to conduct a randomised controlled trial (RCT) of the Toolkit in collaboration with the NGO Raising Voices.[92]

[88] WHO (2017). 10 Facts about Violence Prevention. Retrieved from https://www.who.int/features/factfiles/violence/en/. Accessed 5 September 2019

[89] Hillis S et al (2016) Global prevalence of past-year violence against children: a systematic review and minimum estimates. Pediatrics 137(3): e20154079

[90] Devries K, Child J et al. (2014). School violence, mental health and educational performance in Ugandan primary school children: a cross-sectional survey. Pediatrics 133(1): e129-37

[91] Devries et al (2015). The Good School Toolkit for reducing physical violence from school staff to primary school students: a cluster-randomised controlled trial in Uganda. Lancet Global Health 3(7): e378-86

[92] Ibid.

A two-arm cluster-RCT was conducted in 42 schools in the Luwero district of Uganda along with a qualitative study, economic evaluation, and process evaluation. The primary outcome of the study was past-week self-reported violence on children by school staff.[93] Secondary outcomes were children's mental health, well-being at school, and educational outcomes.

The trial results showed that past-week physical violence was lower in the intervention schools than in the control schools (based on a survey of 3820 students).[94] Overall, the Good School Toolkit helped to reduce violence against children by 42% in the space of 18 months. The Toolkit seems to be equally effective at reducing violence towards boys as well as girls, although there is some evidence that the intervention may have stronger effects in boys than girls.[95] Moreover, the Toolkit is also effective at reducing violence towards children with disabilities[96]. The trial had an impact on the health and wellbeing of the children participating in the trial, supported by the fact that 434 of them were referred to Child Protective Services based on what they disclosed in the follow-up survey.[97]

Evidence from the Good Schools Study has been used to inform a number of policy initiatives. One example is *INSPIRE: Seven Strategies to end Violence against Children*, WHO's technical package for violence prevention.[98] The package includes strategies and interventions for government, civil society organisations, and the private sector to address the problem of violence against children. Use of the Good School Toolkit was also discussed at the 2016 WHO Violence Prevention Alliance Annual Meeting. Finally, the Toolkit was described as a "promising model" in a UNICEF research brief on corporal punishment in schools.[99]

In 2015-16, Dr Devries and a colleague adapted the Good Schools Toolkit for Ugandan secondary schools with funding from the MRC.[100] This intervention is currently being tested in a pilot trial funded by the MRC, DFID and NIHR in Kampala, Uganda[101,102] and a phase 3 RCT is planned for 2020.[103] The Good Schools Toolkit aimed at primary school students is already being used in over 1,000 schools across Tanzania, Kenya, and Rwanda.[104]

[93] Study protocol: Good Schools Study (2012). Retrieved from https://clinicaltrials.gov/ct2/show/NCT01678846. Accessed 5 September 2019.

[94] Devries et al (2015). The Good School Toolkit for reducing physical violence from school staff to primary school students: a cluster-randomised controlled trial in Uganda. Lancet Global Health 3(7): e378-86

[95] Devries et al. (2017). Does the Good Schools Toolkit Reduce Physical, Sexual and Emotional Violence, and Injuries, in Girls and Boys equally? A Cluster-Randomised Controlled Trial. Prevention Science 18(7): 839-853

[96] Devries et al (2018). Reducing Physical Violence Toward Primary School Students with Disabilities. Journal of Adolescent Health 62(3): 303-310

[97] ResearchFish data provided by the MRC.

[98] WHO (2016) INSPIRE: Seven Strategies for Ending Violence Against Children. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/207717/9789241565356-eng.pdf?sequence=1. Accessed 5 September 2019.

[99] Jones & Pells (2016) Undermining Learning: Multi-Country Longitudinal Evidence on Corporal Punishment in Schools. UNICEF Office of Research – Innocenti

[100] LSHTM (no date). Adaptation of the Good School Toolkit for reducing violence in secondary schools. *SAME research online*. Retrieved from https://same.lshtm.ac.uk/projects-2/adaptation-of-the-good-school-toolkit-for-reducing-violence-in-secondary-schools/. Accessed 5 September 2019.

[101] LSHTM (no date). Pilot Trial of Good School Toolkit for secondary schools. Retrieved from https://www.lshtm.ac.uk/research/centres-projects-groups/pilot-trial-of-good-school-toolkit-for-secondary-schools. Accessed 5 September 2019.

[102] Good School Toolkit-Secondary Schools Pilot Trial. Retrieved from https://gtr.ukri.org/projects?ref=MR%2FR022208%2F1. Accessed 5 September 2019.

[103] Raising Voices (no date). Good School Toolkit Adaptations. Retrieved from http://raisingvoices.org/good-school/. Accessed 5 September 2019.

[104] WHO Violence Prevention Alliance (2016). Report of the Violence Prevention Alliance Annual Meeting. Retrieved from https://www.who.int/violenceprevention/VPA2016-AnnualMeetingReport.pdf?ua=1. Accessed 5 September 2019.

Case study 7

Combination interventions for controlling malaria transmitted by pyrethroid resistant mosquitoes: A novel bed net with synergist and IRS formulation (MR/L004437/1, Call 3)

Funding period: 01/03/2014 - 31/01/2019	Funding amount: £ 2,551,857
Lead PI: Prof Mark Rowland	Lead institution: London School of Hygiene and Tropical Medicine, UK

Summary:

- Abundant use of pyrethroid-based insecticides has driven an increase in pyrethroid-resistant mosquitoes, threatening the future success of these control strategies.
- The JGHT-funded trial evaluated the use of two alternative control products in the prevention of malaria transmission in Tanzania: insecticidal nets combining pyrethroid with piperonyl butoxide (PBO LLIN) and an indoor residual spray (IRS) formulation of a non-pyrethroid insecticide. The reference arm (the current standard of care) was pyrethroid-only LLIN. The study was led by the London School of Hygiene and Tropical Medicine in collaboration with two research institutes in Tanzania.
- The trial demonstrated that both products independently reduced malaria infection and transmission compared to standard control strategies. Use of both prevention tools in conjunction did not provide any additional benefit. It was the first trial to measure the impact of PBO LLIN in humans.
- The trial's findings on PBO LLINs were incorporated by WHO into policy, recommending their use in areas where pyrethroid resistance has been confirmed. PBO LLIN are being made available and scaled up across Africa.

Background

Malaria is a potentially fatal disease affecting an estimated 219 million people annually[1]. In 2017, it was estimated that 266,000 (61%) malaria deaths were in children less than 5 years old with the majority of these occurring in Africa[105]. Widespread use of long-lasting insecticidal nets (LLIN) and indoor residual spraying (IRS) has led to a dramatic reduction in the burden of malaria across sub-Saharan Africa[106]. However, both these interventions rely on pyrethroid-based insecticides to which mosquitoes are increasingly becoming resistant[107]. There is a risk that if intense selection via the use of traditional LLIN and IRS continues, cases of malaria will begin to increase.

Prior to the JGHT-funded trial, pyrethroid was the only insecticide recommended by WHO for use on LLIN and was widely used for IRS. In response to this need, WHO encouraged manufacturing companies to develop alternative tools to control mosquitoes[108]. These have included:

- a new type of pyrethroid LLIN that additionally contains piperonyl butoxide (PBO LLIN), a chemical synergist which inhibits mosquitos' defences and knocks out the pyrethroid-resistance mechanism

[105] WHO. World malaria report 2018. Geneva: World Health Organization, 2018.

[106] WHO. World malaria report 2016. Geneva: World Health Organization, 2016.

[107] Ranson H et al (2011) Pyrethroid resistance in African anopheline mosquitoes: what are the implications for malaria control? Trends Parasitol, 27: 91–98

[108] World Health Organization (2012) Report of the 15th WHOPES Working Group meeting, April 2012, Review of Olyset Plus LN, Interceptor LN. WHO/HTM/NTD/WHOPES/2012.

- formulations of alternative non-pyrethroid insecticides that can be used in long-acting IRS, such as the insecticide pirimiphos-methyl

The insecticide-synergist combination nets represent a new product class with the capacity to affect insecticide-resistant populations. At the time of the JGHT award, PBO LLINs had shown promising results in phase II trials[109,110] but had not yet been evaluated in a clinical trial. It was also unclear whether there was an added benefit to using a combination of LLIN and non-pyrethroid IRS[111].

The JGHT award

The JGHT-funded trial investigated if PBO LLIN and a non-pyrethroid IRS are able to mitigate against insecticide resistance and are effective in controlling malaria when compared to traditional control strategies. The trial took place in 40 villages in the Kagera region in northwest Tanzania, a region with both high prevalence of malaria and high levels of pyrethroid resistance in mosquitoes. The cluster randomised controlled trial followed a two-by-two factorial design. The four study groups were: standard LLIN, PBO LLIN, standard LLIN + IRS, and PBO LLIN + IRS.

The project team was led by Professor Mark Rowland, London School of Hygiene and Tropical Medicine in collaboration with two local Tanzanian institutes – the National Institute for Medical Research and the Kilimanjaro Christian Medical Centre. These three institutes form the Pan-African Malaria Vector Research Consortium (PAMVERC), a research alliance focussing on the development and evaluation of new vector control tools in collaboration with industry, WHO and the Bill and Melinda Gates foundation[112]. Strengthening the link to key international stakeholders, the trial steering committee included representatives of WHO, the Global Fund and the (US) President's Malaria Initiative (PMI) (the latter being the two largest funders of programmes addressing malaria[113]).

Trial findings

The trial results, published in The Lancet[114], revealed that use of PBO LLIN was significantly more effective at reducing malaria infection and transmission compared to standard pyrethroid-only LLIN. Households that were part of clusters issued PBO LLIN had a much lower risk of contracting malaria compared to clusters issued a standard LLIN. Similarly, a formulation of non-pyrethroid IRS showed improved control of malaria when compared to standard LLIN. The study found there was no added benefit if the two control interventions were combined.

The trial was the first study to demonstrate the effect of PBO LLIN on malaria transmission control in a natural setting[115]. It also provided the strongest evidence at the time that high-level pyrethroid resistance has a negative effect on the use and efficacy of standard nets. While strong evidence of a negative effect of pyrethroid resistance on the effectiveness of IRS was available, its effect on LLIN had been less clear[116]. The study was incorporated into a recent Cochrane review of the efficacy of PBO LLIN, noting that it

[109] Corbel V et al (2010) Field efficacy of a new mosaic long-lasting mosquito net (PermaNet® 3.0) against pyrethroid-resistant malaria vectors: a multi centre study in Western and Central Africa. Malaria Journal, 9(1): 113

[110] Pennetier C et al (2013) Efficacy of Olyset Plus, a new long-lasting insecticidal net incorporating permethrin and piperonyl-butoxide against multi-resistant malaria vectors. PLoS One 8:e75134

[111] Matowo J et al (2015) Trends in the selection of insecticide resistance in *Anopheles gambiae sl* mosquitoes in northwest Tanzania during a community randomized trial of long-lasting insecticidal nets and indoor residual spraying. Medical and veterinary entomology 29(1): 51-59

[112] http://kcmuco.ac.tz/pan-african-malaria-vector-consortium/ accessed 11 September 2019

[113] Pigott DM et al (2012) Funding for malaria control 2006–2010: a comprehensive global assessment. Malaria J 11(1): 246

[114] Protopopoff N et al (2018) Effectiveness of a long-lasting piperonyl butoxide-treated insecticidal net and indoor residual spray interventions, separately and together, against malaria transmitted by pyrethroid-resistant mosquitoes: a cluster, randomised controlled, two-by-two factorial design trial. The Lancet 391(10130): 1577-1588.

[115] Rowland M & Protopopoff N (2018) Dawn of the PBO-Pyrethroid Long Lasting Net–Light at Last. Outlooks on Pest Management 29(6): 242

[116] Kleinschmidt I et al (2015) Design of a study to determine the impact of insecticide resistance on malaria vector control: a multi-country investigation. Malar J. 14: 282

was the only village trial that had measured the impact of PBO LLIN on malaria infection in humans (all other studies recorded the impact on mosquito populations)[117].

The study was also the first RCT to provide evidence of malaria control of over 1 year for the first long-lasting non-pyrethroid formulation to be developed specifically for IRS[118]. The finding justifies the scale up and use of IRS in sub-Saharan Africa and long-running investment into long-lasting alternatives for indoor spraying between private and public sector organisations.

The trial also improved an important tool for vector control research: it validated use of the 'Furvela trap' for collection of mosquitos in an outdoor environment and improved its design[119]. During the trial, the trap was modified to make it easier to set up in the field without compromising its functionality. The design has since been used in other research studies[120,121].

Policy impact and implementation

Due to the extensive engagement with WHO before, during and after the project, WHO representatives were well aware of the emerging trial findings and were in a position to immediately incorporate these into policy. In 2017, prior to the publication of the trial results, WHO released a conditional recommendation endorsing the deployment of PBO LLIN in regions of confirmed pyrethroid resistance[122]. The JGHT-funded trial was instrumental by providing the data on which the recommendation is based. To further strengthen the evidence available, a second trial of PBO LLINs is currently underway in Uganda, where PBO nets were recently included in a national mass-distribution campaign of the Uganda Ministry of Health[123].

The WHO recommendation provides an important signal: A 2016 study on options for accelerating access to next generation LLIN in Burkina Faso found that "the national policy process is well defined but is dependent on global malaria policymaking and available resources. [...] The absence of global guidance on the role and cost-effectiveness of next-generation LLINs in vector control in countries with insecticide resistance is a critical barrier to donor funding and national adoption of next-generation LLINs"[124]. The recommendation now provides clear guidance to national policy makers and has enabled PBO nets to be financed by donor organisations.

