



EDCTP

The power of sharing science

EDCTP2 portfolio: fellowship programme



2014-2020

Supported by the
European Union



About EDCTP

The European & Developing Countries Clinical Trials Partnership (EDCTP) is a public–public partnership between 14 European and 16 African countries, supported by the European Union.

EDCTP's vision is to reduce the individual, social and economic burden of poverty-related infectious diseases affecting sub-Saharan Africa.

EDCTP's mission is to accelerate the development of new or improved medical interventions for the identification, treatment and prevention of infectious diseases, including emerging and re-emerging diseases, through pre- and post-registration clinical studies, with emphasis on phase II and III clinical trials. Our approach integrates conduct of research with development of African clinical research capacity and networking.

The second EDCTP programme is implemented by the EDCTP Association supported under Horizon 2020, the European Union's Framework Programme for Research and Innovation.

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Contents

Developing capacity for clinical research in sub-Saharan Africa – the EDCTP contribution	4
EDCTP fellowship programme	8
Senior Fellowships	11
Career Development Fellowships	53
Clinical Research & Development Fellowships	123
EDCTP/AREF Preparatory Fellowships	141
Acknowledging our funders	149

Developing capacity for clinical research in sub-Saharan Africa – the EDCTP contribution

Capacity development is a core EDCTP activity, complementing its support for clinical trials and product-focused implementation research. Effective capacity development requires a long-term perspective, an integrated system-wide approach, and strong partnerships with host countries to ensure sustainability. Guided by these principles, EDCTP is making a lasting contribution to the capacity of countries in sub-Saharan Africa to undertake high-quality clinical research – to the benefit of the research community, ethics and regulatory bodies, policymakers and populations.

The European & Developing Countries Clinical Trials Partnership (EDCTP) exists to advance the development and implementation of new and improved medical interventions against key infectious diseases, through support for collaborations between countries and institutions in Europe and sub-Saharan Africa. Since its launch in 2014, the second EDCTP programme (EDCTP2) has awarded more than €750 M in grants to support landmark studies on vaccines, drugs and diagnostics for TB, HIV/AIDS, malaria, diarrhoeal diseases, respiratory infections, and emerging and re-emerging infections.

International collaborative clinical trials lie at the heart of EDCTP's work. But a further important goal is to build the capacity of countries in sub-Saharan Africa to carry out clinical research, including international-standard clinical trials. Support for capacity development is embedded within funding for clinical trials, and also the focus of dedicated funding schemes.

Capacity development is critical for a range of reasons. First and foremost, it enables countries, institutions and individuals to participate in clinical studies, including international consortia. More generally, it creates an enabling environment that attracts further studies. It also benefits countries by promoting greater self-reliance in health research, and by building national human scientific capital – a vital national asset to ensure research growth, ownership and leadership. Furthermore, early experience with evaluation of new and improved interventions is associated with their more rapid introduction to benefit health.

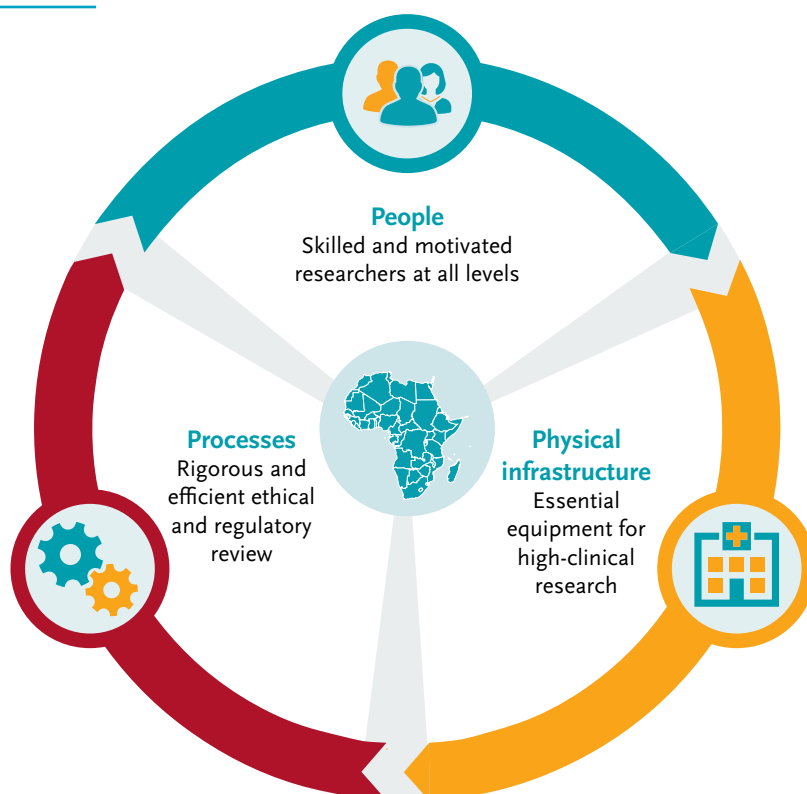


Dr Michael Makanga
Executive Director

EDCTP2 capacity-building funding at a glance

- **244** sub-Saharan African institutions benefiting from enhanced research facilities
- **196** fellows funded in 25 sub-Saharan African countries
- **112** PhD students funded through EDCTP grants
- **9,956** researchers and support staff receiving short-term training
- **35** sub-Saharan African countries benefiting from regulatory and ethics review capacity building
- **42** institutions in 27 sub-Saharan African countries participating in Networks of Excellence.

EDCTP integrated capacity development approach



Key aspects of capacity development

Capacity development requires an integrated, systems-oriented perspective. There are many aspects to clinical research capacity, and benefits will not be fully realised unless all are addressed.

Physical infrastructure such as laboratory, clinical facilities, data management and IT equipment is clearly essential. Development of **human capacity** is fundamental to long-term sustainability. Skills development is essential at all levels, from research leaders through up-and-coming researchers, to master's and PhD students at the start of their careers. Equally important are the laboratory support and research administration staff, who make an essential contribution to the research enterprise.

International networking – both North–South and South–South – is fundamental to capacity development. International connections facilitate the diffusion of knowledge and new experimental techniques. Stronger institutions can support the development of those with less experience. Networks facilitate the building of relationships to underpin mentoring and exchange to build research skills.

From a national perspective, high-quality clinical research depends on effective **systems of research regulation and oversight**. Structures and processes for ethical review of research proposals need to be in place to ensure that the interests of participants are protected, without creating unnecessary obstacles that delay research or deter clinical trial sponsors. These elements are important components of wider **national health research systems**, which also include the capacity of policymakers to use research evidence and scientific advice in decision-making in order to build better health care systems.

EDCTP and physical infrastructure

Support for building of physical infrastructure capacity is strongly tied to the needs of clinical research projects. Funding for essential research-ready clinical space, laboratory equipment, data management and other essential tools is embedded within proposals for clinical trial support, with 229 institutions in 38 countries hosting EDCTP-funded activities in sub-Saharan Africa.

Lack of physical infrastructure is one reason why institutions and countries without a strong track record of clinical research may struggle to compete in international funding calls. One role of the four EDCTP regional **Networks of Excellence** is to work with institutions in disadvantaged countries to build physical infrastructure so they are better able to compete for funding.

EDCTP and personal support

EDCTP provides dedicated **fellowship funding** to build human capacity in clinical research. By December 2020, EDCTP had supported 196 fellows, including 47 Senior Fellows, Africa's research leaders, and 122 Career Development Fellows, the research leaders of the future. EDCTP fellowships play a critical role in retaining and attracting back scientific talent. Senior fellowships also include an element of future capacity building, with funding provided for supervision and mentoring of junior researchers, helping to coalesce a critical mass of researchers around leading scientists.

The **EDCTP Alumni Network** and its associated web platform (<https://edctpalumninetwork.org>) encourage continued networking, collaboration and mentoring. Subsidiary networks have been established for each of the disease areas covered by EDCTP.

EDCTP has worked extensively with partners on fellowship support. Calls have been organised with the WHO Regional Office for Africa, WHO's Special Training Programme in Tropical Diseases (TDR), the Africa Centres for Disease Control (Africa CDC), the Africa Research Excellence Fund (AREF), foundations (such as the Fondation Botnar) and the private sector (including Novartis and GlaxoSmithKline). These calls have provided opportunities to build capacity in targeted areas.

The future of clinical research in the region will depend on a continuing stream of young, motivated and talented **trainee scientists**. EDCTP provides extensive support for master's and PhD studentships, embedded with its support schemes. This ensures that young researchers 'learn by doing', and gain research skills within the context of an ongoing major clinical research study, under the wing of a Senior Fellow, or with the supportive infrastructure provided by a regional Network of Excellence. By now, EDCTP

has supported 111 PhD and 75 master's students.

A further important aspect of skills development is **short-term training**. This provides opportunities for researchers to develop new skills, supported by African or European partners. Training is also used to build the capacity of support staff, for example in laboratory management or clinical study management, as well as in practical areas such as research proposal writing and grant management. Currently, 9,091 people have benefited from short-term training through EDCTP support.

EDCTP and ethics/regulatory capacity building

EDCTP has provided specific funding to develop regulatory and ethical review capacity within countries in sub-Saharan Africa, supporting activities in 37 countries. Although the region still hosts relatively few trials in comparison to its disease burden, more clinical research is being carried out in sub-Saharan Africa. Increasing global interest in conducting trials is increasing pressure on poorly resourced regulatory and ethical review bodies. Furthermore, increasingly complex clinical trial design and ethical issues, such as those surrounding research on vulnerable populations, pose major challenges to national regulatory authorities, as well as national and institutional research ethics committees. Moreover, registration of clinical trials in online registries is now internationally recognised best practice. EDCTP funded the establishment of the Pan-African Clinical Trials Registry (PACTR), the only WHO-endorsed clinical trial database in Africa and the premier source of information on African trials.

National systems therefore need the capacity to evaluate increasing numbers of proposals and to monitor active projects, and the skills to consider a wide range of issues. Dedicated EDCTP funding has enabled countries to strengthen their capacity and improve their efficiency through training programmes for members of ethical review committees, implementation of electronic proposal management and monitoring systems, and strengthening of national, regional and international coordination and networking. EDCTP funding has enabled groups of countries to work together to develop and harmonise regulatory and ethical review procedures, drawing upon links to European partners and

African regional bodies such as the African Vaccines Regulatory Forum (AVAREF).

One specific area of focus has been safety monitoring, with several projects building national capacity in **pharmacovigilance**. These activities are essential for ensuring that possible adverse events are identified and investigated in clinical trials and when new interventions are introduced. Effective pharmacovigilance systems protect populations, highlight possible safety issues with new interventions, and help to build public trust in clinical research and health systems.

EDCTP funding has also enabled projects to examine specific issues in regulatory and ethical review. These have included embedding a gender perspective in ethical review and research design, and capacity building specifically in French- and Portuguese-speaking countries.

EDCTP and networking

International networking allows researchers to tap into global networks, facilitating the spread of knowledge and new experimental techniques and providing access to research resources. It provides opportunities for placements and mentoring, as well as transfer of new technologies.

EDCTP clinical studies are based on collaborations between institutions in Europe and sub-Saharan Africa, and increasingly with partners in other high-income countries. These connect 229 institutions in 38 countries in sub-Saharan Africa with 153 institutions in 19 countries in Europe, as well as 14 institutions from other high-income countries beyond Europe.

In addition, South–South networking provides opportunity to share experience and expertise, and to harmonise and coordinate activities, for example through collaborative development of capacity. A key role in South–South networking is played by the four EDCTP regional **Networks of Excellence** – CANTAM in Central Africa, EACCR in East Africa, TESA in southern Africa and WANETAM in West Africa – which collectively span 42 institutions in 27 countries in Africa. Moreover, there is a North–South networking component with 16 European Institutions in 9 European countries. As well as providing routes for the dissemination of knowledge, they provide an important infrastructure for the training of young and upcoming scientists, help to develop

capacity in countries with less mature health research systems, and carry out preparatory studies that can provide the basis for later interventional studies.

Other important EDCTP-funded networks include two major international networks focusing on **epidemic preparedness**, ALERRT and PANDORA-ID-NET. Bringing together teams in multiple African and European countries, the networks are enhancing the capacity of countries to detect, prevent and respond to outbreaks of emerging and re-emerging infectious diseases.

National health research systems

The above examples illustrate how EDCTP is contributing to the development of multiple aspects of research capacity in sub-Saharan African countries. This integrated perspective aligns with the approach taken by the WHO Regional Office for Africa to develop sustainable national health research capacity in the region, and EDCTP and the WHO Regional Office have developed a strategic partnership to advance this agenda.

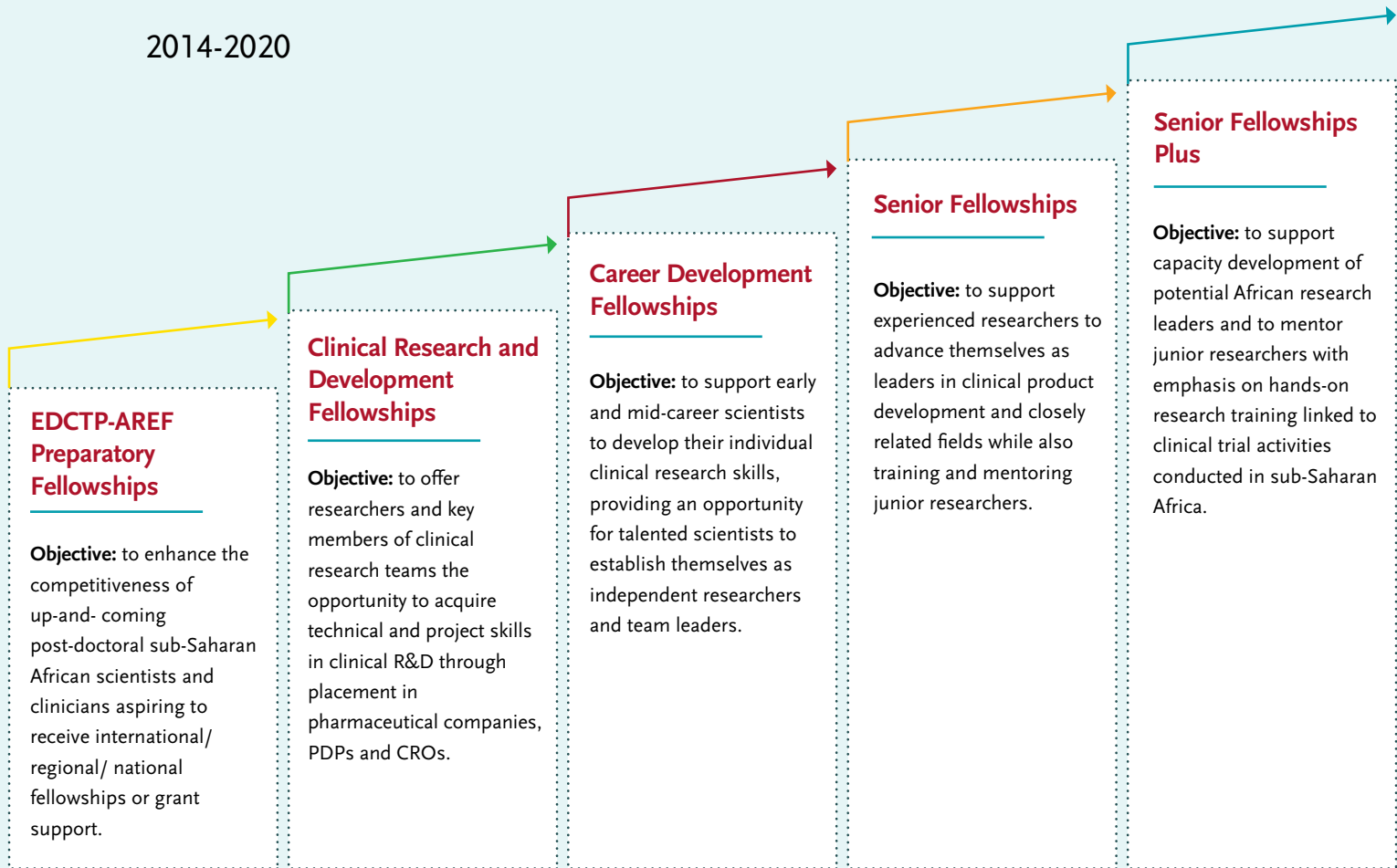
A series of high-level meetings have been held to discuss benchmarking of national health research systems in the region, using a tool developed by the WHO Regional Office. The most recent survey has revealed promising progress in national capacity development, and EDCTP is providing funding to support collection of data to the region's Health Observatory to facilitate ongoing monitoring of health research capacity.

Conclusions

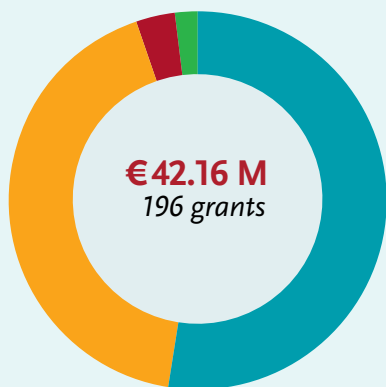
EDCTP grant funding and other activities are contributing to the development of high-quality and sustainable health research systems in sub-Saharan Africa. They are helping to support increasing numbers of clinical trials, and providing a firm foundation to support further extension of clinical research activity – in pursuit of a vision of research conceived, designed and executed in sub-Saharan Africa. This will ensure that countries in the region can identify and enact research agendas shaped by local health priorities, including capacity that can be mobilised to address emerging and re-emerging health challenges – such as Ebola, COVID-19 or whatever threat next emerges.

EDCTP fellowship programme

2014-2020

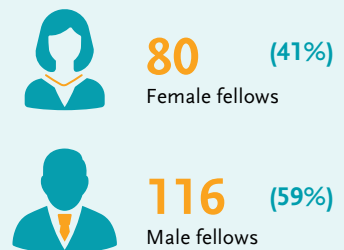


EDCTP fellows by type



- Senior Fellowships, 47 grants
€22.20 M
- Career Development Fellowships, 122 grants
€17.79 M
- EDCTP-TDR Clinical Research and Development Fellowships, 15 grants
€1.40 M
- EDCTP-AREF Preparatory Fellowships, 12 grants
€0.77 M

EDCTP fellows by gender



EDCTP fellows in sub-Saharan Africa





Senior Fellowships

2014-2020



47 grants

€22.20 M

to support experienced researchers to advance themselves as leaders in clinical product development and closely related fields while also training and mentoring junior researchers.



Combating HIV drug resistance in children

Dr Immaculate Nankya is monitoring for early signs of resistance to antiretroviral drugs in young children with HIV.

The challenge

Despite the great success of programmes to eliminate mother-to-child transmission of HIV – an estimated 1.3 million cases were averted between 2010 and 2015 – large numbers of infants continue to be infected with HIV in Africa. In 2016, around 160,000 children became infected with HIV.

In addition, death rates from HIV are highest in infants aged 0–4 years. Infants who acquire HIV via maternal transmission are thus a highly vulnerable group.



Dr Immaculate Nankya
Uganda

The project

Co-Director of the Uganda Laboratory Core C, part of the Joint Clinical Research Centre, Dr Immaculate Nankya has contributed to numerous landmark trials of HIV/AIDS treatment and clinical studies on HIV/AIDS. She has a particular interest in the detection of mutations that confer resistance to antiretroviral drugs.

In her EDCTP Senior Fellowship, Dr Nankya aims to ensure that HIV-infected infants receive the best possible care. Currently, infants are started on antiretroviral treatment regimens without any assessment of the presence of drug resistance mutations. Dr Nankya is using next-generation DNA sequencing technology to determine the prevalence of drug resistance mutations, including extremely rare ones, using dried blood spot samples. Infants will be monitored for three years to determine whether the mutations detected have any impact on response to therapy.

Importantly, next-generation DNA sequencing may detect rare HIV variants not identified by standard DNA sequencing technologies. Under drug selection pressure, these rare variants may expand and ultimately trigger treatment failure.

Impact

Dr Nankya's Senior Fellowship project will provide key data on how drug resistance mutations affect treatment responses in a very vulnerable population. They will have the potential to feed directly into national and international guidelines

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Immaculate Nankya, Joint Clinical Research Centre, Uganda

Year funded: 2017

EDCTP funding: €0.4 M

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/03ba2a65-acbe-4c49-85da-13df6f8eab0a>

of recommended programmes of care for HIV-infected infants.

The Uganda Laboratory Core C has also developed into a sophisticated centre for molecular virology and immunology. It provides an ideal site for the training of young scientists from Uganda and elsewhere in Africa on the latest laboratory techniques, including next-generation DNA sequencing. Dr Nankya's fellowship will include training of two master's students.

Reference

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Building capacity in clinical pharmacogenomics



Professor Collen Masimirembwa is establishing new training schemes on genetic factors affecting drug responses.

The challenge

Genetic factors can have a significant impact on responses to drugs – predisposing to harmful side effects or affecting the efficacy of standard dosing regimens. Greater attention to genetic factors is ushering in an era of ‘precision medicine’, with treatments more tailored to patients’ genetic make-up.

Africa is the most genetically varied continent on Earth, yet relatively little is known about how genetic diversity in Africa affects drug responses. Notably, genetic factors affecting drug responses may be unique to Africa, emphasising the importance of research in African settings.

The project

Professor Collen Masimirembwa is one of Africa’s leading experts in pharmacogenomics. Following his scientific training, he spent 10 years working in industry in Europe before returning to Africa. He set up the African Institute of Biomedical Science and Technology to promote drug discovery and drug development in Africa. In 2018, Professor Masimirembwa was awarded the HUGO African Prize for his contribution to genetics in Africa.

Professor Masimirembwa carried out some of the earliest pharmacogenomics studies in Africa, identifying genetic factors influencing responses to anti-parasitic drugs and antiretrovirals, including African-specific variants of drug-metabolising enzymes. His work has important implications for the safe use of the antiretroviral drug efavirenz.

In his Senior Fellowship project, Professor Masimirembwa will be building on this unique experience to develop new training schemes and research opportunities in pharmacogenomics for early-career researchers. Building on existing and new international links, he is establishing a five-week course in clinical pharmacogenomics and an 18-month master’s course in genomic medicine, in association with the University of Zimbabwe. The project will also support the training of two PhD students in the field of pharmacogenomics in the treatment of HIV and schistosomiasis.

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Professor Collen Masimirembwa, African Institute of Science and Technology, Zimbabwe

Year funded: 2017

EDCTP funding: €0.5 M

Fellow profile: <https://edctpalumnnetwork.org/fe/profiles/view/92ba7a36-22a8-471d-8756-4c8e8f795f46>

Impact

Professor Masimirembwa’s Senior Fellowship will enable him to establish a platform for the training of the next generation of pharmacogenomics researchers in Africa – a field that will become increasingly important as more insights are gained into the genetic diversity of African populations and their implications for drug responses. A new master’s programme will be established at the University of Zimbabwe during the fellowship, to ensure sustainability and continuity of training for young researchers.

Reference

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Prof. Collen Masimirembwa
Zimbabwe



Chronic conditions in older people living with HIV

Dr Barbara Castelnovo is setting up a cohort of older people living with HIV, to determine the health risks they face in later life.

The challenge

The rollout of antiretroviral therapy has saved millions of lives. Increasingly, people living with HIV are surviving to old age.

Although these are very positive developments, older people are at increased risk of a range of non-communicable diseases, such as heart disease, respiratory disease and diabetes. In addition, these risks may be greater in people living with HIV, as HIV infections are associated with accelerated ageing, because of factors such as chronic inflammation and long-term exposure to antiretroviral drugs.



Dr Barbara Castelnovo
Uganda

The project

Dr Barbara Castelnovo has been based in Uganda for more than 10 years. She has established a range of cohorts monitoring people receiving antiretroviral therapy and exploring interactions between HIV and TB infections. Her work has identified a shift in health conditions affecting people living with HIV away from AIDS-related opportunistic infections towards non-communicable diseases.

In her EDCTP Senior Fellowship, Dr Castelnovo is setting up a new cohort of older people (60 years of age or older) with HIV. Participants will undergo regular screening for high blood pressure, cardiovascular disease, respiratory function, kidney function and for a range of cancers. They will also undergo tests of physical function and be assessed for frailty and history of falls.

Dr Castelnovo is also establishing a new group of clinicians and researchers with an interest in HIV and non-communicable diseases, which will meet regularly to share experiences and discuss cases. It will also link into an international network of experts and build stronger links with other stakeholders, including communities and policymakers.

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Barbara Castelnovo, Infectious Diseases Institute, Uganda

Year funded: 2018

EDCTP funding: €0.5 M

Fellow profile: <https://edctpalumninetwork.org/fellow/profiles/view/0f8fb3a6-e0f8-4ae4-bf10-8d8c91970bd5>

Impact

Dr Castelnovo's Senior Fellowship project will generate new data on a health issue of growing importance in sub-Saharan Africa – the comorbidities experienced by older people with HIV who have been taking antiretroviral drugs for many years. The findings will have important implications for prevention of non-communicable disease in this group, as well as for the design of appropriate models of care that reflect the full range of their health conditions. The fellowship will also allow for the development of young clinicians and researchers in a field where there is limited expertise in Africa.

Reference

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Cardiometabolic risk factors and HIV

Professor Andre Kengne is aiming to identify the key risk factors for cardiometabolic disease in people living with HIV in sub-Saharan Africa.



The challenge

More than 20 million people are living with HIV in sub-Saharan Africa. Thanks to increasing access to antiretroviral therapy, more people living with HIV are surviving to older age, when they are at increased risk of a range of cardiometabolic diseases, including high blood pressure, cardiovascular disease and chronic kidney disease. In addition, long-term use of antiretroviral drugs may also increase the risk of these conditions.

Non-communicable diseases are already more common in people with HIV than in the general population, and modelling studies suggest that, by 2030, 84% of people with HIV will have at least one non-communicable disease and about one-third will have three or more.

The project

Currently, care of people living with HIV is provided in parallel with other healthcare provision, and focuses primarily on the infectious diseases they are at risk of acquiring. This limits opportunities to address non-communicable disease risk factors in this group. In addition, there is a limited understanding of the nature and extent of non-communicable disease risk factors in people living with HIV.

In his EDCTP Senior Fellowship, Professor Andre Kengne is building on existing links to establish a network to generate additional evidence on non-communicable disease risk factors. The network brings together the South African Medical Research Council, the Nigerian Institute of Medical Research, and the Clinical Research, Education and Consultancy Network in Cameroon.

Professor Kengne's research will draw on the resources of three existing large-scale projects. In Nigeria, data on risk factors for chronic kidney disease will be collected from a cohort of nearly 24,000 people living with HIV who are receiving antiretroviral therapy and have been followed for nearly 15 years. In Cameroon, information on cardi-metabolic risk factors will be obtained from a cohort of nearly 20,000 people living with HIV. And in South Africa, Professor Kengne is evaluating a text messaging intervention designed

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Professor Andre Kengne, South African Medical Research Council, South Africa

Year funded: 2019

EDCTP funding: €0.5 M

to improve adherence to anti-hypertensive medicines in people with HIV and high blood pressure.

Impact

Professor Kengne's Senior Fellowship project will gather additional information on the risk factors for non-communicable disease in sub-Saharan African populations. A clearer understanding of the most important risk factors could underpin the design of integrated services for people living with HIV that address both infectious and non-communicable co-morbidities.

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Prof. Andre Kengne
South Africa



Gut health, HIV and diabetes

Dr George PrayGod is investigating whether damage to the gut is linked to the increased risk of diabetes in people living with HIV.

The challenge

People living with HIV are significantly more likely to have type 2 diabetes than those without HIV. In part, this may reflect a higher prevalence of well-established risk factors for non-communicable diseases in people living with HIV. Long-term use of antiretroviral therapy may also increase the risk of diabetes.

One factor that might be mediating this increased risk of diabetes is environmental or HIV-related enteropathy – inflammation of the gut that disrupts gut function and leads to wider systemic inflammation. Gut abnormalities may include reduced release of hormones that promote insulin release, while systemic inflammation may promote insulin resistance, both of which would drive the development of diabetes.



Dr George PrayGod
Tanzania

The project

Despite its potential importance, enteropathy has been little studied in African populations with HIV. In his EDCTP Senior Fellowship, Dr George PrayGod will take advantage of the ongoing CICADA cohort study, which is examining risk factors for diabetes (but not enteropathy) among people living with HIV in Tanzania.

Complementing the wealth of health, demographic and metabolic data being gathered in the CICADA study, Dr PrayGod will analyse a wide range of biomarkers associated with enteropathy. He will then look for correlations between the levels of these markers and the development of diabetes. His project will also provide capacity-building research opportunities for a PhD and a master's student.

Impact

Dr PrayGod's Senior Fellowship project will shed light on the possible involvement of enteropathy in the development of diabetes in people in sub-Saharan Africa living with HIV. Encouraging progress is being made in the development of therapies for enteropathy, so evidence of a link would suggest a possible new approach to diabetes prevention among people living with HIV.

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr George PrayGod, National Institute for Medical Research, Tanzania

Year funded: 2018

EDCTP funding: €0.5 M

Fellow profile: <https://edctpalumninetwork.org/fellow/profiles/view/2ed076bf-d2b8-4b5f-a316-3f5a1170fa68>

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An innovative approach to HIV cure

Dr George Kyei is exploring new ways to enhance the 'shock and kill' approach to eradicate HIV from the body.

The challenge

Although the numbers of new HIV infections are in decline, around one million new infections occurred in Africa in 2017. In addition, millions of people living with HIV have to take antiretroviral drugs daily to keep HIV infection under control.

The need for daily treatment is a huge drain on resources, exposes people to powerful drugs throughout their lives, and increases the risk that drug resistance will arise due to lack of adherence to long-term treatment.

The project

These issues could be overcome if it were possible to cure rather than just control HIV infections. The main obstacle to cure is the persistence of HIV in a reservoir of quiescent T cells – HIV-derived DNA is integrated into the T cell genome but is dormant. One suggested approach to cure, known as 'shock and kill', is to reactivate these quiescent cells while patients are taking antiretroviral drugs, to eliminate residual HIV and enable patients to stop taking medication. However, to date, it has not proven possible to reactivate cells sufficiently to achieve eradication.

In his EDCTP Senior Fellowship, Dr George Kyei is testing new strategies to reactivate HIV replication in quiescent cells. In such cells, HIV replication is suspended because of the compact folding of DNA around HIV DNA integrated into the genome. Dr Kyei is screening a library of compounds that have the potential to unfold DNA, potentially kick-starting HIV replication.

Compounds showing the most promising DNA unfolding effects will be tested on resting T cells obtained from HIV patients taking antiretroviral drugs. To do this, Dr Kyei will monitor virus levels in a cohort of patients receiving antiretroviral therapy and select those in whom viral reproduction is being effectively suppressed by medication.

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr George Kyei, Noguchi Memorial Institute for Medical Research, Ghana

Year funded: 2018

EDCTP funding: €0.5 M

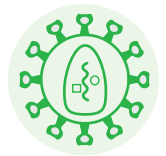
Fellow profile: <https://edctpalumninetwork.org/fellow/profiles/view/9e253a0f-cf4b-42ca-87b5-6fc6e20386bf>

Impact

As well as providing new data on the effectiveness of antiretroviral treatment in Ghanaian patients, Dr Kyei's Senior Fellowship project could identify novel compounds that make it more likely that the shock and kill approach is successful. Achieving HIV cure would have a huge impact on management of HIV in sub-Saharan Africa. More immediately, the project will increase regional capacity for HIV cure studies, including training of graduate students, and establish a biobank of samples for future HIV-related research and training.

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Dr George Kyei
Ghana



Understanding the impact of pre-exposure prophylaxis on immunity

Dr Derseree Archary is investigating how pre-exposure prophylaxis (PrEP) to prevent HIV infection affects immune responses in women.

The challenge

PrEP, pre-emptive use of antiretroviral drugs to prevent infection, is increasingly seen as a crucial HIV prevention strategy. Although it has been shown to be safe and effective, PrEP involves the administration of powerful drugs to people who are not unwell, and its long-term impact is unclear.

In particular, it is not known how PrEP affects immune responses or the composition of the body's microbial communities (the microbiome), which play key roles in defence against infection. This is an important question, given that PrEP may also be used in combination with HIV vaccines.



Dr Derseree Archary
South Africa

The project

Combined PrEP and vaccine use may be a particularly attractive combination for preventing HIV infection in women, in whom PrEP has shown mixed results. Dr Derseree Archary is therefore examining the immunological and microbiological impact of PrEP specifically in women.