The Global Fund[125] and PMI[126] have since encouraged national control programmes to make provision for PBO LLIN in their distribution campaigns across Africa, and the Global Fund has funded purchases

[117] Gleave K et al (2018) Piperonyl butoxide (PBO) combined with pyrethroids in insecticide-treated nets to prevent malaria in Africa. Cochrane Database of Systematic Reviews, Issue 11

[118] Protopopoff N et al (2018) Effectiveness of a long-lasting piperonyl butoxide-treated insecticidal net and indoor residual spray interventions, separately and together, against malaria transmitted by pyrethroid-resistant mosquitoes: a cluster, randomised controlled, two-by-two factorial design trial. The Lancet, 391(10130): 1577-1588.

[119] Charlwood JD (2017) The Furvela tent-trap Mk 1.1 for the collection of outdoor biting mosquitoes. PeerJ 5: e3848

[120] Charlwood JD (2018) Studies on the resting behaviour and host choice of Anopheles gambiae and An. arabiensis from Muleba, Tanzania. Medical and veterinary entomology 32(3): 263-270

[121] Charlwood JD (2018) 'We like it wet': a comparison between dissection techniques for the assessment of parity in Anopheles arabiensis and determination of sac stage in mosquitoes alive or dead on collection. PeerJ 6: e5155

[122] World Health Organisation. Conditions for deployment of mosquito nets treated with a pyrethroid and piperonyl butoxide. Programme GM. Geneva; 2017. WHO/HTM/GMP/2017.17 https://www.who.int/malaria/publications/atoz/use-of-pbo-treated-llins/en/

[123] Staedtke SG et al (2019) LLIN Evaluation in Uganda Project (LLINEUP) – Impact of long-lasting insecticidal nets with, and without, piperonyl butoxide on malaria indicators in Uganda: study protocol for a cluster-randomised trial. Trials 20: 321

[124] Tesfazghi K et al (2016) Challenges and opportunities associated with the introduction of next-generation long-lasting insecticidal nets for malaria control: a case study from Burkina Faso. Implement Sci. 11:103

[125] https://www.theglobalfund.org/media/4754/psm_categoryproductlevelprocurementdeliveryplanning_guide_en.pdf?u=637001819690000000, accessed 16 September 2019, via https://www.theglobalfund.org/en/sourcing-management/health-products/long-lasting-insecticidal-nets/

[126] PMI. U.S. President's Malaria Initiative technical guidance.(2018) https://www.pmi.gov/docs/default-source/default-document-library/tools-curricula/pmi-technical-guidance-(march-2016).pdf accessed 16 September 2019

of PBO LLIN, e.g. for Burkina Faso (USD4.2m transaction value, Jan 19)[127]. The trial and subsequent WHO recommendation have also informed the Bill and Melinda Gates Foundation, in conjunction with MedAccess and Clinton Health Access Initiative, to encourage development of new PBO LLIN products under a potential volume guarantee[128,129]. It is anticipated that such an agreement will drive manufacturing and decrease purchase costs for low income countries.

In 2018, five PBO LLIN were in production[130]. While this expansion of PBO LLIN products on the market is expected to help reduce pricing, it can make it difficult for countries to choose the most appropriate option: Each product varies in the distribution of PBO across the net and it is unclear if these differences will affect the observed reduction in mosquito populations and malaria prevalence.

To address this issue, a new study led by Professor Rowland and Dr N'Guessan is now comparing the efficacy of different PBO nets before and after washing 20 times, funded by the Global Fund ($150,000)[131]. The study is running small-scale field trials (comparative experimental hut trials), rather than full disease control trials, as WHO recognises that latter cannot be conducted for every type of PBO LLIN[132] - thus accelerating deployment and reducing research costs.

Concurrently, a new JGHT-funded trial is evaluating the newest generation of LLIN, bi-treated nets incorporating mixtures of insecticides or insecticide synergists, led by Dr Protopopoff with Prof Rowland as a co-investigator (MR/R006040/1[133]). Data or strategy emerging will be relevant to malaria control programmes in areas with a growing insecticide resistance problem, in Tanzania as well as neighbouring countries (Kenya, Uganda, Burundi, DRC and Malawi) and countries in West Africa.

[127] Global Fund Transaction Summary database: https://public.tableau.com/profile/the.global.fund#!/vizhome/PQRTransactionSummary_V1/TransactionSummary. Accessed 20 Sep 2019

[128] https://www.unicef.org/supply/files/6_BMGF_CHAI_update_next_generation.pdf Accessed 20 September 2019

[129] A volume guarantee reduces a company's risk of producing products by guaranteeing a pre-determined purchasing commitment over a set time period.

[130] Gleave K et al (2018) Piperonyl butoxide (PBO) combined with pyrethroids in insecticide-treated nets to prevent malaria in Africa. Cochrane Database of Systematic Reviews, Issue 11

[131] Prof Mark Rowland, personal communication. 19 Sep 2019.

[132] World Health Organisation (2017) Meeting report of the WHO Evidence Review Group on Assessing Comparative Effectiveness of New Vector Control Tools. Geneva. https://www.who.int/malaria/mpac/mpac-oct2017-erg-comparative-effectiveness-report-session5.pdf?ua=1, accessed 20 Sep 2019

[133] https://gtr.ukri.org/projects?ref=MR%2FR006040%2F1, accessed 16 Sep 2019

Case study 8

Evaluation of a rapid test for tuberculous meningitis: Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis (MR/M007413/1, full trial /Call 4)

Funding period: 01/03/2015 - 28/02/2018	Funding amount: £888,672
Lead PI: Dr David Meya	Lead institution: Makerere University, Uganda

Summary:

- The JGHT-funded ASTRO-CM trial aimed to evaluate whether addition of the drug sertraline to standard treatment improved survival of HIV patients with cryptococcal meningitis. The trial was led by Dr David Meya, Infectious Diseases Institute in Uganda. The trial results showed that adjunctive sertraline did not improve survival.
- Data collected as part of a study nested within the trial, but not directly related to the issue the trial addresses, has informed WHO policy: During screening of potential trial participants for Cryptococcal meningitis, the ASTRO-CM team also compared diagnostic TB tests and found that the new TB Xpert Ultra assay detected significantly more tuberculous meningitis than the other tests. This contributed to an update of a WHO recommendation in March 2017.

The JGHT-funded ASTRO-CM trial aimed to evaluate whether treatment with the drug sertraline improves survival of HIV patients with cryptococcal meningitis (a fungal infection of the protective membranes covering the brain and spinal cord). Dr David Meya, from the Infectious Diseases Institute (IDI) in Uganda, led the trial, working in collaboration with researchers from Mbarara University of Science and Technology, Uganda; Ifakara Health Institute, Tanzania; and the University of Minnesota, USA. While a previous study showed that adjunctive sertraline resulted in faster clearance of the fungal pathogen from cerebro-spinal fluid[134], the ASTRO-CM trial did not show an improvement in survival. Hence, sertraline should not be used to treat patients with HIV-associated cryptococcal meningitis[135].

The project also informed policy in other ways, and contributed to a decision by WHO to change its recommendation for TB meningitis diagnostic assays used in the detection of *Mycobacterium tuberculosis* in patients with suspected TB meningitis[136]:

Tuberculosis (TB) is one of the top 10 causes of death worldwide. In 2017, 10 million people fell ill with TB, and 1.6 million died from the disease[137]. The disease is a leading killer of HIV-positive people. Central nervous system TB, including tuberculous meningitis, is one of the most devastating clinical manifestations of TB. Early diagnosis and prompt initiation of TB treatment offer the best chance of a good neurological outcome; however, diagnosis through bacterial culture has low sensitivity and is too slow for initial clinical decision-making[138].

In the past years, nucleic acid amplification technology has enabled improved detection of *Mycobacterium tuberculosis*, the bacterium causing TB. In 2011, WHO recommended the Xpert

[134] Rhein J et al (2016) Efficacy of adjunctive sertraline for the treatment of HIV-associated cryptococcal meningitis: an open-label dose-ranging study. Lancet Infect Dis. 16(7):809-818

[135] Rhein J et al (2019) Adjunctive sertraline for HIV-associated cryptococcal meningitis: a randomised, placebo-controlled, double-blind phase 3 trial. Lancet Infect Dis. 19(8):843-851

[136] https://www.who.int/tb/features_archive/Xpert-Ultra/en/ Accessed Aug 2019

[137] WHO fact sheet: Tuberculosis (2018): https://www.who.int/en/news-room/fact-sheets/detail/tuberculosis

[138] Chin JH (2017) Xpert MTB/RIF Ultra: the long-awaited game changer for tuberculous meningitis? European Respiratory Journal 50: 1701201

MTB/RIF assay ('Xpert', Cepheid, Sunnyvale, USA) test for the diagnosis of pulmonary TB[139]. Since 2013, this assay has also been recommended for use in children and to diagnose specific forms of extrapulmonary TB[140]. However, while sensitivity for diagnosis of pulmonary TB is high for Xpert, detection of tuberculous meningitis varies widely and is low[141]. Delaying or failing to initiate TB treatment on the basis of a negative result can have serious and potentially deadly consequences.

At the time of the JGHT award, a new diagnostic assay, Xpert Ultra, had become available. This re-engineered test sought to improve the analytical sensitivity for MB detection, but its performance had not yet been compared with that of the standard Xpert assay for TB meningitis using cerebrospinal fluid. The ASTRO-CM team collaborated with the group that had developed the new test, and used both assays to screen 129 HIV-infected adults for suspected tuberculous meningitis during the trial recruitment phase [142]. This was the first evaluation of diagnostic performance of Xpert Ultra for this disease.

The study found that Xpert Ultra detected significantly more tuberculous meningitis than did either Xpert (95% compared to 45%) or culture. It hence showed that in clinical practice, the high sensitivity of Xpert Ultra could facilitate diagnosis of TB at earlier stages of disease, including in patients with HIV, a population with high mortality. These findings were published in an article in Lancet Infectious Diseases in 2018[143], which has since been cited in 67 articles (Scopus, 22 Aug 2019).

The assays were also evaluated in a larger study involving 1520 HIV-negative individuals and children, published in November 2017[144]. In March 2017, WHO summarised available evidence in a technical report[145], and recommended the use of Xpert Ultra as a replacement for the current Xpert cartridges in all settings[146]. The ASTRO-CM trial results informed this decision.

By 2018, South Africa was using Xpert Ultra as the initial TB diagnostic test[147]. However, despite its improved performance and the WHO recommendation, the transition to this assay has been limited - in part due to its short shelf-life.

Dr Meya is currently leading a second JGHT-funded trial, the HARVEST trial, investigating whether a high dose of oral rifampicin (an antibiotic) improves survival of adult patients with TB meningitis[148]. As in the ASTRO-CM trial, the trial includes a nested study which will evaluate a novel test, the Fujifilm SILVAMP TB LAM (FujiLAM) assay[149], for diagnostic accuracy of TB meningitis.

[139] Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. Policy statement. Geneva, World Health Organization, 2011 (http://whqlibdoc.who.int/publications/2011/9789241501545_eng.pdf)

[140] WHO Global Tuberculosis Report 2018 https://www.who.int/tb/publications/global_report/en/

[141] Denkinger CM et al (2014) Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. Eur Respir J 44: 435–446

[142] Bahr NC et al (2018) Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study. Lancet Infect Dis 18: 68–75

[143] Bahr NC et al (2018) Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study. Lancet Infect Dis 18: 68–75

[144] Dorman SE et al (2018) Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. Lancet Infect Dis 18: 76–84

[145] https://www.who.int/tb/publications/2017/XpertUltra/en/ Accessed Aug 2019

[146] https://www.who.int/tb/features_archive/Xpert-Ultra/en/ Accessed Aug 2019

[147] WHO Global Tuberculosis Report 2018 https://www.who.int/tb/publications/global_report/en/ Accessed Aug 2019

[148] High Dose Oral Rifampicin to Improve Survival from Adult TB Meningitis - (HARVEST) Trial. MR/S004963/1, Jun 19 - May 23; £3,881,422

[149] Broger T et al (2019) Novel lipoarabinomannan point-of-care tuberculosis test for people with HIV: a diagnostic accuracy study. Lancet Infect Dis. 19(8): 852–861

Case study 9

Interrupting transmission of soil-transmitted helminths: cluster randomised trial evaluating alternative treatment strategies in Kenya (TUMIKIA) (MR_N00579X_1/Call 5)

Funding period: 01/11/2015 - 31/10/2018	Funding amount: £1,027,818
Lead PI: Dr Rachel Pullan	Lead institution: London School of Hygiene and Tropical Medicine, UK

Summary

- Soil-transmitted helminths (STH) are among the most common infections worldwide and affect the poorest and most deprived communities.
- The TUMIKIA trial investigated whether it is possible to *interrupt* the transmission of STH, evaluating the impact of school-based and community-based treatment on the prevalence and intensity of STH infection. It was co-funded by the Government of Kenya, the Children's Investment Fund Foundation, and the Bill and Melinda Gates Foundation. The trial was led by Dr Rachel Pullan, LSHTM and included collaborators from the Kenya Medical Research Institute (KEMRI) and other investigators at LSHTM.
- The trial found that community-wide treatment was more effective in reducing hookworm prevalence and intensity than school-based treatment, with little additional benefit of treating every 6 months compared to once per year.
- The results fed into the development of the Breaking Transmission Strategy of the Kenyan government for 2019-2023, which targets STH, and other NTDs, with a package of interventions[150]. Implementation is currently being piloted to prepare for nation-wide roll-out. TUMIKIA findings are also informing WHO discussions on community- vs school-based treatment, and on effective monitoring and surveillance strategies.
- Broadening coverage is faced with a key challenge: Deworming programmes are mainly driven by donations that are limited to children in their use. Unless donor programmes chose to purchase drugs, only a shift in this limitation will enable broader uptake of community-based deworming.
- A longer-term study in Malawi, Benin, and Sri Lanka - the DeWorm3 trial funded by BMGF and led by the Natural History Museum London - is currently expanding on the trial's results. Findings are likely to guide BMGF strategy and inform WHO and other international organisations.