In her EDCTP Senior Fellowship, Dr Archary is taking advantage of the CAPRISA 082 trial, which is following a cohort of women at risk of HIV in South Africa, some of whom will be taking PrEP. She will examine antiretroviral drug levels in blood and the genital tract of these women, as well as antibody production and immune cell characteristics before and after the initiation of PrEP. She will also explore any changes in the composition and properties of the microbiome of the genital tract.

Impact

Dr Archary's Senior Fellowship project will generate key data on the impact of oral PrEP on immune responses and the microbiome of the female genital tract. The findings will be crucial to anticipating the possible impact of PrEP on immune responses stimulated by an HIV vaccine,

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Derseree Archary, Centre for the AIDS Programme of Research in South Africa (CAPRISA), South Africa

Year funded: 2019

EDCTP funding: €0.5 M

Fellow profile: <https://edctpalumnetwork.org/fellow/profiles/view/3015d7f7-a5b7-4e3f-ac58-8623d796fbf7>

of great importance when combined use of the two therapeutic strategies is being considered.

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Identifying the true burden of Kaposi's sarcoma

Dr Georgia Schafer aims to develop a clearer picture of Kaposi's sarcoma-associated herpesvirus in HIV-related disease.

The challenge

TB is a major cause of death and ill-health in sub-Saharan Africa, particularly for those with HIV infections: a third of all HIV-related deaths are due to TB. However, because it is so common, TB is often presumed to be the cause of symptoms, leading to significant levels of misdiagnosis.

One infection that is common in sub-Saharan Africa and has pathological features similar to TB is Kaposi's sarcoma-associated herpesvirus (KSHV). Despite 32,500 cases being identified in 2018, leading to 17,500 deaths, KSHV is relatively little studied and its exact contribution to HIV-related disease not fully understood.

The project

In her EDCTP Senior Fellowship, Dr Georgia Schafer aims to work with well-defined cohorts of people living with HIV to determine the burden and characteristics of KSHV-related disease. As well as Kaposi's sarcoma, a cancer of the skin, respiratory system and other organs, the virus can cause a range of other conditions.

KSHV can establish dormant or 'latent' infections, which can be reactivated, leading to extensive viral replication. A key hypothesis is that this 'lytic reactivation' is a key contributor to the risk of severe symptoms and death.

Dr Schafer has carried out studies showing that high KSHV viral load is a strong predictor of death in people with HIV. Among nearly 700 people hospitalised and investigated for TB, 31% had KSHV infections. The 6% with high KSHV viral load were at 6.5 times higher risk of death. Dr Schafer has also shown that variants in the receptor used by KSHV to gain access to cells, known as EPHA2, are associated with susceptibility to infection and risk of developing Kaposi's sarcoma.

In her Senior Fellowship, Dr Schafer will undertake an intensive analysis of a new cohort of HIV patients. As well as screening for KSHV infections and investigating links between viral load and poor outcomes, she will also

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Georgia Schafer, University of Cape Town, South Africa

Target population(s): Adults living with HIV

Year funded: 2019

EDCTP funding: €0.5 M

characterise EPHA2 variant status and subtype KSHV infections to see if any are associated with severity of disease.

Impact

Born in Germany, Dr Schafer has worked in South Africa for many years. She has established an extensive programme of research in cancer-causing viruses, including human papillomavirus (HPV), the main cause of cervical cancer. The EDCTP Senior Fellowship will allow Dr Schafer to strengthen her research presence in KSHV and KSHV-linked disease. The work should also highlight the importance of an underappreciated cause of illness in people living with HIV and may suggest new ways in which the burden of KSHV-related disease could be minimised.

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Dr Georgia Schafer
South Africa



Innate immunity and control of HIV

Dr Christina Thobakgale is studying rare individuals able to keep HIV replication in check, focusing on key cells of the innate immune system.

The challenge

Despite some progress, HIV/AIDS remains a huge disease burden in sub-Saharan Africa. In South Africa alone, 7.5 million people are living with HIV and 200,000 new infections occur each year.

Intriguingly, a small number of people – known as HIV controllers – seem naturally able to repress HIV replication even without antiretroviral drugs. In so-called ‘elite controllers’, virus replication is undetectable. Less positively, HIV controllers are at increased risk of a range of health complications, particularly inflammatory conditions, as are people on antiretroviral therapy, even if they are controlling HIV replication.



Dr Christina Thobakgale
South Africa

The project

In her Senior Fellowship, Dr Christina Thobakgale is investigating the role of the innate immune response in HIV control and vulnerability to HIV-associated complications. The innate immune response is an early, non-specific defence response, and there is growing interest in its contribution to control of HIV.

Dr Thobakgale will be analysing the properties of different types of innate immune cell from HIV controllers and elite controllers, comparing them to those from people showing more typical responses to HIV infection.

For example, she will be investigating particular types of dendritic cell, which can orchestrate more powerful immune responses to HIV, and natural killer cells, which destroy virus-infected cells. She will also be exploring the properties of monocytes, white blood cells that can also be infected by HIV, which may act as a reservoir of virus and could also contribute to the vulnerability to complications. A particular focus will be on cell metabolism and energy production by mitochondria, which may be altered by HIV infection.

The Senior Fellowship builds on Dr Thobakgale's past work on the innate immune system and HIV infection, particularly the role of natural killer cells and HIV mutations that enable the virus to evade host responses. In recognition of

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Christina Thobakgale, University of Witwatersrand, South Africa

Target population(s): Adults living with HIV

Year funded: 2020

EDCTP funding: €0.5 M

her promising early research, the South African Ministry of Science and Technology named her runner up in its distinguished young women in science award and she has been nominated to join the Academy of Science of South Africa and the African Academy of Science.

Impact

Dr Thobakgale's studies are addressing a health problem of particular relevance in South Africa. Her findings will provide insight into the elements of the innate immune response important to HIV control, and those linked to inflammatory complications. The results will have important implications for both the treatment and potential prevention of HIV infections, as well as for minimising the risk of inflammatory complications.

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Improving detection of pneumonia

Dr William Worodria is aiming to generate a clearer picture of the causes of pneumonia and the prevalence of antibiotic resistance in a high-HIV setting.



The challenge

Lower respiratory tract infections are responsible for a huge burden of disease. Up to 17% of patients die during hospitalisation and a third of patients die within a month. Individuals with HIV infections are at particular risk of lower respiratory tract infections. A further challenge is the alarming growth in antibiotic resistance, leading to treatment failures.

There are multiple potential causes of lower respiratory tract infections, and treatment is typically empiric – based on knowledge of pathogens circulating locally and local patterns of antibiotic resistance rather than specific diagnostic tests. These methods lack sensitivity, and better approaches are needed to manage patients in low-resource settings, particularly those at high risk of poor outcomes.

The project

In his Senior Fellowship, Dr William Worodria is aiming to generate a better understanding of the causes of pneumonia in a high-HIV setting in Uganda, the current state of antibiotic resistance, and key factors affecting clinical outcomes.

Focusing on emergency units at three public hospitals in Uganda, he is recruiting a cohort of pneumonia patients and collecting extensive data on the patients, their infections and their clinical progression. As well as using a range of conventional and molecular diagnostics to characterise infections, he is testing additional methods such as bronchoalveolar lavage as well as readily available point-of-care tests for blood markers associated with the severity of infection, such as C-reactive protein and procalcitonin. Monitoring of these markers could provide an early warning sign of treatment failure and the need for additional care or alternative treatments.

As well as shedding light on the local epidemiology of lower respiratory tract infections and drug resistance, this information will help to identify factors associated with treatment failures. Data will be used to develop simple-to-apply diagnostic algorithms for assessing the severity of illness in low-resource settings and for triaging of patients, identifying those in need of most intensive care. Dr Worodria's findings should also guide more appropriate use of antibiotics, reducing the risk of antibiotic resistance.

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr William Ofuti Worodria, Infectious Disease Institute, Uganda

Target population(s): Adults with pneumonia

Year funded: 2020

EDCTP funding: €0.5 M

The Senior Fellowship will build Dr Worodria's expertise, as well as clinical and laboratory capacity at participating centres. Dr Worodria will also be training one master's and one PhD student through his project.

Impact

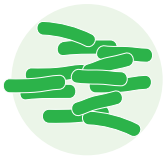
Dr Worodria's research will reveal key causes of community-acquired pneumonia in a high-HIV setting in sub-Saharan Africa, as well as the current state of antibiotic resistance. As well as generating new tools to improve clinical assessment and management of patients, the project will also create a foundation for future clinical trials on treatment of community-acquired pneumonia.

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**Dr William Ofuti
Worodria**
Uganda



Assessing next-generation TB diagnostics

Professor Grant Theron is evaluating the performance and potential for implementation of a new generation of diagnostics for TB.

The challenge

TB remains the leading cause of death in sub-Saharan Africa, accounting for more than 400,000 lives every year. Sensitive and rapid point-of-care tests could ensure that more people begin timely treatment, but currently used tests have so far had limited impact.

However, a new wave of improved diagnostics are beginning to be introduced. A key challenge is not only to assess their performance in real-life settings, but also to determine how they can best be deployed in existing health systems.



Prof. Grant Theron
South Africa

The project

Professor Grant Theron is an emerging authority on TB diagnostics. He was part of the team that demonstrated the practicability of the Xpert molecular diagnostic platform, informing WHO recommendations on its use. However, he also played a key role in highly influential EDCTP-funded studies revealing that, in practice, Xpert had less impact than expected because clinicians' treatment choices were only partly based on diagnostic results – emphasising the importance of understanding the context in which diagnostic tests are used.

In his EDCTP Senior Fellowship, Professor Theron is undertaking a range of studies on a new generation of Xpert-based and other TB diagnostics. These include studies of the performance and impact of Xpert Ultra and AlereQ TB point-of-care testing for pulmonary TB in clinics, as well as the potential to use automated digital chest radiography to optimise the use of molecular tests.

A second study will assess the impact and accuracy of Xpert Ultra and AlereQ TB testing for extra-pulmonary TB in a hospital setting. A third study is focusing on next-generation tests to detect drug resistance, MTBDRsl v2.0 and Xpert XDR, using laboratory samples. These tests have the advantage that they can be performed directly on patient specimens, removing the need for time-consuming culture.

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Professor Grant Theron, Stellenbosch University, South Africa

Year funded: 2017

EDCTP funding: €0.5 M

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/b45ea8f0-f9f6-4dec-aa0b-7772ca7b879f>

Impact

Professor Theron's Senior Fellowship will provide key evidence from a high-burden setting on both the performance and the impact of potentially highly significant new tools for TB diagnosis, including how they can be optimally used, for example with other technologies such as radiography. Findings will be of great relevance to policymakers considering whether to implement the new technologies.

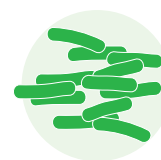
The project will also create a biobank of well-characterised samples to serve as a platform for future research, including the training of new researchers. At least three PhD students will be trained as part of the project, building capacity in a priority area for sub-Saharan Africa.

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Applying new technologies in TB research

Professor Keertan Dheda is building the capacity of African researchers to apply genomics and other new technologies in the battle against TB.



The challenge

An estimated 2.5 million people fall ill with TB in sub-Saharan Africa every year, with more than 400,000 deaths. These figures include 1 million new infections in children and 250,000 deaths.

The challenges of TB are being exacerbated by the emergence of multidrug-resistant TB and extensively drug-resistant TB, which require long periods of hospitalisation and treatment.

The project

Professor Keertan Dheda is one of Africa's leading authorities on TB. He is Head of the Division of Pulmonology at the University of Cape Town, having built up a large research group from scratch. His group's work has a strong focus on developing improved services for local populations in the Western Cape, and in South Africa and Africa more generally. He has pioneered the adoption of new techniques into clinical practice, and developed research programmes in all areas of TB diagnosis, treatment and care. He has led several successful EDCTP-funded projects on TB diagnostics, and was awarded the 2018 EDCTP Scientific Leadership Prize.

In his EDCTP Senior Fellowship, Professor Dheda aims to further develop his own leadership capabilities, and build local capacity in new genomics and other 'omics' technologies. This will include setting up a genome sequencing platform to support the training of early-career researchers in a technology increasingly central to infectious disease research.

His fellowship will build on a trial being funded by the South African Medical Research Council, NExT RCT, led by Professor Dheda, which is evaluating a new six-month needle-free regimen for multidrug-resistant TB. Biobanked samples will be used in a range of projects. One study is evaluating biomarkers potentially associated with response to TB treatment – current trials are long and costly because no good markers currently exist that predict treatment responses. A second study will use next-generation genome sequencing to identify resistance mutations. A third study will investigate methods to enable genome sequence information to be derived directly from clinical samples.

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Professor Keertan Dheda, University of Cape Town Lung Institute, South Africa

Year funded: 2017

EDCTP funding: €0.4 M

Fellow profile: <https://edctpalumnetwork.org/fe/profiles/view/5cf67de5-451b-4ee4-835f-79762318a127>

Impact

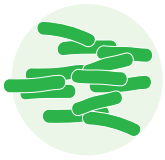
Professor Dheda's Senior Fellowship will enable him to undertake professional development activities so he can extend his leadership role in the African and global TB research community. In addition, it will support the introduction of new technologies that will accelerate research on diagnosis and treatment of this critical disease, and facilitate the training of junior researchers (a postdoctoral fellow and a PhD student).

References

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Prof. Keertan Dheda
South Africa



Strengthening clinical research capacity in Tanzania

Dr Stellah Mpagama is testing a possible approach for avoiding the deafness caused by some anti-TB treatments, while also building local capacity to carry out high-quality clinical trials.

The challenge

Kanamycin is a commonly used component of combination treatments for multidrug-resistant TB. Unfortunately, in a significant number of patients, kanamycin use is associated with damage to the auditory system and loss of hearing.

There is some evidence that N-acetylcysteine protects against kanamycin-induced hearing loss. However, there are limited data on its use in Africa and in people infected with HIV as well as TB.



Dr Stellah Mpagama
Tanzania

The project

Dr Stella Mpagama has wide-ranging interests in the treatment of TB and other emerging and re-emerging infections. Based at the Kibong'oto Infectious Diseases Hospital, she has a strong interest in meeting both clinical and practical programmatic challenges in the treatment of infections, and in the interactions between health conditions. Few patients experience infection in the absence of other conditions; HIV–TB co-infections are common, but many patients have a combination of infections and non-communicable conditions. Dr Mpagama has been part of the EDCTP-funded PanACEA Consortium, which has been evaluating alternative treatment regimens for TB. Dr Mpagama has also carried out research on the first cohort of multidrug-resistant TB patients treated in Tanzania.

In her EDCTP Senior Fellowship, Dr Mpagama is addressing a significant issue associated with treatment of multidrug-resistant TB. As many as half of all patients may experience kanamycin-induced hearing loss, potentially affecting their quality of life and economic wellbeing. Focusing on patients with HIV–TB co-infections, Dr Mpagama is carrying out a randomised controlled phase IIb trial to determine the safety and efficacy of N-acetylcysteine to prevent damage to the auditory system.

Embedded in this project are a range of studies that will support the development of PhD and master's students. Early-career researchers will have opportunities to monitor patient responses to treatment using the bacterial load assay, to use molecular assays to assess susceptibility

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Stellah Mpagama, Kibong'oto Infectious Disease Hospital, Tanzania

Year funded: 2018

EDCTP funding: €0.5 M

Fellow profile: <https://edctpalumnetwork.org/fe/profiles/view/6ba4d9de-ffc7-4be4-af64-2f3134ba2c20>

to second-line drugs, and to carry out whole genome sequencing of isolates showing signs of drug resistance but with no detectable resistance mutations.

Impact

Dr Mpagama's Senior Fellowship project will answer an important question in the management of patients with multidrug-resistant TB, and could ensure that significant numbers of patients are spared serious hearing loss. In addition, it will create sufficient critical mass of researchers to establish a functional clinical trial unit locally.

References

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- Mpagama SG et al. Diagnosis and interim treatment outcomes from the first cohort of multidrug-resistant tuberculosis patients in Tanzania. *PLoS One*. 2013;8(5):e62034.

Understanding HIV's impact on TB immunity

Professor Wendy Burgers is investigating a possible mechanism by which HIV increases susceptibility to active TB disease.

The challenge

More than 10 million people developed TB in 2015, and 2 million people died of TB disease. People living with HIV are at greatly increased risk of TB disease: HIV co-infection increases the risk of TB disease by up to 30 times.

Notably, only one in 10 people with a *Mycobacterium tuberculosis* (Mtb) infection develop TB disease, suggesting that the immune system can usually contain infections. However, factors such as HIV infection compromise the body's ability to keep Mtb under control.

The project

Professor Wendy Burgers has developed an extensive programme of research on the impact of HIV infection on the immune system. As well as HIV vaccine development, her work also has important implications for HIV–TB co-infections.

TB is increasingly seen as encompassing a spectrum from quiescent infection through to active disease. It would be highly advantageous to know who was at risk of progressing to active disease, but development of biomarkers to identify such individuals is held back by a lack of understanding of the drivers of disease. As HIV infection tilts the scales in favour of active disease, studying HIV–TB co-infections may reveal critical disruptions that drive TB disease.

In her EDCTP Senior Fellowship, Professor Burgers is focusing on a class of immune cells called Th22 cells, which produce the cytokine interleukin-22 (IL-22). The numbers of Th22 cells are greatly reduced in HIV infections, and there is some evidence that IL-22 plays a protective role in respiratory infections.

To shed more light on their possible role in TB, Professor Burgers is carrying out a detailed investigation of Th22 cell responses during TB disease and treatment, after HIV infection and during antiretroviral therapy. Th22 cell responses in these different disease states will be compared with those of other immune cell populations potentially involved in TB disease.

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Professor Wendy Burgers, University of Cape Town, South Africa

Year funded: 2017

EDCTP funding: €0.4 M

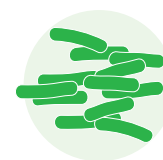
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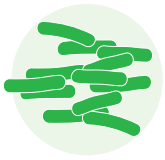
Professor Burgers' Senior Fellowship project will provide key data on Th22 responses, with potential implications for vaccine design and the development of biomarkers predictive of disease progression. The project will also support the clinical research training of two PhD students, one master's student and a postdoctoral fellow, building research capacity in this critical area.

References

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Prof. Wendy Burgers
South Africa



Understanding the impact of diabetes on TB

Professor Dorothy Yeboah-Manu is assessing how diabetes affects TB disease and responses to treatment.

The challenge

In 2016, 2.5 million people developed TB in sub-Saharan Africa, and more than 400,000 people died from TB disease.

It is well-recognised that HIV infection greatly increases the risk of TB disease, but other health conditions also have a significant impact. For example, there are growing concerns that type 2 diabetes – a growing health challenge in sub-Saharan Africa – may affect immune system function and the risk of TB disease.

The project

Professor Yeboah-Manu has developed a wide-ranging programme of research on mycobacterial infections affecting Ghana and other African countries. These include landmark studies on a TB-causing bacterium, *Mycobacterium africanum*, restricted to parts of West Africa. Professor Yeboah-Manu was awarded the Royal Society's Africa Prize in 2018.

In her EDCTP Senior Fellowship, Professor Yeboah-Manu is generating additional information on the interplay between diabetes and TB. She is recruiting patients newly diagnosed with TB, who will undergo testing on their glycaemic control; patients will be categorised as either normal, having impaired glucose control or with full-blown diabetes.

Clinical and demographic data will also be collected, and patients will be tested again after 2, 5 and 6 months of treatment. Professor Yeboah-Manu will also examine interactions between anti-TB and diabetes drugs, monitor TB drug susceptibility, and culture and genotype *M. tuberculosis* isolates.

Impact

Professor Yeboah-Manu's Senior Fellowship project will yield important information on how diabetes affects TB disease and its treatment. The findings will have important implications for the management of TB patients. With diabetes becoming increasingly common in sub-Saharan Africa – three-quarters of diabetes patients live in low-income countries – the results are very timely.

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Professor Dorothy Yeboah-Manu, Noguchi Memorial Institute for Medical Research, Ghana

Year funded: 2018

EDCTP funding: €0.5 M

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Prof. Dorothy Yeboah-Manu
Ghana

Immunological signatures of TB infection

Dr Catherine Riou is aiming to identify cellular markers characteristic of different stages of TB disease.

The challenge

In 2017, TB was responsible for an estimated 1.7 million deaths; more than a quarter of TB deaths occur in Africa.

Most people who are infected with *Mycobacterium tuberculosis* (Mtb) do not develop active disease. However, it is becoming clear that the traditional distinction between active and latent or quiescent TB is too simplistic. Instead, there is likely to be a spectrum of disease states, with people at differing risks of progressing to severe disease.

The project

Dr Catherine Riou is aiming to identify specific immune system markers that are able to differentiate different TB disease states. Her focus is on T cells, specifically the CD4+ class of T cells. She and her colleagues have shown that the properties of CD4+ T cells differ between latent and active TB, in both HIV-infected and -uninfected patients. Furthermore, levels of a specific class of Mtb-specific CD4+ T cells expressing the CD153 marker are significantly higher in people with latent TB compared with those with active disease, and these cells are known to confer protection against TB in mice.

In her EDCTP Senior Fellowship, Dr Riou is studying in more detail the characteristics of T cell populations in different TB disease states. In particular, she is exploring whether people at heightened risk of active TB – with HIV infections or early signs of TB disease – show changes in the properties of Mtb-specific CD4+ T cells. In addition, she will test whether these changes are reversed by prophylactic TB treatment or antiretroviral therapy, which are known to reduce the risk of active TB disease.

Impact

Dr Riou's Senior Fellowship project will improve understanding of a critical aspect of the immune response to Mtb infection. It also has the potential to identify specific markers that could detect those at greatest risk of developing active

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Catherine Riou, University of Cape Town, South Africa

Year funded: 2018

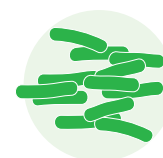
EDCTP funding: €0.5 M

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/66966e4d-7a9c-4b37-9aee-c57d5dce333a>

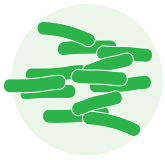
TB and be used to monitor responses to therapy. The project will also build capacity by contributing to the training of two PhD students and a postdoctoral scientist.

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Dr Catherine Riou
South Africa



Dissecting the origins of lung disease

Professor Maia Lesosky is developing new statistical methods to shed light on the risk factors behind childhood lung infections, and building capacity in biostatistics and analysis of complex datasets.

The challenge

Respiratory diseases, including TB and lower respiratory tract infections, are major causes of death and ill-health in sub-Saharan children. In addition, it is increasingly recognised that damage to the lungs in childhood increases the risk of TB and other lung diseases in later life.

Cohort and other clinical studies are generating a wealth of data on infectious diseases and risk factors affecting vulnerability to infection or the likelihood of long-term impacts. However, making full use of these data requires expertise in biostatistics, so new approaches to data analysis can be applied.

The project

With a background in biostatistics and modelling, Professor Lesosky has a particular interest in the development of biomarkers to predict disease progression, particularly in TB. It is highly unlikely that single markers will be informative of disease progression, and complex statistical analysis is likely to be needed to dissect complex biological data to identify predictive patterns across multiple markers.

In her EDCTP Senior Fellowship, Professor Lesosky is developing new methods to extract information on key factors affecting childhood lung health. Her work will draw on two ongoing studies that are exploring the longitudinal determinants of TB and lower respiratory tract infections in African children. She is aiming to develop new approaches that will shed light on how factors such as interactions between pathogens, household and environmental pollution, and clinical and demographic factors affect the risk of TB and lower respiratory tract infections.

Impact

Professor Lesosky's Senior Fellowship project will provide new insight into the origins of common and important lung infections in children, supporting more effective prevention

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Professor Maia Lesosky, University of Cape Town, South Africa

Year funded: 2018

EDCTP funding: €0.5 M

Fellow profile: <https://edctpalumnetwork.org/fellow/profiles/view/f4d14703-86c1-4f45-8bd1-9cc9f5b9053e>

and identification of those at risk of disease. By training two PhD students and four Master's students, her project will also build capacity to analyse and extract more information from complex biological datasets.

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Prof. Maia Lesosky
South Africa

Searching out drug-resistant TB

Dr Mareli Claassens is investigating how best to identify cases of drug-resistant TB in Namibia.

The challenge

More than 500,000 new cases of multidrug-resistant (MDR) TB occur each year, around 10% of which are extremely drug resistant (XDR) TB. Namibia is classified as a high TB burden country, with 11,000 new cases a year; 3.9% of new cases and 8.7% of previously treated cases are MDR-TB.

It is vital that cases of drug-resistant TB are identified in a timely fashion, so that patients can be started on the most appropriate treatment but also to limit the spread of drug-resistant strains. This requires an active case-finding strategy – going out into the community to identify cases rather than waiting them to appear at health facilities.

The project

In her Senior Fellowship, Dr Mareli Claassens aims to develop a clearer picture of drug-resistant TB in Namibia, to investigate the feasibility of targeted case finding to improve TB control, and to develop a TB transmission model to explore the potential impact of case-finding interventions.

Her work will focus on two areas of Namibia thought to be hotspots for transmission of drug-resistant TB, including disadvantaged ethnic minority populations. A wide range of clinical, epidemiological, laboratory and social networking data will be collected to characterise drug-resistant TB cases in these regions and how they are being spread. Through a collaboration with Research Center Borstel in Germany, this work will take advantage of the power of whole genome sequencing to reveal pathways of transmission of drug-resistant TB strains.

These results, plus a systematic review of the literature, will be used to identify a potential strategy for active case finding. Interventions will be tested in a feasibility study focusing on transmission hotspots, households and hospitals.

Data from the drug-resistant TB mapping exercise and from Namibia's national TB programme will feed into a model of drug-resistant TB transmission, which will be used to explore the potential impact of case-finding

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Mareli Claassens, University of Namibia, Namibia

Target population(s): All

Year funded: 2018

EDCTP funding: €0.5 M

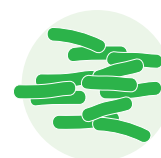
interventions. This strand of work will include a health economic component to provide data on the likely cost-effectiveness of targeted case-finding interventions.

Impact

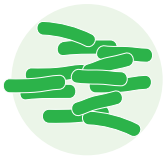
Dr Claassens' research will generate a deeper understanding of drug-resistant TB in Namibia and establish the feasibility and likely costs of locally appropriate case-finding interventions. The findings will contribute to more effective control of drug-resistant TB in Namibia. In addition, it will build local capacity in whole-genome sequencing and further develop Dr Claassens' research career, facilitating her addition to the faculty at the University of Namibia.

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Dr Mareli Claassens
Namibia



Better detection of TB meningitis

Dr Novel Chegou is aiming to develop a new diagnostic tool to more rapidly identify cases of TB meningitis in children.

The challenge

Although commonly viewed as a lung infection, TB can also affect the brain and nervous system. The TB bacterium can infect the membranes surrounding the brain and nervous system, the meninges, causing potentially fatal tuberculous meningitis.

TB meningitis is the most severe form of TB affecting children. However, early symptoms are non-specific and meningitis has multiple possible causes. Furthermore, facilities for brain imaging and analysis of cerebrospinal fluid samples to aid diagnosis are not available in many sub-Saharan African settings, leading to long delays in diagnosis and start of treatment.

The project

In his EDCTP Senior Fellowship, Dr Novel Chegou aims to work with colleagues in the Engineering Faculty of Stellenbosch University to develop a novel point-of-care test for TB meningitis.

Dr Chegou was involved in the EDCTP-funded AE-TBC project, which identified a set of host biomarkers associated with TB meningitis infections in adults. This led to the development of six- and seven-biomarker 'biosignatures' with good potential to be used diagnostically for TB meningitis in adults. The EDCTP-funded ScreenTB project is evaluating the potential of a point-of-care diagnostic based on these biosignatures to detect active TB.

Building on this experience, Dr Chegou is evaluating more than 50 host inflammatory biomarkers with the potential to form the basis of a similar point-of-care diagnostic for TB meningitis in children. His goal is to identify the most promising combination of three or four biomarkers to provide a reliable indicator of TB meningitis. Past work has identified a three-biomarker signature with potential to form the basis of a new test.

His colleagues in the Engineering Faculty have developed novel detection technology based on zinc oxide nanowires. Dr Chegou plans to work with colleagues in Engineering to develop a prototype diagnostic for TB meningitis for

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Associate Professor Novel Chegou, Stellenbosch University, South Africa

Target population(s): Children

Year funded: 2019

EDCTP funding: €0.5 M

use on cerebrospinal fluid or blood samples. Its performance will be assessed on samples from 300 newly recruited children with suspected TB meningitis.

Impact

Through his EDCTP Senior Fellowship, Dr Novel Chegou aims to develop a much-needed new diagnostic that would accelerate the detection of TB meningitis in children, enabling treatment to begin much sooner. Dr Chegou has gained extensive experience in previous EDCTP-funded TB biomarker projects, but this is his first major grant in his own name. The EDCTP fellowship is therefore providing an opportunity for Dr Chegou to establish his credentials as a research leader through additional technical training, mentoring and leadership skills development.

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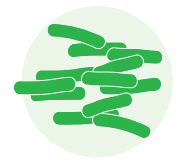
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Assoc. Prof. Novel
Chegou
South Africa

Connecting TB patients to care

Dr Esther Buregyeya is exploring the potential of behavioural interventions to promote healthcare seeking by people diagnosed with TB.



The challenge

TB control is undermined by the large number of likely cases that never undergo confirmatory testing or who are tested but do not start treatment. Globally, an estimated 40% of new cases are not reported to national TB control programmes. This leads to unnecessary mortality and morbidity, and also provides opportunities for the further spread of infection.

Uganda is a country with a high burden of TB, including multidrug-resistant TB. More than 40,000 cases are reported each year, only around half of which are started on treatment. Up to a third of patients are lost to follow up having started treatment.

The project

In her Senior Fellowship, Dr Esther Buregyeya is exploring the patient's perspective of TB care, with a view to identifying obstacles and enablers of health-seeking behaviour to improve linkage to care.

Dr Buregyeya has a particular interest in the use of behavioural interventions to improve health-seeking behaviour. There is some evidence that text messaging can improve adherence to treatment. In some circumstances, financial incentives may also be a way to overcome financial barriers to care seeking.

During her fellowship Dr Buregyeya is recruiting a cohort of individuals with suspected TB and tracking their pathway through testing and treatment. This will identify potential points of intervention to improve linkage to care. Through interviews and consultations with patients and other stakeholders, she plans to design an intervention strategy incorporating text messaging reminders and mobile money payments. These will be rooted in well-established theoretical frameworks for behavioural interventions, the 'COM-B' model. The interventions will then be evaluated (individually and in combination) in a controlled trial.

The project builds on Dr Buregyeya's past work on TB patient pathways and delays. She also heads the Department of Disease Control and Environmental Health at Makerere University, and is spearheading the development of

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Esther Buregyeya, Makerere University, Uganda

Target population(s): All

Year funded: 2020

EDCTP funding: €0.5 M

a master's of public health and business administration, to promote greater consideration of public health within the business world. During her fellowship, she will train one PhD and three master's students.

Impact

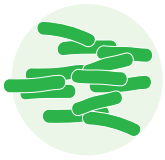
Dr Buregyeya's research will identify and evaluate contextually sensitive behavioural interventions, grounded in strong psychological theory, with the potential to increase retention of TB patients with the healthcare system in Uganda. This will ensure more patients receive the care they need and reduce opportunities for the spread of infection. The project will also generate rigorous evidence on interventions that could be adapted for use elsewhere in sub-Saharan Africa. The fellowship also provides an opportunity for Dr Buregyeya to develop her research leadership abilities, mentoring skills and ability to compete for funding.

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Dr Esther Buregyeya,
Uganda



Reducing infections in HIV-exposed infants

Dr Victoria Nankabirwa is assessing whether BCG vaccination protects HIV-exposed but uninfected infants against serious infections, and developing an innovative 'clinical trials teaching clinic'.

The challenge

Prevention of mother-to-child transmission has markedly reduced the number of infants with HIV infections. However, a million infants are exposed to HIV in sub-Saharan Africa each year, and this exposure appears to have harmful impacts on their health. For example, they are at greater risk of other infections, including lower respiratory tract infections, malaria and diarrhoeal disease, which account for more than 40% of childhood deaths.

There is some evidence that the BCG vaccine for TB has non-specific immune stimulatory effects that protect against other infections. In addition, the timing of BCG vaccination might also influence its ability to stimulate immune responses – later vaccination could generate more powerful immune responses but might leave infants vulnerable in the high-risk period before vaccination. Furthermore, most data are from observational studies rather than well-controlled clinical trials.

The project

In her Senior Fellowship, Dr Victoria Nankabirwa aims to generate rigorous clinical trial data on the protective effect of BCG vaccination on serious infections in HIV-exposed infants. Dr Nankabirwa has been running a clinical trial comparing the risk of serious infections in infants receiving BCG vaccine either within 24 hours of birth or at 14 weeks. Because the number of infections has been much lower than anticipated at study sites, the number of infants recruited needs to be doubled, which will be facilitated by EDCTP fellowship funding.

Dr Nankabirwa is an experienced clinical researcher who has worked in the UK, USA and Bangladesh, as well as at WHO headquarters in Geneva. She is committed to developing up and coming talent and is Director of the Distance Education Master of Public Health programme at Makerere University in Uganda. Through her fellowship, she plans to establish an innovative 'clinical trials teaching clinic' – the first of its kind in the region – to provide hands-on training for graduates and post-graduates within the context of ongoing clinical trials. The clinic will help to bridge the gap between the mainly theoretical teaching that students currently receive, enabling

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Victoria Nankabirwa, Makerere University, Uganda

Target population(s): Infants

Year funded: 2020

EDCTP funding: €0.5 M

them to apply their learning in a practical context.

During her fellowship, Dr Nankabirwa will directly supervise at least five graduate students and at least three PhD students. She will also be developing an online graduate-level course on randomised controlled trial methodology for low-resource settings, which will contribute to clinical research capacity development across the whole of sub-Saharan Africa.

Impact

Dr Nankabirwa's research will provide rigorous trial data on an important but controversial area of medicine, the potential non-specific effects of BCG. The results will have immediate public health relevance and the potential to shape national vaccination policies. In addition, her educational initiatives will play an important role in developing clinical research capacity in the region.

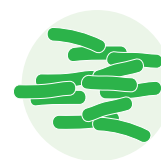
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Dr Victoria Nankabirwa
Uganda

Understanding the evolution of drug-resistant TB



Dr Elizabeth Streicher is using whole genome sequencing to shed light on the evolution and spread of drug-resistant Mycobacterium tuberculosis (Mtb).

The challenge

More than half a million new cases of multidrug-resistant (MDR) TB occurred in 2017 and an estimated 240,000 people died of MDR-TB. Of these cases, around 6% had extremely drug-resistant TB (XDR-TB) which is difficult to diagnose, hard to treat, and has a very high mortality rate. In addition, failure to identify and treat MDR-TB cases promotes the spread of infection in communities.

Control of TB will ultimately depend on a good understanding of the origins and spread of MDR-TB and XDR-TB. However, despite the major TB burden in sub-Saharan Africa in general and South Africa in particular, there is limited understanding of Mtb evolution.

The project

In her Senior Fellowship, Dr Elizabeth Streicher is using whole genome sequencing of MDR-TB and XDR-TB isolates to develop a better understanding of drug-resistant strains, how they have spread, and factors affecting their survival.

Dr Streicher has a long-standing interest in the use of genetic approaches to characterise Mtb strains, having been the first researcher in Africa to introduce a rapid genotyping tool, spoligotyping, and using that and other approaches to investigate the spread of resistant strains. She has also established a valuable biobank of more than 45,000 Mtb samples.

Conventionally, it is assumed that resistance mutations reduce the fitness of bacterial strains, hindering their ability to spread. However, molecular studies have shown that certain MDR-TB and XDR-TB strains have managed to establish themselves, and seeded new outbreaks following migration of infected patients, suggesting that they can compete effectively with non-resistant strains.

Concentrating on the Western Cape Province, which has a very high burden of XDR-TB, Dr

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Elizabeth Streicher, Stellenbosch University, South Africa

Year funded: 2019

EDCTP funding: €0.5 M

Streicher is using whole-genome sequencing to provide a higher resolution view of the genetic make-up drug-resistant Mtb. She plans to map the full range of resistance-associated mutations in different outbreaks, and to determine how changes in diagnostic approaches and recommended treatment regimens affected the spread of different strains. She also plans to assess the extent of drug-resistant TB in other southern African countries.

Impact

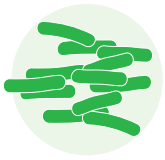
Dr Streicher's Senior Fellowship will improve understanding of the mechanisms driving the emergence and spread of XDR-TB in populations badly affected by both TB and HIV. It will generate important insights to inform control of highly problematic drug-resistant infections having a major impact on individuals and communities.

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Dr Elizabeth Streicher
South Africa



Personalised treatment of drug-resistant TB

Professor Nesri Padayatchi is exploring use of whole genome sequencing to identify resistance genes and facilitate tailored treatment of TB.

The challenge

Drug resistance is a growing problem in TB. In 2018, there were around half a million new cases of drug-resistant TB globally and an estimated 214,000 deaths. South Africa, particularly KwaZulu Natal, is badly affected by drug-resistant TB and has experienced the largest outbreak of extremely drug-resistant (XDR) TB ever reported.

Identification of drug resistance is important to ensure that patients are started on effective drugs as rapidly as possible and are spared the side effects of powerful drugs from which they will derive no benefit. However, culture methods to determine resistance take many weeks, while quicker molecular tests screen for only a few specific resistance genes.

The project

Professor Nesri Padayatchi has contributed to multiple areas of TB research, and was the recipient of the South African Medical Research Council's Silver Scientific Merit Award. She also has extensive practical experience of care for patients with MDR- and XDR-TB. In her Senior Fellowship, Professor Padayatchi is exploring the potential of whole genome sequencing to provide a comprehensive picture of resistance genes to inform treatment of MDR-TB and XDR-TB.

The mechanisms of drug resistance in *Mycobacterium tuberculosis* (Mtb) are complex, and mutations in many genes may contribute to reduced drug susceptibility. Whole genome sequencing is becoming more widely available and has the advantage of providing information relatively quickly across the entire Mtb genome. Recent studies have shown that there is a good correlation between resistance predicted on the basis of genetic information and that observed in tests with cultured bacteria.

In her Senior Fellowship project, Professor Padayatchi is undertaking a trial comparing use of whole genome sequencing with conventional methods for detecting resistance. The trial will focus on patients first screened with the Xpert MTB/RIF diagnostic so are known to have

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Professor Nesri Padayatchi, Centre for the AIDS Programme of Research in South Africa, South Africa

Target population(s): All

Year funded: 2020

EDCTP funding: €0.5 M

drug-resistant TB, and aims to recruit patients with both MDR-TB and XDR-TB. On the basis of genome data, experts will select treatments likely to be most effective in each patient.

Impact

Inadequate treatment of MDR-TB delays recovery, exposes patients to drugs with the potential to cause a range of significant side effects, and increases the risk that more extensive drug resistance develops. Whole genome sequencing is emerging as a tool that could overcome many of these challenges. Professor Padayatchi's study will provide important evidence on the clinical benefits of its use in an area with one of the world's heaviest burdens of MDR-TB and XDR-TB.

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Professor Nesri Padayatchi
South Africa

Building malaria research capacity in Uganda

Dr Peter Olupot-Olupot is aiming to increase the capacity of Uganda to undertake clinical research in malaria, including clinical trials.



The challenge

Malaria is a major public health problem in Uganda. Uganda has the sixth highest number of malaria deaths in Africa, with 16 million cases reported in 2013 and more than 10,000 deaths annually.

Even so, capacity to carry out research on malaria lags behind that of other infections such as HIV. In particular, Uganda hosts relatively few clinical trials in malaria. Malaria trials that do take place in Uganda are generally originated and led from elsewhere, with limited input from local researchers.

The project

Dr Peter Olupot-Olupot is a paediatric infectious disease specialist with extensive experience in clinical research. He founded the Mbale Regional Referral Hospital Clinical Research Unit, and is the local lead for a range of paediatric studies run by the Wellcome–KEMRI Research Programme in Kenya.

Dr Olupot-Olupot has a particular interest in malaria research, and is using his EDCTP fellowship to develop his own skills in this area and to enhance the research capacity of the Mbale clinical research unit. His personal development is focusing on epidemiology, pathophysiology and the conduct of phase II and III trials. Building these skills will enable him to carry out studies on local malaria epidemiology, and on the epidemiology and pathophysiology of acute kidney injury in severe malaria in children, and to undertake a clinical trial on the feasibility of paracetamol use to address acute kidney injury in severe malaria.

In addition, he will use these studies as a platform for training and mentoring of two master's students, expanding expertise in malaria and clinical trials.

Impact

As well as generating new insights into malaria in east Uganda and on the mechanisms of kidney

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Peter Olupot-Olupot, Mbale Regional Referral Hospital, Uganda

Year funded: 2018

EDCTP funding: €0.5 M

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/75752fb2-81ce-4774-afd8-b8509ab25926>

damage in severe malaria, Dr Olupot-Olupot's fellowship will enable him to play a more active role in the development of clinical research relevant to malaria in Uganda, and to build clinical malaria research capacity in east Uganda.

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Dr Peter Olupot-Olupot
Uganda



Understanding malaria parasite diversity

Professor Faith Osier has created an international network to map the malaria parasite diversity across Africa – a key step in the development of more effective malaria vaccines.

The challenge

The diversity of malaria parasites is one of the biggest obstacles to malaria vaccine development. Many malaria proteins come in a wide range of forms and antibodies against one form may not recognise other variants of the same protein.

Immunity to malaria seems to arise because, over time, people generate a repertoire of antibodies spanning the diversity of parasites they encounter, but it is still unclear precisely which immune responses are protective.

The project

Professor Faith Osier's research has focused on understanding the immune response to the malaria parasite, and the elements of it that protect against infection. This understanding is critical to the design of more effective vaccines.

In her EDCTP Senior Fellowship, she has established an international network, SMART, that is sharing samples and epidemiological data on malaria parasites across Africa. The network now spans 12 sites in seven sub-Saharan Africa countries, and has created a dataset of 10,000 samples and data.

Each sample is being systematically analysed to characterise variation in key proteins of interest – creating a unique map of parasite diversity across the continent.

Complementing this focus on the parasite, Professor Osier is also continuing to explore immune responses correlating with protection against malaria (uncomplicated and severe). To this end, she and her colleagues have developed a new 'protein array', known as KILchip, which includes more than 100 parasite proteins that are potential targets of antibody responses. This durable and reliable tool, suitable for use in Africa, opens up the prospect of rapid high-throughput screening to quantify antibody responses to multiple key parasite proteins.

Impact

This EDCTP Senior Fellowship is supporting the career development of one of Africa's

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Professor Faith Osier, Kenya Medical Research Institute, Kenya

Year funded: 2017

EDCTP funding: €0.5 M

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/2c10cd51-85de-4d15-89b6-bbadbe00448d>

leading malaria vaccine researchers. In 2014, Dr Osier received the Fifth Merle A Sande Health Leadership Award from the Accordia Global Health Foundation as well as the Royal Society Pfizer Prize. In 2016, she received a Sofja Kovalevskaja Award from the Alexander Humboldt Foundation, enabling her to establish a lab in Heidelberg, Germany, alongside her work at the KEMRI–Wellcome Trust Programme in Kilifi, Kenya.

Her research is helping to identify candidate antigens to include in a malaria vaccine. In addition, her work on the mechanisms of immunity to the malaria parasite is informing how vaccines should be designed and used. She is also committed to developing malaria research capacity in Africa, the SMART collaboration providing a platform for three PhD students, five master's students and shorter-term training for postdoctoral scientists and postgraduate diploma students.

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Prof. Faith Osier
Kenya

Towards improved vaccines for malaria

Dr John Lusingu is building capacity for trials of new malaria vaccines that are more effective than RTS,S/AS01.



The challenge

Malaria vaccine development has proven hugely challenging. Following decades of work, the first vaccine of proven efficacy, RTS,S/AS01, is beginning to be implemented in Africa.

However, RTS,S/AS01 is of limited efficacy and requires four doses. Alternatives are still urgently needed to improve malaria control and to support the drive towards elimination. One key priority is severe malaria, which in Africa predominantly affects children under 5 years of age, which can be rapidly fatal without prompt treatment.

The project

Dr John Lusingu was one of the researchers involved in the clinical trials evaluating RTS,S/AS01. He is aiming to build on this experience to advance the development of other vaccine candidates and to build the capacity for malaria research and vaccine field trials in Tanzania.

In his EDCTP Senior Fellowship, Dr Lusingu is focusing on a highly variable malaria parasite protein known as PfEMP1, which is found on the surface of infected red blood cells and promotes binding of infected cells to blood vessel walls. Antibodies against PfEMP1 are associated with protection against malaria, but because it is such a highly variable protein, it takes time for people to develop a repertoire of protective antibodies. However, there is also evidence that protection against specific forms of malaria – such as malaria in pregnancy and severe malaria in children – could develop relatively quickly when antibodies against specific PfEMP1 variants are generated.

Dr Lusingu's research is focusing on PfEMP1 variants that bind to a protein on blood vessel walls known as endothelial protein C receptor (EPCR), which Dr Lusingu and his colleagues in Denmark have found is associated with severe malaria in children. A vaccine blocking binding to EPCR could therefore reduce the risk of one of the most deadliest manifestations of malaria.

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr John Lusingu, National Institute for Medical Research, Tanzania

Year funded: 2017

EDCTP funding: €0.5 M

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/fe8d6fe4-6200-42ce-88ef-61b7cd0387d4>

Impact

Dr Lusingu's fellowship will build capacity for vaccine-related research, with the aim of developing a vaccine suitable for pregnant women and young children, those most vulnerable to severe malaria. It will also establish a field site in Korogwe, Tanzania, able to carry out field-based studies on candidate vaccines. Dr Lusingu's fellowship will also facilitate the training of junior researchers (two master's and two PhD students).

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Dr John Lusingu
Tanzania



Understanding natural immunity to malaria

Dr Francis Ndungu is studying individuals who are seemingly resistant to malaria infection, to identify immune responses correlating with protection against infection.

The challenge

Malaria still has a major impact on the health and economic wellbeing of people in sub-Saharan Africa. Half the population live in areas affected by malaria.

Although the first effective malaria vaccine, RTS,S/AS01, is beginning to be rolled out, it is only partially protective and alternatives are urgently needed. However, a major challenge in malaria vaccine development is that it is still unclear which specific immune responses are most important in conferring protection against infection.



Dr Francis Ndungu
Kenya

The project

Dr Francis Ndungu has been involved in numerous studies exploring naturally acquired immunity to malaria, as well as trials of the RTS,S/AS01 vaccine and follow up of vaccinated children. Recently, he has also worked on 'controlled human infection' studies, a newly introduced approach in Africa in which individuals are deliberately infected with malaria parasites. This approach provides a great opportunity to understand more about the immune responses to malaria parasites and their association with infection and protection.

In his EDCTP Senior Fellowship, Dr Ndungu will follow up on an intriguing preliminary finding that about one in 10 people previously exposed to malaria parasites do not develop blood-stage infections when injected with sporozoites – the parasite stage transmitted to people by mosquitoes. This suggests that these individuals mount immune responses that stop parasites from invading and multiplying within red blood cells (so-called pre-erythrocytic immunity).

RTS,S/AS01 also induces pre-erythrocytic immunity. However, most studies of naturally acquired immunity have focused on responses to erythrocytic rather than pre-erythrocytic stages. Hence, the current understanding of naturally acquired immunity may not be a useful guide to the design of pre-erythrocytic vaccines. Using the controlled human infection model, Dr Ndungu will be able to gain a detailed understanding of the mechanisms and antibody responses

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Francis Ndungu, African Research Collaboration for Health Ltd/ KEMRI-Wellcome Trust Research Programme, Kenya

Year funded: 2018

EDCTP funding: €0.5 M

Fellow profile: <https://edctpalumnnetwork.org/fellow/profiles/view/8dc99f37-fb81-474e-8ef2-c95708a574a9>

associated with pre-erythrocytic immunity in individuals that do not develop blood-stage infections after exposure to sporozoites.

Impact

Dr Ndungu's Senior Fellowship project will provide important data on the association between specific immune responses and outcomes of infection. By identifying parasite antigens eliciting protective immune responses that prevent red blood cell infection, it will provide important input into the prioritisation of targets for pre-erythrocytic vaccine development.

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Optimising malaria treatment for people living with HIV

Professor Pauline Byakika-Kibwika is investigating how antiretroviral therapy affects the metabolism of antimalarial drugs.

The challenge

Many populations with a high burden of HIV are also exposed to malaria. In addition, the two infections show reciprocal interactions – HIV infections leave people at greater risk of malaria, while malaria leads to increased viral replication.

Inevitably, therefore, many people are simultaneously treated for both HIV and malaria. Furthermore, treatments for both infections involve multiple drug combinations, increasing the risk of drug–drug interactions that affect their therapeutic effectiveness.

The project

Professor Pauline Byakika-Kibwika has been involved in studies revealing how antiretroviral drugs affect bloodstream levels of commonly used antimalarial combinations. In particular, efavirenz-based antiretroviral therapy has a significant impact on levels of artemether and its active metabolite, dihydroartemisinin, as well as those of its long-acting partner drug lumefantrine.

In her EDCTP Senior Fellowship, Professor Byakika-Kibwika is exploring the possible clinical implications of these drug–drug interactions, by monitoring outcomes of malaria treatment in people with HIV infections receiving antiretroviral therapy.

She is also undertaking pharmacokinetic studies to generate more data on the interactions between antiretroviral and antimalarial drugs.

Impact

Professor Byakika-Kibwika's Senior Fellowship project will reveal the clinical impact of drug–drug interactions between commonly used antimalarial and antiretroviral drugs. It will also identify the optimal dosage to overcome these interactions, which could then be evaluated in a formal clinical trial.

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Professor Pauline Byakika-Kibwika, Infectious Diseases Institute, Uganda

Year funded: 2018

EDCTP funding: €0.5 M

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Prof. Pauline Byakika-Kibwika
Uganda



Identifying hidden malaria infections

Dr Makhtar Niang is evaluating new diagnostic technology that could make it easier to identify asymptomatic malaria infections.

The challenge

Despite some progress, more than 400,000 people die of malaria every year, the vast majority in sub-Saharan Africa. Nevertheless, with effective drugs and other control measures such as bednets available, the prospect of malaria elimination is increasingly being discussed.

A major obstacle to malaria elimination is likely to be the existence of asymptomatic infections. Parasite numbers may be so low that they do not cause symptoms, but they can still be transmitted via mosquitoes and cause new infections. The other major challenge with asymptomatic infections is that they may be beyond the limits of detection by commonly used rapid diagnostic tests.



Dr Makhtar Niang
Senegal

The project

In his EDCTP Senior Fellowship, Dr Makhtar Niang aims to test a new, highly sensitive malaria diagnostic suitable for community-based screening. The AnyMDx test detects parasite DNA using 'loop-mediated isothermal amplification' (LAMP) technology, which, unlike standard polymerase chain reaction (PCR) approaches, does not require repeated cycles of heating and cooling. It therefore requires less complex equipment and is significantly cheaper.

Dr Niang has spent his research career working on malaria, spending time in laboratories in Europe, the USA and Singapore before returning to Senegal to take up a position at the Institut Pasteur de Dakar. He has made important discoveries about the STEVOR family of proteins, which may play a key role in protecting the parasite from the host immune system.

In Senegal, his work has increasingly focused on low-level and asymptomatic malaria parasite infections. He identified the presence of a less common species of malaria parasite, *Plasmodium vivax*, in Senegal, and has undertaken an extensive study of asymptomatic infections in two test-bed villages, Dielmo and Ndiop. These studies found significant levels of asymptomatic infections, 7.6% and 9.5% respectively, at the two sites. Importantly, 98% of subsequent infections occurred in households affected by asymptomatic infections.

Dr Niang has already made significant contributions to malaria research, including

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Makhtar Niang, Institut Pasteur de Dakar, Senegal

Target population(s): All

Year funded: 2020

EDCTP funding: €0.5 M

through his collaborations with researchers in the extensive Institut Pasteur network and beyond. He also co-supervises a PhD student with EDCTP Senior Fellow Professor Faith Osier. Through his Senior Fellowship, he will strengthen his collaborations and undertake training at the Institut Pasteur, Paris, where his mentor, Professor Didier Ménard, is based.

Impact

Dr Niang's project will provide important data on a diagnostic tool that could play an essential role in malaria elimination, which will depend on the ability to screen populations and identify all residual infections, including asymptomatic ones. His fellowship will also enable Dr Niang to consolidate his reputation in malaria research and nurture additional master's and PhD students to build malaria research capacity.

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Hepatitis B virus and malaria

Dr Kwado Kusi aims to determine whether infection with hepatitis B virus impairs immune responses to the malaria parasite.



The challenge

An estimated 60 million people in sub-Saharan Africa are infected with hepatitis B virus (HBV), which can lead to long-term liver damage and potentially fatal cancer. Many people face the dual risk of HBV and malaria, and co-infections are common.

Both HBV and the malaria parasite infect liver cells, and it is possible that infections with one pathogen may influence immune responses to the other. HBV infections could also impair immune responses to malaria vaccines, but as HBV-infected people are excluded from malaria vaccine trials this is not known for certain.

The project

Dr Kwado Kusi has carried out a series of studies examining immune responses to malaria, including responses that might have the potential to be used as markers of recent infection. His studies have also identified responses associated with protection against malaria, highlighting possible antigens to include in malaria vaccines.

In his Senior Fellowship, Dr Kusi aims to find out more about the impact of HBV infection on immune responses against the liver stage of the malaria parasite. More specifically, he will test the idea that chronic HBV infections have a generalised inhibitory effect on immune responses, dampening down the responses required to protect against malaria liver-stage infections.

In his project, Dr Kusi is recruiting people in Accra, Ghana, with chronic HBV infections and following them monthly for a year. He will measure antibody levels against a sporozoite protein, to provide a measure of *Plasmodium* infection, as well as levels of asexual blood-stage parasites, an indication of how well the parasite has survived the liver stage of infection.

He will also gather data on liver function and HBV viral load to provide an indication of how a malaria infection affects HBV and liver disease.

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Kwado Kusi, University of Ghana, Ghana

Target population(s): Patients with HBV infection

Year funded: 2020

EDCTP funding: €0.5 M

Impact

Dr Kusi's work will fill a key evidence gap, shedding light on the impact of HBV and malaria parasite co-infections on immune responses. The findings will have important implications for the treatment of people with HBV who contract malaria. In addition, as malaria vaccines move closer to routine use, the results will help to determine how effective a vaccine is likely to be in populations with high levels of HBV infection.

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Dr Kwado Kusi
Ghana



Malaria prevention in school-age children

Dr Karim Traoré is evaluating the potential of a new drug combination to prevent malaria in school-age children at high-risk times of year.

The challenge

Although much progress has been made in the battle against malaria, it still kills more than 400,000 people in sub-Saharan Africa every year, most of them children.

One of the most successful strategies for malaria prevention has been seasonal malaria chemoprevention, in which antimalarial drugs – usually sulfadoxine–pyramethamine (SP) and amodiaquine – are given to healthy young children to prevent malaria at times of year when they are at greatest risk, generally during the rainy season.

However, there are concerns that SP-based chemoprevention is becoming less effective due to the spread of drug resistance. In addition, the success of malaria prevention in young children means that they are not acquiring natural immunity to infection, leading to increasing numbers of infections in older, school-age children. Such children may also act as a reservoir facilitating the spread of malaria during times of low transmission.

The project

Dr Karim Traoré has contributed to a wide range of malaria studies in Mali, including work on mechanisms of drug resistance, genetic and other risk factors for malaria, and phase I testing of a candidate malaria vaccine.

In his Senior Fellowship, Dr Traoré is evaluating an alternative to SP–amodiaquine, dihydroartemisinin–piperaquine (DHA–PQ). Dihydroartemisinin is a fast-acting drug while piperaquine has a longer half-life and therefore a more sustained effect.

To test its use in seasonal malaria chemoprevention, Dr Traoré is carrying out a trial comparing DHA–PQ with SP– amodiaquine in school-age children during Mali's rainy season (October to January).

Impact

Dr Traoré's project will provide important data on the ability of DHA–PQ to prevent malaria

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Karim Traoré, Université des Sciences, des Techniques et des Technologies de Bamako, Mali

Target population(s): School-age children

Year funded: 2019

EDCTP funding: €0.5 M

in school-age children and reduce community transmission of malaria. This evidence will inform decision-making on use of seasonal malaria chemoprevention in older children and the most appropriate drug combination to use. As well as supporting Dr Traoré's development as a senior researcher, the project is also helping to build capacity through the training of master's and PhD students.

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Dr Karim Traoré
Mali

Controlled blood-stage malaria infection

Dr Ally Olotu is introducing controlled human infection with blood-stage malaria parasites into Africa.



The challenge

The malaria parasite has a complex life cycle. In humans, it first invades and multiplies in liver cells, before infecting red blood cells; gametocytes released from erythrocytes are taken up when mosquitoes bite, and develop into the forms that can establish new human infections.

Controlled human infection studies, in which malaria parasites are introduced into volunteers in highly controlled settings and then treated with drugs before serious symptoms develop, have generated a wealth of information on the mechanisms of infection. They are also increasingly key to new vaccine development, providing a highly efficient way to test and compare candidate vaccines for further evaluation. Controlled human infection models have been introduced in several African countries, but have to date focused on the first stage of malaria infection.

The project

Dr Ally Olotu has played a key role in the evaluation of the most advanced malaria vaccine, RTS,S/AS01, which is undergoing pilot implementation studies in three African countries. His work has also covered the relationship between vaccine efficacy and past exposure to malaria and immunological markers of vaccine-induced and natural post-infection immunity.

In his Senior Fellowship, Dr Olotu is introducing a new type of controlled human infection model into Tanzania, focusing on the bloodstream stage of infection. This model has been used in Australia and Europe but not so far in Africa.

Work on the bloodstream stage will provide important information on parasite multiplication and factors affecting transmission to mosquitoes. It is also essential for testing transmission-blocking vaccines, which target the bloodstream (gametocyte) form of Plasmodium and are designed to break the cycle of malaria transmission. Establishment of the model in Africa is essential to ensure that findings are directly relevant to affected populations.

Having established the model, Dr Olotu plans to investigate factors affecting the efficiency of

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Ally Olotu, Ifakara Health Institute, Tanzania

Target population(s): Male volunteers (18–35 years)

Year funded: 2020

EDCTP funding: €0.5 M

transmission to mosquitoes, including immune responses to different parasite antigens, parasite loads, and the sex ratio of male and female gametocytes.

Impact

Dr Olotu's project will extend the range of controlled human infection models being used in Africa. It will generate new insights into a key stage in the parasite life cycle that drives transmission. It will facilitate studies on candidate transmission-blocking vaccines, efficiently identifying those showing greatest promise so that expensive phase III trials are only carried out on those with the greatest likelihood of being effective.

References

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Dr Ally Olotu
Tanzania



Rapid diagnosis of visceral leishmaniasis

Dr Dawit Wolday is evaluating two new options for rapid and simplified diagnosis of visceral leishmaniasis, an important neglected infectious disease in East Africa.

The challenge

An estimated 350 million people are at risk of developing leishmaniasis, infection with the single-celled *Leishmania* parasite. The most severe form of the disease, visceral leishmaniasis or kala azar, is particularly common in East Africa.

Treatment and control would benefit greatly from reliable point-of-care diagnostics to detect new infections as well as 'test-of-cure' tools to assess the success of treatment. However, methods to detect parasites or antibodies against *Leishmania* are either not available in East Africa or perform poorly, especially in people living with HIV. Although molecular tests show excellent performance, they require specialist training and facilities and are expensive.



Dr Dawit Wolday
Ethiopia

The project

In his EDCTP Senior Fellowship, Dr Dawit Wolday is evaluating two possible alternative methods for diagnosing new *Leishmania* infections and for monitoring treatment responses.

The first is based on a method for amplification of parasite DNA that does not require repeated cycles of heating and cooling, central to conventional tools based on the polymerase chain reaction (PCR). Loop-mediated isothermal amplification (LAMP) methods show good specificity, generate easy-to-interpret results and require no cold chain. However, despite this promise, there are few data on their use in Africa.

Dr Wolday will also evaluate a novel PCR-based test, known as db-PCR-NALFIA, which can be used directly on blood samples without the need for extraction of DNA.

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Dawit Wolday, Mekelle University College of Health Sciences, Ethiopia

Year funded: 2018

EDCTP funding: €0.5 M

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/d8e85731-b21b-4936-b7b7-acb4c5caff18>

Impact

Dr Wolday's Senior Fellowship project will provide key data on two new point-of-care tools for diagnosing visceral leishmaniasis and for monitoring patient responses and test of cure. The two tools will be tested in people with and without HIV, and results compared with rigorous laboratory-based assessments.

The results will provide policymakers in Ethiopia and other East African countries with key evidence of the effectiveness of the new tests. The project will also build capacity in research on neglected infectious diseases at Mekelle University College of Health Sciences in Ethiopia, including the training of two master's and one PhD student.

Shortening treatment of Buruli ulcer

Professor Richard Phillips is exploring whether a dressing generating nitric oxide speeds up healing of Buruli ulcer.

The challenge

Buruli ulcer is a neglected infectious disease caused by *Mycobacterium ulcerans*. It is mainly found in rural regions of West Africa, and is characterised by large, unsightly ulcers leading to extensive scarring.

Buruli ulcer can be treated effectively with a combination of antibiotics, but treatment lasts eight weeks and response rates vary markedly between patients.

The project

Professor Richard Phillips has established an extensive programme of research on Buruli ulcer in Ghana, in partnership with collaborators in Europe. His research has provided significant input into WHO-recommended treatments for Buruli ulcer.

During his EDCTP Senior Fellowship, Professor Phillips is testing a possible way to shorten treatment times for Buruli ulcer. There is some evidence from laboratory and clinical studies that nitric oxide is toxic to *M. ulcerans*. To generate further evidence, Professor Phillips is running a clinical trial that will evaluate use of a dressing designed to release nitric oxide as an addition to standard treatment (oral rifampicin and clarithromycin).

Embedded within the study will be a programme of activities to develop expertise in specialised diagnostics and laboratory techniques, as well as generic research skills such as research methodologies, statistics, research governance and administration.

Impact

Professor Phillips's Senior Fellowship will generate important data on a potential way to shorten treatment of a neglected infectious disease that is extremely common in Ghana and neighbouring countries. By training three PhD and two master's students, it will also build local capacity to undertake clinical studies, including controlled trials, on Buruli ulcer or other locally important infectious diseases.

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Professor Richard Phillips, Kwame Nkrumah University of Science and Technology, Ghana

Year funded: 2018

EDCTP funding: €0.5 M

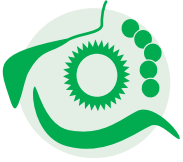
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Prof. Richard Phillips
Ghana



Parasitic infections and cardiometabolic disease

Professor Marielle Bouyou-Akotet is exploring whether common parasitic infections affect the risk of cardiometabolic disease.

The challenge

There are growing concerns about the rise of non-communicable disease in Africa. Although lifestyle factors, such as diet, tobacco use and lack of exercise are important contributory factors, infectious diseases may also increase the risk of non-communicable diseases.

Even so, there is very little evidence from Africa on the impact of infectious diseases on non-communicable disease.



Prof. Marielle Bouyou-Akotet
Gabon

The project

Professor Marielle Bouyou-Akotet has carried out extensive research on multiple aspects of malaria, and taken part in several influential international trials on antimalarial treatments. She also has research interests in other parasitic diseases affecting West Africa.

In her EDCTP Senior Fellowship, Professor Bouyou-Akotet is gathering more evidence on the contributions that intestinal parasitic diseases make to the risk of developing cardiometabolic disease. In the first phase of her project, she is enrolling adults aged 18–49 years at four sites – two urban (Libreville and Melen) and two rural (Koulamoutou and Bitam) locations – in Gabon. A questionnaire will be used to gather information on demographics and lifestyle risk factors, and biometric data on height, weight, blood pressure and other variables will be collected. Participants will be screened for multiple parasitic diseases, and laboratory tests will be used to identify metabolic and inflammatory abnormalities. A 10-year cardiovascular risk score will be calculated for each participant.

In phase 2 of the project, participants with and without parasite infections will be followed for 18 months and monitored for any cardiometabolic event or risk factor. Statistical analyses will then be used to determine whether the presence of a parasitic infection affects the risk of cardiometabolic disease.

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Professor Marielle Bouyou-Akotet, La Faculté de Médecine, Université des Sciences de la Santé, Gabon

Year funded: 2018

EDCTP funding: €0.5 M

Impact

Professor Bouyou-Akotet's Senior Fellowship project will provide insight into the prevalence of cardiometabolic disease risk factors in urban and rural populations in a Central African country. It will also reveal whether intestinal parasites, including important neglected tropical diseases, affect the risk of cardiometabolic disease in either traditional rural or more westernised urban settings. The study will add to the evidence base on the burden of parasitic diseases in sub-Saharan Africa, including their contributions to non-communicable diseases.