Background

Soil-transmitted helminths (STH) are among the most common infections worldwide and affect the poorest and most deprived communities[151]. STH are transmitted by eggs present in human faeces which in turn contaminate soil in areas where sanitation is poor. The main species infecting humans are the roundworm *Ascaris lumbricoides*, the whipworm *Trichuris trichiura* and hookworms *Necator americanus* and *Ancylostoma duodenale*.

Globally, over 1.5 billion people, or just under a quarter of the world's population, are infected with STH, and more than 800 million preschool- and school-age children live in areas where these parasites are intensively transmitted. These children are in need of treatment and preventive interventions: STH infections can adversely affect physical and mental growth in childhood and contribute to malnutrition

[150] The Kenya National Breaking Transmission Strategy for Soil-Transmitted Helminthiasis, Schistosomiasis, Lymphatic Filariasis and Trachoma 2019-2023. Republic of Kenya, Ministry of Health 2019, p. 10: "The BTS will use a community-based platform to implement the expanded STH and SCH MDAs while maintaining schools as one of the fixed, service delivery points.", with reference to TUMIKIA trial protocol.

[151] Pullan R et al (2014) Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. Parasites & Vectors 7: 37

and iron-deficiency anaemia. In 2017, the global burden of STH infections was estimated at 3.3 million disability-adjusted life years (DALYs)[152].

In 2012, the London Declaration on neglected tropical diseases (NTDs) was launched, a coordinated cross-sectoral effort aimed at intensifying control of, or eliminating, 10 neglected diseases by 2020[153]. The declaration includes a target to provide regular anthelmintic treatment to at least 75% of children in districts with high prevalence of any STH infection (>20%) in schoolchildren, thereby reducing the burden of disease[154]. By 2016, school-based deworming programmes had reached nearly 70% of these children[155]. Based on this success, policy makers are starting to consider the next step in combatting STH: interruption of transmission.

While schools provide a good entry point for deworming activities, allowing easy provision of the health and hygiene education components, mathematical models suggest that treating only school-age children is insufficient to interrupt STH transmission, and that community-wide treatment would be more effective[156]. Other programmes combatting infectious diseases, such as lymphatic filariasis, had achieved treatment of entire communities with community health workers (CHWs) or volunteers[157]; however, the impact and cost-effectiveness of this approach had not yet been evaluated for STH infections.

In 2009, the Government of Kenya launched its national school-based deworming programme (NSBDP), treating over 4.6 million preschool and school children in 2013/14[158]. As a school-based programme, it was not fully integrated within community health structures that were being established in Kenya at the time, and hence did not utilise CHWs who had started to deliver a range of other public health interventions in the country, and there was a lack of evidence to compare the effectiveness, cost-effectiveness, and equity of these two delivery systems.

The JGHT award

The TUMIKIA trial (Tuangamize Minyoo Kenya Imarisha Afya; Swahili for Eradicate Worms in Kenya for Better Health) investigated the question whether it is possible to *interrupt* the transmission of STH[159]. It evaluated the impact of school-based and community-based treatment on the prevalence and intensity of STH infection, and was the first trial to address the potential for transmission control, rather than focussing on morbidity reduction only (i.e. a decrease of the intensity of infection). The trial also assessed the costs, cost-effectiveness, acceptability and feasibility of different treatment strategies and delivery systems.

The trial involved 120 community units (a government health-service delivery structure serving approximately 1000 households) in Kwale County, Kenya. This county had benefitted from previous mass drug administration for a difference parasitic disease, lymphatic filariasis, and hence had better established community-based treatment delivery structures than other counties. TUMIKIA was led by

[152] GBD 2017 DALYs and HALE Collaborators (2018) Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392: 1859–1922

[153] https://www.who.int/neglected_diseases/London_meeting_follow_up/en/ Accessed 19 Aug 2019

[154] WHO (2012) Eliminating soil-transmitted helminthiases as public health problem in children: progress report 2001–2010 and strategic plan 2011–2020; WHO Guideline: preventive chemotherapy to control soil-transmitted helminth infections in at-risk population groups. Geneva: World Health Organization, 2017

[155] WHO. Schistosomiasis and soil-transmitted helminthiases: number of people treated in 2016 (2017) Wkly Epidemiol Rec 49: 749–60

[156] Truscott JE et al (2014) Can chemotherapy alone eliminate the transmission of soil transmitted helminths? Parasit Vectors 7: 266; Anderson R et al (2014) The coverage and frequency of mass drug administration required to eliminate persistent transmission of soil-transmitted helminths. Philos Trans R Soc B 369: 20130435

[157] https://www.who.int/lymphatic_filariasis/elimination-programme/en/ Accessed 19 Aug 2019

[158] The 2nd Kenya National Strategic Plan for control of Neglected Tropical Diseases 2016-2020. Kenya Ministry of Health

[159] Pullan RL et al (2019) Effects, equity, and cost of school-based and community-wide treatment strategies for soil-transmitted helminths in Kenya: a cluster-randomised controlled trial. The Lancet 393: 2039–50

Dr Rachel Pullan, London School of Hygiene and Tropical Medicine (LSHTM) and included a team of researchers from the Kenya Medical Research Institute (KEMRI) and other investigators at LSHTM.

The TUMIKIA trial compared three approaches: 1) routine deworming of school children, 2) annual deworming of the entire community, and 3) biannual deworming of the entire community, and assessed the impact of each approach on the prevalence of hookworm infection within the community (the dominant STH species in this setting). It was embedded within existing public health programmes, to maximise public health relevance, and was nested within the ongoing NSBDP. Additional treatment in the community-based trial arms was delivered by CWHs to all who were not covered by the school-based strategy. Working within these local delivery structures also meant that the trial team had a direct route to community engagement.

- Funding for the TUMIKIA trial

The TUMIKIA trial drew on funding and resources from across sectors, with the JGHT award contributing to the study: The JGHT award financed the cost-effectiveness assessment of the interventions and the evaluation of whether the interventions are acceptable to the community, feasible given the existing health system, and scaleable to other regions.

The full costs of treatment and its delivery through both schools and communities were covered by the Government of Kenya (teacher and health worker salaries), the Children's Investment Fund Foundation (CIFF) (which funds the NSBDP and provided additional funding to support the delivery of treatment in the community-based treatment groups as part of the trial), and GlaxoSmithKline (GSK) (providing the deworming drug free-of-charge). The parasitological survey to determine the level of STH infection was funded by the Bill & Melinda Gates Foundation (BMGF).

- Stakeholder engagement

At the inception of the trial, Kenya's health programmes were being decentralised, moving from nationally controlled programmes to increased decision making and authority at the county level. The Kwale county government and Kwale Minister of Health were particularly interested in evidence on how best to institutionalise deworming into their community health programmes, and open to research evidence to inform policy making. Members of the trial team had previously worked in this area, e.g. as part of research evaluating the school-based deworming programme in Kenya, and had established links with key government stakeholders. When developing the proposal for the trial, the team held discussions with officials at national and county levels, CHWs and community members; the Kenya Ministry of Health and county government (led by the County Executive Committee, CEC) provided input into the project design as well as letters of support to accompany the trial proposal. The trial team also kept the relevant WHO offices informed of the trial and findings, including the WHO country office in Kenya, the WHO neglected tropical disease (NTD) and community health programmes, the WHO STH guidance committee, and the WHO Africa regional office.

Trial findings

The TUMIKIA trial found that community-wide treatment was more effective in reducing hookworm prevalence and intensity than school-based treatment, with little additional benefit of treating every 6 months compared to once per year[160]. Community-wide treatment was similar for different demographic and socioeconomic subgroups, i.e. equitable in coverage and effects. Cost-per-person treated through community-wide treatment was higher than that reported by the NSBDP, but was projected to be lower when considering a scale-up scenario that removed costs associated with the trial. These findings highlight the potential of community-wide treatment targeting all ages to reduce infection prevalence and potentially interrupt transmission of hookworm, and provide evidence to inform the scaling-up of this delivery strategy for the control of STH and other NTDs, in Kenya and beyond. The study also highlighted key strategies that were instrumental for effective drug delivery relevant to informing

[160] Pullan RL et al (2019) Effects, equity, and cost of school-based and community-wide treatment strategies for soil-transmitted helminths in Kenya: a cluster-randomised controlled trial. The Lancet 393: 2039–50

planning of community-wide drug distribution[161]. Qualitative investigations conducted at all levels of the health system suggested that in addition to scale up of mass drug administration, Kenyan stakeholders identified several other areas requiring investment: changes in institutional structures and culture to reduce working in silos; building community demand and ownership; and increased policymaker engagement on underlying socioeconomic and environmental causes of STH[162].

Impacts

The results of the TUMIKIA trial fed into the development of the Breaking Transmission Strategy of the Kenyan government for 2019-2023, which targets STH - as well as other NTDs - with a comprehensive package of interventions[163]. The strategy is currently being introduced across three counties, building the framework for implementation in a number of key settings before national roll-out[164].

Discussions on whether to move towards community treatment rather than school-based treatment are ongoing within the global community, e.g. WHO is currently going through a consultation process to determine the 2030 goals in this respect. Evidence from the TUMIKIA trial has informed these discussions (but strategies are yet to be formalised). Data from the TUMIKIA trial is also being used by WHO to look at effective monitoring and surveillance strategies[165].

While the trial showed that community-wide treatment is more effective than targeting of school-age children only, broadening coverage is faced with a key challenge: Deworming programmes are mainly driven by donations that are limited to children in their use. WHO do also recommend including women of child bearing age and pregnant women, but there is no donation in place for these groups. Unless programmes chose to purchase drugs, only a shift in this limitation will enable broader uptake of community-based deworming.

Data collected and tools developed and as part of the TUMIKIA trial have helped other public health and research efforts. For example, the trial developed a linked smartphone survey and sample collection tool, which includes scanning of QR codes on sample pots, enabling linking of household and individual data collected through a questionnaire with laboratory results. Standard Operating Procedures based on this tool were adapted for another trial (DeWorm3, see below) and are currently used for data collection in Benin, India and Malawi[166]. The trial team also supported the Kenyan Ministry of Health in the use of the survey tool and platform for other programmes, including the national programme to eliminate lymphatic filaraisis (surveys and drug delivery). Data on sanitation collected as part of the TUMIKIA trial were shared with the environmental health department at the Kwale Ministry of Health who used this information to refine their community sanitation strategy, in particular the roll out of community-led total sanitation.

Capacity building within the trial

The trial built local capacity in three main areas:

- The pathological dissections (examination of stool samples) to determine the presence and level of STH infection required a team of around 38 technicians throughout the trial. Working with KEMRI and the Ministry of Health, more than 70 technicians from across Kenya were recruited and trained.

[161] Legge H et al (2019) Implementer and recipient perspectives of community-wide mass drug administration for soil-transmitted helminths in Kwale County, Kenya. PLOS Negl Trop Dis. In press.

[162] Khan MS et al (2019) "For how long are we going to take the tablets?" Kenyan stakeholders' views on priority investments to sustainably tackle soil-transmitted helminths. Social Science & Medicine 228: 51-59

[163] The Kenya National Breaking Transmission Strategy for Soil-Transmitted Helminthiasis, Schistosomiasis, Lymphatic Filariasis and Trachoma 2019-2023. Republic of Kenya, Ministry of Health 2019, p. 10: "The BTS will use a community-based platform to implement the expanded STH and SCH MDAs while maintaining schools as one of the fixed, service delivery points.", with reference to TUMIKIA trial protocol.

[164] Dr Rachel Pullan, LSHTM, personal communication (10 Oct 2019)

[165] Dr Rachel Pullan, LSHTM, personal communication (10 Oct 2019)

[166] http://www.nhm.ac.uk/our-science/our-work/sustainability/deworm3.html Accessed Sep 2019

This resulted in a large skilled 'rotating' team of technicians including nationally recruited expert technicians, who worked to train local technicians recruited from health centres across Kwale county.

- The TUMIKIA trial helped strengthen the nascent community health structure across Kwale county. While policy and guidance for community health units was in place at the start of the trial, actual units were covered only approx. 50% of the county. Working with the local Ministry of Health, TUMIKIA established informal community health units where needed, which involved recruitment and training of CHWs[167]. Once in place, these structures were then also used for other public health interventions, e.g. distribution of bed nets for malaria control, and implementation of the lymphatic filariasis treatment programme.
- Conduct of the trial required recruitment and training of a large number of field officers, who conducted all field work. During the periodic cross-sectional surveys, 120 field officers were recruited locally, and provided training in a number of key areas including research ethics, electronic data capture, field logistics and the conduct of household and community-based surveys.

Further research

The TUMIKIA trial was the first trial to address the potential for STH transmission control, and provided a first proof-of-concept for community-based deworming programmes. However, with funding limited to 2 years, the trial could not fully explore transmission interruption. In addition, longer-term data could not be collected, as the trial sites were affected by a scaling up of the Kenyan lymphatic filariasis programme, which provides drug also effective against STH - the TUMIKIA trial hence 'lost' its control group.

A longer-term study with trials in Malawi, Benin, and Sri Lanka - the DeWorm3 trial funded by the BMGF and led by the Natural History Museum London[168] - is currently expanding on the TUMIKIA results. DeWorm3 is expected to conclude at the end of 2022[169] and its findings are likely guide BMGF future strategy as well as inform international organisations such as WHO. TUMIKIA's lead investigator, Dr Pullan, and other members of the trial team were asked to support the design of DeWorm3 in 2016, bringing in their experience from Kenya[170]. Members of the TUMIKIA team continue to be involved in the DeWorm3 project (e.g. LSHTM acts as the Trial Conduct and Coordination Support Unit for DeWorm3, and Dr Pullan is a Principal Investigator for the Malawi trial site[171]).