References

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Combating parasitic worm infections

Dr Alexander Debrah is evaluating a novel approach to mass drug administration that could accelerate elimination of important neglected infectious diseases.

The challenge

Parasitic worm infections such as onchocerciasis (the cause of river blindness) and lymphatic filariasis (responsible for elephantiasis) affect some 200 million people and have major health, social and economic impacts.

The availability of safe and effective treatments and use of mass drug administration programmes have led to great progress in disease control and the prospect of disease elimination. However, current drug treatments have drawbacks: they do not kill adult worms effectively, which can continue to produce microfilariae that can be transmitted to others, and they cannot be used in areas where people may also be infected with another parasitic worm, *Loa loa*, since death of *L. loa* parasites can trigger a potentially deadly inflammatory response in the brain.

The project

In his Senior Fellowship, Dr Alexander Debrah is testing a new mass drug administration that overcomes these challenges and could provide an alternative or complementary strategy for disease elimination.

His project takes advantage of the fact that the parasitic worms responsible for onchocerciasis and lymphatic filariasis are dependent on a commensal bacterium known as *Wolbachia*, but *L. loa* is not. Laboratory studies have shown that existing drugs can kill *Wolbachia*. These include doxycycline, although it is relatively slow-acting, and rifampicin, a mainstay of TB treatment.

In practice, however, rifampicin is less potent than laboratory studies suggest, because of the way that the drug is metabolised in the body. This has encouraged testing of high-dose rifampicin, which has been found to be safe in TB trials. Furthermore, pre-clinical studies have revealed a synergistic interaction between rifampicin and albendazole, one of the drugs currently used in mass drug administration programmes, so shorter treatment regimes could be possible.

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Assistant Professor Alexander Yaw Debrah, Kwame Nkrumah University of Science and Technology (KNUST), Ghana

Target population(s): Adults

Year funded: 2020

EDCTP funding: €0.5 M

The core of Dr Debrah's project will be two phase II trials comparing the efficacy of high-dose rifampicin and albendazole (for 7 days or 14 days) and 28 days of doxycycline or ivermectin (another commonly used drug in mass drug administration programmes). One trial will focus on onchocerciasis and the second on lymphatic filariasis.

Impact

Dr Debrah's research will provide important data on an innovative new approach for control of parasitic worm infections, based on currently available drug treatments. It would have the potential to provide an alternative strategy for mass drug administration, particularly important for the 20% of geographic areas where the presence of *Loa loa* restricts use of existing drugs and for locations where resistance to existing treatments is beginning to emerge.

References

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**Assistant Professor
Alexander Yaw Debrah**
South Africa



Enhancing rotavirus protection in children

Dr Roma Chilengi is exploring whether an additional dose of rotavirus vaccine provides infants with additional protection against this important gastrointestinal pathogen.

The challenge

Diarrhoeal disease kills more children than HIV/AIDS and measles combined. Globally, diarrhoea is the second biggest killer of children, and rotavirus is the leading cause of severe diarrhoea in children under 5 years of age.

Many countries have introduced rotavirus vaccination into their national immunisation programmes, leading to a significant drop in diarrhoeal disease and hospitalisation. However, the performance of rotavirus vaccines is generally lower in low- and middle-income countries (LMICs) than in high-income countries.



Dr Roma Chilengi
Zambia

The project

Dr Roma Chilengi returned to his home country of Zambia in 2011, having held positions in Europe and Kenya. He is head of the Centre for Infectious Disease Research in Zambia, and has worked with the Ministry of Health and NGOs on projects that have significantly cut child mortality locally, including rollout of rotavirus vaccination.

In his EDCTP Senior Fellowship, Dr Chilengi is assessing whether adding a third dose of rotavirus vaccine at nine months boosts rotavirus-specific immune responses at 1 year, providing longer-lasting protection. More than 200 mother–infant pairs are being recruited just before first vaccination and half will receive an additional dose at nine months. As well as antibody responses at 1 year, the study will monitor safety, analyse infants' immune responses and assess the impact of diarrhoeal disease on growth rates.

The project will also contribute to research capacity building in Zambia. One PhD and one master's student will receive training through the project.

Impact

Dr Chilengi's Senior Fellowship project will determine whether a third dose of rotavirus vaccine compensates for the reduced effectiveness of such vaccines in LMICs –

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Roma Chilengi, Centre for Infectious Disease Research, Zambia

Year funded: 2017

EDCTP funding: €0.4 M

Fellow profile: <https://edctpalumnetwork.org/fe/profiles/view/7ab542b0-1115-41c1-b6d3-1233280a1d66>

information that will be highly relevant not just to Zambia but also to other LMICs. Findings may also identify elements of the immune response indicative of protection. The project will also add to clinical research capacity at the University of Zambia.

References

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- Chilengi R et al. Association of maternal immunity with rotavirus vaccine immunogenicity in Zambian infants. *PLoS One.* 2016;11(3):e0150100.
- Mwape I et al. Immunogenicity of rotavirus vaccine (Rotarix™) in infants with environmental enteric dysfunction. *PLoS One.* 2017;12(12):e0187761.

Strengthening vaccine research in Gabon

Dr Selidji Agnandji is carrying out a range of studies that will strengthen both laboratory and social science capacity in Gabon.



The challenge

Vaccines hold great promise for controlling and eliminating infectious diseases in sub-Saharan Africa. However, vaccines often perform less well in Africa than in high-income countries, emphasising the importance of vaccine studies in African populations.

Realising the full potential of vaccines will therefore depend on the strengthening of vaccine research capacity in Africa. In addition, it is important to understand the reasons underlying the lower efficacy on vaccines in Africa. As more trials are undertaken in sub-Saharan Africa, there is also an increasing need to develop social science expertise to ensure effective community engagement.

The project

Dr Selidji Agnandji has been involved in key clinical trials of vaccines in sub-Saharan Africa. These include influential trials of the most advanced malaria vaccine (RTS,S/AS01) and Ebola vaccine (rVSV-ZEBOV).

In his EDCTP Senior Fellowship, Dr Agnandji aims to strengthen vaccine research in the Centre of Medical Research Lamberéné (CERMEL) in Gabon. In the area of biomedical research, he will carry out a systematic review of studies of immune responses to vaccination in sub-Saharan Africa, India, Europe and North America, to determine whether lower performance is specific to certain vaccines or a common phenomenon. In laboratory studies, he will explore whether immune responses before, during and after vaccination with an experimental malaria and Ebola vaccine influence the kinetics of vaccine-induced responses. He will assess whether Ebola vaccination affects responses to currently used vaccines.

In the social science element of his fellowship, Dr Agnandji will examine how well the biomedical sciences are integrated in sub-Saharan African societies. He will also develop a novel framework to better capture the social and economic impacts of biomedical research in sub-Saharan Africa.

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Selidji Agnandji, Centre of Medical Research Lamberéné, Gabon

Year funded: 2018

EDCTP funding: €0.5 M

Impact

Dr Agnandji's Senior Fellowship project will provide additional information on immune responses to vaccination in sub-Saharan Africa populations, data that will inform the design of vaccines that are more effective in this setting. He will also strengthen social science research in the region, of growing importance as more vaccines become available for testing.

References

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Dr Selidji Agnandji
Gabon



A clearer picture of adverse drug reactions

Professor Jonathan (Jonny) Peter is developing the capacity to identify – and ultimately prevent – rare immune-mediated adverse reactions to drugs.

The challenge

Drugs shown to be safe and effective in clinical trials may nevertheless cause rare adverse reactions of varying degrees of severity. Adverse drug reactions may mean drug treatment has to be halted, and in the most severe cases can be life-threatening.

As genetic factors influence the risk of adverse drug reactions, their prevalence varies globally, emphasising the importance of regional studies. In addition, relatively little is known about their underlying mechanisms.



Dr Jonathan Peter
South Africa

The project

Professor Jonny Peter is the first registered adult allergist in South Africa. He has been focusing on severe cutaneous adverse reactions (SCAR) – potentially deadly drug reactions affecting the skin. These are known to be mediated by the immune system and are relatively common in sub-Saharan Africa, in part because of the nature of the drugs used in the region and the impact of regionally prevalent infectious diseases – adverse reactions are 100-fold more common in people with HIV infections.

In his EDCTP Senior Fellowship, Professor Peter is building on an existing study monitoring for SCAR in South Africa, which is beginning to provide important data on reactions to antiretroviral and anti-TB drugs. He is now extending this work by developing a network, AfriSCAR, across five sub-Saharan African countries. This will enable data on the epidemiology of SCAR to be captured from four additional countries, as well as samples for laboratory analysis.

The fellowship will also enable Professor Peter to develop both his technical skills, particular in advanced immunology and ‘omics’ technologies, and his project management and leadership abilities. These skills will be passed on to a PhD and two master’s students involved in the project.

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Dr Jonathan (Jonny) Peter, University of Cape Town Lung Institute, South Africa

Year funded: 2018

EDCTP funding: €0.5 M

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/7ab542b0-1115-41c1-b6d3-1233280a1d66>

Impact

Dr Peter’s Senior Fellowship project will reveal more about the prevalence of severe drug reactions in sub-Saharan Africa, and which drugs are most likely to trigger them – not straightforward when many patients are taking multiple medications. It will also shed light on possible genetic and immunological risk factors, which will improve understanding of underlying mechanisms and suggest new approaches to prevent or treat severe adverse reactions. In addition, it will create a regional network able to carry out clinical trials of new treatments or prevention of these devastating conditions.

References

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Immunological selection of recombinants following HIV-1 superinfection

Dr Deogratus Ssemwanga investigates the role of immune responses among individuals with established HIV infection who acquire new HIV strains.

The challenge

The challenge is to understand the role of immune responses among individuals with established HIV infection who subsequently acquire new HIV strains, a phenomenon known as HIV superinfection (SI), and delineate the evolutionary pathways of mosaic recombinant viruses between initial and SI strains.

The hypothesis is that HIV-1 recombination has a high rate immediately after superinfection; is not random but due to immune selection; facilitates immune escape; and accelerates disease progression.

The project

The objective of the study is to determine the recombination rate following superinfection, its causes, and its consequences for the virus (i.e. persistence by immune escape) and for the host (i.e. accelerated disease progression).

Initially, 15 individuals will be included in the study. These participants are previously confirmed SI (n=8) and multiple infected (n=7) cases among female sex workers. Other SI cases identified during an on-going screening from three cohorts will also be included in the study. These cohorts are the female sex worker cohort in Kampala, the fisherfolk communities along the shores of Lake Victoria, and the General Population Cohort in rural South-western Uganda.

Participants with superinfection are defined as having phylogenetically distinct HIV-1 strains using next-generation sequencing (NGS) of partial p24 and gp41 genomic regions. The SI cases will be confirmed by full envelope Single-Genome Sequencing. In SI cases, near full-length genome NGS will be performed on longitudinal plasma samples taken after SI and analysed for recombination using the Iterative Virus Assembler pipeline, REGA subtyping tool, jumping profile Hidden Markov Model, and Simplot software.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Deogratus Ssemwanga, Uganda National Health Research Organisation, Uganda

Year funded: 2017

EDCTP funding: €148,848

Fellow profile: <https://edctpalumninetwork.org/fellow/profiles/view/17907f55-8de3-406e-9f0f-3fa9ea0fbde0>

In SI cases, the team will generate pseudotyped virus stocks from autologous viral envelope genes representing the initial infecting virus, the SI virus and their recombinant strains. These pseudoviruses will be tested against autologous longitudinal serum (pre- and post-SI). The NAb assays will be done using autologous pseudoviruses and TZM/bl cells expressing the reporter gene luciferase. CTL epitopes will be evaluated by comparing full HIV proteomes from SI cases and controls to analyse and identify predicted Human Leucocyte Antigen (HLA)-restricted CTL epitopes with a special interest in epitopes mapped to recombination sites. High-resolution HLA typing on SI cases and controls will be done to evaluate if there is genetic predisposition to HIV-1 superinfection and emergence of recombinants.

Impact

Dr Ssemwanga had the opportunity to train and develop biomedical clinical research skills. Moreover, a panel of envelope pseudoviruses representing pre-SI, SI and recombinant strains will be made freely available for future evaluation of vaccine candidates.



Dr Deogratus Ssemwanga
Uganda

A reminder intervention to promote adherence to ART

Dr Ilse Marion Sumari-de Boer investigates the effect of a short message service (SMS) and real-time medication monitoring (RTMM) on antiretroviral treatment.

The challenge

HIV-positive individuals have to take lifelong treatment which is taxing. The challenge is to alleviate this burden and find ways to support adherence.

With this study we aim to introduce an innovative, accessible and affordable means of improving adherence to antiretroviral treatment, that exploits the large use of mobile phones in Tanzania and sub-Saharan Africa and involves patients in their own care.

The project

The objective of the study is to investigate the effect of short message service (SMS) and real-time medication monitoring (RTMM), which both generate reminder cues and adherence performance reports for tailored feedback on adherence to treatment among HIV-positive individuals in the Kilimanjaro region, Tanzania.

We will conduct a randomised controlled three-armed clinical trial in which one arm will receive reminder SMS messages and another arm will use an RTMM device that generates SMS messages in case of no medication intake. Both systems will be used to generate reminder cues and adherence performance reports. These reports will be the basis for tailored feedback on adherence to treatment. The third arm is the control arm that will receive standard care only. We will compare adherence to treatment and virological outcome in all three arms to investigate the effect of SMS and RTMM messaging.

Impact

The interventions may improve adherence to HIV therapy, thus contributing to a lower social and economic burden of HIV/AIDS in Tanzania. Secondly, the study will contribute to research capacity development at the Kilimanjaro Clinical

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Ilse Marion Sumari-de Boer, The Good Samaritan Foundation (Kilimanjaro Christian Medical Centre), Tanzania

Year funded: 2017

EDCTP funding: €148,494

Fellow profile: <https://edctp.alumninetwork.org/fellow/profiles/view/0a1a27fd-a6dd-40be-98bf-25a2e4197218>

Research Institute (KCRI), an institute with wide experience in the conduct of clinical trials. A mid-career postdoctoral researcher will acquire more experience in conducting and managing research while continuing her career in sub-Saharan Africa with greater seniority. In addition, a PhD student will be trained, which will lead to new opportunities for postdoc positions. The institutional capacity at KCRI will also be expanded (human resources and equipment).



Dr Ilse Marion Sumari-de Boer
Tanzania



Tracing HIV-positive pregnant women and their babies

Dr Agnes Kiragga helps mothers and infants to return to HIV care and thus seeks to diminish high drop-out rates which hinder elimination of mother-to-child HIV transmission.

The challenge

Sub-Saharan Africa carries the heaviest burden of HIV and more than 70% of persons presenting to care are women. Women who initiate ART and disengage from care are at risk of transmitting the HIV virus to their infant pre and post-delivery. The alarmingly high dropout rates observed among HIV-positive pregnant women may alter the general success of option B+* and hinder the successful elimination of mother-to-child transmission. The challenge is to trace HIV-positive pregnant women and bring them back to treatment.



Dr Agnes Kiragga
Uganda

The project

The study aims to trace HIV-positive pregnant women who were previously started on antiretroviral therapy through the Option B+ strategy and later dropped out of care. The aim is to trace these disengaged women and link them back to care while ascertaining the HIV status of babies born to these women as compared to those born to women who were retained in care. Furthermore, the study aims to use the estimates of vertical transmission in the retained and non-retained women to produce estimates of vertical transmission with option B+, while adjusting for loss to follow-up among these women.

Impact

The study will contribute to maternal and child health by reducing mother-to-child transmission by bringing mothers back to care. The data generated may be critical to the roll-out of option B+ in sub-Saharan Africa. Dropout rates among HIV-positive pregnant women may alter the success of option B+ and hinder successful elimination of mother-to-child transmission.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Agnes Kiragga, Infectious Diseases Institute Limited (IDI), Uganda

Year funded: 2017

EDCTP funding: €149,825

Fellow profile: <https://edctpalumminetwork.org/fe/profiles/view/e7f0f303-99be-43d6-9c14-5b7b9b6e4ac2>

* Option B+: prevention of vertical transmission for pregnant women living with HIV in which treatment for life is immediately offered regardless of CD4 count)

The epidemiology of human papillomavirus in HIV-positive men



Dr Admire Chikandiwa intends to describe the epidemiology of anogenital and oropharyngeal cancer patterns and trends in South African men (1994-2010)

The challenge

Globally, the incidence of human papillomavirus-associated anal and oropharyngeal cancers (OPCs) in men is increasing. Anogenital warts (AGWs) cause significant morbidity in men and result in high medical costs worldwide. Fewer data exist for men in sub-Saharan Africa, including South Africa, due to paucity of research and poor quality of cancer registries. The challenge is to quantify the burden of disease in South Africa and sub-Saharan Africa.

The project

There is enough data suggesting that HPV infection is a primary underlying cause of AGWs and these cancers. Available data from other settings suggests that HIV alters the susceptibility and the natural history of HPV-associated diseases, leading to higher rates of pre-cancerous lesions. Studies suggest that antiretroviral therapy (ART) increases the regression of Cervical Intraepithelial Neoplasia (CIN) lesions, indicating immune reconstitution. However, the incidences for Anal Intraepithelial Neoplasia (AIN) and oropharyngeal lesions seem to increase steadily despite ART initiation. It is therefore important to additionally understand the natural history of anogenital and oral HPV infection in HIV-positive men and the factors associated with HPV-disease progression.

Dr Chikandiwa intends to describe the epidemiology of anogenital and oropharyngeal cancer patterns and trends in men, including incidence and mortality rates and differences by ethnicity in South Africa between 1994 and 2010. Furthermore, to explore the influence of HIV status on the epidemiology of these cancers.

His second objective is to determine the prevalence of anogenital and oropharyngeal HPV infection, genotype distribution and associations with anogenital disease, according to HIV-related factors and exposure to ART. Finally,

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Admire Chikandiwa, Wits Health Consortium (Pty) Ltd, South Africa

Year funded: 2017

EDCTP funding: €150,000

Fellow profile: <https://edctpalumnetwork.org/fe/profiles/view/87d5f76c-de97-49cd-896d-690695422411>

he will determine the incidence, persistence, and clearance of type-specific anogenital and oropharyngeal HPV infection and anal cytological lesions over 18 months and the effects of HIV-related factors and concomitant exposure to ART on these outcomes.

Impact

Quantification of the burden of these diseases in South Africa and sub-Saharan Africa is an important first step as fewer data exist for men in South Africa due to paucity of research, poor quality of cancer registries, and high costs of screening. Further steps needed may comprise investigation of biomarkers such as HPV viral load to identify men at high risk of progression to cancer. HPV DNA testing could be used to screen for OPCs, however, the best sampling method for oropharyngeal HPV DNA infection is yet to be agreed on.



Dr Admire Chikandiwa
South Africa



Drug resistance and HIV-1 variability in adolescents

Dr Joseph Fokam will monitor adolescents living with HIV for a year as they go through treatment transitions to ascertain how they respond.

The challenge

Nine out of every ten children living with HIV globally are in sub-Saharan Africa. Monitoring remains suboptimal even as these children grow older. Over 2.1 million HIV-infected children are growing towards adolescence with the potential to reach adulthood. However, despite HIV-related mortality decreases overall, it is increasing among adolescents living with HIV (ALHIV). The challenge is to develop strategies for the transition of adolescents from paediatrics to adult-healthcare. This is critical to ensure successful treatment response, longer life expectancy and their future contribution to their society.



Dr Joseph Fokam
Cameroon

The project

The study is an observational, prospective and open cohort-study conducted among 250 ALHIV (10-19 years old) receiving ART, in the central region of Cameroon. Dr Fokam monitors the response to first- and second-line regimens and profiles drug resistance and HIV-1 variability during a 12 months follow-up. Specifically, the study evaluates the rate of immune-virologic failure at enrolment, month 6 and month 12; acquired mutations associated with drug resistance; HIV-1 subtype distribution; genetic variability in circulating (plasma) versus archived (cellular) viral strains; and early warning indicators of HIV drug resistance. Survival analysis will be performed during the 12 months follow-up. Primary outcomes are rates of virological failure, acquired HIVDR, and mortality.

Impact

Dr Fokam expects that the findings will provide evidence-based recommendations to ensure a successful transition from paediatrics to adult ART regimens. Secondly, the results will highlight further needs of active ART combinations to achieve reduced morbidity and mortality in

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Joseph Fokam, International Reference Centre Chantal Biya (CIRCB), Cameroon

Year funded: 2017

EDCTP funding: €149,656

Fellow profile: <https://edctpalumnnetwork.org/fellow/profiles/view/bf03a808-03d0-4e9d-9df5-6fb42b0eafe3>

populations of adolescents living with HIV in sub-Saharan Africa. Without a successful transition of adolescents, the success rate of paediatric ART might be quickly jeopardised, with possible HIV-1 drug-resistance emergence, especially after years of paediatric ART exposure.

Proximal tubular renal dysfunction among HIV patients on tenofovir versus tenofovir-sparing regimens



Dr Mercy Karoney conducts a study to acquire better data on proximal tubular renal dysfunction in African HIV-patients on ART.

The challenge

Tenofovir disoproxil fumarate (TDF) is the most widely used antiretroviral drug (ART) due to its antiviral potency, safety profile and tolerability. However, TDF causes proximal tubular renal dysfunction (PTRD) leading to Fanconi syndrome, acute kidney injury and chronic kidney damage.

The challenge is to get better data on the association of TDF and PTRD in African HIV patients.

The project

Dr Karoney is conducting the TREND study, a cross-sectional analytic study of HIV-infected patients attending the Academic Model Providing Access to Healthcare programme in Western Kenya. Laboratory tests will be carried out to determine the outcomes of interest.

The primary outcome for this study is PTRD while the secondary outcome is estimated glomerular filtration rate (GFR). TDF-induced renal toxicity can be missed because it is initially subclinical and manifests as PTRD. Studies investigating TDF toxicity using estimated GFR report only 2-4% prevalence while studies investigating PTRD report up to 22% prevalence. PTRD is determined through urinalysis for glucose and tubular proteinuria, serum phosphate, and bone fracture rate.

The TREND study will compare PTRD among HIV-infected patients on a TDF regimen and patients on TDF-sparing regimen and compare the estimated GFR among HIV-infected patients on TDF regimen and patients on TDF sparing regimen. This study will also assess the determinants of the association between PTRD and TDF use in HIV-infected patients and determine the sensitivity and specificity of normoglycemic glucosuria in assessing proximal

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Mercy Karoney, Moy University, Kenya

Year funded: 2017

EDCTP funding: €99,877

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/f9359d75-bced-415e-a3c5-b53eaaaa5632>

tubular renal dysfunction in HIV patients on ART.

Impact

There is limited data on TDF-induced PTRD among African patients and lack of proper guidelines on lab monitoring. This study will add new knowledge on subclinical tubular injury and improve monitoring guidelines as well as validate the use of simpler markers for detection of PTRD.



Dr Mercy Karoney
Kenya



Motivating adolescents to adhere to ART

Dr Obinna Ekwunife aims to develop an intervention to support adolescents in south-east Nigeria to remain in care and better adhere to antiretroviral therapy.

The challenge

Adolescent HIV patients face enormous challenges in accessing HIV care services. Given their risk-taking behaviour, this group also has worse treatment outcomes compared to other age groups. Poor treatment outcomes will impact negatively on HIV/AIDS management and control. The challenge is to get better evidence on the effectiveness of service delivery interventions to support adolescents' linkage from HIV diagnosis to antiretroviral therapy (ART) initiation, retention on ART and adherence to ART.



Dr Obinna Ekwunife
Nigeria

The project

Dr Ekwunife's Adolescent Retention and Adherence Trial (ARA Trial) aims to improve the retention in care and adherence to antiretroviral therapy of adolescents living with HIV. The trial evaluates an incentive scheme to improve their retention in care and adherence to antiretroviral therapy. The scheme comprises a cash incentive conditioned on meeting the viral load target in combination with motivational interviewing. Motivational interviewing will help to sustain the demand for care and adherence to therapy aiming for attitude change.

The study is a cluster-randomised, controlled trial conducted in selected HIV treatment hospitals in Anambra State, Nigeria. Based on sample size calculation, twelve HIV treatment hospitals from Anambra have been selected, which were randomised to either intervention (six) or control arm (six). The control clinics provide routine HIV care without the intervention. The trial successfully recruited 251 HIV adolescents (126 in the intervention and 125 in the control arm). The trial was in its seventh month as at June 2019. We published the research protocol in *Trials* and presented two abstracts. Preliminary work was presented at the 13th INTEREST conference in Accra, Ghana; the trial protocol was presented at the 9th EDCTP Forum in Lisbon, Portugal.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Obinna Ekwunife, Nnamdi Azikwe University (NAU), Nigeria

Year funded: 2018

EDCTP funding: €148,782

Fellow profile: <https://edctpalumnnetwork.org/fe/profiles/view/aca4bf97-52aa-4c8d-8bae-1c9db38c8e8d>

Impact

As more than 80% of HIV-infected adolescents live in sub-Saharan Africa, improve retention in care and adherence to antiretroviral therapy of HIV-positive adolescents will have a huge potential impact.

Regarding the capacity development impact, Dr Ekwunife as the principal investigator already improved his qualifications substantially by successfully taking nine clinical trial short courses offered by The Global Health Network. He also has a mentor. Moreover, he also guides and trains 36 health personnel involved in the trial (3 per HIV treatment hospital). Additionally, he trains two collaborators, i.e. a research assistant (PhD candidate), a laboratory technologist (in charge of the central virological laboratory).

Pharmacogenetics of ART

Dr Yaya Kassogue investigates enzymes that influence ARV drug metabolism and thus treatment response.

The challenge

The introduction of highly active antiretroviral therapy reduced the morbidity and mortality related to HIV infection. However, the occurrence in certain patients of invalidating side effects or resistance related to antiretroviral treatment (ART) may be a source of nonadherence and results in an inadequate response.

The project

The differences in treatment response observed in patients could be due to various factors such as age, gender, and ethnicity. However, genetic factors also play a significant role in the variability of the response to treatment. Thus, interindividual differences in DNA sequence as a result of single nucleotide polymorphisms (SNP) may explain the variability of therapeutic responses.

Dr Kassogue will focus on the pharmacogenetics aspects of ART treatment and will investigate the impact of selected SNPs from three major classes of drug metabolising enzymes. These most relevant enzymatic classes influencing drug metabolism are the cytochrome P450, the multidrug resistance gene-1, and the glutathione S-transferase.

Impact

In addition to supporting the development of the research skills of the fellow, the project may further insight into genetic factors influencing ART treatment response. This may contribute to avoid invalidating side effects in certain patients.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Yaya Kassogue, Université des Sciences, des Techniques et des Technologies de Bamako (USTTB), Mali

Year funded: 2018

EDCTP funding: €147,585

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/68709908-ccd2-49a8-a254-0342138144bb>



Dr Yaya Kassogue
Mali



Assessing how to enroll and retain adolescents at risk of HIV infection

Dr Yunia Mayanja aims to assess ways to involve at-risk adolescents (14-19 years old) in HIV prevention and prevention research.

The challenge

Despite the fact that adolescents are involved in risky behaviours such as early sexual debut, multiple sexual relationships, alcohol and substance use, there are not many adolescent-friendly services, whether for research, prevention or treatment. However, there are substantial benefits to the involvement of adolescents in health research for both HIV-positive and HIV-negative adolescents and their peers.

The challenge is to devise ways to involve adolescents in research, prevention and treatment.

The project

Dr Mayanja and her team are conducting a feasibility cohort study to assess whether at-risk adolescents in the age 14-19 years can be enrolled from hotspots and followed up regularly in a research clinic.

A three-year cohort study is conducted which uses recruitment and retention strategies to enrol and follow up a closed cohort of 500 adolescents (20% male) aged 14-19, resident in Kampala and involved in sex work. At baseline data on social demographics, sexual behaviour and knowledge and uptake of HIV prevention methods contraceptive use, substance use, gender-based violence are collected. Qualitative data are collected on individual and contextual barriers to participation in HIV prevention research.

Secondly, participants will receive biological testing for hepatitis B, gonorrhoea and chlamydia at enrolment, HIV testing every 3 months and syphilis testing every 6 months. HIV counselling and testing, risk reduction counselling for HIV, STIs, and substance abuse, contraception, STI screening are provided as well as treatment at baseline and periodic presumptive treatment at follow-up, with free condoms and health education every three months.

The primary objectives are to: assess the feasibility of recruiting at-risk adolescent volunteers into a research clinic; determine baseline HIV prevalence

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Yunia Mayanja, Uganda National Health Research Organisation, Uganda

Year funded: 2018

EDCTP funding: €149,412

Fellow profile: <https://edctp.alumninetwork.org/fe/profiles/view/59de3044-d884-4541-9e06-fe9e59a7d3c5>

and estimate HIV incidence; and, estimate the annual retention rate. Secondary objectives are to: estimate the baseline prevalence of sexually transmitted infections; determine the acceptability of periodic presumptive treatment for sexually transmitted infections; determine reproductive health outcomes of volunteers; determine the prevalence of substance use and gender-based violence; and, explore facilitators and barriers to participation in HIV prevention research using qualitative methods.

Impact

Dr Mayanja expects that the study will provide preliminary data on the burden of health problems of adolescents residing in hotspots and/or involved in sex work. It will also inform the improvement of recruitment and retention strategies for a larger study to deliver a combination of HIV prevention services (including an education intervention on biomedical HIV prevention) and assess the preparedness of volunteers for HIV prevention trials.



Dr Yunia Mayanja
Uganda

Mucosal type I IFN desensitisation and the risk of HIV acquisition

Dr Aida Sivro aims to disentangle the mechanisms that govern the positive and negative effects of host interferon on HIV susceptibility.

The challenge

Host interferon (IFN) antiviral response is an important determinant of HIV transmission during sexual exposure. Recent data from animal models suggest that mucosal application of type I IFNs can block viral infection and might represent an HIV prevention strategy.

However, in a prospective cohort analysis of the CAPRISA 004 trial increased mucosal type I IFN expression was associated with an increased risk to acquire HIV. One of the explanations for this discrepancy could be the timing and duration of IFN exposure. In the animal model, exogenous IFN exposure was brief, whereas, in humans, endogenous IFN expression can be maintained at high levels for a prolonged period of time. The challenge is to disentangle the mechanisms that govern the positive and negative effects of IFN on HIV susceptibility.

The project

Dr Sivro hypothesises that chronic type I IFN expression in the female reproductive tract causes dysregulation of IFN responsiveness, therefore increasing the susceptibility of HIV target cells in the mucosa. She and her team will measure patterns of type I IFN expression longitudinally at the female reproductive tract. Type I IFN levels will be plotted over time and cumulative IFN score will be calculated. Participants with persistently high and low type I IFN levels will be identified. Type I IFN levels will then be correlated to demographic, clinical, behavioural and reproductive variables. Finally, they will correlate the high/low IFN status with IFN responsiveness and altered HIV susceptibility of mucosal target cells.

Impact

This study aims to contribute to an understanding of how basic immunological mechanisms are exploited by HIV. Resolving the controversy around IFNs and HIV transmission is critical if IFN therapies are going to be considered for clinical translation. The Centre for the AIDS Programme of Research in South Africa

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Aida Sivro, Centre for the AIDS Programme of Research in South Africa (CAPRISA), South Africa

Year funded: 2018

EDCTP funding: €150,000

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/9cc087a3-5215-487c-81da-9a95b2c7850b>

(CAPRISA) is one of South Africa's best-known research organisations and will provide the fellow with the necessary support and international research environment to further her development as an independent researcher. Furthermore, through this fellowship Dr Sivro will supervise students from the University of KwaZulu- Natal, transferring her skills and knowledge to a new generation of researchers in South Africa.



Dr Aida Sivro
South Africa



Immunological markers of HIV-2 infection

Dr Boris Kevin Tchounga aims to establish epidemiological data for HIV-2, improve the diagnosis of HIV-2 patients and better understand HIV-2 disease progression, with a view to improving the holistic care of people living with HIV-2.

The challenge

Human immunodeficiency virus type 2 (HIV-2) is a retrovirus responsible for an AIDS epidemic localised in West Africa, where the circulation of both HIV-1 and HIV-2 leads to co-infections with both viruses. The HIV-2 infection is characterised by a longer asymptomatic phase and a slower disease progression than HIV-1 infection, as well as the intrinsic resistance of HIV-2 to non-nucleoside reverse transcriptase inhibitors. It is mandatory to differentiate HIV-1 from HIV-2 infection before initiating antiretroviral therapy (ART), but the diagnosis is still challenging, especially for the HIV-1 and HIV-2 dually infected individuals

The challenge is to explore new diagnostic algorithms based on routinely used HIV rapid tests, to ensure the peripheral diagnosis of patients with dual infection in West Africa. The related challenge is to describe the epidemiology of HIV-2 and dual infection in West Africa.

The project

Guidelines for antiretroviral therapy neglect HIV-2 infected patients due to conflicting reports on the epidemic trend of HIV-2 infection and a lack of recent data. Furthermore, the important mortality reported among HIV-2 infected individuals may be the consequence of immune activation and persistence of soluble biomarkers as demonstrated in HIV-1 infection.

Dr Tchounga's three-year research project relies on the West African HIV-2 cohort, and the related biobank to evaluate a new diagnostic algorithm for HIV-1 and HIV-2 dual infection. The study will also produce more accurate and updated epidemiological data on HIV-2 infection. Finally, it is exploring disease progression and the prognostic role of immunologic and inflammatory markers in HIV-2 infection.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Boris Kevin Tchounga, Association PAC-CI (PAC-CI), Côte d'Ivoire

Year funded: 2018

EDCTP funding: €149,958

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/0a62b539-b927-4765-a7c9-b23ce503b0ad>

Impact

The project aims to provide the much needed accurate epidemiologic data, improved diagnosis of HIV-2 patients and a better understanding of the dynamics and correlates of disease progression. These results may help inform specific guidelines for HIV-2 infection. Capacity development is integrated into the project through training of graduate students in epidemiology, immunology and biostatistics.



Dr Boris Kevin Tchounga
Côte d'Ivoire

Subclinical atherosclerosis and treated HIV infection

Dr Tecla Temu aims to assess the relative contributions to subclinical atherosclerosis of persistent inflammation and immune activation in HIV-infected subjects.

The challenge

Despite the high prevalence of HIV in sub-Saharan Africa, cardiovascular diseases (CVD) are the leading causes of morbidity and mortality in this region. Predictors of CVD are well established in resource-rich countries, but whether these same risk factors are strongly associated with CVD in sub-Saharan Africa is not known. Growing evidence from Europe suggests that HIV itself may be a risk factor for CVD. The challenge is to establish whether HIV infection contributes to the risk of early CVD in sub-Saharan Africa. As it remains unclear whether inflammation and immune activation truly predict the early risk of CVD in African HIV-infected subjects.

The project

Dr Temu and her team hypothesise that systemic immune activation and inflammation associated with HIV infection contribute to the early risk of CVD in HIV-positive individuals and that Cytomegalovirus (CMV) infection and microbial translocation may contribute to this process.

Therefore she aims to determine if HIV-infected individuals have increased inflammation and immune activation compared to the uninfected controls, and is testing whether the markers of immune activation and inflammation are associated with an increased risk of subclinical atherosclerosis.

The study is a cross-sectional, case-control study of 200 HIV-positive and 100 HIV-negative subjects nested in the ongoing Kenya study of cardiovascular diseases during HIV infection with a cohort of 300 HIV-infected on long-term antiretroviral treatment and 300 HIV-uninfected subjects. Dr Temu's study analyses banked blood from the study for markers of inflammation, CMV infection, microbial translocation and cellular immune activation, selected for their association with CVDs in HIV-uninfected populations.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Tecla Temu, University of Nairobi, Kenya

Year funded: 2018

EDCTP funding: €149,000

Fellow profile: <https://edctpalumninetwork.org/fellow/profiles/view/f31bf03f-ef7e-4775-906c-0a5de656cbb8>

Associations with subclinical atherosclerosis in HIV-positive patients (adjusting for age, sex, HIV-related and traditional risk factors) are also investigated. A set of candidate biomarkers may be derived for prospective validation.

Impact

This innovative and important clinical study on a well-characterised cohort will illuminate the mechanisms leading to increased risk of CVD in HIV-infected individuals and provide data that will be critical to developing targeted, feasible intervention trials to combat CVD in sub-Saharan Africa over the next decade.



Dr Tecla Temu
Kenya



Understanding adherence among individuals initiating ART

Dr Jane Frances Namukasa Wanyama aims to assess treatment outcomes among individuals initiating antiretroviral therapy (ART) under test-and-start guidelines.

The challenge

Recent WHO guidelines recommend antiretroviral therapy (ART) initiation for everyone diagnosed with HIV regardless of CD4+ cell count and pre-exposure prophylaxis for those at substantial risk of HIV infection. However, there are fears that initiating healthy people on treatment may instead result in poor treatment outcomes due to non-adherence. The challenge is to understand what may contribute to or diminish their adherence.



**Dr Jane Frances
Namukasa Wanyama**
Uganda

The project

Dr Wanyama seeks to assess treatment outcomes, barriers and facilitators of adherence and linkage to care among individuals initiating ART under test-and-start guidelines in an urban HIV clinic in Uganda. She and her team will conduct a mixed-methods study. Key informant interviews and sessions will be conducted among healthcare providers to assess their experiences with patients initiating ART under test-and-start guidelines. In order to assess barriers and facilitators for adherence to ART, a purposively selected sample of 24 individuals will participate in-depth interviews. Participants will be classified as adherers if they reported adherence =95% with corresponding viral suppression. Non-adherers will be categorised as irregular (inconsistent or reporting adherence < 95%) or as lost to follow-up.

The quantitative study will involve a retrospective analysis of medical records of all HIV-positive individuals (>18 years) initiated on ART under a test-and-start approach at the Kawaala Health Centre III between January 2017 and January 2018 who were followed up for two years. Participants' longitudinal data on socio-demographic characteristics, adherence, CD4 counts, viral loads (VLs), opportunistic infections and patient retention at 6, 12 and 24 months on ART will be abstracted. The study will determine the proportion of participants with

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Jane Frances Namukasa Wanyama, Infectious Diseases Institute Limited (IDI), Uganda

Year funded: 2018

EDCTP funding: €149,891

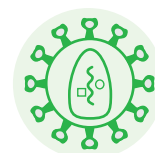
Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/ad6fc505-60da-4c3e-9047-bc078c573946>

viral suppression (VL =1000 copies/mL), the mean adherence using self-reports, the incidence of opportunistic infections, mortality rates, and retention in care rates at 6, 12 and 24 months.

Impact

Uganda has had three policy changes in HIV treatment guidelines. The test-and-start policy guidelines require ART initiation for everyone testing HIV-positive or at higher risk of HIV acquisition. This appears to be too ambitious. In Uganda, the majority of the population does not know their HIV status, while resources to meet the ART demand are insufficient. Findings from this study may therefore directly inform the policy debate on the pace of the fight against HIV/AIDS in Uganda. Additionally, findings from this study will inform interventions to address challenges in treatment adherence and linkage to care, especially among healthy individuals living with HIV.

Inducible, replication-competent latent HIV-1 as an impediment to HIV/AIDS cure



Dr Edward Maina aims to detect how much of the inducible HIV-1 virus is left after ART through a longitudinal, descriptive study, looking for ways to describe and reduce this latent reservoir of HIV-infection.

The challenge

In 2014, the Joint United Nations Program on HIV/AIDS (UNAIDS) issued treatment goals for HIV, the 90-90-90 target. The 90-90-90 target specifies that by 2020, 90% of individuals living with HIV will know their HIV status, 90% of people with diagnosed HIV infection will receive antiretroviral treatment (ART), and 90% of those taking ART will be virally suppressed. However, achieving viral suppression will not lead to an HIV-free society by 2030. Although tracking progress towards the 90-90-90 target is important, the challenge of achieving an HIV-free society depends also on detecting the inducible virus and expunge it.

The project

Although ART can suppress HIV-1 infection to undetectable levels of plasma viraemia, HIV DNA integrates and persists in resting CD4+ T cells. Latent HIV-1 genomes that encode replication-competent virus can resurface once ART is discontinued. This is believed to be the largest impediment to a cure by ART alone. The vast majority of HIV-infected individuals currently live in sub-Saharan Africa where fully suppressive ART is expanding rapidly. A large number of patients is expected to achieve viral suppression. To date, there have been no systematic studies to quantify the latent reservoir in virally suppressed HIV-infected patients in Africa.

Dr Maina proposed to detect how much of the inducible virus is left in the human body after ART through a longitudinal, descriptive study. He aims to: document the antiviral cocktail in a-viraemic HIV-1 patients, viral suppression and incidences of rebound; measure the size of the latent HIV reservoir in virally suppressed HIV-infected individuals; and examine the immunological correlates of the latent reservoir.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Edward Maina, Kenya Medical Research Institute, Kenya

Year funded: 2019

EDCTP funding: €149,500

Impact

Data generated through this study will provide a clear framework for high-burden countries to reduce gaps at each stage of the HIV care continuum, maximise linkage, retention and health outcomes. These data may also inform strategies to reduce HIV-1 reservoirs, inflammation and activation which persist despite ART. The study results may also enable identification of eligible candidates for latency reactivation treatment once one becomes available.



Dr Edward Maina
Kenya



Preterm birth and HIV-acquisition risk

Dr Gbolahan Ajibola aims to quantify the extent to which preterm birth – 1 in 5 infants exposed to HIV are born preterm – confers an increased risk of mother-to-child transmission of HIV.

The challenge

As countries in sub-Saharan Africa scale up antiretroviral treatment (ART) programs, more in utero exposure to antiretroviral (ARV) drugs will occur among children born to HIV-infected women. ART use in pregnancy has been associated with preterm birth (birth < 37 weeks gestational age). This further increases the already elevated risk for preterm birth among HIV-exposed infants and preterm birth is associated with increased neonatal mortality. However, among HIV-exposed infants born preterm, neither differential risk of HIV-acquisition nor toxicity of antiretroviral prophylaxis in the first month of life has been well studied.



Dr Gbolahan Ajibola
Botswana

The project

Dr Ajibola conducts an evaluation of the relationship between preterm birth and a) mother-to-child HIV transmission (MTCT), and b) antiretroviral prophylaxis toxicity. The specific aims of the study are, first, to describe the prevalence and timing (in utero versus peripartum) of MTCT in HIV-exposed infants delivered preterm vs those delivered at term in the setting of ART. Secondly, Dr Ajibola aims to assess the haematologic safety of ARV prophylaxis among HIV-exposed infants born preterm in the first month of life, evaluating for anaemia and/or neutropenia. He uses data collected from infants that participated in a randomised controlled trial looking at the effect of cotrimoxazole on mortality in HIV-exposed but uninfected children in Botswana (the Mpepu study, R01HD061265).

He proposes to analyse the number of infants with positive HIV-DNA PCR at birth or within 72 hours postdelivery (for in utero transmission) and at 4-6 weeks post-delivery (for peripartum transmission) and compare these rates for preterm birth vs at term infants. To conduct the analysis of adverse haematologic comparisons between HIV-exposed preterm and at term

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Gbolahan Ajibola, Botswana-Harvard AIDS Institute Partnership, Botswana

Year funded: 2019

EDCTP funding: €75,431

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/2b08616b-0e8d-4b96-a0d0-254efd1106f3>

infants receiving ARV prophylaxis, the occurrence of anaemia and neutropenia will be compared, using a grade 3 or greater value of haemoglobin or absolute neutrophil count per the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events version 2 (November 2012), using data from infants enrolled in the Mpepu Study.

Impact

The findings of the study will quantify the extent to which preterm birth confers an increased risk of mother-to-child transmission of HIV. The study has the potential to inform public policy with regards to testing and prophylaxis strategies for preterm HIV-exposed infants. As 1 in 5 HIV-exposed infants are born preterm in resource-constrained settings, these findings may contribute to improved survival and a reduction in overall neonatal and infant mortality. Furthermore, the study will provide data on the efficacy and haematological safety of prophylactic ARV regimens in preterm infants.

HIV self-testing in adolescents and young people

Dr Grace McHugh investigates new strategies to reach adolescents and young people to improve the uptake of HIV self-testing.

The challenge

HIV testing and counselling (HTC) is the critical entry point for access to HIV treatment, and also a means of accessing prevention for those who test HIV-negative. UNAIDS has set an ambitious target of 90% of individuals living with HIV to be identified by 2020. Adolescents and young people have the highest incidence of HIV in sub-Saharan Africa of any age-group, with particularly high rates among women. Adolescents and young people face both supply and demand barriers to HTC. Generally, this age group is comprised of infrequent users of health care. Moreover, healthcare provider attitudes towards young people seeking HTC can be stigmatising and discriminatory. They often perceive the risk of HIV acquisition as low. Therefore, access to age-appropriate information about HIV for adolescents and young people, resulting in HIV testing and counselling, is considered neither necessary nor important.

The project

Dr McHugh aims to investigate innovative age-appropriate strategies, youth-friendly approaches to explore the feasibility and acceptability of HIV self-testing. The study will conduct a study to investigate the effectiveness of two different community-based strategies for delivering HIV self-testing to adolescents and young people at educational institutions and within communities in areas frequented by adolescents and young people, using peer distribution. A mixed-methods process evaluation will be used to assess the intervention.

Impact

It is expected that this study will be useful to inform and facilitate the scale-up of HIV self-testing services for adolescents and young people in Zimbabwe and inform on how to make the connection with HIV health care and prevention through the HIV self-testing process.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Grace McHugh, Biomedical Research and Training Institute (BRTI), Zimbabwe

Year funded: 2018

EDCTP funding: €141,745



Dr Grace McHugh
Zimbabwe



Strategies for HIV-control in pregnant women

Dr Tacilta Nhampossa aims to identify the factors that influence the effectiveness of HIV control strategies in pregnant women exposed to malaria.

The challenge

Current guidelines for HIV management and mother-to-child-transmission prevention in Mozambique rely on lifelong administration of antiretroviral therapy (ART) (option B+) from the time of HIV diagnosis during pregnancy. Thus, HIV-infected pregnant women need to self-administer an average of five tablets from different medications daily. Available information suggests that adherence to these medications is poor and retention rate is low, while there is little understanding of the factors affecting this.

Moreover, there are no data on the proportion and clinical presentation of pregnant women with advanced HIV disease, which is needed for the implementation of new management guidelines for individuals with advanced HIV disease.

With malaria in pregnancy, HIV-infected pregnant women cannot receive intermittent preventive treatment (IPTp) with sulphadoxine-pyrimethamine for malaria prevention due to potential drug interactions with cotrimoxazole prophylaxis (CTXp), which is administered to prevent opportunistic infections.

The project

Dr Nhampossa aims to identify the factors that influence the effectiveness of HIV control strategies in pregnant women exposed to malaria in rural southern Mozambique, in order to assist policymakers in the implementation of the appropriate interventions for this group of women most vulnerable to both infections. Specific objectives of the project are: 1) to assess perceptions, acceptability and behaviour of HIV-infected pregnant women regarding the administration of the recommended multiple medications; 2) to assess the retention rate to Option B+ and its determinants; 3) to determine the proportion, characteristics and clinical presentation of pregnant women attending the antenatal care clinic with HIV advanced disease.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Tacilta Nhampossa, Fundação Manhiça, Mozambique

Year funded: 2019

EDCTP funding: €149,098

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/a387b71e-20e4-458d-b960-d9331e7c7e8f>

In this project the fellow is using three sources of information: 1) participants in a randomised placebo-controlled trial to evaluate the safety and efficacy of dihydroartemisinin-piperaquine for IPTp in HIV-infected pregnant women receiving CTXp; 2) pregnant women attending the same antenatal care clinic who do not participate in the above-mentioned trial, 3) retrospectively collected data from HIV-infected pregnant women attending the antenatal care clinics.

Impact

Importantly, the results of the research that is part of this fellowship, may help to guide public health policies contributing to the improvement of maternal and child health in the most vulnerable populations.

As regards capacity development, this fellowship will train a junior African researcher in epidemiology, qualitative research and statistical analysis. Additionally, the fellow will have the opportunity to interact with collaborators from other African and European research institutions.



Dr Tacilta Nhampossa
Mozambique

Albuminuria and the long-term health of HIV-patients

Dr Mosepele Mosepele aims to address the knowledge gap regarding albuminuria with inflammation (and its reduction) as a factor in the long-term health of African HIV-infected patients.

The challenge

HIV infection is associated with a five-fold risk of albuminuria. Albuminuria causes HIV-infected patients up to four times more likely to die. It is well known from Western populations that persistent albuminuria with inflammation is a marker of excess end-organ dysfunction and mortality among HIV-infected adults with undetectable HIV-1 RNA (viral load suppression on antiretroviral treatment or ART).

As more HIV-infected patients attain viral suppression and prolonged survival globally, they are faced with multiple non-communicable diseases mostly characterised by accelerated end-organ dysfunction which threatens their long-term health and longevity. It is believed that persistent inflammation despite viral suppression drives most of the observed end-organ dysfunction. Studies involving HIV-infected and HIV-uninfected persons outside Africa have shown albuminuria to be a marker of end-organ dysfunction (e.g. cardiovascular disease, renal dysfunction, and even cognitive impairment), and demonstrate that albuminuria is highly correlated with inflammation.

However, the burden of albuminuria with inflammation has not been well characterised among black African patients. In addition, although angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) are widely available, their role in reducing albuminuria with inflammation in African HIV-infected patients has not been studied.

The project

Dr Mosepele proposed a prospective observational non-interventional study to determine the prevalence and longitudinal changes in albuminuria in a clinical setting with high rates of viral suppression. He will also

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Mosepele Mosepele, University of Botswana, Botswana

Year funded: 2019

EDCTP funding: €148,403

assess if longitudinal changes in albuminuria are associated with ACEI/ARB exposure over a 12-month period in a clinical setting. The association between longitudinal changes in albuminuria and inflammatory markers and whether this association is affected by the use of ACEI/ARB will also be assessed. Finally, dr Mosepele plans to enrol a cohort to assess long-term HIV-Cardiovascular Disease outcomes. Biospecimens will be stored for future testing of other inflammation markers as well as data on host genetics (e.g., APOL-1 allele variant frequency). Five-year mortality in the death registry will be linked to longitudinal changes in albuminuria.

Impact

Results of this study will provide baseline data to inform the design of a clinical trial to assess whether HIV disease is a compelling indication for early ACEI/ARB prescription among hypertensive HIV-infected patients given the positive pleiotropic effects of these medications on albuminuria, inflammation and cardiac remodelling. As the fellow plans to lead such a study, the current fellowship may facilitate further career development.



Dr Mosepele Mosepele
Botswana



Early immune responses with virological control in HIV-1 infection

Dr Andrew Ekii Obuku aims to identify the most potent phenotypes of CD8 T cells for controlling HIV-1 infection.

The challenge

Natural immune responses are able to control viral replication from peak viraemia to viral set point in acute HIV-1 infection. However, these natural immune responses have not been fully characterised. Immune correlates of protection from HIV acquisition and progression to AIDS are not known, neither are the phenotypes of cells needed to be induced by HIV vaccines to confer protection.

The project

Defining the precise correlates of the cellular immune response to HIV-1 that are associated with control of HIV-1 replication in acute infection, has been the focus of intense study over the past two decades. The identification of such correlates has been pursued as part of a rational strategy to produce an HIV-1 vaccine capable of best mimicking the cellular immune response associated with control of HIV-1 viraemia. Once defined, such correlates will also help establish the necessary benchmarks for candidate vaccine down selection and efficacy testing.

In this study, Dr Obuku will attempt to delineate the different T cell phenotypes (including lymph node resident memory T cells) and their ability to inhibit viral replication. He will characterise the CD8 T cell phenotypes, before peak viraemia, at peak viraemia, at set point and post set point from blood and lymph nodes. He will also investigate the cell death pathways associated with the death of CD8 T cells from peak viraemia to set point. Moreover, he will compare the ability of the different CD8 T cell phenotypes to inhibit HIV-1 replication in a viral inhibition assay and identify the most potent phenotypes of CD8 T cells at controlling HIV-1 infection.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Andrew Ekii Obuku, MRC/UVRI & LSHTM Uganda Research Unit, Uganda

Year funded: 2019

EDCTP funding: €149,911

Impact

The results of this study will contribute to the body of research that aims to determine how HIV vaccines can induce the immune system to confer protection.



Dr Andrew Ekii Obuku
Uganda

Epidemiology of invasive fungal diseases

Dr Beatrice Achan aims to establish epidemiological baseline data for invasive fungal diseases, specifically cryptococcal meningitis and common opportunistic fungal diseases in immunosuppressed patients.

The challenge

The epidemiology of invasive fungal diseases has been evolving for the past two decades. In Uganda, HIV/AIDS has highlighted cryptococcal meningitis as a leading invasive fungal disease caused by *Cryptococcus neoformans*. Associated mortality is high, as 10-week survival rates in routine care are less than 50% after cryptococcal meningitis. Furthermore, the incidence of the common opportunistic fungi causing invasive disease in other immunosuppressive conditions such as cancer is not known.

The project

Dr Achan aims in this study to determine the molecular epidemiology of *Cryptococcus species* causing cryptococcal meningitis and to describe the epidemiology of *Candida*, *Cryptococcus* and *Aspergillus species* that cause fungaemia in immunosuppressed individuals in Uganda. Additionally, the epidemiology of *Madurella mycetomatis*, which causes eumycetoma, will be described.

To characterise the epidemiology of invasive fungal diseases in Uganda, fungal isolates retrieved from blood culture will initially be identified to species level using the standard algorithm for identification. Identification methods will include India Ink stain, germ tube test, 10% potassium hydroxide mount, lactofuchsin stain, culture on Chrom-Candida, Niger birdseed, I-Canavanine glycine bromothymol blue agar, and use of biochemical tests such as API 20C. Antifungal susceptibility testing will be performed using the EUCAST method for yeasts and moulds. Environmental samples will include birds' guano, tree barks, soil and inanimate objects in the vicinity of the patient. Mycetoma granules from patients who present with the triad features of mycetoma

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Beatrice Achan, Makerere University, Uganda

Year funded: 2019

EDCTP funding: €149,250

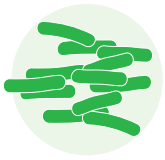
will be assessed by direct microscopy using 10 % potassium hydroxide, culture on Saboraud dextrose agar while the tissue biopsy will be examined using histological stains like Haematoxylin and Eosin, Periodic Acid Schiff and Grocott Methamine Silver stains.

Impact

Findings from this study will provide important baseline information on the epidemiological trend of invasive fungal diseases in Uganda for patient management and research.



Dr Beatrice Achan
Uganda



Predicting unsuccessful MDR-TB treatment response

Dr Ali Esmail develops and validates an appropriately weighted dynamic clinical prediction rule which can predict the unfavourable or favourable outcome of treatment of MDR-TB.

The challenge

The emergence of multidrug-resistant TB (MDR-TB) in Africa is a serious public health concern. It is extremely expensive to treat and has high associated mortality, with rates of MDR-TB increasing in countries like South Africa, (32,000 MDR-TB cases were diagnosed last year), the situation is becoming unsustainable with a potential to destabilise TB programmes in Africa.

The introduction of newer agents such as bedaquiline and linezolid have renewed hope in the treatment of drug-resistant TB. However, clinical trials of new treatments for MDR-TB are expensive and prolonged, which delays registration and access to the drug. One of the major challenges in trials of new treatments for MDR-TB is the lack of tools to predict outcomes.

The project

As there are no validated biomarker profiles that will identify patients who are likely to have a favourable versus unfavourable outcome, the goal of the proposed project is to evaluate a package of treatment response biomarkers for MDR-TB.

Dr Esmail will aim to formulate a weighted prediction rule incorporating clinical, radiological, mycobacterial, serum and urine biomarkers, which can predict unfavourable from favourable outcomes. The project is nested within the NexT clinical trial, a randomised control trial that is evaluating a new 6-month injection-free regimen for MDR-TB. This South African MRC-funded study will recruit 300 patients with MDR-TB randomised to a WHO-approved or intervention regimen. Data and clinical samples required for the project are available in a biobank.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Ali Esmail, University of Cape Town Lung Institute (Pty) Ltd, South Africa

Year funded: 2017

EDCTP funding: €148,400

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/441d5673-1ad5-40e9-a364-54d887b3309d>

Impact

The successful development and validation of an appropriately weighted dynamic clinical prediction rule that can predict outcome in the treatment of MDR-TB would have an impact on both patient management and the clinical development of new regimens.

TB clinicians would be able to intervene earlier in a patient who is likely to have an unfavourable outcome, as opposed to current standards that use sputum culture, a process which delays such critical decisions by months.

Reduced follow-up times would result in shorter studies. Phase II studies could be conducted to identify the most promising candidate regimens that could then move on to phase III trials in a shorter time. Several trials are currently planned for testing various regimens for the treatment of MDR-TB and with bedaquiline treatment failures starting to emerge the need for new drugs will likely increase over time.



Dr Ali Esmail
South Africa

Drug-resistant TB: optimising linezolid use in African patients

Dr Sean Wasserman will define the optimal use of linezolid in South African patients with drug-resistant tuberculosis (DR-TB).

The challenge

New evidence-based treatment options are urgently needed to improve the outcomes of drug-resistant tuberculosis. Linezolid improves culture conversion and cure rates in complicated multidrug-resistant (MDR) and extensively drug-resistant TB and has the potential to allow for injection-free regimens for MDR-TB.

Because of its impressive impact on outcomes, linezolid is likely to become a key component of treatment regimens for drug-resistant TB in sub-Saharan Africa. However, it has never been systematically studied in its populations and there are critical knowledge gaps that need to be addressed prior to the expanded use of this important agent.

The project

To support the scale-up of safer and more effective drug-resistant TB regimens, the study aims to address several knowledge gaps. First, mitochondrial toxicity associated with long-term use of linezolid leads to treatment-limiting adverse events in over a third of patients. It is unclear whether attempts to reduce this by reducing dosage compromise efficacy and facilitate the emergence of linezolid resistance. Second, the risk of toxicity may potentially be different in patients from sub-Saharan Africa because of high rates of HIV co-infection, different population pharmacokinetics, and unique polymorphisms in mitochondrial DNA (mtDNA). Published reports of linezolid use for drug-resistant TB include outcomes data for only 239 patients worldwide; fewer than 10% of these were HIV-infected and only 55 cases have been reported from Africa.

Dr Wasserman and his team will conduct a large prospective pharmacokinetic and pharmacodynamic (PK/PD) study aimed at defining the optimal use of linezolid in South

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Sean Wasserman, University of Cape Town (UCT), South Africa

Year funded: 2017

EDCTP funding: €149,606

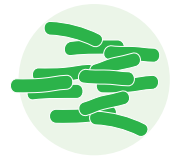
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African patients with DR-TB. The specific objectives of the project are to develop a population PK model of linezolid in South African patients with drug-resistant TB; to determine the effects of linezolid exposure on toxicity, treatment response, and linezolid resistance; and to define the relationships between linezolid PK parameters, functional mitochondrial activity, and clinical toxicity, and explore the association of polymorphisms in mtDNA with the risk of linezolid toxicity in this population.

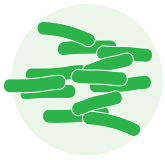
Impact

The study findings will likely inform international guidelines for linezolid use, ultimately translating into improved outcomes for patients with drug-resistant TB.

This project will also enable Dr Wasserman to acquire further skills to lead future clinical and translational studies in the fields of HIV and TB.



Dr Sean Wasserman
South Africa



The impact of lower respiratory tract infections in young children

Dr Marieke van der Zalm investigates the impact of Mycobacterium tuberculosis and other common bacterial and viral pathogens in young South African children.

The challenge

Tuberculosis (TB) and acute pneumonia are important causes of morbidity and mortality in children in the developing world. Although the importance of viral and bacterial infections, including pulmonary TB during respiratory illnesses is well recognised, key questions regarding the long-term sequelae of these infections remain unclear. These are especially relevant in developing countries where the burden of these diseases is high. The challenge is to collect better data on lung function in young children living in low and middle-income countries.



Dr Marieke van der Zalm
South Africa

The project

In a major recent advance, a portable device to measure lung function in infants and young children has been developed and validated. The Whistler LFMi® takes measurements using the single occlusion technique (SOT) and the interrupter resistance technique. Both measure airway resistance while the SOT also measures airway compliance during tidal breathing. It is the first handheld device for performing pulmonary function tests on babies and young children which can readily be used in clinical settings. Both techniques have been shown to be feasible and reliable in infants and young children in studies conducted in Europe.

Dr Van der Zalm's study aims to investigate the impact of *M. tuberculosis* and other common bacterial and viral pathogens in young South African children by using this practical and novel tool for lung function measurements. Children will be classified into bacteriologically confirmed, clinically diagnosed TB and not TB (pulmonary TB excluded), with or without other respiratory pathogens. Both baseline and long-term lung function in these children after 6 months will be assessed. As early lung function is a predictor of lung function later in life, clinical and epidemiological research in young children with

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Marieke van der Zalm, Stellenbosch University, South Africa

Year funded: 2017

EDCTP funding: €147,764

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/dbbfc7bf-4a81-49f6-a3d5-fe9d436d00ea>

pulmonary TB and other respiratory pathogens may benefit substantially from lung function measurements to assess the functional impact of these infections.

Impact

Improved knowledge of pulmonary TB and lung function impairment will allow for the development and implementation of possible preventative and therapeutic strategies in high-risk children. These include tailored anti-tuberculosis treatment approaches, targeted vaccination for influenza or respiratory syncytial virus, and immune-modulating antibiotics.

Avoiding TB drug-resistance with host-directed therapies

Dr Nelita du Plessis evaluates sildenafil to determine its effect on Mycobacterium tuberculosis survival in myeloid-derived suppressor cells, with a view to shorten TB treatment by focusing on host processes.

The challenge

There is no vaccine which protects against infection or pulmonary tuberculosis (TB) and TB therapeutics require a cumbersome lengthy (6 months) regimen in the case of drug-susceptible *Mycobacterium tuberculosis* (Mtb). This often leads to poor compliance or discontinued treatment, which also facilitates the development of antibiotic resistance.

An innovative treatment approach (host-directed therapy) focuses on host processes to shorten treatment without inducing drug-resistance. In this case, the project sets as its goal to determine the effect of sildenafil on Mtb survival in myeloid-derived suppressor cells.

The project

Myeloid-derived suppressor cells (MDSCs) accumulate during inflammatory conditions to suppress host immunity to limit tissue pathology. We and others showed that MDSCs represent a critical element in the pathogenesis of pulmonary TB. MDSCs increase during TB disease, contain Mtb bacilli, suppress protective host immunity and modulate lung inflammation.

Recently, PDE-5 inhibition was tested in mouse tumour models and shown to reverse tumour-induced immunosuppression and induce antitumor immunity that delayed tumour progression. Subsequently, PDE-5 inhibitors (including sildenafil/Viagra®) are being repurposed, tested in human clinical trials for the treatment of malignancies. In particular, sildenafil has shown to improve cancer therapy by up-regulating T-cell numbers in tumours, increase T-cell activation and T-cell IL-2 production. Importantly, sildenafil mediated this improved response by dampening MDSC recruitment and down-regulating MDSCs-derived T-cell suppression. Reports show that the therapeutic treatment of Mtb-infected mice with sildenafil accelerated lung sterilisation when

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Nelita du Plessis, Stellenbosch University, South Africa

Year funded: 2018

EDCTP funding: €149,627

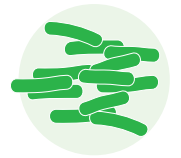
Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/07b3e3e5-f0ef-4cfc-bef3-24cba8be8c05>

added to the standard TB-treatment regimen, but the mechanism of action remains unknown.

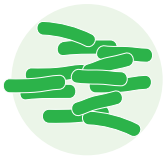
The role of sildenafil on human MDSCs in the context of TB has not been evaluated and further groundwork is needed to better understand how PDE-5 inhibitors might be beneficial in combination with standard TB-treatment. Dr Du Plessis and her team hypothesise that delivery of sildenafil to MDSC from TB patients could alter MDSCs phenotype and function. They will test this in two ways by 1) evaluating the immunomodulatory capacity of sildenafil on the function and phenotype of MDSC from lungs and blood of TB patients, and 2) determining the effect of sildenafil on Mtb survival in MDSCs.

Impact

The immediate impact will be to further Dr Du Plessis career development by facilitating increased scientific output (peer-reviewed publications), increased student training, broadening her local and international network and establishing her myself as a leader in the field of MDSCs research in TB.



Dr Nelita du Plessis
South Africa



Improving TB case detection with informal healthcare providers

Dr Sylvie Kwedi evaluates the effect of integrating informal healthcare providers into the National Tuberculosis Programme of Cameroon in order to improve TB case detection.

The challenge

With about 35,000 TB cases expected annually, Cameroon is a country with a relatively high incidence and prevalence of tuberculosis. The strategies adopted in Cameroon by the National Tuberculosis Control Program (NTCP) address all facets in the fight against tuberculosis as recommended by the WHO. The NTCP's main objective of case finding is to identify patients with pulmonary tuberculosis (PTB) who are responsible for the transmission of the infection. However, based on a survey, the NTCP estimates that one of the main bottlenecks in finding TB cases is the fact that many people frequent informal health care providers, who give substandard care.