Another further trial, the EDCTP-funded STOP project, was awarded in September 2018 and will investigate different drug combinations for deworming school-children in Kenya, Mozambique and Ethiopia[172]. The STOP consortium includes researchers from KEMRI and LSHTM (modelling and health economics support) who were involved in TUMIKIA and are now able to contribute their knowledge and experience to the project. The Kenya STOP study site will be group of communities from Kwale county, the selection of which will be directly informed by results from the TUMIKIA trial.

[167] Dr Rachel Pullan, personal communication, July 2019

[168] http://www.nhm.ac.uk/our-science/our-work/sustainability/deworm3.html Accessed Sep 2019

[169] https://clinicaltrials.gov/ct2/show/NCT03014167 Accessed Sep 2019

[170] Ásbjörnsdóttir KH (2018) Assessing the feasibility of interrupting the transmission of soil-transmitted helminths through mass drug administration: The DeWorm3 cluster randomized trial protocol. PLoS Negl Trop Dis 12(1): e0006166

[171] https://www.nhm.ac.uk/our-science/our-work/sustainability/deworm3/who-we-are.html Accessed Sep 2019

[172] https://www.isglobal.org/en/new/-/asset_publisher/JZ9fGljXnWpI/content/arranca-stop-un-proyecto-que-busca-interrumpir-la-transmision-de-parasitos-intestinales Accessed Sep 2019

Case study 10

Menstrual solutions in adolescent schoolgirls in western Kenya: an acceptability, feasibility and safety study (G1100677/1/Call 1)

Funding period: 01/04/2012 - 30/09/2013	Funding amount: £716,200
Lead PI: Penelope Anne Phillips-Howard	Lead institution: Liverpool School of Tropical Medicine

Summary:

- Little evidence is available on Menstrual Health Management (MHM) by schoolgirls in LMICs and its impact on education and health outcomes. The JGHT-funded feasibility study responded to this gap and compared three different approaches to MHM (menstrual cups, sanitary pads, no intervention). The study was led by the London School of Hygiene and Tropical Medicine, with partners in Kenya and the UK.
- The feasibility study provided important evidence for the design of a full trial, subsequently funded by the JGHT (ongoing). It has also stimulated further international research activity on the topic.
- Expertise developed through the JGHT award enabled the study team to contribute to committees and fora addressing issues in MHM, both in Kenya and internationally. This has included feeding into the Kenyan National Menstrual Hygiene Management Policy and Strategy, currently under development by the Kenyan Ministries of Health, Education and Gender.

Background

Menstrual Health Management (MHM) is an important contributor influencing schoolgirls' sexual and reproductive health.[173] Lack of money to purchase menstrual products leads to girls use unsanitary items (rags, paper, cotton wool etc) to manage the menstrual cycle, which can cause reproductive tract infections. Moreover, girls may engage in transactional sex (sex in return for money or favours) to afford sanitary products, which increases the risk of contracting sexually transmitted infections (STIs) and may lead to unwanted pregnancy.[174] [175]

Prior to the JGHT-funded trial, few studies had addressed the issue of MHM, and limited evidence existed on the link between poor MHM and school absenteeism. In 2012, at the time of the JGHT award, pilot studies carried out in Ghana[176] and Nepal[177] had shown a weak relationship between MHM and school absenteeism. However, the studies' small sample sizes did not allow findings to be generalised and appropriate policy to be formulated and their short duration (3 months) did not provide evidence on long-term compliance and acceptability. No randomised controlled trial (RCT) assessing the effect of using menstrual cups on school absenteeism and other harmful outcomes had been undertaken.

[173] Sommer M & Sahin M (2013) Overcoming the taboo: advancing the global agenda for menstrual hygiene management for schoolgirls. Am J Public Health 103(9): 1556–1559

[174] Prof P Phillips-Howard, Personal communication, July 2019

[175] Sommer M & Sahin M (2013) Ibid.

[176] Scott L et al (2009). Impact of Providing Sanitary Pads to Poor Girls in Africa. Retrieved from https://www.doublexeconomy.com/wp-content/uploads/2010/09/University-of-Oxford-Sanitary-Pad-Study.pdf. Accessed 5 September 2019

[177] Oster E & Thornton A (2010) Determinants of Technology Adoption: Peer Effects in Menstrual Cup Take-Up. Retrieved from https://www.povertyactionlab.org/sites/default/files/publications/Determinants%20of%20Technology%20Adoption.pdf. Accessed 5 September 2019

Policymakers in Kenya had become increasingly aware of the effect poor MHM on schoolgirls' educational outcomes[178], but were lacking robust evidence on which to base policy decisions. The JGHT-funded trial aimed to address this issue.

The JGHT study team had initially put in an application for funding for a full trial. Following feedback from the JGHT assessment panel, the decision was made to first carry out a feasibility study to inform the design of a full trial; latter was funded by the JGHT in 2015 (see section 1.3.2).

The JGHT award

The JGHT-funded study "Menstrual solutions in adolescent schoolgirls in western Kenya: an acceptability, feasibility and safety study" assessed the feasibility of using menstrual cups in a rural environment by Kenyan schoolgirls.[179] It compared the use of menstrual cups, sanitary pads and usual practice (control) in a three-armed cluster-randomised controlled trial. The study was designed to explore multiple outcomes[180]: The primary outcome was the effectiveness of menstrual cups in reducing school absenteeism or drop-out. Secondary outcomes were the incidence of sexually transmitted infection (STI), reproductive tract infection including bacterial vaginosis and safety relating to toxic shock syndrome or vaginal Staphylococcus aureus, and cup contamination.

The study was conducted in Siaya, a rural area in Western Kenya with high rates of HIV, STIs, sexual and reproductive harm and school absenteeism, benefitting from a well-established health and demographic surveillance system. In total, 751 girls between the ages of 14 and 16 who had started menstruating were enrolled in the feasibility study and followed for a median of 10.9 months. The study also included a baseline survey on water, sanitation and hygiene (WASH) conditions in schools[181] and focus group discussions with parents to determine cultural acceptability of menstrual cups[182].

The study team was led by Professor Penelope Phillips-Howard from the Liverpool School of Tropical Medicine who had extensively collaborated with two of the Kenyan institutions involved in the study, the Kenyan Institute for Medical Research (KEMRI) and the Kenyan-based US Centre for Disease Control and Prevention (CDC) in her previous work (in the field of malaria). Other collaborating institutions were Bangor University from the UK, the Safe Water and AIDS Project in Kisumu Kenya, and the Kenyan Ministry of Public Health and Sanitation.

The study team engaged with stakeholders from national and regional government during the preparation and implementation phases of the trial. The Kenyan Ministry of Health and Education provided an endorsement letter for the study[183], which aided the recruitment process and focus groups.

[178] UNESCO (2014). Puberty Education & Menstrual Hygiene Management. *Good Policy and Practice in Health Education, booklet 9*. Retrieved from https://asanteafrica.org/wp-content/uploads/2018/03/UNESCO-Puberty-rpt.pdf. Accessed 5 September 2019.

[179] Phillips-Howard PA et al (2016). Menstrual cups and sanitary pads to reduce school attrition, and sexually transmitted and reproductive tract infections: a cluster randomised controlled feasibility study in rural Western Kenya. BMJ Open 6:e013229

[180] Ibid.

[181] Alexander KT et al (2014) Water, Sanitation and Hygiene Conditions in Kenyan Rural Schools: Are Schools Meeting the Needs of Menstruating Girls? Water, *6*(5): 1453-1466

[182] Mason L et al (2013). 'We Keep It Secret So No One Should Know' – A Qualitative Study to Explore Young Schoolgirls Attitudes and Experiences with Menstruation in Rural Western Kenya. PLoS ONE 8(11): e79132

[183] Prof P Phillips-Howard, Personal communication, July 2019

Local Education and Health Offices were directly involved in the study and are co-authors on some of the publications. [184] [185] [186] [187] [188] [189]

Results of the development award and research impact achieved

- Results of the development award

The feasibility study produced four main publications, of which one is based on a nested qualitative study[190].

The main findings of the study are:

- The use of cups or pads did not reduce absence from school (primary outcome)[191].
- The use of menstrual cups or pads reduced the incidence of STIs by almost half compared the control arm (7.7% versus 4.2%), and menstrual cups reduced the incidence of bacterial vaginosis (12.9% vs approx. 20% for pads and control group). No adverse events relating to toxic shock syndrome were identified (secondary outcomes) [192] [193].

- Research outcomes and impact

Findings of the JGHT feasibility study constitute the first robust evidence in this little-researched area and have stimulated a variety of further work on MHM.

In 2015, the study team received further funding from the JGHT to carry out a larger RCT in secondary schools entitled "Menstrual cups and cash transfer to reduce sexual and reproductive harm and school drop-out in adolescent schoolgirls in Western Kenya". The trial received funding for £2,635,762; it started in October 2015 and is expected to complete in June 2020.

The preceding feasibility study provided important information for the design of the full trial. As a result, the full trial's primary outcome measure was shifted from the level of absenteeism to the level of school drop-out and level of sexually transmitted infections, as the feasibility study showed this to be a more reliable indicator. Another finding related to girls' sexual and reproductive health being affected by financial constraints, exposing them to coerced sex in order to receive basic essentials, including sanitary

[184] Alexander K et al (2014) Water, Sanitation and Hygiene Conditions in Kenyan Rural Schools: Are Schools Meeting the Needs of Menstruating Girls? Water 6(5): 1453-1466

[185] Mason L et al (2015) Adolescent schoolgirls' experiences of menstrual cups and pads in rural western Kenya: a qualitative study. Waterlines 34(1)

[186] Juma J et al (2017) Examining the safety of menstrual cups among rural primary school girls in western Kenya: observational studies nested in a randomised controlled feasibility study. BMJ Open 7: e015429

[187] Phillips-Howard PA et al (2016) Menstrual cups and sanitary pads to reduce school attrition, and sexually transmitted and reproductive tract infections: a cluster randomised controlled feasibility study in rural Western Kenya. BMJ Open 6:e013229

[188] Van Eijk AM et al (2018) Use of menstrual cups among schoolgirls: longitudinal observations nested in a randomised controlled feasibility study in rural western Kenya. Reproductive Health 15: 139

[189] Mason L et al (2019). Comparing use and acceptability of menstrual cups and sanitary pads by schoolgirls in rural Western Kenya. International Journal of Reproduction, Contraception, Obstetrics and Gynaecology 8

[190] Mason L et al (2015) Adolescent schoolgirls' experiences of menstrual cups and pads in rural western Kenya: a qualitative study. Waterlines 34(1): http://dx.doi.org/10.3362/1756-3488.2015.003

[191] Phillips-Howard PA et al (2016) Menstrual cups and sanitary pads to reduce school attrition, and sexually transmitted and reproductive tract infections: a cluster randomised controlled feasibility study in rural Western Kenya. BMJ Open 6:e013229

[192] Kerubo E et al (2016) Prevalence of reproductive tract infections and the predictive value of girls' symptom-based reporting: findings from a cross-sectional survey in rural western Kenya. Sex Transm Infect 92(4): 251-6

[193] Juma J et al (2017) Examining the safety of menstrual cups among rural primary school girls in western Kenya: observational studies nested in a randomised controlled feasibility study. BMJ Open 7: e015429

pads[194]. The full trial hence examines whether cups, cash, or cups and cash provided together, prevent school drop-out and improve girls' sexual and reproductive health.

The PI has also been involved in further research, e.g. at KEMRI/CDC funded by CDC (Atlanta) and the United States' President's Emergency Plan for AIDS Relief (PEPFAR), investigating menstrual needs in connection to sexual harm in Kenyan women between the ages of 13 and 29 (i.e. not limited to schoolgirls).[195] Professor Phillips-Howard is frequently asked by international organisations (e.g. UNFPA, UNICEF[196], Grand Challenges Canada) to provide expert input.

The feasibility study also led questions relating to MHM to be included in the HDSS[197], a wide-scale a wide-scale community survey monitoring 250,000 persons in Western Kenya.[198] Since 2012, KEMRI/CDC include menstrual and behavioural questions in their Health and Demographic Surveillance System (HDSS). These additional questions aim to investigate specific menstrual or sexual behaviours in association with respondents' HIV status.

Informed by the JGHT-funded research, further studies on the topic of MHM are currently underway. Nested as a sub-study within the current full trial, a team of researchers at the University of Illinois, USA is investigating the effect of menstrual cups on the vaginal microbiome in Kenyan schoolgirls[199]. The research is based on the feasibility study's finding that use of menstrual cups resulted in lower incidence of bacterial vaginosis.

Policy impact in Kenya and beyond

As a result of the expertise the study team was able to develop through the JGHT award, the study team is now in a position to inform various committees working on MHM intervention policy, both in Kenya and internationally.

- Impact on Kenyan policy

Following on from the feasibility study, Professor Phillips-Howard was invited by the Government of Kenya to join an advisory panel tasked with developing national policy guidelines for MHM and training tools for government officials. The process, coordinated by the Kenyan Ministry of Health (MoH), brings together key stakeholders in MHM including NGOs, community-based organisations, UN agencies, the private sector and social enterprises[200]. A draft Menstrual Hygiene Management Policy and Strategy currently awaits endorsement from the Kenyan Ministries of Health, Education and Gender.[201] In

[194] Oruko K et al (2015) 'He is the one who is providing you with everything so whatever he says is what you do': A Qualitative Study on Factors Affecting Secondary Schoolgirls' Dropout in Rural Western Kenya. PLoS One 10(12): e0144321

[195] Phillips-Howard PA et al (2015) Menstrual Needs and Associations with Sexual and Reproductive Risks in Rural Kenyan Females: A Cross-Sectional Behavioral Survey Linked with HIV Prevalence. Journal of Women's Health 24(10): 801–811

[196] See https://www.unicef.org/wash/schools/files/India_-_MHM_for_Schoolgirls.pdf. Accessed 28 Sep 2019

[197] ResearchFish data, provided by MRC.