Dr Sylvie Kwedi
Cameroon

The project

A survey conducted by the NTCP revealed that numerous informal healthcare providers (IHPs) were operating in major cities in Cameroon. The IHPs are not yet integrated into the NTCP network, but they are likely to provide health care to a significant number of TB suspects.

In 2015, Dr Kwedi, in collaboration with the NCTP, conducted a study to assess the feasibility of integrating IHPs into the NTCP in order to improve TB case detection in Yaoundé (intervention city) as compared to Douala (control city). This feasibility study showed that the IHPs were willing to collaborate with the NCTPs. They accepted to be trained, using NCTP tools and referring suspected TB cases to the NTCP for confirmation.

For this study, Dr Kwedi proposed to evaluate the effect of integrating the informal healthcare providers into the NTCP in order to improve TB case detection. The project takes place in three main cities in Cameroon: Douala, Buéa and Bafoussam. Informal healthcare providers receive proper training for handling TB suspects

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Sylvie Kwedi, University of Yaoundé I (UYI), Cameroon

Year funded: 2018

EDCTP funding: €149,963

Fellow profile: <https://edctpalumnetwork.org/fe/profiles/view/21fc4075-716a-4869-a3c5-efd1a65945ca>

and their ability to refer TB suspects to the NCTP is intensively monitored. The project is a prospective quasi-experimental (pre/post) study to test an intervention that utilises a training tool intended to improve the IHPs ability to handle TB suspects and further refer them to the NCTP for case detection.

Impact

The study is innovative in that it taps into a non-traditional TB case-finding strategy in the community. The results from this study will provide actionable evidence that may guide policy to transform the contribution of IHPs from a liability into an asset for TB control. Dr Kwesi expects that a formal path to integrate the IHPs into the official TB control services can be implemented.

Lung imaging to evaluate 4 and 6 months treatment of pulmonary TB

Dr Stephanus Malherbe aims to facilitate the discovery of biomarkers which evaluate successful TB treatment regardless of treatment duration and would allow for individualised treatment duration.

The challenge

Shortening of tuberculosis (TB) treatment to 16 weeks or shorter is a main priority of TB research to decrease cost, improve treatment adherence and decrease the development of drug resistance. Clinical trials of treatment shortening have thus far all failed but have consistently found 80-85% treatment success rates in the 16-week arms. This suggests that the majority of patients are cured within 16 weeks. The challenge is to identify these patients, so for this subset treatment shortening could be successfully accomplished.

The project

Identification of said patients needs a better understanding of biomarkers to monitor the treatment of pulmonary tuberculosis. Recently, 18F-Fluorodeoxyglucose Positron Emission Tomography / Computed tomography (PET/CT) has shown promise as a tool to stratify risk, monitor response and provide insight into the dynamics of Mtb versus host interaction during TB treatment.

Dr Malherbe conducts the Evaluate 4mTB study as a substudy of the Predict-TB trial. The parent study's aim is to demonstrate that the 72-weeks (18-months) treatment success rate of standard treatment stopped after 16 weeks is not inferior to treatment stopped after 24 weeks, in subjects classified as low risk by new criteria, based on PET/CT scans at baseline and week 4.

Dr Malherbe's study aims to validate and optimise the functional and anatomical characteristics, previously identified by 18F-FDG PET/CT scans on patients with pulmonary TB (with a focus on scans at 16 and 24 weeks), and use this information to provide insight into the dynamics of Mtb versus host interaction, serve as a prognostic indicator and facilitate

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Stephanus Malherbe, Stellenbosch University, South Africa

Year funded: 2018

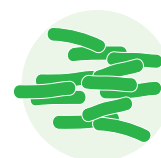
EDCTP funding: €149,696

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/dd5a17ab-b52d-41e2-bc4a-095e3e912d7e>

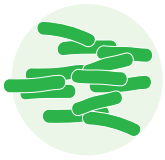
the discovery of biomarkers to monitor and understand treatment response during 16 and 24 week treatment courses. In this prospective randomised non-inferiority phase IIb trial, he and his team recruit and follow up 516 patients with pulmonary TB for 72 weeks, and perform PET/CT scans at Dx, 4 weeks and 16 weeks. Those that meet early treatment criteria, will be randomised to a treatment of either 16 or 24 weeks.

Impact

As scans at the end of treatment are more accurate than early treatment scans and provide a better understanding of lung pathology after shortened treatment, this should facilitate the discovery of biomarkers to evaluate the end-of-treatment status of the TB infection in the lung, regardless of treatment duration. This, in turn, would be a major step towards easy and affordable tests to allow individualised treatment duration.



Dr Stephanus Malherbe
South Africa



New treatment regimens for TB/HIV-co-infected patients on ART

Dr Christine Sekaggya-Wiltshire studies the safety of high-dose rifampicin regimens in TB-HIV co-infected patients on efavirenz-based ART.

The challenge

The current WHO goal of ending the global TB epidemic by 2035 will not be achieved without considerable new advances in TB treatment. A growing body of evidence has indicated that the current dose of rifampicin (10mg/kg) is inadequate. Several studies have suggested that dose escalation (to 20-35mg/kg) is safe and that higher doses (35mg/kg) may accelerate clearance of TB bacteria from the sputum of infected individuals. However, these studies have almost entirely been completed on HIV-negative TB patients, or TB-HIV-co-infected patients without severe immunosuppression who are not yet receiving antiretroviral therapy (ART). The challenge is to establish that a higher dose of rifampicin is safe for these patient groups.



Dr Christine Sekaggya-Wiltshire
Uganda

The project

As Uganda moves towards early initiation of ART, drug-drug interactions between rifampicin and efavirenz need to be assessed. It is also not clear if high dose rifampicin is safe in patients on efavirenz-based ART. Dr Sekaggya-Wiltshire proposed to determine the effect of higher doses of rifampicin (20mg/kg and 35mg/kg) on efavirenz concentrations and the safety of TB regimens containing high-dose rifampicin in TB-HIV-infected patients also receiving efavirenz-based ART.

She and her team are enrolling 160 TB-HIV-co-infected patients at the Infectious Diseases Institute for a randomised open-label phase IIb clinical trial. Patients diagnosed with TB will be randomised to one of three rifampicin doses of 10 (control), 20 or 35mg/kg for the first 8 weeks of TB treatment. Isoniazid, pyrazinamide and ethambutol will be given in their standard doses. Patients who are not on ART will be initiated on efavirenz-based ART after two weeks of TB treatment. Alanine transaminase will be done two weekly and sputum culture performed after 8 weeks of treatment.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Christine Sekaggya-Wiltshire, Infectious Diseases Institute Limited, Uganda

Year funded: 2018

EDCTP funding: €150,000

Fellow profile: <https://edctpalumnetwork.org/fe/profiles/view/2a0c4e76-a3e2-4093-a292-64f75e999cbc>

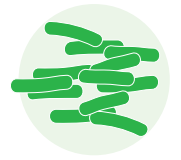
The study aims to determine whether TB-HIV-co-infected patients on efavirenz-based ART and higher doses of rifampicin (20mg/kg and 35mg/kg) have lower concentrations of efavirenz, develop liver toxicity more frequently compared to patients on standard dose (10mg/kg). It will also determine the proportion of patients who remain sputum culture-positive after 8 weeks of treatment in each treatment arm.

Impact

The results of this study will inform phase III clinical trials in a larger group of TB-HIV-co-infected patients to determine the utility of higher doses of rifampicin in this population. As regards capacity development, Dr Sekaggya-Wiltshire aims to enhance her capabilities in patient-oriented research and ability to perform pharmacokinetic-focused clinical trials and learn new model-based approaches for the analysis of pharmacokinetic data.

TB rates among HIV health care workers

Dr Evaezi Okpokoro aims to measure the additional risk of TB infection to HIV health care workers with a view to better training on infection control



The challenge

The dual epidemic of HIV and TB has heightened the risk of TB among health care workers especially in sub-Saharan Africa which bears the highest burden of both diseases. Health care workers primarily working in HIV clinics are seemingly at greater risk of *Mycobacterium tuberculosis* (Mtb) infection as an estimate of 25% of persons living with HIV will have active TB at the initial visit to HIV clinics. The challenge is to measure the additional risk they are exposed to and how they can be protected.

The project

Dr Okpokoro aims to measure the additional risk of Mtb infection in health care workers and identify the factors associated with the infection rates among health care workers in HIV care and treatment settings. These findings then should be incorporated in a TB infection control training for health care workers.

He and his team conduct a prospective cohort study that will recruit healthcare workers in hospitals with a high burden of HIV and TB in two states in the Northcentral region of Nigeria. This part of the region has the highest HIV prevalence in the region (i.e. Abuja & Nasarawa). Thirteen hospitals with dedicated PEPFAR-funded HIV care and treatment centres in Abuja and Nasarawa have been selected. A 25% latent TB infection rate among the unexposed group (general health care workers) is assumed and a 35% latent TB infection rate (anecdotal evidence) among the exposed group (health care workers primarily working in the HIV clinics). A minimum of 656 health care workers needs to be recruited. Following informed consent, a TB risk assessment questionnaire is administered and 5ml blood for QFT-Plus and 5ml blood for PBMC is collected from eligible study participants.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Evaezi Okpokoro, Institute of Human Virology Nigeria (IHVN), Nigeria

Year funded: 2018

EDCTP funding: €150,000

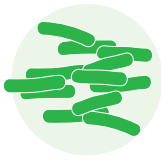
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Impact

Prevalence of Mtb infection among all participants will be calculated as measured by the QFT-Plus. Summaries of Mtb rates will be presented by age, gender, residential district; years of employment at the hospital, etc. Additional analysis will be based on the exploration of immune correlates of protection or risk.



Dr Evaezi Okpokoro
Nigeria



Development of a candidate TB vaccine protecting children and adults

Dr Babatunde Adeagbo focusses on the development of a thermostable single-vial TB vaccine formulation.

The challenge

Tuberculosis (TB) remains a foremost poverty-related disease with a high rate of mortality despite the global immunisation with the only available vaccine, Bacille Calmette-Guérin (BCG). However, this vaccine only provides some protection against the severe forms of paediatric TB but is not completely protective against the disease in infants or pulmonary TB in adults. There is an urgent challenge to develop an affordable, effective and safe vaccine that can protect against the disease in infants and adults.



Dr Babatunde Adeagbo
Nigeria

The project

Dr Adeagbo aims to develop a strategy for the presentation of a vaccine as a single vial through conjugation and lyophilisation.

An adjuvanted recombinant protein vaccine, developed at the Infectious Disease Research Institute, Seattle, USA, is one of the vaccines that are in clinical development for the prevention of pulmonary TB. The current composition comprises two vials, one containing the antigen and one containing an adjuvant, which is bedside mixed immediately prior to inoculation. The mode of association of the adjuvant to the antigen influences immunogenicity, thus appropriate adjuvant-coupled antigens are expected to be suitable for the development of vaccines that induce humoral and cellular immunity. Moreover, lyophilisation has facilitated the formulation of thermostable pharmaceuticals containing proteins with enhanced shelf life and reduced degradation in the presence of heat stress.

The study will explore the use of chemical conjugation strategies to associate the antigen to the liposome. It will also develop and optimise a lyophilisation process for the formulation of a thermostable single-vial vaccine. Field stability of these formulations will be evaluated in selected health facilities in Nigeria. The physicochemical

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Babatunde Adeagbo, Obafemi Awolowo University, Nigeria

Year funded: 2018

EDCTP funding: €149,999

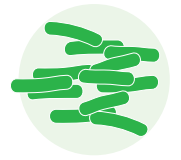
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stability of these formulations will be studied using HPLC, dynamic light scattering, and SDS-PAGE while the bioactivity will be tested by evaluating cytokine stimulation using fresh whole blood from donors in order to determine the most stable and bioactive formulation. The study will also involve an evaluation of the differential response of individuals to the vaccine.

Impact

The findings of this study will render a stability profile of a conjugated or lyophilised single-vial vaccine with enhanced immunogenicity and thermostability, ready for storage outside a cold chain facility, thereby enabling delivery to remote populations. This proposal will also enhance capacity for vaccine research in the African scientific community and build a team of young scientists who will be part of the global search for vaccines for infectious diseases in Africa.

Dosing drugs for children with uncomplicated TB



Dr Hadija Hamisi Semvua is evaluating the pharmacokinetics and safety/ tolerability of higher doses of rifampicin in children with newly diagnosed, uncomplicated tuberculosis.

The challenge

Tuberculosis (TB) treatment outcome is not only impaired by co-morbidities such as HIV infection, but also by insufficient consideration of the relationship between the dosing of the administered TB drugs, the concentrations achieved, and eventually, the desirable and undesirable responses. Especially dosing of TB drugs for children is not well substantiated and the concept of using higher doses of rifampicin has not been translated to the treatment of children.

The project

Dr Semvua proposed to conduct a phase IIa dose-finding clinical study to find the rifampicin dose in children that yields plasma concentrations similar to those achieved in adults after a 35 mg/kg daily dose. This will answer an important scientific question of direct public benefit.

As regards capacity development, the fellow will receive hands-on training from a mentor of the Radboudumc, an academic research hospital in the Netherlands, during all parts of the study. Skills to perform bio-analysis of TB drugs will be obtained through the pharmacokinetic laboratory at Radboudumc. The fellow will also attend courses on bioanalytical method validation and pharmacokinetic data analysis as well as relevant conferences. All this will enable the development and validation of bioanalytical methods for TB drugs at the Biotechnology Laboratory in the Kilimanjaro region. The fellow will mentor two next-generation scientists on the principles of bio-analysis of drugs and pharmacokinetic data analysis through PhD and Master training at the Kilimanjaro Christian Medical University College.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Hadija Hamisi Semvua, The Good Samaritan Foundation, Kilimanjaro Christian Medical Centre (GSF KCMC), Tanzania

Year funded: 2019

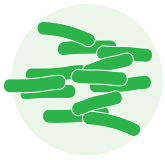
EDCTP funding: €149,621

Impact

The team of experts developed through this proposal will continue to design and conduct pharmacokinetic studies focused on infectious disease threats in Tanzania and contribute to the global effort to fight poverty-related infectious diseases.



**Dr Hadija Hamisi
Semvua**
Tanzania



Understanding mechanisms of TB drug resistance

Dr Marisa Klopper is testing the hypothesis that Mycobacterium tuberculosis mutations causing drug resistance also contribute to retain the metabolic fitness of the pathogen.

The challenge

Drug-resistant tuberculosis (TB) remains a world-wide crisis. Despite early work indicating that drug-resistant *Mycobacterium tuberculosis* is less fit than its drug-susceptible counterparts, *M. tuberculosis* resistant to increasing numbers of drugs continues to emerge and spread. It has been shown that compensatory mutations exist that may explain the ability of the resistant bacilli to retain fitness. The challenge is to understand this mechanism.



Dr Marisa Klopper
South Africa

The project

Mutations in the *inhA* promoter are well known to cause resistance to at least two drugs. These mutations have been suggested to be a gateway to extensively drug-resistant TB (resistant to at least 4 key drugs). Dr Klopper proposes that, in addition to causing resistance, *inhA* promoter mutations act as compensatory mechanisms, overcoming negative effects of drug-resistance.

She will test this hypothesis by targeted mutagenesis and fitness assays. In particular, *inhA* promoter mutations cause the upregulation of two genes involved in mycolic acid synthesis (*mabA* and *inhA*), as well as one gene involved in haem biosynthesis (*hemZ*). Dr Klopper aims to show that this upregulation causes an increase in the number of mycolic acids synthesised, which in turn increases the functionality of mycolic acids. She will show that this function is to facilitate the sequestration of ferrous iron, nitric oxide or oxygen by isolation of mycolic acids and measurement of the concentration of these molecules in a solution containing mycolic acids.

Impact

The study focuses on an important drug-resistance mechanism and will aid in elucidating additional functions of this mechanism. This will contribute to a better understanding of the

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Marisa Klopper, Stellenbosch University, South Africa

Year funded: 2018

EDCTP funding: €150,000

physiology of the bacillus and may lead to novel insights for drug design.

The fellowship will not only allow Dr Klopper to conduct this study plan but also plan longer-term projects emanating from its results, including the investigation of further structure-function relationships of different mycolic acids, as well as the related role of haem in the utilisation of reactive oxygen or -nitrogen species. Building out the project will increase opportunities for postgraduate student supervision, as well as international collaborations and publications.

Understanding progression to active TB

Dr Virginie Rozot aims to understand NK and B cell determinants of immunity to Mycobacterium tuberculosis in humans.

The challenge

Tuberculosis (TB) is the major human killer from a single infectious agent. A better understanding of the immunopathogenesis of *Mycobacterium tuberculosis* (Mtb) infection and disease is critical for the rational development of improved interventions needed to control and eradicate TB. The mechanisms that govern how humans control infection with Mtb are not understood. Recent studies have shown that CD4 T cell responses are necessary but not sufficient for immunological protection against TB.

The project

Dr Rozot proposes that NK and B cells participate alongside antigen-specific Th1 responses in the successful immune response to Mtb and are dysregulated in persons who progress to active disease. She aims to identify new NK and B cell subsets involved in tuberculosis progression.

First, the study aims to re-analyse a longitudinal mass cytometry CyTOF dataset of 37 progressors who transitioned from Mtb infection to incident TB disease, and 37 matched Mtb-infected controls who remained asymptomatic during 2 years of follow-up. This complex dataset was generated to primarily study T cell response correlates of TB disease risk. Re-analysis will now allow us to characterise changes in NK and B cell phenotypes and functions in the context of the Mtb-specific T cell response using 16 NK-specific and 17 B-cell specific markers.

Secondly, she and her team will investigate the mechanisms of activation of NK cells whether they are directly activated by the pathogen or through nonspecific cytokine stimulations. Further, the relevance of the findings made in the peripheral blood will be defined by analysing post-mortem tissue samples from the site of Mtb-infection from TB patients and healthy Mtb-infected individuals who died from trauma/accidents. A new 40 marker mass cytometry antibody panel will be defined to deeply decipher

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Virginie Rozot, University of Cape Town (UCT), South Africa

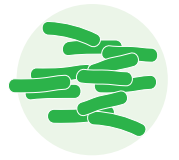
Year funded: 2019

EDCTP funding: €149,990

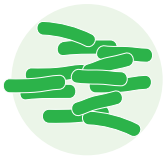
phenotype and functions of NK and B cells at the site of infection in humans after stimulation with Mtb. The role of NK cells in IL-22 production will be defined as well as the memory profile and cytokine production capabilities of B cells and their contribution to the milieu at the site of infection.

Impact

The study will uncover new potential targets for host-directed therapies, early diagnosis and vaccine design and will provide the fellow with the opportunity to expand her knowledge and technical capacities as well as her international network of collaborations, essential skills to become a research leader in the field of infectious diseases and particularly tuberculosis in South Africa.



Dr Virginie Rozot
South Africa



The possible role of the microbiome in TB treatment outcome

Dr Charissa Naidoo studies the longitudinal microbiome of TB patients, symptomatic culture-negative controls and healthy household contacts, and its association with treatment outcome.

The challenge

Despite being curable, tuberculosis (TB) remains the single biggest infectious cause of death globally and, in South Africa, kills more people than any other condition. Many cases of TB are never diagnosed and, despite good adherence to treatment, a significant proportion of cases encounter unfavourable treatment outcomes, in some settings as high as ~20%.

Therefore, there is not only a need for TB diagnostics but also for novel methods of prognosticating patients likely to have unfavourable outcomes. The microbiome (the collection of microbial genetic material within a specific environment) is an emerging research area as the microbiome has been implicated in disorders ranging from obesity to cystic fibrosis to survival in HIV-positive pneumonia patients. However, there are very little data in the context of tuberculosis. Moreover, the capacity in Africa to study the intersection of TB and the microbiome is also limited.



Dr Charissa Naidoo
South Africa

The project

Dr Naidoo participates in an international multidisciplinary team comprised of a young TB researcher with emerging experience in computational biology (the fellow), mycobacteriologists and diagnosticians, pulmonologists with experience in the microbiome and lung disease, and immunologists.

In the MOSAIC study (Microbiome of South African Incident TB Cases), we propose to characterise the gut microbiome in 100 Xpert MTB/RIF-positive, culture-positive cases (pre-treatment, 2- and 6-months into treatment, and 6-, 12- and 18-months post-treatment), 50 matched symptomatic controls (Xpert-negative, culture-negative), and 200 healthy household contacts (two per case; culture-negative) in Cape

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Charissa Naidoo, Stellenbosch University, South Africa

Year funded: 2019

EDCTP funding: €149,996

Fellow profile: <https://edctp.alumninetwork.org/fe/profiles/view/34e678af-bb7e-4682-8551-5ecd68a097fe>

Town, South Africa. We will leverage the SAMRC-funded project (BAR-TB) recruiting patients with presumptive TB, performing testing (Xpert, culture), microbiological and clinical follow-up. In MOSAIC, the team will, in addition to the work in BAR-TB, collect microbiome specimens, recruit and collect the same specimens from healthy contacts.

Impact

The study is expected to result in advances regarding the role of the microbiome in TB. In the long term, this may lead to targeting the microbiome for diagnosis or treatment outcome. The fellowship will develop the scientific, management and mentorship skills of the fellow, supports trainees and will enhance local computational biology capacity. Moreover, the study will collect additional specimens for future microbiome research.

New ways to predict MDR-TB treatment outcome early

Dr Willy Ssengooba evaluates how other methods of treatment monitoring than by sputum culture may predict outcomes of a shorter MDR-TB treatment regimen

The challenge

Effective treatment monitoring is vital not only for proper patient management but also for preventing the unnecessary continuation of failing treatment and emergence of more drug-resistant *Mycobacterium tuberculosis* (Mtb). Treatment monitoring by sputum culture is the gold standard for TB treatment. However, this method has several problems, including high operational cost and long turnaround time.

The challenge is to develop better alternatives which will protect the currently effective drugs and streamline the development of new drugs for multi-drug resistant tuberculosis (MDR-TB).

The project

Dr Ssengooba proposes to evaluate the effectiveness – compared with culture colony forming units (CFUs) determination – of alternative methods for measuring the response to therapy during the initial 16 weeks of MDR-TB treatment. These methods will be analysed to determine how well they predict MDR-TB patient treatment outcome.

A prospective study will enrol patients 18 years of age or older and diagnosed with MDR-TB according to local standards. Two sputum samples, a spot and an overnight sample, will be taken at weeks 0, 1, 2, 3, 4, 5, 6, 7, 8 and once during month 3 and 4. Follow-up will be active during the intensive phase and passive during the continuation phase up to 18 months of MDR-TB treatment to document treatment outcomes.

Samples will be pooled and homogenised and divided into three portions. Portion one will be used for respectively, 1) FDA- treated AFB smear microscopy, 2) PMA-Xpert/ULTRA assay, and 3) liquid culture for Mtb-TTP. Portion two will be used for 16s rRNA detection in an MBLA assay and portion three for CFUs/mL determination. Data will be analysed for correlation of the results of the alternative methods with results based on reducing culture CFUs.

Project at a glance

Project: EDCTP Career Development Fellowship

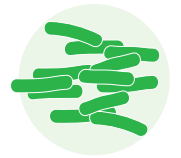
Project lead: Dr Willy Ssengooba, Makerere University, Uganda

Year funded: 2019

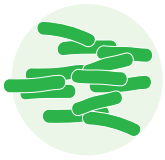
EDCTP funding: €149,750

Impact

Potentially, this study may validate alternative methods of monitoring MDR-TB treatment response in resource-limited settings. Allowing quicker decision making, alternative ways of monitoring may help to protect the available treatment regimens and novel TB drugs, improve the efficiency of phase II trials/treatment regimens and lead to reduced delayed-results costs in the development of new MDR-TB drugs.



Dr Willy Ssengooba
Uganda



Resistance to *Mycobacterium tuberculosis* infection in HIV patients

Dr Elouise Kroon studies innate immune response to TB infection and the exact cells involved in HIV-infected persons.

The challenge

Mycobacterium tuberculosis is a pathogen spread via the inhalation of airborne droplets containing the bacteria from an infected individual. However, some individuals, despite persistent and heavy exposure to *M. tuberculosis* do not become infected and are so-called resisters.

The existence of resistance to infection in tuberculosis (TB) pathogenesis is supported by multiple lines of evidence and is also observed in HIV-infected persons. HIV infection predisposes to TB. However, some HIV-infected persons do not become infected with *M. tuberculosis* and have no history of previous or current TB, despite low CD4 counts and living in environments with high TB incidence.

The contribution of the innate immune system and the exact cells involved in innate immune resistance to infection are not yet completely clear.

The project

Neutrophils are some of the first phagocytes recruited from the pulmonary vasculature to the pulmonary interstitium to control infection and are prominent candidates for possible involvement as primers for microbial clearance. Dr Kroon hypothesises that resistance of HIV-infected individuals to *M. tuberculosis* is due to neutrophils acting as effector cells. In that case, significant transcriptional differences and effector functions will exist in the neutrophil response between hosts who do not develop immune sensitisation to *M. tuberculosis* – as evidenced by IGRA/TST or innate resisters – and those who develop immune sensitisation, or infection susceptible (individuals).

For this study, Dr Kroon will use samples previously collected from a total of 60 HIV-infected persons screened and enrolled in the NIH-funded ResisTB study in Cape Town, South Africa. The samples are subdivided into 4 groups

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Elouise Kroon, Stellenbosch University, South Africa

Year funded: 2019

EDCTP funding: €150,000

based on IGRA/TST results (positive/negative) and age category (18- 25 years, 35-60 years). Age is used as a surrogate for exposure intensity in an area of high *M. tuberculosis* transmission.

The objectives of the study are to compare neutrophil numbers, phenotype and activation markers between the specified study groups. Secondly, genomic total RNA will be extracted from the *M. tuberculosis*-infected and -uninfected neutrophils at different time points and characterised for the difference in transcriptional responses using RNA sequencing. Finally, differences in effector mechanisms of neutrophils, such as NETosis, will be investigated for the study groups using microscopy.

Impact

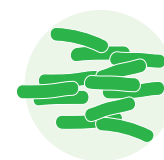
By gaining a better understanding of the resister phenotype and the potential role of neutrophils in *M. tuberculosis* infection resistance, the study may reveal clinically important activities for prevention and treatment development.



Dr Elouise Kroon
South Africa

Pulmonary TB and the role of the microbiome

Dr Kateete will study microbiome composition in relation to immune responses in patients with pulmonary TB and household control groups (HIV+ or HIV-/TB-).



The challenge

The microbiota or microbiome, complex communities of microbes in mammals, play an important role in health and disease including for the induction and functioning of the immune system. However, baseline information on their composition and potential role(s) in pulmonary tuberculosis (TB) in sub-Saharan Africa, is lacking.

The project

The overall purpose of Dr Kateete's study is to determine the microbiome composition in patients with pulmonary tuberculosis and examine its relationship with treatment and immune response in these patients relative to their household healthy contacts without TB-infection and HIV-infection.

Specific aims of the study are, first, to examine the relationship between sputum and gut microbiome diversity and disease and the relationship between sputum and gut microbiome composition and treatment response among patients on first-line TB therapy, including whether dysbiosis resolves in patients who get cured of TB after successfully completing anti-TB therapy. Secondly, Dr Kateete will investigate the relationship between sputum and gut microbiome composition and inflammatory cytokine production capacity.

He will conduct a longitudinal study nested in a project at the Mulago National Referral Hospital in Kampala, Uganda, which maintains a cohort of 320 Xpert-positive, treatment-naïve adult TB patients with follow-up at months 2, 5, 12, 18 and 24. Sputum, stool and blood samples from 160 participants (purposive sampling) at baseline (day 0) and months 2, 5, 12, 18 & 24 for microbial and cytokine profiles. Out of the 160 participants, 100 will be pulmonary TB cases randomly selected from the parent MTI-cohort of whom 50 will be HIV-positive (TB+/HIV+) and 50 HIV-negative (TB+/HIV-). Sixty (60) household contacts will be similarly investigated

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr David Kateete, Makerere University, Uganda

Year funded: 2019

EDCTP funding: €150,000

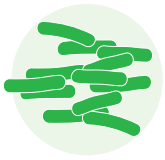
as the comparator group (controls). Household contacts will be TB-negative family members of the 100 TB cases, of whom one half (30) will be HIV-positive without respiratory/pulmonary symptoms based on interferon- γ release assay (i.e. HIV+/TB- sub-group) while the other half (30) will be both HIV-negative and TB-negative i.e. the healthy contacts (HIV-/TB-).

Impact

The study will deliver human microbiota profiles in tuberculosis from a TB-endemic/HIV-burden setting. Such results could be used as a reference for other settings in sub-Saharan Africa. The data also may reveal potential markers of TB-treatment response or failure. Such information is vital in devising novel region- or country-specific interventions.



Dr David Kateete
Uganda



Understanding the genetics of TB-drug resistance for clinical use

Dr Navisha Dookie aims to optimise the clinical utility of whole-genome sequencing to enable individualised treatment of patients with drug-resistant TB.

The challenge

Resistance to antituberculosis drugs has emerged as a key public health challenge. The last decade has seen an unprecedented increase in resistance to rifampicin and isoniazid (defined as multidrug resistance) and has been supplanted by additional resistance to fluoroquinolones and second-line injectable agents: amikacin, kanamycin and capreomycin (defined as extensive resistance).

Multidrug-resistant TB and extensively drug-resistant TB (XDR-TB) drive approximately a quarter of the global TB-related mortality, are unsustainably costly to treat and pose a major threat of continued transmission. Current treatment options for XDR-TB fail to cure 30-75% of patients with XDR-TB, contributing to an emerging public health crisis. The first challenge is to improve current diagnostics, which have a limited capacity to detect drug resistance and slow turnaround times.

The project

Dr Dookie proposed a study embedded in the CAPRISA 020 Index Study. This study is the first of its kind, utilising the most robust sequencing technology to provide an individualised treatment regimen for patients with drug-resistant TB. In the fellowship study, Dr Dookie will focus on improving understanding of the development of resistance in patients undergoing treatment, optimise the extraction of DNA directly from sputum and assess the contribution of the various pathogen factors that impact on drug-resistant TB outcomes.

Impact

The fellowship will translate basic science studies which will improve the utility of sequencing technology to provide a robust real-time diagnostic assay. It will also provide a comprehensive algorithm for the inclusion

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Navisha Dookie, Centren for the Aids Programme of Research in South Africa (CAPRISA), South Africa

Year funded: 2019

EDCTP funding: €139,550

and exclusion of drugs, based on the clinical relevance of resistance mutations. Moreover, it will improve understanding of the differential pathogenesis and disease outcomes by strain type and thus inform targeted interventions for interrupting transmission. This study may pave the path for new therapeutic and management approaches for drug-resistant TB.



Dr Navisha Dookie
South Africa

Comprehensive genetic profiles of drug resistance

Dr Anzaan Dippenaar aims to guide treatment of rifampicin-resistant TB through early drug susceptibility testing.

The challenge

TB treatment strategies rely on the use of combination therapy to reduce the risk of antibiotic selection of resistance and thus to protect the limited repertoire of anti-tuberculosis drugs available.

Optimising the treatment regimen for patients with drug-resistant tuberculosis is dependent on knowledge of genetically encoded resistance. *M. tuberculosis* develops drug resistance through mutations in target genes. Identifying these mutations creates a drug susceptibility profile of the infecting pathogen.

Sequencing the whole genome of *M. tuberculosis* offers the opportunity to identify mutations conferring drug-resistance in all genes known to be involved in resistance. This technology has already been implemented in the United Kingdom and in the USA to guide patient management, diagnostic policy and surveillance. In South Africa, whole-genome sequencing has been used to describe the epidemiology of extensively drug-resistant tuberculosis with particular emphasis on transmission and the evolution of resistance. This technique has also questioned the reliability of routine testing for drug susceptibility in high-throughput laboratories.

The project

Dr Dippenaar proposed to harness the resolution of whole-genome sequencing to provide comprehensive genetic drug resistance profiles on all rifampicin-resistant tuberculosis isolates from patients resident within the Western Cape Province. The objective is to provide clinicians with these profiles in such a way that informed therapy changes can be made at their discretion to improve treatment outcome.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Anzaan Dippenaar, Stellenbosch University, South Africa

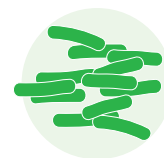
Year funded: 2019

EDCTP funding: €149,984

Impact

Successfully establishing the genetic drug resistance profiles of all rifampicin-resistant tuberculosis isolates will assist the case management of patients with drug-resistant tuberculosis, enabling doctors to make informed therapy changes and improve outcomes.

The data generated by whole-genome sequencing will also enable to longitudinally measure the impact of policy changes on the drug-resistant tuberculosis epidemic.



Dr Anzaan Dippenaar
South Africa



Emerging drug resistance and prevention of malaria in pregnancy

Dr Atinuke conducts an observational study on parasite resistance in the context of intermittent preventive treatment of pregnant women.

The challenge

Malaria in pregnancy is an issue of public health concern due to the risk of significant adverse maternal and infant outcomes. Nigeria currently has the highest infection and transmission rates, as well as the highest at-risk population for malaria disease globally.

Intermittent preventive treatment in pregnancy (IPTp) is strongly advocated to reduce the occurrence of this disease, but resistance to the currently prescribed drug i.e. sulphadoxine-pyrimethamine (SP) is already being reported. However, data on the occurrence of IPTp-SP resistance in Nigeria and West Africa is scarce.



Dr Atinuke Olaleye
Nigeria

The project

This project aims to describe the burden of sulphadoxine-pyrimethamine (SP) resistance and determinants of its occurrence among pregnant women receiving Intermittent Preventive Treatment (IPTp) in Nigeria. It will also identify connections between SP drug resistance markers and efficacy of IPTp-SP, as well as assess maternal and neonatal health outcomes.

A prospective observational study will be conducted for 24 months within a malaria-endemic community. Pregnant women will be counselled during their antenatal clinic visits and consenting women meeting the inclusion criteria will be recruited for the study. Relevant socio-demographic and obstetric information will be obtained, and blood samples will be taken pre- and post-IPTp-SP administration at scheduled intervals, for analysis. Microscopically confirmed parasitaemic samples will be analysed using PCR to detect drug resistance markers (pfdhfr and pfdhps). Participants will be followed up until 7 days post-delivery and assessed for maternal and fetal outcomes (anaemia, low birth weight, preterm delivery, placental parasitaemia, stillbirth, early neonatal death).

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Atinuke Olaleye, Babcock University, Nigeria

Year funded: 2017

EDCTP funding: €85,875

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/73f76229-e4f6-4c66-beae-061b16b7bcec>

Impact

As data on the occurrence of IPTp-SP resistance in Nigeria and West Africa is scarce, this study will contribute to filling this gap in the relevant body of knowledge. The study is the first in this region of Nigeria and will generate data to complete the picture of sulphadoxine-pyrimethamine resistance. The data may form a reference and benchmark for other studies replicated in other regions to produce a national overview of sulphadoxine-pyrimethamine resistance. This will also help government public health officials to review current practices pertaining to intermittent malaria chemoprophylaxis in pregnancy. Moreover, the project will improve local clinical research capacity providing other researchers and scientists with data and equipment for genotypic detection of resistance traits in South-West Nigeria.

Assessing the safety of primaquine added to standard malaria treatment



*Dr Richard Mwaiswelo assesses the safety and efficacy of low-dose primaquine for *P. falciparum* gametocyte clearance and transmission blocking in patients with reduced or null CYP2D6 activity.*

The challenge

The World Health Organization (WHO) has now recommended the addition of a 0.25 mg/kg single-dose primaquine (PQ) to standard artemisinin-based combination therapy for the elimination of *Plasmodium falciparum* malaria in low-transmission settings and for containment in areas threatened by artemisinin resistance. The dose has shown to be safe even in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency and is efficacious for clearance of *P. falciparum* gametocytes. However, due to remaining safety concerns, most malaria-endemic sub-Saharan African countries have not adopted the PQ recommendation.

Some individuals with normal G6PD status nonetheless developed adverse events, including acute hemolysis following treatment with this single low-dose PQ. Furthermore, a failure rate of =5 has also been reported in gametocyte clearance and transmission-blocking after treatment with even high doses of PQ, which suggests other factors being involved in determining PQ safety and efficacy. This study aims to collect better information regarding the effect of CYP2D6 isoenzyme polymorphism on PQ safety and its efficacy in sterilizing mature *P. falciparum* gametocytes.

The project

Dr Mwaiswelo and his team aim to assess the safety and efficacy of 0.25 mg/kg single-dose PQ when added to standard artemether-lumefantrine regimen for clearance and blocking transmission of *P. falciparum* gametocytes in patients with CYP2D6 reduced/null activity as compared to those with normal/increased enzyme activity.

Children 1-10 years of age and with uncomplicated *P. falciparum* malaria will be enrolled (155) and treated with standard artemether-lumefantrine regimen plus a 0.25 mg/kg single-dose of PQ and then followed up on days 0, 1, 2, 3, 7, 14, 21 and

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Richard Mwaiswelo, Tropical Pesticides Research Institute, Tanzania

Year funded: 2018

EDCTP funding: €148,050

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/47f95e75-6b4d-4858-96cb-c703c9489634>

28 for clinical and laboratory assessment.

Primaquine is administered with the first dose of artemether-lumefantrine. Safety assessment is performed using the PQ Roll-Out Monitoring Pharmacovigilance Tool.

Gametocytes are being detected and quantified by microscopy and Pfs25 mRNA quantitative nucleic acid sequence-based amplification (QT-NASBA) on days 0 and 7. For a subset of 100 participants, post-treatment infectiousness will be assessed by mosquito feeding assays on day 7. The CYP2D6 status will be determined using PCR followed by restriction fragment length polymorphism (RFLP) analyses.

Impact

The expected impact will be to establish the much-needed information on the safety and efficacy of 0.25 mg/kg single-dose PQ in individuals with reduced/null compared to those with normal/increased CYP450 2D6 isoenzyme activity. This information is needed before the WHO PQ policy can be implemented, especially in sub-Saharan Africa.



Dr Richard Mwaiswelo
Tanzania



Preventing malaria in pregnancy while avoiding the development of further drug-resistance

Dr Jean-Bertin Bukasa Kabuya aims to improve standard intermittent presumptive treatment outcomes by introducing a rapid test for SP-resistant parasites at the first antenatal care visit.

The challenge

Malaria in pregnancy (MIP) may result in serious clinical consequences for mother and child. In moderate- to high-transmission areas of sub-Saharan Africa, the World Health Organization (WHO) recommends the use of long-lasting insecticidal nets (LLINs) together with Intermittent Preventive Treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP) and/or treatment of confirmed cases.

However, there are concerns that IPTp-SP efficacy is becoming less as a consequence of the ever-increasing parasite resistance to SP. Continued use of SP for IPTp would result in further reduction of IPTp-SP efficacy and compromise the prevention of MIP-associated adverse outcomes. As SP needs to remain the recommended antimalarial drug for IPTp, the challenge is to devise strategies to prevent and treat which avoid furthering SP-resistance of the parasite.

The project

Reducing SP interaction with the already mutated parasite would prevent further selection of mutated parasites, reduce resistance to SP and improve its efficacy. This may be achieved by introducing at the first antenatal care (ANC) visit, a malaria Rapid Diagnostic Testing (mRDT). Mothers testing positive will then be treated with a fully effective antimalarial drug before being administered SP; mothers testing negative will receive SP as per current recommendations.

Therefore, Dr Kubuya proposed to compare the current IPTp-SP treatment with IPTp-SP in combination with an mRDT and treatment at the first ANC visit (IPTp-SP+) in terms of efficacy at clearing peripheral maternal parasitaemia and prevention of adverse outcomes associated with MIP. Volunteer mothers not infected with

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Jean-Bertin Bukasa Kabuya, Tropical Diseases Research Centre (TDRC), Zambia

Year funded: 2018

EDCTP funding: €150,000

Fellow profile: <https://edctpalumninetwork.org/fellow/profiles/view/f86f5f24-2acc-42cf-9473-3b93610b94f8>

HIV and meeting the inclusion criteria will be recruited for this clinical trial. Relevant socio-demographic and clinical information is collected and blood samples are taken for haemoglobin and malaria molecular testing at enrolment, days 14, 28, 42 and 63, and at delivery. In addition, cord blood and a placental biopsy will be collected, and babies' haemoglobin will be measured to determine malaria parasitology and histopathology.

Impact

Data from this study may directly help MIP leaders to review current practice for the prevention of malaria in pregnancy. Positive outcomes will expand the available medical interventions for this special population and contribute to averting resistance to SP.



Dr Jean-Bertin Bukasa Kabuya
Zambia

Biomarkers for malaria detection and population level surveillance



Dr Kingsley Badu evaluates the possible role of infectious-bite biomarker PSOP24-377 in tracking malaria transmission intensity to improve control efforts.

The challenge

The tools used in measuring malaria transmission intensity have different sensitivities at different geographical scales over time and space. This reflects changes in vector exposure, parasite infections and the dynamics of changing human immunity. Therefore, the intrinsic sensitivity of tools to detect short term changes in transmission is highly desirable. Accurate data on transmission intensity will be crucial for directing control efforts, developing and testing new interventions, as well as predicting the effects of these interventions under various conditions.

However, current tools have limitations in sensitivity at low-level transmission or lack the inherent ability to track short-term changes. Changes measured by traditional tools reflect either parasite or vector exposure but not both. The challenge is to develop an 'ideal' tool for tracking malaria transmission intensity. It should reflect both exposure to the vector, parasite infection and human immunity, detect short-term changes and be applicable at both individual and population level.

The project

Sporozoite and ookinete proteins have been identified as a promising marker for an infectious bite as human immune response correlates with seasonal vector and parasite exposure and thus. The role of infectious-bite markers to detect short-term changes in malaria transmission has not been thoroughly studied.

Dr Badu proposed to evaluate candidate biomarkers to address the current challenges regarding tools to measure malaria transmission. It is hoped that these biomarkers will prove to be sensitive for the identification of transmission hotspots, vulnerable populations and inform focused interventions to speed up malaria elimination. Using longitudinal community

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Kingsley Badu, Kwame Nkrumah University of Science and Technology (KNUST), Ghana

Year funded: 2018

EDCTP funding: €144,500

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/dd9b80eb-9878-464e-a1e6-70a743d58f62>

cohorts, under varying transmission levels, Dr Badu is studying the dynamics of antibody response to candidate biomarkers in comparison to other salivary proteins to validate infectious-bite markers.

Impact

The research capacity of the fellow will be enhanced for protein chemistry, bioinformatics and project management. Moreover, standard infectious-bite markers developed in the study may be applied in other parts of Africa.



Dr Kingsley Badu
Ghana



Implementing a WHO-recommended malaria treatment regimen in routine healthcare

Dr Dominic Mosha evaluates the safety of single low-dose primaquine coadministered with ACT in routine healthcare practices.

The challenge

The success of malaria control programmes has contributed to a decrease in malaria mortality rates by approximately 50% worldwide over the past 15 years. To maintain this gain, WHO recommends use of primaquine, in conjunction with artemisinin-based combination therapy (ACT), to block *Plasmodium falciparum* transmission in areas approaching malaria elimination and/or facing artemisinin resistance. East Africa including Tanzania faces artemisinin resistance which may justify adopting the recommendation.



Dr Dominic Mosha
Tanzania

Only one African country, Swaziland, has included PQ as part of the first-line treatment for *P. falciparum* in its national policy. Concerns related to safety monitoring of this new treatment recommendation is likely the key barrier for adoption of the regimen.

The project

Primaquine (PQ) may cause haemolytic side effects in individuals who have G6PD deficiency; the potential for haemolysis depends on the dose. The current WHO-recommended dose of 0.25mg/kg is low enough to mitigate the side risk of haemolysis in G6PD deficiency individuals. This low dose also enables treatment without requiring G6PD testing.

Dr Mosha aims to determine the readiness, challenges and policy options for the effective roll-out of PQ with ACT in routine healthcare. He is conducting a repeated cross-sectional study involving clinicians as a primary study population, who are treating uncomplicated malaria patients with ACT+PQ regardless of their G6PD status, with a 7 days follow-up and management of adverse events. Malaria patients are therefore the secondary study population.

The project will assess 16 randomly selected facilities in two rural districts (human resources, laboratory capacity and medical supplies)

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Dominic Mosha, Ifakara Health Institute (IHI), Tanzania

Year funded: 2019

EDCTP funding: €149,720

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/d3bbcd76-1320-4783-8999-cbf933934d5c>

and equip 6 randomly sampled intervention facilities with the tools and supplies needed for monitoring and managing G6PD adverse events. Health care providers will then be trained to use the PQ Roll-Out Monitoring Pharmacovigilance Tool, which will subsequently be adopted and used by healthcare providers in malaria treatment using ACT+PQ, for a period of six months with minimal supervision. Healthcare provider challenges will be assessed and the training package will be revised. The revised training package and safety monitoring tool will then be used for four months. Finally, a comprehensive safety training package will be developed, including on the basis of in-depth interviews. 'Key Informant' interviews will be used to determine the needs for a successful roll-out of the PQ+ACT treatment regimen. The interviews will involve officers from the Ministry of Health, the National Malaria Control Programme, and the Safety Drug Monitoring Board.

Impact

The study's findings may provide useful evidence to facilitate the roll-out of the PQ+ACT regimen thus contributing to lowering the barriers for countries in sub-Saharan Africa to adopt the WHO recommended regimen when confronted with growing artemisinin resistance.

Field-based screening model for *P. vivax* and *P. ovale* malaria infection



Dr Laurent Dembele aims to establish a screening model for malaria liver-stage infection by Plasmodium vivax and Plasmodium ovale using field-isolated sporozoites from infected mosquitoes.

The challenge

Research focusing on *Plasmodium vivax* and *Plasmodium ovale* has been severely limited as most malaria control programmes have focused on *P. falciparum* malaria. However, *P. vivax* and *P. ovale* have the unique attribute to cause malaria relapses, resulting from the activation of quiescent hepatic hypnozoites. This hinders global efforts to control and eliminate malaria.

Currently, primaquine is the only licensed drug able to eradicate hypnozoites. However, primaquine is not a well-tolerated drug. The challenge is to develop better drugs.

The project

Very few tools are available to support biological studies and screening efforts for *P. vivax* and *P. ovale*. There is also no reliable robust culture system for the blood-stage forms of *P. vivax* and *P. ovale*, nor for the most closely related simian malaria species, *P. cynomolgi*. Thus, access to *P. vivax* and *P. ovale* is dependent on field isolates. These major obstacles have limited molecular and cellular investigation of *P. vivax* and *P. ovale* malaria biology.

An optimised in vitro liver-stage model supporting biological studies and screening efforts which would be easily accessible to all researchers is critically needed to enable the discovery of new drugs. In a first step, the simian parasite, *P. cynomolgi* which is related to *P. vivax*, was used to establish an in vitro culture system in which the full liver-stage life-cycle of the parasite including the hypnozoite stage, was recapitulated. It was demonstrated that this system could be used for testing candidate drugs or exploring the liver-stage biology including hypnozoite.

Dr Dembele now aims to accelerate research towards an optimised drug assay to evaluate the anti-hypnozoite activity of candidate drugs. The

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Laurent Dembele, Université des Sciences, des Techniques et des Technologies de Bamako, Mali

Year funded: 2018

EDCTP funding: €130,125

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/d1b62f56-b8d1-492a-9363-ac19d13628fc>

project comprises field and clinical activities: experimental infection of *P. vivax* and *P. ovale* to *Anopheles* spp in Addis Ababa and Bamako; routine production of sporozoites from *P. vivax*- and *P. ovale*-infected mosquitoes. Ultimately, Dr Dembele aims to establish an in vitro optimised malaria liver-stage infection and screening model using field-isolated sporozoites from *P. vivax*- and *P. ovale*-infected mosquitoes.

Impact

The successful development of a malaria liver-stage infection and screening model for *P. vivax*- and *P. ovale* would be an important contribution to more effective malaria control efforts (focused on *P. falciparum* malaria) as *P. vivax* and *P. ovale* have the ability to cause malaria relapses.



Dr Laurent Dembele
Mali



Pharmacokinetics of piperazine administered to prevent malaria among pregnant women on standard ART

Dr Clifford George Banda aims to determine the impact of dolutegravir-based ART on the pharmacokinetic profile and placental penetration of piperazine used in the intermittent preventive treatment of malaria in pregnant women.

The challenge

In malaria-endemic settings in Africa, HIV infection is also highly prevalent and HIV-infected pregnant women are on antiretroviral therapy (ART) and trimethoprim-sulphamethoxazole.

In the case of malaria in pregnancy, dihydroartemisinin-piperazine (DP) is an effective alternative to sulfadoxine-pyrimethamine (SP) for intermittent preventive treatment of malaria in pregnancy (IPTp) in areas where SP resistance is high. However, it has been shown that the current efavirenz-based ART reduces exposure to piperazine (the longer-acting partner drug of DP) below purported efficacious concentrations during IPTp. Therefore, different dosing regimens for DP have been suggested and a number of countries with malaria-endemic settings plan to adopt a dolutegravir-based ART regimen for first-line treatment of HIV-infection.

Unfortunately, recently, concerns have arisen regarding possible dolutegravir-associated neural tube defects among children born to women on dolutegravir-based ART (at the time of conception or during the first trimester of pregnancy). This has prompted national HIV programmes to delay the roll-out of dolutegravir in women of childbearing potential and for first-line ART initiation during pregnancy. The challenge is to meet this urgent need to understand their impact on the pharmacokinetic profile and placental penetration of DP.

The project

With the PENETRATE study, Dr Banda aims to determine the impact of standard ART on the pharmacokinetic profile and placental penetration of piperazine administered as DP for intermittent preventive treatment of malaria in pregnant women in Malawi.

A pharmacokinetic cohort study – nested within two large on-going EDCTP-MRC funded clinical trials (IMPROVE I & II) – will be conducted in two steps among HIV-uninfected and matched

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Clifford George Banda, University of Malawi, Malawi

Year funded: 2018

EDCTP funding: €149,999

HIV-infected pregnant women who started dolutegravir-based ART.

First, plasma blood samples will be collected over a period of 28 days following intake of DP to compare pharmacokinetic (PK) parameters of piperazine between the HIV-infected and HIV-uninfected groups.

Secondly, two similar separate cohorts of women from the IMPROVE trials will have a paired maternal plasma and umbilical cord vein sample collected at delivery to compare the ratio of maternal/umbilical cord piperazine concentrations between HIV-uninfected and HIV-infected pregnant women on standard ART.

Impact

Findings of the PENETRATE study will inform accurate dosing of DP when co-administered with standard ART, thereby informing the dosing regimen of dihydroartemisinin-piperazine in the IMPROVE II clinical trial and contributing to the pool of evidence needed by WHO to recommend the use of DP for IPTp among HIV-uninfected and -infected pregnant women on standard ART in sub-Saharan Africa.



Dr Clifford George Banda
Malawi

Extended benefits of the RTS,S/AS01 malaria vaccine



Dr Symon Kariuki aims to establish the impact of RTS,S/AS01 vaccination (combined with insecticide-treated bednets) on preventing neurobehavioural impairment in children.

The challenge

P. falciparum malaria is still an important cause of mortality and morbidity. Over half a million malaria deaths were reported in 2015 particularly in children, and malaria was associated with 795 per 100,000 disability-adjusted life years in 2016.

Severe malaria causes neurobehavioural impairments (behavioural disorders, seizures and cognitive and language impairments). The effect of chronic parasitisation and repeated episodes of mild malaria on neurobehavioural outcomes is not well documented. Young children (< 2 years) are particularly susceptible since this is the period of maximum brain growth postnatally.

The project

Phase III, RTS,S/AS01 vaccine showed efficacy of up to 55% against all episodes of malaria, and 45% against cases of severe malaria. Insecticide-treated bednets (ITBN) prevented severe malaria morbidity in 44% of children under 5 years in Kilifi, Kenya. Therefore, by preventing malaria, RTS,S/AS01 and ITBN may have prevented neurobehavioural impairments attributable to malaria, and may also improve school participation and performance especially because the vaccine and the ITBN were given in the first two years of life.

Dr Kariuki proposes to follow up Kenyan children vaccinated with RTS,S/AS01 during the first two years of life and who used ITBN during the first five years of life. Those who were not vaccinated are to be examined for neurobehavioural impairments and school participation approximately nine years after initial vaccination and eleven years after ITBN intervention.

Dr Kariuki will perform the primary study on the Kenyan coast on a sample of 600 children in a phase II RTS,S/AS01 trial undergoing active surveillance for malaria, and in a random sample

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Symon Kariuki, African Research Collaboration for Health Ltd, Kenya

Year funded: 2019

EDCTP funding: €149,623

of 1052 children who participated in the ITBN intervention in Kilifi, Kenya. The phase II RTS,S/AS01 findings in Kilifi will be used to conduct an external validation study using children in a phase III RTS,S/AS01 trial from areas with passive surveillance in Western Kenya. Trained clinicians will take clinical history to diagnose seizure disorders and to document medical history. Behavioural disorders, cognitive impairments and school participation will be examined using assessment tools adapted to the local populations and these will be administered by trained neuropsychological assessors.

Impact

Dr Kariuki aims to provide evidence of possible extended benefits of the malaria vaccine RS,S/AS01 for the prevention of neurobehavioural impairment in young children.



Dr Symon Kariuki
Kenya



Impact of seasonal malaria chemoprevention on protective immunity

Dr Mariama Combassere-Cherif will conduct a proof of concept study for improving interventions which target the asymptomatic malaria parasite reservoir.

The challenge

Seasonal Malaria Chemoprevention (SMC) is a new strategy to reduce the malaria burden in young children in Sahelian countries. SMC consists of the administration of full treatment courses at regular intervals during the malaria high-transmission season. However, it is not clear if there is a cumulative effect of SMC on the acquisition of antibodies to malaria antigens.



Dr Mariama Combassere-Cherif
Burkina Faso

The project

Dr Combassere-Cherif intends to establish the key elements for understanding the potential role of seasonal malaria chemoprevention (SMC) in the buildup of immunity against clinical malaria in Burkina Faso. Specifically, she proposed to study how SMC during low and high transmission affects parasite presence, density, and diversity (or clones), and host antibodies response. She aims to establish the relationship between asexual parasite densities, multiclonal infections with *Plasmodium falciparum* and immune responses before and after SMC.

Building on existing collaborations, she and her team will conduct a prospective cohort study following the national health policy of SMC in Burkina Faso. It is a full treatment course of sulfadoxine-pyrimethamine plus amodiaquine (SP+AQ) given to 6-59 months old children at monthly intervals during the malaria high-transmission season from July to October. The project comprises five cross-sectional surveys to establish the relationship between SMC, malaria prevalence, parasite densities, the number of new *P. falciparum* clones as well as the immune responses across surveys, before and after SMC.

Impact

The approach used in this project could be implemented as part of a surveillance program to explain the impact of SMC in Burkina Faso where malaria is endemic, stable and seasonal. This

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Mariama Combassere-Cherif, Université Nazi Boni (UNB), Burkina Faso

Year funded: 2019

EDCTP funding: €149,120

study will serve as a proof of concept in order to optimise the design of interventions targeting the asymptomatic reservoir of the parasite.

Combining seasonal malaria chemoprevention with nutrients and vitamin supplementation



Dr Paul Sondo aims to establish whether a combined strategy of seasonal malaria chemoprevention (SMC) with nutrients and vitamin A-Zinc supplementation will improve SMC outcomes and reduce malnutrition.

The challenge

Malaria and malnutrition represent major public health concerns worldwide and especially in sub-Saharan Africa. In Burkina Faso, the burden of malaria and associated mortality among children under 5 years old remains high, despite the implementation of Seasonal Malaria Chemoprophylaxis (SMC), an intervention aimed at reducing malaria prevalence among children aged 6-59 months.

This raises the question which hidden factors possibly affect the responsiveness of SMC intervention negatively. Malnutrition, and in particular micronutrient deficiency, is one of the factors that may negatively affect the effectiveness of SMC, while treating micronutrient deficiencies is known to reduce malaria mortality prevalence in highly prevalent malaria zones such as rural settings.

The project

Dr Sondo hypothesises that a combined strategy of SMC with a daily oral nutrients supplement, either Vitamin A-Zinc or Plumpy'Nut®, a fortified peanut butter-like paste, will enhance the immune response. This would decrease the incidence of malaria in this population and also reduce the burden of malnutrition among children under SMC coverage.

Prior to the SMC implementation by the National Malaria Control Program, children under SMC coverage will be identified through the Health and Demographic Surveillance System (HDSS). Children will be randomly assigned to one of three groups: a) SMC alone, b) SMC + Vitamin A-Zinc, or c) SMC+Plumpy'Nut®.

After each SMC monthly distribution, children will be visited at home to confirm drug administration and followed up for six months. Anthropometric indicators will be recorded at each visit. Blood samples will be collected

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Paul Sondo, Institut de Recherche en Sciences de la Santé, Burkina Faso

Year funded: 2019

EDCTP funding: €147,500

for thick and thin film and haemoglobin measurement and spotted onto filter paper for further PCR analyses.

The primary outcome will be measured by the incidence of malaria in each group. Secondary outcome measures include mid-upper arm circumference gain and weight gain from baseline measurements, coverage and compliance to SMC, and prevalence of molecular markers of antimalarial resistance Pfcr1, Pfmdr1, Pfdhfr and Pfdhps.

Impact

If successful, this project may serve as a pilot demonstrating the value of an integrated strategy. While relying on existing strategies, implementation of a joint intervention will be scalable to country and regional levels.



Dr Paul Sondo
Burkina Faso



Malaria in pregnancy and the uterine microenvironment

Dr Caroline Kijogi aims a better understanding of macrophage polarisation in placental malaria pathogenesis, ultimately to improve outcomes of malaria in pregnancy.

The challenge

Macrophages account for one of the most abundant leucocytes infiltrating the uterine lining during pregnancy. They play a key role in the maintenance of a healthy pregnancy by promoting implantation, trophoblast invasion, placentation, tissue remodelling and angiogenesis.

Macrophages are present at all stages of pregnancy unlike other leukocytes and are integral in the immunological adaptations that facilitate tolerance of the semi-allogenic fetus. Due to their plasticity and heterogeneity, they may act as either pro- or anti-inflammatory mediators. The activation state and function of macrophages is dependent on the local tissue microenvironment, enabling their polarisation into either of the two distinct subsets; the classically activated, M1 macrophages which are proinflammatory and the alternatively activated, M2 macrophages which are anti-inflammatory and immunoregulatory.

During the course of pregnancy, an M1 bias is observed transiently at the initial immunological phase then a switch to M2 phenotype ensues till delivery. Secreted cytokines, chemokines, growth factors, hormones as well as interactions with related cells are important in the acquisition of the unique phenotypes and functions of macrophages.

The project

Infections during pregnancy can disrupt the uterine microenvironment and have profound effects on macrophage activity and subsequently the pregnancy outcome. *Plasmodium falciparum* infection during pregnancy causes massive recruitment of monocytes and macrophages to the intervillous space of the placenta, the site of sequestration of infected erythrocytes. Dr Kijogi

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Caroline Kijogi, Mount Kenya University, Kenya

Year funded: 2019

EDCTP funding: €149,875

hypothesises that the accumulation of these cells causes an M1/M2 imbalance that skews polarisation to M1 phenotype possibly with deleterious effects on the growing fetus.

She will test this hypothesis by examining the expression of cell surface markers for M1 and M2 macrophages (CD80, CD86, CD68 for M1 and CD163, CD206, CD209 for M2) by flow cytometry. She will also assess the localisation of placental M1 and M2 macrophages by immunohistochemistry. To assess the functional capacity of these cells, the expression levels of related angiogenic factors and cytokines upon stimulation with PMA-ionomycin will be examined. Also, for *in vitro* polarisation studies, decidual macrophages will be cultured in the presence of malarial antigens.

Impact

Findings from this study will lead to a better understanding of *P. falciparum*-mediated macrophage polarisation during placental infection and could be probed further in the development of immuno-therapeutic tools to improve outcomes during malaria in pregnancy. Such treatment could be explored to reverse M1 polarisation and may have potential as adjunctive treatment for malaria in pregnancy.



Dr Caroline Kijogi
Kenya

Scaling up mass malaria test-treat-track programmes for children



Dr Ndong Ignatius Cheng aims to identify ways to scale up test-treat-track, programmes to include whole communities thus reducing overall parasite load prior to specific interventions.

The challenge

Asymptomatic malaria parasitaemia poses a serious threat to malaria control efforts. Persons carrying the malaria parasite but showing no symptoms, constitute a reservoir that fuels the transmission process.

Mass parasite clearance can deplete these parasite reservoirs and lower the transmission potential. Therefore, efforts are made to scale up current effective interventions such as the use of long-lasting insecticidal nets (LLIN), intermittent preventive treatment in children (IPTc), and test, treat and track (TTT) programmes. However, in designing interventions to reduce the burden of malaria in children under five, mass TTT has largely been left out. Adults, usually not targeted, remain reservoirs for transmission. Mass testing, treating and tracking (MTTT) of the whole population is needed to reduce the parasite load before implementing the interventions mentioned.

The project

Seasonal malaria chemoprophylaxis (SMC) has been adopted for selected localities in Ghana. The impact of these interventions could be enhanced if associated with MTTT at baseline to reduce the parasite load. In a pilot with MTTT in Ghana, coverage of more than 75% was achieved in target communities. This reduced asymptomatic parasitaemia by 27.4% from July 2017 to July 2018. It is important to continue this work so as to generate time-series data to better analyse and understand the prevalence trends and bottlenecks. However, questions remain on what we need for MTTT scale-up and must be addressed.

The hypothesis is that implementing MTTT complemented by community-based case management can reduce the prevalence of asymptomatic malaria parasite carriage in endemic communities. Thus, Dr Cheng will

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Ndong Ignatius Cheng, University of Ghana

Year funded: 2019

EDCTP funding: €146,537

conduct an MTTT programme in the Pakro subdistrict of Ghana among household members two months and older. All cases of confirmed asymptomatic parasitaemia or clinical malaria will be treated. The entire population will be followed up in two years. Hospital records will be studied to document trends in malaria admissions in the area during the study.

Impact

In addition to bringing a concrete community health benefit and documenting trends in asymptomatic malaria parasitaemia in the study population, this implementation study will also analyse the challenges and bottlenecks associated with scaling up mass test, treatment and tracking programmes. In addition, the project will have a strong capacity development component, not only for the fellow and his development as a researcher and trainer of junior scientists but also for his research team. This comprises nurses, community health workers (HWs) and research assistants who will be trained on ethics, good clinical practice, population engagement and sensitisation techniques.



**Dr Ndong Ignatius
Chenge**
Ghana



Highly-sensitive rapid diagnostics and malaria in pregnancy case management

Dr Marc Christian Tahita studies the impact of additional screening with highly-sensitive rapid diagnostic tests on placental malaria and low birth weight.

The challenge

National malaria control strategies in pregnant women rely primarily on effective case management along with the use of long-lasting insecticide-treated nets (LLINs) throughout pregnancy. This includes intermittent preventive treatment with sulfadoxine-pyrimethamine (IPTp-SP) in the second and third trimesters in malaria-endemic regions in sub-Saharan Africa.

For IMPTp, three 3 or more doses are recommended by the national malaria control programme of Burkina Faso but available data suggests that only 19% of eligible women received this in 2016 despite observed high attendance to the antenatal clinic. Therefore, adherence to IPTp may be affected by perceptions, acceptability and contextual factors which need to be understood better to improve the effectiveness of these health interventions.

In addition, all malaria cases should be confirmed either by microscopy or using a rapid diagnostic test (RDTs) before any treatment. Despite the crucial role of RDTs in improving malaria case management, many malaria cases are missed in pregnant women due to the recommended RDTs which are unable to detect very low parasitaemia. Identifying lower density infections in pregnant women using highly-sensitive RDTs (HS-RDTs) and clearing them with an effective ACT could improve the outcome of the pregnancy.

The project

Dr Tahita aims to determine operational feasibility and impact of additional screening with HS-RDTs and treatment with dihydroartemisinin-piperaquine (DP) on placental malaria (PM) and low birth weight (LBW) in a context of IPTp-SP, in rural central Burkina Faso. Dr Tahita devised a 2-arm randomised controlled trial with a nested qualitative behavioural study to address three specific questions.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Marc Christian Tahita, Institut de Recherche en Sciences de la Santé, Burkina Faso

Year funded: 2019

EDCTP funding: €149,138

First, the study will determine the benefit of additional screening with HS-RDTs and treatment with DP relative to PM, LBW and peripheral malaria infection at delivery. Secondly, the study will assess the determinants of poor coverage and improve the number of IPTp doses received using reminders (phone call or text message). Finally, Dr Tahita aims to assess the performance of the new HS-RDTs in comparison to the RDTs currently deployed by the National Malaria Control Program in Burkina Faso.