[198] Odhiambo F et al (2012). Profile: the KEMRI/CDC Health and Demographic Surveillance System—Western Kenya. Int J Epidemiol 41(4): 977-87

[199] National Institutes of Health. Menstrual cups, maturation of the adolescent vaginal microbiome, and STI/HIV risk, University of Illinois at Chicago. Retrieved from http://grantome.com/grant/NIH/R01-HD093780-02. Accessed 5 September 2019.

[200] FSG (2016) Menstrual Health in Kenya, Country Landscape Analysis. Retrieved from https://menstrualhygieneday.org/wp-content/uploads/2016/04/FSG-Menstrual-Health-Landscape_Kenya.pdf. Accessed 5 September 2019.

[201] IRC (2019) Integrating, collaborating and building capacity for menstrual hygiene management. Retrieved from: https://www.ircwash.org/news/integrate-collaborate-build-capacity-%E2%80%93-kenyans-advise-mhm. Accessed 5 September 2019.

addition, a number of MHM training tools were developed and government officials from across ministries in Kenya and Malawi were trained in 2016 and 2017.[202] [203]

- Other influence on international policy

The MHM intervention feasibility study has raised awareness of the issue of MHM internationally, and the study team has taken on advisory roles for research projects and programmes, including WHO, UNFPA, WSSCC[204] initiatives, as well as initiatives across Africa (Kenya, Malawi, Uganda, Tanzania, São Tomé and Príncipe) and in Asia (India). [205] [206] The outcomes of JGHT-funded research and the experience of disseminating the findings led to the initiation of the 'Cup Coalition' in 2018, bringing together organisations working with school children on the topic of MHM in various African countries, consolidating the movement for better menstrual health in African girls [207]. Professor Phillips-Howard is providing research advice and guidance to the coalition and its members.

Further evidence to inform MHM policy is expected as a result of the ongoing full trial, adding to the body of evidence on which to base policy decisions in this area.

[202] WSSCC (2016) First National Training of Trainers on Menstrual Hygiene Management – Kenya. Retrieved from: https://www.wsscc.org/resources-feed/first-national-training-trainers-menstrual-hygiene-management-kenya/. Accessed 5 September 2019

[203] WSSCC (2017) Second Training of Trainers on Menstrual Hygiene Management in Kenya empowers officials to champion MHM. Retrieved from https://www.wsscc.org/2017/10/13/second-training-trainers-menstrual-hygiene-management-kenya-empowers-officials-champion-mhm/. Accessed 5 September 2019.

[204] Prof P Phillips-Howard, Personal communication, July 2019

[205] Prof P Phillips-Howard, Personal communication, July 2019

[206] UNICEF (2015) WASH in Schools Empowers Girls' Education, Proceedings of the Menstrual Hygiene Management in School. Virtual Conference 2015. Retrieved from https://www.unicef.org/wash/schools/files/MHM_fourth_annual_virtual_conference_proceedings.pdf. Accessed 5 September 2019.

[207] Menstrual Cup Coalition. Retrieved from https://menstrualcupcoalition.org/. Accessed 5 September 2019.

Case study 11

Intermittent screening and treatment or intermittent preventive therapy for control of malaria in pregnancy in Indonesia (G1100654/1 /Call 1)

Funding period: 01/10/2011 - 30/06/2017	Funding amount: £ 2,426,004
Lead PI: Prof Feiko ter Kuile	Lead institution: Liverpool School of Tropical Medicine

Summary:

- Infection with malaria in pregnancy (MiP) can have severe consequences for both mother and baby. Interventions recommended by WHO for the control of MiP are largely based on findings from sub-Saharan Africa; the Asia-Pacific region on the other hand does not have a standardised strategy for the prevention of MiP.
- The JGHT-funded study was the first trial in the Asia-Pacific region to determine the effectiveness of several strategies designed to prevent malaria in pregnancy. It was led by the Liverpool School of Tropical Medicine, in collaboration with researchers from institutions in the UK, Indonesia, and Australia.
- Comparing the current strategy with two alternatives revealed that intermittent preventive treatment (IPT) with the antimalarial dihydroartemisinin-piperaquine was most effective in a high transmission setting to prevent MiP in Indonesia.
- The Indonesian Ministry of Health was engaged throughout the project and has now requested support from the research team to conduct and evaluate a pilot implementation of IPT in the Indonesian healthcare system (subject to LSTM obtaining funding).
- Nested acceptability and systems effectiveness studies were conducted as part of the JGHT award. These provided additional information that will support the implementation of IPT in terms of key priority areas that need to be addressed in the implementation pilot.

Background

Infection with malaria in pregnancy (MiP) can have severe consequences for both mother and baby. Many malaria infections in pregnancy are asymptomatic and therefore remain undetected and untreated, yet are a major cause anaemia in the mother and interfere with the growth of the foetus. In other women, fever resulting from the malaria infection may trigger preterm onset of labour or pregnancy loss. Interventions recommended by WHO for the control of MiP are largely based on findings from sub-Saharan Africa[208]. These include intermittent preventive treatment in pregnancy (IPT), consisting of curative doses of an effective antimalarial given at predefined intervals in the 2nd and 3rd trimester.

The Asia-Pacific region on the other hand does not have a standardised drug-based strategy for the prevention of MiP. Many countries in this region have successfully reduced prevalence of malaria, however MiP remains a major public health problem[209]. However, MiP in areas of low or unstable transmission, where women have little acquired immunity, is more likely to result in symptomatic malaria, severe disease and death of the mother or baby than in areas of moderate-to-high transmission[210]. In Indonesia alone, 6.4 million pregnancies are exposed to malaria annually[211].

[208] WHO (2004) A strategic framework for malaria prevention and control during pregnancy in the African region. http://whqlibdoc.who.int/afro/2004/AFR_MAL_04.01.pdf

[209] Rogerson SJ et al (2018) Burden, pathology, and costs of malaria in pregnancy: new developments for an old problem. Lancet Infect Dis 18(4): e107-e118

[210] Desai M et al (2017) Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis. 7(2):93-104

[211] Dellicour S et al (2010) Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study. PLoS Med. 7:e1000221

In 2012, Indonesia became the first country in Asia to introduce systematic screening of pregnant women to reduce the burden of MiP. However, since this 'Single Screening and Treatment' (SST) strategy targets women during their first antenatal visit, it cannot detect infection acquired in later pregnancy. An alternative strategy, in addition to IPTp, is intermittent screening and treatment (IST), consisting of 3 to 6 screening events with rapid diagnostic tests (RDTs) using the same schedule as recommended for focused antenatal care. Women who test RDT positive are provided with long-acting anti-malarial treatment to clear the infection while providing additional post-treatment prophylaxis to minimise the risk that a new infection will become symptomatic[212].

The JGHT award

Prior to the JGHT-funded trial, there had been no evaluation to determine which of these strategies - IPT, SST or IST - is the most effective in Indonesia. The aim of the trial was to determine whether IST or IPT are superior to SST.

The study was conducted at two sites: Sumba, an area with low malaria transmission, and Papua, an area of moderate malaria transmission. It was led by Prof Feiko Ter Kuile, Liverpool School of Tropical Medicine, in collaboration with researchers from institutions in the UK, Indonesia and Australia[213].

In order to facilitate translation of results into policy, the study team established a policy liaison group before the start of the trial including representatives from the Indonesian Ministry of Health. This group met independently from the project steering committee and was instrumental in ensuring that the trial was embedded in the context of the local health infrastructure.

Trial findings

The trial found that IPT was the most effective strategy in a moderate transmission setting (Papua) to prevent malaria during pregnancy, and concluded that this may be a suitable strategy for other areas of moderate or high transmission in the region[214].

The trial also included a number of nested studies. An acceptability study revealed that pregnant women were accepting of all interventions, but that health care providers were reluctant to provide antimalarials presumptively i.e. without a confirmatory test (a fundamental component of IPT) due to fears of potential harm to the patients and emergence of drug resistance[215]. This has identified the need to educate healthcare providers on this issue as a priority area to address if IPT is to be implemented.

Next steps

The research team is now planning to support the Indonesian government to conduct a pilot implementation study and LSTM is seeking funding from the MRC to support the implementation and evaluation. The team has received letters of support from the Indonesian government and from the Indonesian office of UNICEF who currently support the Indonesia Ministry of Health's malaria programme. Should the pilot implementation prove successful, it is likely IPT will be adopted as the recommended policy to prevent MiP in moderate or high transmission areas of Indonesia.

[212] Desai M et al (2018) Prevention of malaria inpregnancy. Lancet Infect Dis. 18(4): e119–32

[213] London School of Hygiene and Tropical Medicine; Menzies School of Health Research, Australia; Centre of Tropical Medicine, Oxford University; Universitas Gadjah Mada, Indonesia; Eijkman Institute for Molecular Biology, Indonesia

[214] Ahmed R et al (2019) Efficacy and safety of intermittent preventive treatment and intermittent screening and treatment versus single screening and treatment with dihydroartemisinin–piperaquine for the control of malaria in pregnancy in Indonesia: a cluster-randomised, open-label, superiority trial. Lancet Infect Dis. 19(9) 973-987

[215] Hoyt J et al (2018) Intermittent screening and treatment or intermittent preventive treatment compared to current policy of single screening and treatment for the prevention of malaria in pregnancy in Eastern Indonesia: acceptability among health providers and pregnant women. Malaria journal, 17(1), 341

Case study 12

Community randomised evaluation of socioeconomic intervention to prevent TB (MR/K007467/1/Call 2)

Funding period: 01/10/2012 - 01/10/ 2021	Funding amount: £3,168,125
Lead PI: Carlton Evans	Lead institution: Imperial College London

Summary

- Tuberculosis (TB), one of the top 10 causes of death worldwide, is associated with poverty. Therefore, socioeconomic interventions have a large role to play in addressing this problem.
- A team led by Professor Carlton Evans (Imperial College London; Universidad Peruana Cayetano Heredia, Peru) is evaluating a combined socioeconomic intervention aimed at tackling TB in the CRESIPT trial in Peru. The intervention comprises household visits, community meetings and conditional cash transfers towards TB-associated costs.
- The findings so far show that households receiving the intervention are less likely to incur catastrophic costs, uptake of preventive therapy among household contacts is increased and TB treatment success in TB patients is improved.
- The trial team has engaged with local, national and international stakeholders; influenced the training of health professionals; empowered recovering patients to become community leaders and contributed to improved understanding of TB in the community. Publications emerging from the project have been referenced in WHO's handbook for conducting TB patient costs surveys and the team has helped to roll out such cost surveys in 15 countries.

Tuberculosis (TB) is one of the top 10 causes of death worldwide. In 2017, 10 million people suffered from the disease and 1.6 million people died from it[216]. TB is treatable and curable, however multidrug resistant TB (MDR-TB) remains a threat to health security. These are among the many compelling reasons for including ending the TB epidemic by 2030 as one of the health targets in the Sustainable Development Goals.

TB is also associated with poverty. Poverty is manifested in terms of overcrowding, malnutrition, poor health knowledge and impaired access to healthcare owing to an inability to pay, all of which increase the risk of getting TB and reduce the ability to control TB. Therefore, there is increasing consensus that socioeconomic interventions have a large role to play in ending TB[217].

Against this backdrop, Professor Carlton Evans (Imperial College London; Universidad Peruana Cayetano Heredia, Peru) and a team of researchers from the UK, Peru and the US[218] set up a trial (acronym CRESIPT) in Peru to evaluate the impact of a combined socioeconomic intervention for reducing poverty, improving access to TB care and reducing the risk of TB. The trial is funded by multiple funders including Wellcome Trust, JGHT, DfID, World Bank, BMGF and Innovation for Health And Development (IFHAD, Peru)[219] and is expected to run until 2021.

The team is testing an integrated community-based intervention which it had developed previously[220]. The social aspect of the intervention comprises household visits and participatory community meetings (for patients and their household contacts) aimed at providing information about TB, its treatment and prevention; education about household finances; mutual support and empowerment. The economic

[216] WHO (2018) *Global tuberculosis report 2018*. Geneva: World Health Organization.

[217] Hargreaves J et al (2011) The Social Determinants of Tuberculosis: From Evidence to Action. American Journal of Public Health 101(4): 654-662

[218] Institutions include Imperial College London, UK; Innovation For Health And Development (IFHAD), Universidad Peruana Cayetano Heredia, Peru; Institute of Infection and Global Health, Liverpool; Innovación Por la Salud Y Desarrollo (IPSYD), Peru; London School of Hygiene & Tropical Medicine, UK; Johns Hopkins Bloomberg School of Public Health, US.

[219] Isrctn.com. (2019). *PREVENT TB: Improving determinants of TB cure, prevention & diagnosis*. [online] Available at: http://www.isrctn.com/ISRCTN17820976?q=&filters=&sort=&offset=8&totalResults=15064&page=1&pageSize=10&searchType=basic-search Accessed 9 Sep. 2019

[220] Rocha C et al (2011) The Innovative Socio-economic Interventions Against Tuberculosis (ISIAT) project: an operational assessment. Int J of Tuberculosis and Lung Disease 15(6): 50-57

aspect consists of conditional cash transfers for payments towards TB-associated costs in a household, thereby mitigating TB risk factors and incentivising care. The intervention was shown to be associated with increases in household contact TB screening (from 82% to 96%), successful TB treatment completion (from 91% to 97%) and patient HIV testing (from 31% to 97)[221].

The initial phase of the CRESIPT study involved a household-randomised controlled pilot study with 1,579 participants in 2014–2015[222]. The results of this pilot helped to refine the intervention ready for impact assessment[223]. The study showed that households receiving the intervention were less likely to incur catastrophic costs (30% versus 42%)[224]. Moreover, the intervention led to increased uptake of preventive therapy among household contacts and greater TB treatment success in TB patients[222]. However, the effects of the social and economic components of the intervention cannot be separated as yet and the study was insufficiently powered to show a statistically significant effect of the intervention. The ongoing larger CRESIPT study seeks to address these points.

To date, stakeholder engagement has been a prominent part of the trial in both the design and implementation phases. Stakeholders engaged include the Peruvian Ministry of Health, the Peruvian National TB Program, the WHO Global TB Program, LMIC healthcare professionals, World Bank, community organisations and people living with TB (through community workshops)[225]. In turn, members of the project team have acted as experts for the Global TB caucus, WHO Global TB program's expert consultations and the Peruvian Ministry of Health[225]. For instance, one team member, Thomas Wingfield, is a core contributor to WHO's handbook for conducting TB patient cost surveys[226], which also refers to two publications[227,228] emerging from the project. To date, the team has helped to roll out and interpret cost surveys in 15 countries around the world. WHO's End TB strategy document also refers to one of the project's publications in relation to defining a threshold for catastrophic costs[227].

In addition, the project team has run workshops for frontline health workers in Peru to educate them about the risk factors for TB, advising them on how to help patients and households to overcome barriers to accessing healthcare and reduce simple daily costs[225]. Similarly, they have influenced the training of practitioners with regard to improving diagnosis for MDR-TB. Information materials produced for the project such as videos, instruction guides, information booklets and certificates for peer mentors have helped to people who were previously isolated and stigmatised and empowered them to become community leaders (as peer mentors). The materials have also contributed to a better understanding of TB in the community, and have promoted access to social programmes around TB[225].

To conclude, the initial phase of the study has shown promising results in terms of the feasibility and potential economic and health benefits of the intervention tested, thus raising expectations that this could be an effective socioeconomic intervention to complement the ongoing drug-based treatment and prevention strategies. Strengthening TB control using such an intervention has the potential to help millions of people annually.

[221] Rocha et al (2011) The Innovative Socio-economic Interventions Against Tuberculosis (ISIAT) project: an operational assessment. Int J of Tuberculosis and Lung Disease 15(6): 50-57

[222] Wingfield T et al (2017) A randomized controlled study of socioeconomic support to enhance tuberculosis prevention and treatment, Peru. Bulletin of the World Health Organization 95(4): 270-280

[223] Wingfield T et al (2015) Designing and implementing a socioeconomic intervention to enhance TB control: operational evidence from the CRESIPT project in Peru. BMC Public Health 15(1)

[224] Wingfield T et al (2016) The economic effects of supporting tuberculosis-affected households in Peru. European Respiratory Journal 48(5): 1396-1410

[225] ResearchFish data

[226] WHO (2017). *Tuberculosis patient cost surveys: a handbook*. Geneva: World Health Organization.

[227] Wingfield T et al (2014) Defining Catastrophic Costs and Comparing Their Importance for Adverse Tuberculosis Outcome with Multi-Drug Resistance: A Prospective Cohort Study, Peru. PLOS Medicine 11(7): e1001675.

[228] Wingfield T et al (2017) Socioeconomic support to improve initiation of tuberculosis preventive therapy and increase tuberculosis treatment success in Peru: a household-randomized, controlled evaluation. The Lancet 389: S16.

Case study 13

Primary Care Strategies to Reduce High Blood Pressure: A Cluster Randomised Trial in Rural Bangladesh, Pakistan and Sri Lanka (COBRA-BPS) (MR/N006178/1/Call 5)

Funding period: 01/09/2015 - 30/11/2019	Funding amount: £2,233,623 (COBRA-PBS), £201,806 (feasibility study)
Lead PI: Professor Tazeen H. Jafar	Lead institution: Duke-National University of Singapore Medical School, Singapore

Summary

- Hypertension is a leading risk factor of cardiovascular disease, a major cause of mortality and disability. Many affected people in rural South Asia remain undiagnosed and undertreated and are at risk of serious adverse effects. A potential strategy to reduce rates of hypertension is a multicomponent intervention (MCI).
- Professor Jafar, from the Duke-National University of Singapore Medical School, led a feasibility study with funding from the JGHT to optimise the delivery of an MCI. The MCI was designed to be embedded in the existing healthcare infrastructure and encompassed the screening and referral of at-risk individuals, family education on mitigation strategies, training of healthcare providers, and a financing model.
- The feasibility study indicated that a full-scale trial in the rural settings of Pakistan, Bangladesh and Sri Lanka was viable. It also supported the development of training manuals and protocols needed to deliver the intervention. Comprehensive stakeholder engagement ensured the intervention was supported by local and national healthcare officials.
- The full-scale COBRA-BPS trial was undertaken following the feasibility study. The final trial results will be published shortly, however a number of other publications have already emerged including a qualitative assessment of the barriers to accessing healthcare. The stakeholder engagement, established during the feasibility study, has since developed into a regional policy forum centred on cardiovascular disease and hypertension.

Background

Hypertension is a leading cause of mortality and morbidity associated with cardiovascular disease (CVD) in South Asia[229]. Understanding the risks of the condition and strategies to reduce these risks is vital in reducing the health and economic burden associated with hypertension. This is particularly vital in the South Asian context where over a quarter of the population (27%) is estimated to be affected[230]. Reducing blood pressure can be achieved with medications and adopting a healthy lifestyle but, due to its asymptomatic nature, many individuals living with high blood pressure may not be aware of their condition,[231] and adherence to medication schedules under traditional care pathways is reportedly low[232].

[229] Forouzanfar MH et al (2017) Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. Jama 317(2): 165-182

[230] Neupane D et al (2014) Prevalence of hypertension in member countries of South Asian Association for Regional Cooperation (SAARC): systematic review and meta-analysis. Medicine (Baltimore) 3(13):e74

[231] Chow CK et al (2013). Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. Jama, 310(9): 959-968.

[232] Elliott WJ (2008) What factors contribute to the inadequate control of elevated blood pressure?. The Journal of Clinical Hypertension 10: 20-26

Interventions focussed on education, lifestyle adjustments and care from trained providers have been shown to be effective in the urban setting in Pakistan[233] but these findings may not generalisable to rural populations where healthcare infrastructure is different. Addressing hypertension in rural populations is important because cardiovascular case fatality rates are higher in these populations[234] and most of South Asia's population is rural[235].

The JGHT award

In a previous clinical trial, COBRA[236], Professor Jafar, from the Duke-National University of Singapore, demonstrated that blood pressure could be managed via Home Health Education (HHE) combined with care from local general practitioners trained in the management of hypertension. However, the COBRA trial relied upon access to urban healthcare infrastructure which is different from healthcare in rural settings where a larger proportion of the South Asian population resides[237].

Given the variability in healthcare provision between the rural and urban areas[238], a pilot feasibility study (MR/L004224/1[239]), funded by the JGHT, was run across Bangladesh, Pakistan and Sri Lanka to evaluate if a similar intervention was possible and acceptable when delivered using an enhanced public healthcare infrastructure. This study involved assessment of a multicomponent intervention (MCI) for controlling high blood pressure to gather preliminary information for designing a larger full-scale trial. The MCI was initially made up of four components. These were:

- HHE delivered by trained government community health workers
- Blood pressure monitoring and stepped-up referral to a trained general practitioner
- Training healthcare providers in blood pressure monitoring and management
- A financing model to compensate the district health office for the additional healthcare services

HHE teaches patients and their families about a healthy lifestyle for hypertension using behavioural change communication strategies, and helps create an educated support network for patients. Stepped-up referral ensures patients with uncontrolled blood pressure are identified (using a checklist) and referred to a general practitioner or hospital. Including the training of healthcare providers ensures that the public health system is able to provide the required care. Finally, the financing model involves compensating community health workers for the additional health services and providing patient subsidies. Compensation of health workers is expected to increase compliance from the healthcare team.

Results from the feasibility study were promising in terms of lowering the enrolled patients' blood pressure. Critically, the feasibility study also incorporated a stakeholder engagement component involving high level officials (national and provincial), district health managers, public and private providers, health workers, hypertensive individuals and family members. This ensured that the intervention was supported and trusted by the stakeholders who would eventually be responsible for delivering the intervention.

The current, full-scale JGHT-funded trial, COBRA-BPS, builds on the success of the pilot and aims to evaluate the MCI in a stratified cluster randomised controlled trial, and to determine if the MCI is effective and cost-effective for blood pressure control in the trial countries. On the recommendation of

[233] Jafar TH et al (2009) Community-based interventions to promote blood pressure control in a developing country: a cluster randomized trial. Annals of Internal Medicine 151(9): 593-601

[234] Yusuf S (2014) Cardiovascular risk and events in 17 low-, middle-, and high-income countries. N Engl J Med 371(9): 818-827

[235] World Bank. Rural population (% of total population). https://data.worldbank.org/indicator/SP.RUR.TOTL.ZS Accessed 20 Sep 2019

[236] Jafar TH et al (2009) Community-based interventions to promote blood pressure control in a developing country: a cluster randomized trial. Annals of Internal Medicine 151(9): 593-601

[237] World Bank. Rural population (% of total population). https://data.worldbank.org/indicator/SP.RUR.TOTL.ZS Accessed 20 Sep 2019

[238] Yusuf S (2014) Cardiovascular risk and events in 17 low-, middle-, and high-income countries. New England Journal of Medicine 371(9): 818-827

[239] Gateway to Research entry. Available https://gtr.ukri.org/projects?ref=MR%2FL004224%2F1, Accessed 20 Sep 2019

key stakeholders, the MCI being tested in the full trial includes an additional (fifth) component: hypertension triage counters and hypertension care coordinators at government clinics to facilitate the stepped-up referrals.

The feasibility study and the full trial have been conducted by a team of researchers from across South Asia, including the International Centre for Diarrhoeal Disease Research (Bangladesh), Aga Khan University (Pakistan), University of Kelaniya (Sri Lanka), Duke-NUS Graduate Medical School (Singapore), and London School of Hygiene & Tropical Medicine (United Kingdom). A national or project advisory committee from each trial country provides feedback on issues and solutions tailored to local conditions. The national advisory committees were established through the project and include leaders of professional societies; hypertension, non-communicable disease (NCD) and public health experts; representatives from government authorities and key provincial health departments, relevant pharmaceutical industry, and non-governmental organisations.

Research findings and outcomes

The feasibility study confirmed the need for a full-scale trial, finding that more than two thirds of hypertension patients in the study areas had uncontrolled blood pressure[240]. Encouragingly uptake was high indicating a large-scale randomised control trial was possible. Exploration of the barriers to implementation informed the development of training manuals for healthcare workers and protocols for the full trial. As such, the COBRA-BPS trial filled gaps with regard to the lack of a standardised hypertension treatment protocol for quality of care across health facilities and guidelines for the promotion of lifestyle modifications to mitigate the risk of CVD among hypertensive patients. The standard treatment protocol 'The Hypertension Management Manual for Clinic Providers' was developed in collaboration with medical experts and local dieticians and tailored to the local context. Since the treatment varied according to the patients' blood pressure and medical history, a medication treatment algorithm[241] was developed to guide the decision making of healthcare providers building upon National Institute for Health and Care Excellence (NICE) guidelines[242]. A Nutrition and Lifestyle Curriculum was also developed for community health workers with information on healthy lifestyles taking into consideration the local culture and environment as well as diets in the three countries.

Furthermore, throughout the feasibility study, stakeholders[243] were consulted to establish support for the MCI and identify potential barriers or facilitators. These engagement activities continued into the full trial and the meetings eventually evolved into a regional forum on NCD (Policy Forum on Hypertension and Cardiometabolic Diseases-Impact on Health Systems in Sri Lanka, Bangladesh, Pakistan, and Regional Countries) bringing together representatives from Sri Lanka, Bangladesh and Pakistan. In these forums, government officials were invited to present their countries' strategies and plans to tackle the burden of NCD. Governments could then learn from each other and reported a sense of responsibility to act in line with the other countries. A video of the Policy Forum held in Columbo, Sri Lanka in 2018 has been shared online[244]. These forums gave the research team a direct link to the people who would be responsible for implementing the findings of the trial and gave the policy makers the opportunity to voice their questions and concerns. These relationships highlight a key potential benefit of a smaller scale development award.

Analysis of the results of the full trial is ongoing, and the findings will be presented in a Featured Science Oral Session at the 2019 Scientific Meeting of the American Heart Association on 17 November 2019.

[240] Jafar TH et al (2016) Control of blood pressure and risk attenuation: a public health intervention in rural Bangladesh, Pakistan, and Sri Lanka feasibility trial results. Journal of Hypertension 34(9): 1872-1881

[241] Appendix 6 of the study protocol. Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5469065/ Accessed 27 Aug 2019

[242] National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management. 2016. https://www.nice.org.uk/guidance/cg127. Accessed 27 Aug 2019

[243] High level officials (national and provincial), district health managers, public and private providers, health workers, hypertensive individuals and family members

[244] Session 1: https://www.youtube.com/watch?v=bZqdJ8-WzVE; Session 2: https://www.youtube.com/watch?v=puiUgz5yH08

Nonetheless, a number of publications have emerged already. Firstly, the study protocol[245] and statistical analysis plan[246] have been published. Also published are the results of the nested qualitative assessment of patients' experiences on accessing healthcare services for management of hypertension[247]. The study identified specific barriers to accessing healthcare that could be addressed within the local health infrastructure (inadequate services and poor-quality facilities, shortage of medicine, busyness of doctors, appointment wait times, long distance to facilities, and cost) and adds to the body of evidence required for implementing the trial interventions. To further facilitate the dissemination of these results, Prof Jafar has created a twitter[248] account and a Facebook[249] page to engage with other researchers and interested parties.

While many implementation barriers and enablers were identified and addressed during the feasibility study, challenges inevitably arose during the full trial. One of these unexpected challenges was the high turnover of research staff and the limited number of researchers with the required knowledge of NCD[250]. This meant that additional time had to be spent training essential staff.

To date, the trial has helped to elevate awareness of NCD in Bangladesh, Sri Lanka and Pakistan. This was achieved locally via the training of healthcare providers and nationally via the regional forum and the research team's and advisory committee's connections with government think tanks and health departments[251]. Co-investigators from Sri Lanka including Dr Anuradhani Kasturiratne had an advisory role in a recent USD200m loan agreement between Sri Lanka and the World Bank[252]. The loan will address primary healthcare services in the context of management and prevention of NCD and will build on a Ministry of Health plan that Professor Rajitha Wickremasinghe, another co-investigator contributed to[253]. Dr Aamir Hameed, a co-investigator from Pakistan led the drafting of updated Hypertension Treatment guidelines for the Pakistan Hypertension League[254] with Dr Mohammad Ishaq, a member of the COBRA-BPS National Advisory Committee from Pakistan[255]. Dr Aliya Naheed, COBRA-BPS principal investigator in Bangladesh, presented policy recommendations for the development of an operational plan on NCD as part of the NCD Control Program of Bangladesh's Ministry of Health and Family Welfare in June 2016[256].

Next steps

The results from the full trial are currently being analysed but if the MCI is shown to be effective and cost effective, implementation is very likely because of ongoing engagement with policy makers, healthcare providers and other relevant stakeholders in the three trial countries. Moreover, implementation was an important consideration in designing the intervention and hopefully this will facilitate its sustainability and scalability beyond the trial. For instance, the MCI is embedded within existing public health infrastructure. Moreover, the trial team decided against providing medication free

[245] Jafar TH et al (2017) Multicomponent intervention versus usual care for management of hypertension in rural Bangladesh, Pakistan and Sri Lanka: study protocol for a cluster randomized controlled trial. Trials 18(1): 272

[246] Gandhi M et al (2018) Statistical analysis plan for the control of blood pressure and risk attenuation-rural Bangladesh, Pakistan, Sri Lanka (COBRA-BPS) trial: a cluster randomized trial for a multicomponent intervention versus usual care in hypertensive patients. Trials 19(1): 658

[247] Legido-Quigley H et al (2019). Patients' experiences on accessing health care services for management of hypertension in rural Bangladesh, Pakistan and Sri Lanka: A qualitative study. PloS One 14(1): e0211100

[248] https://twitter.com/bpscobra Accessed 27 Aug 2019

[249] https://www.facebook.com/cobra.bps/ Accessed 27 Aug 2019

[250] Personal Communication, Prof Jafar (1 July 2019)

[251] Personal Communication, Prof Jafar, (1 October 2019)

[252] Personal Communication, Prof Jafar, (1 July 2019)

[253] Ministry of Health, Nutrition and Indigenous Medicine Sri Lanka, 2017, '*Reorganising Primary Health Care in Sri Lanka*'. Available from www.health.gov.lk/moh_final/english/public/elfinder/files/publications/2018/ReorgPrimaryHealthCare.pdf accessed 27 Aug 2019

[254] Pakistan Hypertension League. Available from http://www.phlpk.org/history.html. Accessed 10 October 2019

[255] Personal Communication, Prof Jafar (1 October 2019)

[256] Personal Communication, Prof Jafar (1 October 2019)

of charge during the trial as this would not be financially sustainable if the intervention was implemented. Instead, physicians were encouraged to prescribe low cost, high quality generic drugs. Furthermore, a financing model is part of the MCI, and evidence collected on this aspect will also have implications on any future implementation of the intervention.

Following final analysis, Professor Jafar plans to seek funding for scale-up of the MCI across the three trial countries (Bangladesh, Pakistan and Sri Lanka) with the potential to expand the intervention to Nepal, Myanmar, India, and other low and middle income countries in Asia[257]. The nature and size of this scale up will depend on the final results.

[257] Personal Communication, Prof Jafar (1 July 2019)

Case study 14

Two-month Regimens Using Novel Combinations to Augment Treatment Effectiveness for drug-sensitive Tuberculosis: the "TRUNCATE-TB" trial (MR/L004356/1 / Call 3)

Funding period: Nov 2014 – Mar 2022	Funding amount: £5,012,977
Lead PI: Angela Crook	Lead institution: University College London, UK

Summary

- Tuberculosis (TB) presents a high disease burden worldwide, particularly in LMICs. Furthermore, multidrug resistant TB (MDR-TB) has emerged as a serious threat to health security. Patients often fail to adhere to treatment, leading to poor outcomes and drug resistance. Therefore, alternative management strategies are the need of the hour.
- Dr Angela Crook from University College London is leading a team of researchers from the UK and Singapore to test a new management strategy comprising a variety of novel 2-month combination drug regimens against the current 6-month treatment in the TRUNCATE-TB trial. The trial is being conducted in Indonesia, the Philippines and Thailand.
- The TRUNCATE-TB trial is one of the first trials to use the multi-arm multi-stage (MAMS) design in the context of global health trials. This design allows researchers to test multiple intervention arms against a single control arm and drop unpromising intervention arms as well as add new ones part way through the trial. Hence, this approach is more efficient and cost-effective than a traditional two-arm trial and offers a greater chance of finding an effective treatment.
- The study is still ongoing and findings are yet to emerge. However, the trial has already contributed to enhancing the scientific knowledge, technical skills and professional networks of the researchers working at the trial sites, and stakeholders are being engaged.

Background

While Tuberculosis (TB) is treatable and curable, it presents a high disease burden globally, particularly in LMICs. Worldwide, 10 million people developed the disease in 2017 and 1.6 million people died from it[258]. 23% of the world's population is estimated to have a latent TB infection and is thus at risk of developing TB during their lifetime. Besides, multidrug resistant TB (MDR-TB) is emerging as a serious threat to health security. Globally, 3.5% of new TB cases and 18% of previously treated cases were shown to have MDR-TB or TB resistant to rifampicin, the most effective first-line drug[259].

The current management strategy is to treat TB with multiple drugs for 6 months[260]. However, patients often fail to adhere to treatment, leading to poor clinical outcomes as well as drug resistance. To solve these problems, alternatives that are more clinically effective and economically efficient are required.

The JGHT award

The TRUNCATE-TB trial is testing a new management strategy comprising a variety of novel 2-month combination regimens against the usual 6-month treatment for drug-sensitive TB[261]. The underlying rationale is to focus resources on optimising treatment over a short period (2 months) before stopping and following up patients, treating only those that relapse (with the 6 months standard of care treatment). If relapse rates are low, this strategy would save precious resources and stopping treatment after 2 months would reduce selection pressure for generating new strains of MDR-TB. A shorter treatment cycle might also lead to better treatment adherence.

Design-wise, TRUNCATE-TB is a randomised, open-label, multi-arm multi-stage (MAMS), non-inferiority trial, allowing multiple regimens to be tested against a single control group and treatment

[258] WHO (2018). *Global tuberculosis report 2018*. Geneva: World Health Organization.

[259] Ibid.

[260] Clinicaltrials.gov: Two-month regimens using novel combinations to augment treatment effectiveness for drug-sensitive tuberculosis (TRUNC*ATE-TB)*. https://clinicaltrials.gov/ct2/show/NCT03474198 Accessed 11 Sep 2019

[261] Gateway to Research: Two-month regimens using novel combinations to augment treatment effectiveness for drug-sensitive tuberculosis: the "TRUNCATE-TB" trial. UKRI https://gtr.ukri.org/projects?ref=MR%2FL004356%2F1 Accessed 11 Sep 2019

arms to be dropped or added during the trial if necessary[262]. 180 people each will be recruited to 4 intervention arms and one control arm (maximum 900)[260]. The interventions will consist of boosted regimens that will include new drugs (licensed drugs, repurposed drugs) and optimised doses of standard drugs, selected after due consideration of the maximal sterilising effect, absence of drug-drug interactions, safety and tolerability.

The trial is sponsored by University College London (UCL) with Dr Angela Crook as Principal Investigator, while Professor Nick Paton at the National University of Singapore is leading the study. UCL (within the MRC Clinical Trials Unit) has relevant methodological expertise for this trial having applied the MAMS design successfully in the STAMPEDE prostate cancer trial[263].

Currently, trial participants are being recruited from 12 centres in Indonesia, the Philippines and Thailand[264], with further trial sites opening soon in Uganda and India[265].

Findings

The trial is one of the first trials to use the MAMS design in the context of global health trials. While the PanACEA consortium funded by the European and Developing Countries Clinical Trials partnership (EDCTP), the German Ministry for Education and Research (BmBF), and the Medical Research Council UK (MRC) used a MAMS design, it was a smaller Phase 2 study and tested a different combination of drugs[266].

A MAMS trial starts with multiple arms and as it progresses, arms that do not show promising results can be dropped part way[267]. Recruitment to the control arm and remaining arms is continued until sufficient numbers of participants have been recruited to enable robust assessment of the primary outcome. Decisions regarding the continuation or discontinuation of arms are made by an Independent Data Monitoring Committee on the basis of safety and efficacy data. As such, the approach is more efficient and cost-effective than the traditional approach of evaluating each new regimen against a control in separate two-arm trials[268]. Besides, as multiple regimens are being tested in parallel, there is a greater chance of finding an effective treatment, and because researchers can stop and start arms during the trial, emerging new treatments can be tested within an existing MAMS trial if suitable[269]. In this way, the usual time lag between stopping a trial and starting a new one could be avoided. This design also enhances patient safety as a smaller number of patients are randomised to ineffective regimens before they are dropped[270].

Although the trial still ongoing, capacity building and dissemination outcomes are already visible. Co-investigators from Indonesia and the Philippines have enhanced their scientific knowledge and technical skills owing to their involvement in the TRUNCATE-TB trial[271], improving their ability to conduct other

[262] Papineni P et al (2016) TRUNCATE-TB: an innovative trial design for drug-sensitive tuberculosis. International Journal of Infectious Diseases 45: 404

[263] James N et al (2016) Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. The Lancet, 387(10024): 1163-1177

[264] Clinicaltrials.gov: Two-month regimens using novel combinations to augment treatment effectiveness for drug-sensitive tuberculosis (TRUNC*ATE-TB)*. https://clinicaltrials.gov/ct2/show/NCT03474198 Accessed 11 Sep 2019

[265] Dr Angela Crook, Personal Communication (3 October 2019)

[266] Boeree MJ et al (2017) High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. The Lancet infectious diseases 17(1): 39-49

[267] Papineni P et al (2016) TRUNCATE-TB: an innovative trial design for drug-sensitive tuberculosis. Int J Infectious Dis 45: 404

[268] Phillips PP et al (2012) Innovative trial designs are practical solutions for improving the treatment of tuberculosis. Journal of infectious diseases 205(suppl_2): S250-S257

[269] MRC website: Clinical trials: why multi-arms are better than two. https://mrc.ukri.org/news/blog/clinical-trials-why-multi-arms-are-better-than-two/ Accessed 11 Sep 2019

[270] Phillips, P.P., Gillespie, S.H., Boeree, M. et al. (2012). Innovative trial designs are practical solutions for improving the treatment of tuberculosis. Journal of infectious diseases 205(suppl_2): S250-S257

[271] JGHT co-investigator survey results

international global health trials in the future. Further, it had expanded their research and policy networks both locally and globally, influenced the work of others in their organisation, improved research leadership and increased their knowledge of local health systems and policy contexts.

Members of the trial team are also engaging with international audiences. They attended the Global TB Community Advisory Board meeting in 2015 to discuss the TRUNCATE-TB trial and to receive input on the protocol and share the trial design for dissemination to other patient groups[272]. The trial design was also presented at the Annual Meeting of the Working Group on New Drugs of the STOP TB Partnership in 2015[273]. This is the main forum for discussing drug development in TB.

Next steps

The trial team plans to create a new Asian TB research network to strengthen the global capacity for TB clinical trials[274]. The dissemination strategy includes presentations about the trial and findings at local, national and international levels as well as a policy brief at the end of the study[275]. The team had already engaged national TB programme managers and other key decision makers at the application stage and hope to engage with health ministries and WHO towards the end of the trial[276].

The scientific achievements, as with any large clinical trial, will only be apparent after the conclusion of the trial and analysis of the resulting data. This is anticipated to be in February 2022, at which time we can expect the trial to yield new knowledge with the potential to transform the approach to TB clinical trials and possibly the approach to TB treatment in future years.

[272] Gateway to Research: Two-month regimens using novel combinations to augment treatment effectiveness for drug-sensitive tuberculosis: the "TRUNCATE-TB" trial. UKRI https://gtr.ukri.org/projects?ref=MR%2FL004356%2F1 Accessed 11 Sep 2019

[273] Ibid.

[274] TRUNCATE-TB: Pathways to impact statement

[275] Ibid.

[276] Ibid.

Case study 15

Develop an interventional study on reducing antibiotic over-prescribing among children with Upper Respiratory Tract Infections in rural Guangxi, China (MR/M022161/1, Call 5)

Funding period: 01/04/2015 - 31/12/2017	Funding amount: £151,260 (development award)
Lead PI: Professor Xiaolin Wei	Lead institution: Shandong University

Summary

- Overuse of antibiotics promotes the development of antimicrobial resistance, a major global health problem. Antibiotic over-prescription is widespread in the treatment of upper respiratory tract infections (URTIs) and this challenge is particularly pressing in low- and middle-income countries.
- A JGHT-funded pilot study aimed to inform the design of a randomised controlled trial aiming to reduce antibiotic over-prescription in the treatment of URTIs in children in rural Guangxi, China. The pilot study tested the feasibility of a multidimensional intervention consisting of clinical guidelines, training material and workshops in two groups (clinicians only; clinicians and caregivers) against a control group.
- Findings of the pilot study informed the design of a full trial which was funded by DfID. This trial showed that the intervention reduced the antibiotic prescription rate by about a third (29%) and that the effect was sustained for at least a year in the intervention hospitals.
- Implementation of the interventions as part of the feasibility study and the full trial had a positive impact in reducing over-prescription of antibiotics regionally.

Antimicrobial resistance (AMR) is a global health problem since it makes treatment ineffective and lets infections persist in the body, resulting in prolonged illness, disability, and death of patients contracting infectious diseases.[277] It is estimated that a failure to address this problem could result in 10 million deaths per year globally by 2050.[278] Further, overuse of antibiotics can promote the development of AMR.

Antibiotic over-prescription is widespread in the treatment of upper respiratory tract infections (URTIs) in primary care settings.[279] This challenge is particularly pressing in LMICs, where 80% of URTIs, which are mostly viral, are inappropriately treated with antibiotics.[280] In fact, a cross-sectional study across 10 provinces of Western China showed that the majority of antibiotic prescriptions were for treating URTIs and of these, a quarter were for children aged 0-10 years.[281] Several studies have shown that educational interventions targeting clinicians and parents can help reduce antibiotic prescribing for childhood URTIs.[282] However, such interventions had not been assessed in a large-scale randomised controlled trial in an LMIC rural primary care setting.

To this end, Professor Xiaolin Wei of Shandong University led a team of Chinese and British researchers in conducting a feasibility study (funded by the JGHT) to test the effect of a multidimensional intervention on reducing antibiotic over-prescription for children with URTIs in rural Guangxi, China. The intervention comprised clinical guidelines, training material (leaflets and a video) and

[277] WHO (2018) Antimicrobial resistance. https://www.who.int/en/news-room/fact-sheets/detail/antimicrobial-resistance. Accessed 5 September 2019

[278] GOV.UK (2015) Health matters: antimicrobial resistance. https://www.gov.uk/government/publications/health-matters-antimicrobial-resistance/health-matters-antimicrobial-resistance. Accessed 5 September 2019.

[279] Andrews T et al (2012) Interventions to influence consulting and antibiotic use for acute respiratory tract infections in children: a systematic review and meta-analysis. PloS One 7(1): e30334

[280] Zhang Z et al (2017) Antibiotic prescribing for upper respiratory infections among children in rural China: a cross-sectional study of outpatient prescriptions. Global Health Action 10(1): 1287334

[281] Dong L et al (2008) Antibiotic prescribing patterns in village health clinics across 10 provinces of Western China. The Journal of antimicrobial chemotherapy 62(2): 410-415

[282] Hu Y et al (2016) Interventions to reduce childhood antibiotic prescribing for upper respiratory infections: systematic review and meta-analysis. J Epidemiol Community Health 70:1162-1170.

workshops.[283] The study was conducted in six township hospitals divided into three groups: (1) targeting clinicians only, (2) targeting clinicians and caregivers, and (3) where usual practice was continued.[284]

The multidimensional intervention was received positively by clinicians, patients and caregivers in the feasibility study. In the intervention groups, doctors became more confident about treating URTIs without antibiotics and patients/caregivers understood more about antibiotics and the long-term impact of the inappropriate use of antibiotics.[285] These findings ultimately informed the design of a larger cluster-randomised controlled trial[286] funded by DfID through the Communicable Diseases (COMDIS) Health Services Delivery Research Consortium.

Findings of the full trial showed that the intervention was effective in reducing the antibiotic prescription rate by about a third (29%).[287] [288] A follow-up study showed a sustained reduction in antibiotic prescription (36%) in the intervention hospitals 12 months after the end of the trial.[289] Moreover, the intervention cost only $400 per healthcare facility.[290] Further, across both the feasibility study and trial, the intervention led to improved knowledge and skills among clinicians and changed public attitudes on the over-prescription of antibiotics.[291]

Both the studies provide evidence on an intervention that can effectively reduce inappropriate antibiotic prescription in China. The effect appears to be sustainable and the intervention is inexpensive. Hence, the findings from the study have the potential to be applied to other LMIC settings following adaptation and testing.

[283] Gateway to Research: Develop an interventional study on reducing antibiotic over-prescribing among children with URIs in rural Guangxi, China. UKRI https://gtr.ukri.org/projects?ref=MR/M022161/1. Accessed 5 September 2019

[284] Ibid.

[285] Dalla Lana School of Public Health (2019). U of T study finds long-term success in reducing unnecessary antibiotics prescriptions in China. Retrieved from http://www.dlsph.utoronto.ca/2019/02/u-of-t-study-finds-long-term-success-in-reducing-unnecessary-antibiotics-prescriptions-in-china/. Accessed 5 September 2019.

[286] ISRCTN14340536 Educational interventions on reducing antibiotic over-prescribing among children with upper respiratory infections (URIs)

[287] Wei X et al (2017) Effect of a training and educational intervention for physicians and caregivers on antibiotic prescribing for upper respiratory tract infections in children at primary care facilities in rural China: a cluster-randomised controlled trial. The Lancet Global Health 5(12): PE1258-E1267

[288] COMDIS-HSD (2017) Research Brief https://assets.publishing.service.gov.uk/media/5ae6cd70ed915d42f7c6bbb8/Improving-rational-use-of-antibiotics-in-childhood-UR-track-infections-in-China-research-brief-final.pdf. Accessed 5 September 2019.

[289] Wei X et al (2019) Long-term outcomes of an educational intervention to reduce antibiotic prescribing for childhood upper respiratory tract infections in rural China: Follow-up of a cluster-randomised controlled trial. PLoS Medicine 16(2):e1002733

[290] Dalla Lana School of Public Health (2019). Ibid.

[291] ResearchFish data, provided by MRC

Case study 16

WHO's Parent Skills Training for developmental disorders: Piloting task-shifting to non-specialists in Ethiopia (MR/P020844/1, Call 7)

Funding period: 01/08/2017 - 30/04/2019	Funding amount: £ 147,849 (development award)
Lead PI: Dr Rosa Anna Hoekstra	Lead institution: King's College London

Summary

- Developmental disorders are common yet under-resourced in low- and middle-income countries. To address this gap, WHO has developed a Caregivers Training Skills (CTS) programme to educate and support caregivers of children with developmental disorders. The programme, designed to be delivered by non-specialists, had not been adapted to or tested in the Ethiopian context prior to this study.
- A pilot study led by King's College London, funded by a JGHT development award, aimed to evaluate whether CST can be implemented in the Ethiopian context and determine if the measures to assess its impact are reliable and appropriate. The full results are not yet published, but the qualitative study indicates that the CST is acceptable and can be implemented in Ethiopia.
- The study team placed emphasis on local stakeholder engagement, ensuring that the project became locally owned. The CST has since been taken up by the community: It is now used in Ethiopia's state-run child mental health clinics and rolled out to all caregivers who attend these.
- The research team is currently collaborating with a team in Kenya to conduct a full multi-country randomised control trial. Findings from the pilot study will feed directly into this planned work.

Background

Developmental disorders such as autism and intellectual disability are common yet grossly under-resourced in low income countries[292]. There is little understanding of the conditions and limited support services for caregivers. To address this, WHO developed a training programme for caregivers of children with developmental disorders, the 'Caregiver Skills Training' (CST) programme[293]. CST is designed to be delivered by non-specialists to maintain low running costs, with a structure and content that can be adapted to incorporate the characteristics of local health and educational systems and in different cultural settings.

While CST draws on the best available evidence, most of this stems from research conducted in high-income countries, and the programme had not been implemented in very low-income contexts, such as Ethiopia, prior to the JGHT award[294]. There was hence a need to demonstrate that the programme is acceptable and feasible when implemented in these settings.

Ethiopia has a shortage of trained health personnel and a severe lack of service provision for children with developmental disorders and their families[295]; CST may be able to address this unmet need.

[292] Nielsen M et al (2017) The persistent sampling bias in developmental psychology: A call to action. J Exp Child Psychol 162: 31-38

[293] *Training parents to transform children's lives*. https://www.who.int/mental_health/maternal-child/PST/en/ Accessed 19 Aug 2019

[294] Tekola B et al (2019) Adapting and pre-testing the World Health Organization's Caregiver Skills Training programme for autism and other developmental disorders in a very low-resource setting: Findings from Ethiopia. Autism: https://doi.org/10.1177/1362361319848532

[295] Tekola B et al (2016) Challenges and opportunities to improve autism services in low-income countries: lessons from a situational analysis in Ethiopia. Glob Ment Health (Camb) 3: e21

The JGHT award

The JGHT development award funded a pilot study to evaluate whether CST can be implemented in the Ethiopian context and to determine if the measures to assess its impact are reliable and appropriate. The study was led by Dr Hoekstra, King's College London in collaboration with the WHO CST team and in-country researchers[296].

The pilot study has recently concluded and while quantitative analysis of the primary outcomes is still ongoing, preliminary results from the qualitative analysis support that a full-scale randomised control trial evaluating CST is warranted. It provided evidence that, through stakeholder engagement, CST can be adapted to the local context and meets a need in the Ethiopian community[297]. Caregivers participating in the study reported that their perceptions regarding their child's development had changed and that they felt less stressed. Caregivers also reported positive changes in their child's behaviour as a direct result of the programme such as acquiring new skills (e.g. washing hands) and speaking their first words[298]. The participation of two fathers in the study was an unanticipated but welcomed result since childcare is traditionally viewed as a woman's role in Ethiopian society[299]. Findings to date indicate that CST is acceptable in the Ethiopian context and preliminary results of the training's implementation are positive.

To deliver the programme the trial team adapted the WHO CST material to meet the local Ethiopian context including translation of materials and converting training texts to be more accessible for caregivers with poor literacy skills. The adapted CST material is now in use at Ethiopia's state-run child mental health clinics and is being rolled out to all caregivers who attend the clinics[300,301]. This is facilitated by the fact that the clinics' psychiatry resident trainees participated in the trial and are fully trained in the material's use. The materials and other outputs of the study have also been shared with WHO and several adaptations and recommendations made by the research team have been incorporated into new versions of the programme[302].

Stakeholder engagement

Local stakeholder engagement was integral to the trial. Ethiopian specialists with a knowledge of the communities and local context ensured the intervention was well received and materials were adapted such that the project became "locally owned"[303]. The importance of this aspect was discussed further in a publication, co-written with a local autism advocate, which highlights the need to include local collaborations in research about autism (with the tag line "Nothing about us, without us")[304]. Buy-in from the local communities was encouraging, with local administrations providing training spaces free of charge and organising transport for caregivers to attend the training sessions[305].

Next steps

Work is now underway to set up a full RCT to evaluate the CST. To this end, the study team is linking up efforts with a research team in neighbouring Kenya, who also conducted a pilot study, testing

[296] Addis Ababa University, Yekatit 12 Hospital Medical College, Ethiopia, St. Paul's Hospital Millennium Medical College, Joy Center for Children with Autism, Ethiopia

[297] Tekola B et al (2019) Adapting and pre-testing the World Health Organization's Caregiver Skills Training programme for autism and other developmental disorders in a very low-resource setting: Findings from Ethiopia. Autism: https://doi.org/10.1177/1362361319848532

[298] Personal communication, R Hoekstra (21 June 2019)

[299] Personal communication, R Hoekstra (21 June 2019)

[300] Gateway to Research: https://gtr.ukri.org/projects?ref=MR%2FP020844%2F1 UKRI. Accessed 17 Sep 2019

[301] Personal communication, R Hoekstra (21 June 2019)

[302] Gateway to Research: https://gtr.ukri.org/projects?ref=MR%2FP020844%2F1 UKRI. Accessed 17 Sep 2019

[303] Personal communication, R Hoekstra (21 June 2019)

[304] Hoekstra RA et al (2018) Nothing about us without us: the importance of local collaboration and engagement in the global study of autism. BJPsych Int. 15(2): 40-43

[305] Personal communication, R Hoekstra (21 June 2019)

acceptability and feasibility of CST implementation in the Kenyan context[306,307]. While the pilot studies were run separately, the teams had coordinated and used several similar outcome measures to allow findings to be compared across the two sites and facilitate joint working going forward. The two teams have now applied for joint funding to conduct a full trial in Ethiopia and Kenya. Dr Hoekstra was awarded funding by the NIHR to organise an interactive workshop in Kenya for Ethiopian and Kenyan stakeholders. This workshop aims to inform the full research plan which will be submitted as part of the second phase of the funding application with the Kenyan research team.

Awareness of the research was raised when Dr Hoekstra was interviewed in a feature article on autism in Africa[308]. The article was republished in The Independent and later developed into a podcast[309].

[306] Personal communication, R Hoekstra (21 June 2019)

[307] International Society for Autism Research meeting, 1-4 May 2019 Quebes, Panel discussion: The Acceptability, Feasibility and Preliminary Evaluation of the Who Caregiver Skill Training Programme in Rural and Urban Kenya. https://insar.confex.com/insar/2019/webprogram/Paper30478.html Accessed 2019-Sep-17

[308] Zeliadt N (2017 Dec 13). Why autism remains hidden in Africa. https://www.spectrumnews.org/features/deep-dive/autism-remains-hidden-africa/ Accessed 19 Aug 2019

[309] Brogan J (2018 Jan 30). Spectrum Stories: Shifting cultural views about autism abroad. https://www.spectrumnews.org/features/multimedia/podcasts/spectrum-stories-shifting-cultural-views-autism-abroad/ Accessed 19 Aug 2019

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