Impact

In addition to its capacity development impact on the fellow and his team, the study results once disseminated properly may contribute to improving outcomes of malaria in pregnancy in sub-Saharan Africa.



Dr Marc Christian Tahita
Burkina Faso

Molecular markers of resistance to artemisinin and partner drugs



Dr Vito Baraka uses high-throughput next-generation sequencing to determine genetic profiles of drug resistance and population structure of Plasmodium falciparum.

The challenge

The emergence and spread of *Plasmodium falciparum* resistance present major challenges for malaria control and elimination. Thus, molecular monitoring of drug resistance is considered important for the detection and tracking of drug-resistant parasites. The recent advancement in next-generation sequencing (NGS) facilitates cost-effective high-throughput detection of resistance and the origin of parasite populations with different genetic backgrounds. This is relevant for monitoring antimalarial drug resistance and tracking the geographic spread of parasite populations.

The project

Dr Baraka will use NGS-based approaches to determine molecular markers of resistance to both artemisinin and partner drugs, parasite genetic diversity and population structure in African settings. In addition, the study will also generate evidence on the *ex vivo* susceptibility of antimalarial drugs.

Samples will be collected from sentinel sites of the national malaria control programmes (NMCPs) in Burkina Faso, the Democratic Republic of the Congo, and Tanzania. The detection of molecular markers of drug resistance will be carried out using a high-throughput NGS platform (Illumina®-based technology) for targeted amplicon sequencing. Following multiplexing PCR amplification of the targeted sequences and indexing, pooled gene fragments will be sequenced using the Illumina Miseq® platform.

To determine the geographical origin and spread of *P. falciparum* population to other regions, polymorphisms (SNPs barcode) in the organellar genome will be used. Photo-induced electron transfer real-time PCR (PET-PCR) assay will be used to detect plasmepsin 2-3 and *pfmdr1* copy

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Vito Baraka, National Institute for Medical Research, Tanzania

Year funded: 2019

EDCTP funding: €149,799

number of *P. falciparum*. *Ex vivo* tests will be performed using the HRP-2 assay.

Impact

The study is expected to generate *P. falciparum* temporal genotyping data of molecular markers of resistance to artemisinin (Pfk13), parasite background mutation (*mdr2*, *fd*, *arps10*, *pfap2mu* and *pfubp1*) and resistance to partner drugs (*Pfmdr1*, *Pfcr1* and *Plasmepsin 2-3* copy numbers). The molecular evidence is critical to inform NMCPs, WHO and others on the efficacy of ACTs as well as drugs used in chemoprevention strategies in the region.

Data on the geographical origin and spread of parasite populations is crucial to signal the dispersal of artemisinin-resistant strains to African settings. Furthermore, data generated on *ex vivo* sensitivity of antimalarial partner drugs is highly relevant as resistance against long-acting partner drugs is likely to accumulate due to post-treatment selection.

Furthermore, the capacity building in next-generation sequencing and bioinformatics will enhance local capacity and further interaction with partner institutions in addressing global health challenges.



Dr Vito Baraka
Tanzania



Schistosomiasis and urinary tract pathology

Dr Humphrey Kariuki Njaanake assesses the usage of the cytokine ELISA tool in assessing S. haematobium-related urinary tract pathology before and after treatment.

The challenge

Schistosoma haematobium infects more than 110 million individuals causing urinary schistosomiasis, which results in more than 150,000 deaths annually in tropical and sub-tropical countries. Several countries have started and others are about to start mass praziquantel administration in endemic areas. This approach is expensive and may be required for a long time. This places enormous demands on limited national resources. There is a need for accurate, easy-to-use, cheap and easily available tools to monitor the performance of such morbidity control programmes.



**Dr Humphrey Kariuki
Njaanake**
Kenya

The project

Infections with schistosomes result in cytokine-mediated urinary tract inflammation. These cytokines, particularly interleukin (IL)-6 and IL-10 are present in the urine of infected individuals and their levels reflect the intensity of the infection and the urinary tract pathology. The general objective is to assess urinary IL-6 and IL-10 ELISA as a tool for assessing *S. haematobium*-related urinary tract pathology before and after treatment in an *S. haematobium*-endemic community of Kenya. We will use a commercially available cytokine ELISA kit. Specific objectives are to 1) correlate levels of urinary IL-6 and IL-10 to *S. haematobium*-related pathology; 10 assess levels of urinary IL-6 and IL-10 in relation to children's age; 3) compare changes in urinary IL-6, IL-10 and ECP (eosinophil cationic protein) levels before and after treatment; 4) determine the rate of degradation of urinary IL-6 and IL-10 at selected temperature ranges.

Urine samples will be collected from *S. haematobium*-infected primary schoolchildren (308) and examined for *S. haematobium* eggs using microscopy, IL-6, IL-10 and ECP levels using ELISA at baseline and at 3, 12 and 24 months after baseline. The children will be treated with praziquantel before baseline and at 12 months after initial treatment (before the

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Humphrey Kariuki Njaanake, University of Nairobi, Kenya

Year funded: 2017

EDCTP funding: €149,646

Fellow profile: <https://edctpalumnetwork.org/fe/profiles/view/004ca5e3-d641-4f8c-ae22-404ccb4d12af>

second follow-up sample collection). In addition, levels of urinary IL-6 and IL-10 will be compared in urine samples stored at -20 °C, 4 °C and 25 °C for two weeks.

Impact

Demonstrating that treatment success of *S. haematobium*-related urinary tract pathology can be successfully assessed using a commercially available cytokine ELISA kit, may validate a way to faster, easier and cheaper monitoring of control programmes involving mass drug administration.

Rapid detection of Buruli ulcer

Dr Michael Frimpong explores the potential of recombinase polymerase amplification (RPA) as a tool for the rapid diagnosis of Mycobacterium ulcerans infections.

The challenge

Buruli ulcer is a neglected tropical disease, principally in West African countries, that causes large disfiguring ulcers. It is caused by infection with *Mycobacterium ulcerans* in the subcutaneous layer of the skin. There are no proven preventive strategies against BU, so early diagnosis and treatment are crucial to avoid physical disabilities that occur if not managed early.

Polymerase chain reaction (PCR) for the IS2404 repeat sequence of *M. ulcerans* plasmid DNA is regarded as the gold standard for case confirmation due to its high sensitivity and specificity but its use is limited by high cost and the need for a sophisticated laboratory setup, not usually available in resource-poor endemic communities. Research to develop a point-of-care diagnostic test is a major priority.

The project

Dr Frimpong's research explores the potential of recombinase polymerase amplification (RPA) as a tool for the diagnosis of Buruli ulcer. RPA has emerged as a novel isothermal technology for use in molecular diagnosis of infectious diseases. The study has several goals. The first is to optimise an RPA assay for the diagnosis of Buruli ulcer and test its sensitivity and specificity in clinical samples compared with the gold standard, PCR for IS2404. This is followed by an assessment of the feasibility and acceptability of the technique for implementation in resource-limited health facilities and laboratories by health staff. The development of a lateral flow RPA detection system will be explored and initiated.

His preliminary investigations in the laboratory have shown great promise of RPA to detect *M. ulcerans* DNA by targeting the IS2404 insertion sequence, the same target used in PCR diagnostics. Initial results have shown that DNA from multiple strains of *M. ulcerans* (Mu1082, Mu5114, Mu912, and Mu560) can be accurately detected with this assay. However, this is not the

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Michael Frimpong, Kwame Nkrumah University of Science and Technology (KNUST), Ghana

Year funded: 2017

EDCTP funding: €149,263

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/43a9b618-d30b-4309-9618-d224e3ef6442>

case for other mycobacteria (e.g. *M. tuberculosis*, *M. chelonae*, *M. avium*, *M. marinum*, *M. celatum* and *M. vaccae*).

Impact

Dr Frimpong expects that the project will lead to the development of a point-of-care RPA assay for the detection of *M. ulcerans* in clinical samples.



Dr Michael Frimpong
Ghana



Towards elimination of lymphatic filariasis

Dr Dzedzom de Souza tests the hypothesis that biannual mass treatment of lymphatic filariasis (LF) in endemic communities will accelerate the interruption of LF transmission.

The challenge

The Global Program for the Elimination of Lymphatic Filariasis has been operational since 2000 with 5-6 rounds of effective annual mass drug administration (MDA). The treatment regimen is ivermectin (IVM) in combination with diethylcarbamazine (DEC) or albendazole (ALB). The objective is to eliminate the disease by 2020,

In Ghana, MDA has been done since 2001. While the disease has been eliminated in many areas, its transmission has persisted in some implementation areas that had experienced 15 or more rounds of MDA. In some settings of high transmission intensity, alternative intervention strategies, including twice-yearly MDA and sleeping under insecticidal nets, have significantly accelerated transmission interruption. The challenge is to identify new intervention strategies that eliminate the residual infection in areas of persistent transmission and speed up the LF elimination process.

The project

Two cluster randomised trials will be implemented in LF endemic communities in Ghana. The interventions will be yearly or twice-yearly MDA delivered to entire endemic communities. Allocation to study group will be by clusters identified using the prevalence of LF. Clusters will be randomised to one of two groups: receiving either (1) annual treatment with IVM+ALB; (2) annual MDA with IVM+ALB, followed by an additional MDA 6 months later. The primary outcome measure is the prevalence of LF infection, assessed by four cross-sectional surveys. Entomological assessments will also be undertaken to evaluate the transmission intensity of the disease in the study clusters. Costs and cost-effectiveness will also be evaluated. Among a random subsample of participants, microfilaria prevalence will be assessed longitudinally. A nested process evaluation, using semi-structured interviews, focus group discussions and a stakeholder analysis, will investigate the

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Dzedzom de Souza, Noguchi Memorial Institute for Medical Research (NMIMR), Ghana

Year funded: 2017

EDCTP funding: €149,885

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/26dc15a9-965d-4e19-9ff5-9cdfb2ae6680>

community acceptability, feasibility and scale-up of each delivery system.

Impact

Establishing an acceptable, feasible and cost-effective alternative intervention strategy (i.e. biannual treatment of LF endemic communities) to support the Global Program for the Elimination of Lymphatic Filariasis, would accelerate the interruption of LF transmission.



Dr Dzedzom de Souza
Ghana

Impact of secondary bacterial infection on filarial lymphoedema

Dr Alexander Kwarteng aims to identify the bacteria that likely aggravate the condition of patients suffering from lymphoedema due to lymphatic filariasis.

The challenge

Filarial infections affect more than 150 million people in the tropics. One of the major forms is lymphoedema caused by *Wuchereria bancrofti* in Africa. The chronicity and morbidity of lymphatic filariasis (LF) are associated with the longevity of the adult worm (>5 years) and the production of millions of microfilariae, which populate the blood. Existing WHO control programmes rely on mass administration of mainly microfilaricidal drugs (MDA) that have the potential to reduce microfilariae loads in infected humans and, thus, transmission by the insect vector.

Several challenges, however, may impede sustainable control and there have been calls to search for an alternative and effective approach to understanding the pathogenesis of lymphoedema and offering a possible option of providing support for individuals with this stage of lymphatic filariasis.

The project

Dr Kwarteng's project will address lymphoedema caused by *Wuchereria bancrofti*. Morbidity is imposed not by microfilariae, but by adult worms that induce an alteration of the lymphatic vessels where they reside, causing both vessel obstruction and dilatation. This results in lymphatic pathology, with two manifestations being hydrocele and lymphoedema. Furthermore, exogenous bacteria that enter through skin lesions are believed to aggravate lymphoedema through secondary infections.

Therefore, Dr Kwarteng hypothesises that exogenous bacteria are major mediators of lymphoedema and that this could lead to complementary chemotherapy approaches against lymphatic filariasis. This is very important as current WHO control programmes can target transmission with the existing microfilaricidal drugs, but morbidity from lymphoedema and hydrocele (from which more than 40 million

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Alexander Kwarteng, Kwame Nkrumah University of Science and Technology (KNUST), Ghana

Year funded: 2018

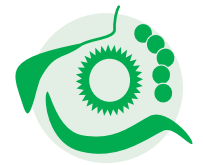
EDCTP funding: €149,263

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/4f23768a-4082-4da1-b6f5-2cb7cecc1e41>

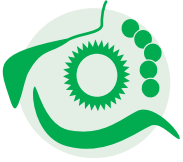
people suffer), cannot be sufficiently addressed by antifilarial chemotherapy. Moreover, the bacteria which are believed to contribute to lymphoedema progression in Ghana remain to be studied.

Impact

Africa bears one-third of the lymphatic filariasis cases. Current chemotherapy used for mass drug administration programmes (diethylcarbamazine, ivermectin and albendazole), shows no or only partial macrofilaricidal effect. Therefore, it is not able to target the adult worms. The results of this project potentially will have a great impact on the possibilities to support patients suffering from lymphoedema.



Dr Alexander Kwarteng
Ghana



Mapping hepato-intestinal schistosomiasis in children

Dr Justin Nono Komguez aims to determine the molecular mechanisms behind differential schistosomiasis-driven liver pathology in children in Cameroon.

The challenge

Intestinal schistosomiasis, specifically at the chronic stage, constitutes a health risk for 230 million people worldwide. The disease morbidity primarily results from the infected individuals' poor ability to immune-regulate their response to parasite eggs trapped in their liver. A progressive fibroproliferative response ensues leading to organ impairment, pathology and - when left untreated - death. The molecular mechanisms behind schistosomiasis-driven liver fibrosis remain elusive. The challenge is to determine these mechanisms.



Dr Justin Komguez Nono
South Africa

The project

Dr Nono reasons that a differential expression profile in schistosomiasis-diseased patients with a comparable egg burden but a different stage of advancement of the liver fibrosis may unveil candidate factors in the host that, by their sole differential expression, alter the progression of liver fibrosis in those patients.

The present study conducted by Dr Nono and his team investigates through full-genome mRNA sequencing of blood cells the factors which are differentially expressed by school children with schistosomiasis, factors that associate with the rapid onset and/or fast progression of liver fibrosis.

The study takes place at a highly endemic site for schistosomiasis in the locality of Yoro in Cameroon around the Mbam river and is rooted in a cross-sectional study on 1000 school children. The study specifically aims to define the knowledge, habits and practices of school children regarding schistosomiasis and the risk the disease represents in the area. Egg-defined prevalence of the disease will be related to individual habits. Secondly, the study assesses the advancement of liver fibro-pathology in the recruited children by ultrasonography and defines comparative clusters of individuals

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Justin Komguez Nono, University of Cape Town (UCT), South Africa

Year funded: 2018

EDCTP funding: €140,277

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/96d007e5-6b94-4607-ad33-5bc840e3b108>

with similar parasitological status but different fibro-pathological (liver) status. Finally, the study determines by next-generation sequencing of children's PBMCs-derived mRNA the differences in transcriptional profiles between children with fibrotic and non-fibrotic livers.

Impact

The different aims of our project are expected to yield an updated map of the prevalence of schistosomiasis in the locality of Yoro. Unprecedentedly, it will define an ultrasonographic profile of the liver pathology in the children of this hepato-intestinal schistosomiasis endemic area. Potentially, it may unveil a unique library of host factors involved in the progression of pathological liver fibrosis in general and during schistosomiasis in particular.

Novel plasma biomarkers for diagnosing stage of sleeping sickness patients

Dr Charles Drago Kato aims to establish biomarkers for diagnosing early or late-stage T. b. gambiense trypanosomiasis.

The challenge

Sleeping sickness progresses in two stages, the early stage with parasites in blood and the late stage in which parasites invade the central nervous system. Drug treatment for both early- and late-stage disease differs. Therefore, it is mandatory to first determine the disease stage.

However, the current staging criterion using cerebrospinal fluid relies on an invasive lumbar puncture that is also required to monitor treatment efficacy. Since initial disease diagnosis is done using blood, identification of plasma biomarkers to replace current criteria for the evaluation of stage and treatment efficacy is of utmost urgency. The challenge is to establish the clinical utility of several plasma biomarkers.

The project

Previously, novel plasma biomarkers were identified with proteomics methods. The markers discriminate late stage from early-stage patients for *Trypanosoma brucei rhodesiense*. The clinical utility of these biomarkers is not yet known and it is not clear if these markers would also apply to *T. b. gambiense*.

In this study, Dr Kato and his team propose to carry out a clinical validation of these novel plasma biomarkers as stage diagnostic markers. He will conduct a retrospective study using archived samples from the trypanosomiasis biobank at Makerere University to assess disease staging potential. Patient samples will be selected that were recruited at Lwala hospital (North Eastern Uganda) for *T. b. rhodesiense*, and Omugo (West Nile) for *T. b. gambiense*. Through proteomics methods, he aims to find out whether markers identified for *T. b. rhodesiense* also apply to *T. b. gambiense*. Clinical validation of identified markers will involve analysis as a single biomarker and as a panel of two or more analytes to determine the best predictor of late-stage disease.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Charles Drago Kato, Makerere University, Uganda

Year funded: 2019

EDCTP funding: €130,125

Impact

Successful identification of biomarkers will form a basis for translation into field-based dipstick assays for disease staging and inform policy regarding disease staging. This will greatly improve patient management through the abolition of the mandatory requirement of an invasive lumbar puncture which is painful to patients.

Furthermore, the successful execution of this project will build capacity at Makerere University by offering training of critical skills to junior researchers.



Dr Charles Drago Kato
Uganda



Dosing schistosomiasis therapy for children not yet in school

Dr Solomon Mequanente Abay aims to contribute to optimising praziquantel therapy for Schistosoma mansoni infection in preschool-aged children.

The challenge

Schistosomiasis is a worldwide public health problem, particularly in sub-Saharan Africa with approximately 90% of the infections. Schistosomiasis treatment and control relies largely upon therapy with praziquantel and is directed primarily at school-aged children (SAC) living in schistosomiasis-endemic areas.

In recent years, the occurrence of schistosomiasis within African preschool-aged children (PSAC) has been much better documented. It revealed an important burden of disease previously overlooked. However, school-aged children remain the principal target group for prevention with praziquantel, partly because of limited information on efficacy and safety in preschool-aged children and partly because they are wrongly thought to be at low risk of schistosomiasis.

A recent study revealed that praziquantel has a flat dose (20-60 mg/kg)-response and overall a lower efficacy in PSAC as compared with in SAC. The off-label use of praziquantel at a standard dose of 40 mg/kg to treat PSAC is an extrapolation of SAC and adult praziquantel dosages. However, these may not provide a good estimate in view of the maturational differences in absorption, metabolism and elimination.

There is a clear need to have evidence-based dosing recommendations of praziquantel for PSAC, based on pharmacokinetics, pharmacogenetics and intensity of *S. mansoni* infections.

The project

Dr Abay and his team proposed the PrazOPT study which aims to optimise praziquantel therapy in preschool-aged children infected with *S. mansoni*. The study has several objectives. The main objective is to conduct an observational

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Solomon Mequanente Abay, Addis Ababa University, Ethiopia

Year funded: 2019

EDCTP funding: €150,000

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/cc7d40c6-c5a0-4797-90a3-316c1cbc81d5>

prospective study to assess cure rate of PSAC receiving schistosomiasis therapy based on 40 mg/kg single dose praziquantel, assess the pharmacokinetics of praziquantel, and the pharmacogenetic and other biological factors affecting treatment outcome.

Regarding research capacity development, the second objective of the fellow is to support and advise a PhD student on the research for a clinical pharmacology thesis. The third objective is to train on GCP, data management, clinical study management, and pharmacokinetic modelling.

Impact

The research findings are expected to suggest optimised praziquantel therapy for preschool-aged children which may have a major health impact.



**Dr Solomon Mequanente
Abay**
Ethiopia

Understanding the dynamics of human and livestock schistosomiasis transmission

Dr Bruno Senghor aims to improve the understanding of the role of hybridisation in the dynamics of human and livestock schistosomiasis transmission after HIV-1 infection.

The challenge

Human schistosomiasis is a neglected tropical disease caused by schistosome helminth worms with terrifying epidemiological statistics: 800 million people at risk in 78 countries, more than 230 million infected and over 200 000 deaths each year. The disease is highly endemic in sub-Saharan Africa where it persists despite mass drug administration with praziquantel (PZQ).

Some schistosomes are specific to humans and induce two main disease forms (either mesenteric or urogenital) while others are associated with wild animals. However, hybridisation can occur between different schistosome species. In northern Senegal, hybridisation between schistosome species is now known to be frequent with the potential risk of zoonotic transmission. Additionally, hybrids may present greater vigour compared to their pure parental forms and may be less sensitive to PZQ.

The project

Dr Senghor aims to better understand the role that hybridisation plays in the dynamics of human and livestock schistosomiasis transmission in Senegal. The objectives of this study are to 1) determine the current prevalence and intensities of human schistosomiasis; 2) study the outcomes of *S. haematobium* x *S. bovis* hybrids on snail infectivity; 3) evaluate the sensitivity of hybrids schistosome populations to PZQ according to parasite genetic introgression levels; and 4) characterise the frequency of hybrids and their level of genomic introgression.

To achieve these objectives, an integrative approach will be used, i.e. a genetic monitoring study of the parasite communities infecting human populations in areas with high hybrid prevalence in Senegal before and after repeated PZQ treatment. Parental and hybrid life-history

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Bruno Senghor, Institut de Recherche pour le Développement (IRD), Senegal

Year funded: 2019

EDCTP funding: €148,750

traits (i.e. sensibility to PZQ; host spectrum) will be investigated in controlled laboratory experiments.

Impact

This project will allow Dr Senghor to train and initiate a biomedical research career on schistosomiasis in Senegal in the context of the One-health approach. The study also constitutes an opportunity to consolidate partnerships with European and local laboratories, health organisations and universities. The aim is to build a locally managed network to undertake larger projects with the ultimate goal of better understanding the dynamics of schistosome populations and in particular the emergence of hybrids. Eventually, the network will take part in the reflection on the strategies of schistosomiasis elimination in Senegal and more broadly in sub-Saharan Africa.



Dr Bruno Senghor
Senegal



Rapid diagnostics for early detection of Ebola and Marburg virus at point of care

Dr Misaki Wayengera continues to develop an easy-to-use affordable rapid diagnostic test for early detection of filoviruses at point of care; in this study he and his team will characterise receiver operators of novel EBOV/MARV-GP epitopes using 2014-2015 Ebola patient samples from Sierra Leone.

The challenge

Ebola and Marburg viruses (EBOV and MARV) form the two generic members of the filoviridae family of viruses. Filoviruses cause rare but highly fatal viral hemorrhagic fevers (VHFs) within rural villages of equatorial Africa. The 2014-2015 Ebola outbreak in West Africa turned into a public health emergency of international concern (PHEIC). Filoviruses are class A pathogens of potential bioterror. There are no easy to use, affordable rapid diagnostic tests for early detection of filoviruses at the point of care (POC) yet.



Dr Misaki Wayengera
Uganda

The project:

In Jan 2013, Grand Challenges Canada (through its rising Stars in Global Health scheme) funded Dr Wayengera and his team to test novel conserved epitopes of EBOV/MARV glycoprotein (Gp) as potential diagnostic biomarkers (Grant #S4-0280-01). During the 2014 to 2015 outbreak in West Africa, we transitioned to scale. Over this period, we generated and validated a panel of over 12 mice-derived hybridomas and monoclonal antibodies (MAbs- targeting 4 unique epitopes inclusive of the extracellular domain of EBOV/MARV Gp) for their reactivity with recombinant Gp cloned and expressed within HEK mammalian cells.

The overall goal of this fellowship project is to determine receiver operator characteristics of novel EBOV/MARVGP epitopes using Sierra Leonean patient-samples obtained from the 2014-2015 Ebola outbreak, stored at the National Institute for Communicable Diseases (NICD) Center for Emerging Zoonotic Diseases (CEZD) BSL-IV. Two specific aims are contingent on this goal, i.e to 1) Pre-characterise the patient sample by clinical picture and outcome, ELISA, RT-PCR, and viral culture, and 2) Determine the sensitivity, specificity, positive predictive value, negative predictive value and receiver

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Misaki Wayengera, Makerere University, Uganda

Year funded: 2018

EDCTP funding: €149,688

Fellow profile: <https://edctpalumnetwork.org/fe/profiles/view/493e24b5-fcd5-4210-aa4d-5833e695a3cb>

operator curves of our *in vitro* pre-validated novel epitopes.

Impact

These conserved EBOV/MARV-Gp epitopes and their derivative MAbs are potential biomarkers to mount on a lateral flow immunochromatographic strip-test (LFT) for use at a point of care, e.g. in remote village settings of equatorial Africa, or during a bioterror attack.

Our team has initiated testing at the NICDCEZD-BSL-IV in collaboration with LifeAssay Diagnostics but will require more funding to reproduce high-affinity purified MAbs for clinical testing. In addition, the fellow will train 2 Master's students in Laboratory Practice and Standards.

In August 2019, Dr Wayengera received for his research the first prize in the competition for the WHO Innovation Challenge in the category Product development.

Emerging and re-emerging arboviral infections

Dr Moses Masika aims to determine the prevalence and genetic diversity of arboviral infections with a view to contributing to outbreak and epidemic preparedness.

The challenge

Emerging and reemerging infections are a major threat to global health today. Their occurrence is unpredictable and they often cause serious morbidity, mortality as well as economic losses. The world needs to be better prepared to handle an outbreak anytime and this requires surveillance to detect outbreaks. The challenge is to develop the tools to assess and control the threat.

The project

Dr Masika and his team will conduct a cross-sectional study on patients with acute febrile illness in three health facilities in the Kibera informal settlement, Nairobi city, Kenya. Sociodemographic and clinical data, as well as blood and urine samples, will be collected from 384 patients with fever for up to 5 days and no signs of localising.

Samples will be analysed using ELISA for antibodies against flaviviruses, alphaviruses and bunyaviruses. Positive samples will be further analysed using plaque reduction neutralisation assays to differentiate the specific viruses. Group-specific PCR will be done to detect any viruses from the three groups (flaviviruses, alphaviruses and bunyaviruses); Sanger sequencing will be performed on PCR-positive samples to determine the specific virus. In addition, the samples will be analysed using next-generation sequencing to detect any other viruses in the samples. Bioinformatics and phylogenetic analysis will be used to assess the genomic diversity of any arboviruses sequenced. Sociodemographic, clinical and laboratory data will be statistically analysed (SPSS).

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Moses Masika, University of Nairobi, Kenya

Year funded: 2019

EDCTP funding: €149,488

Impact

This study will determine the proportion of acute febrile illness that is due to arboviruses. Any novel or emerging viruses will also be identified and characterised. This information will help in surveillance efforts as well as the selection and development of appropriate diagnostic assays and vaccine targets for common arboviral infections in the study area and beyond.



Dr Moses Masika
Kenya



Mapping immune responses to a cholera vaccine over time

Dr Caroline Cleopatra Chisenga aimed to evaluate the real-world efficacy of an oral cholera vaccine in the context of the national introduction of the vaccine in Zambia.

The challenge

In low- and middle-income countries (LMICs), oral vaccines perform poorly. Several reasons are postulated including maternal breast milk components, environmental enteropathy, nutritional factors, and intestinal infections. Zambia has had a high burden of cholera over the past several years and the government is deploying a new oral cholera vaccine (Shanchol™).

While the vaccine has good efficacy in clinical trials, its real-world immunogenicity is unproven.

For example, the duration of vaccine-induced immune response not well-characterised in LMICs where cholera outbreaks are common. The impact of human genetic predisposition on susceptibility to cholera on vaccine responses is unknown and so is the impact of HIV infection on the functional immune protection. Therefore the challenge is to evaluate the vaccine in real-world settings, specifically in Zambia.

The project

In collaboration with local health officials and scientists in Zambia, the study proposed to leverage the introduction of Shanchol in Zambia to address the following research objectives. First, she profiled the cholera-specific antibody status of a population at risk of cholera before and after receiving 1st and 2nd dose of Shanchol oral cholera vaccine (OCV). Secondly she developed and evaluated a non-invasive proxy measure of OCV immune responses. Thirdly and fourthly, Dr Chisenga measured the effect after immunising HIV-infected individuals through measurement of the OCV-generated antibodies, and assessed the impact of ABO blood groups on cholera antibody generation.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Caroline Cleopatra Chisenga, Centre for Infectious Disease Research in Zambia Limited (CIDRZ), Zambia

Year funded: 2018

EDCTP funding: €149,965

Fellow profile: <https://edctpalumnetwork.org/fe/profiles/view/98fd8994-3e60-413f-8391-13b6238540e4>



**Dr Caroline Cleopatra
Chisenga**
Zambia

Impact

Valuable information on the cholera vaccine efficacy in real-world Zambian settings has been acquired in the context of Zambian health policy. Dr Chisenga also gained new research (laboratory) skills and took a grant writing course at Johns Hopkins University in the U.S. The study established Dr Chisenga as a leader in immunology research in Zambia and prepared her to compete for further peer-reviewed research funding.

Respiratory disease in HIV-positive children

Dr Michael Owusu will describe the nasopharyngeal microbiota of HIV-positive children and determine its association with respiratory diseases.



The challenge

The progression of HIV disease and its associated morbidity and mortality among childhood populations has decreased dramatically over the past decade as a result of an unprecedented global effort at scaling up universal access to antiretroviral therapy. In spite of these successes, many children living with HIV disease continue to die as a result of paediatric pneumonia. Although bacteria agents like *Mycobacterium tuberculosis* complex are often considered as the main agent involved, the role of other bacteria agents and viruses still remains unclear and difficult to determine in clinical practice.

The project

The main objective of this project is to describe the nasopharyngeal microbiota of HIV-positive children and determine its association with respiratory diseases, specifically, the identification of specific microbiota associated with respiratory disease in HIV-positive children.

Dr Owusu's research will be a longitudinal study for which 100 HIV-positive children with respiratory disease will be recruited alongside 100 age-matched HIV-negative controls without respiratory disease. All children will be followed up for 24 months for signs and symptoms of respiratory disease and/or pneumonia. Nasopharyngeal swabs will be taken from all subjects at enrolment and also at the various time points that subjects may present with and recover from respiratory disease. All swab samples will be tested for common respiratory viruses using multiplex real-time PCR. Bacterial agents will also be identified using conventional bacteriological techniques and PCR as well as sequencing techniques that will target the range of bacterial pathogens in the nasopharynx. Clinical data on subject's demography, clinical presentations, antibiotic or antiviral treatment, co-morbidities, tuberculosis status and other clinical indicators of well-being will be retrieved from their folders.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Michael Owusu, Kwame Nkrumah University of Science and Technology (KNUST), Ghana

Year funded: 2017

EDCTP funding: €150,000

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/f27471dd-30a9-4fee-bec4-4369fb9e97da>

Impact

The study will contribute to child health in Ghana by generating baseline data that would determine the pathogens associated with respiratory disease in HIV-positive children.



Dr Michael Owusu
Ghana



Biomarkers of acute pneumonia in children

Dr Charles Sande will contribute to developing new diagnostics for pneumonia, which would enable appropriate use of antibiotics and reduce risks of spreading AMR.

The challenge

Over 90% of the mortality attributed to pneumonia infection occurs in developing countries and pneumonia is second only to malaria as a cause of infant and early childhood mortality in sub-Saharan Africa.

The treatment of pneumonia depends on whether its aetiology is viral or bacterial. Care of most viral pneumonia infections is restricted to symptomatic management. On the other hand, antibiotics are an effective way of treating bacterial pneumonia and timely administration of antimicrobial therapy usually has a positive clinical outcome. In developed countries, these infections are often diagnosed using sophisticated platforms. However, these platforms are generally unavailable in typical health facilities in low-resource countries, where the toll of pneumonia infection is greatest.

The lack of these diagnostic platforms means that clinicians in these settings do not have sufficient clinical information to determine whether antibiotic treatment is appropriate. This has led to the widespread presumptive use of antibiotics as empiric treatment for pneumonia. Antibiotics are being administered to vast numbers of children with viral pneumonia who do not need them. This overuse of antibiotics has been implicated in the alarming spread of antimicrobial resistance (AMR), which is estimated to be the leading cause of paediatric death by 2050 if corrective measures are not devised.

The project

To address this problem, Dr Sande aims to validate host-level biomarkers that can rapidly and reliably distinguish viral and bacterial pneumonia and that can be formulated into a rapid point-of-care test. In a previous study of airway proteomics, 15 host proteins were identified that could distinguish with high sensitivity and specificity between viral and bacterial pneumonia in African children.

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Charles Sande, African Research Collaboration for Health, Kenya

Year funded: 2019

EDCTP funding: €149,217

In his fellowship study, Dr Sande proposes to validate the results from the previous study. He will use an independent retrospective cohort of infants and children who were previously admitted to a hospital with severe pneumonia and whose airway samples were archived in a biobank. By measuring the expression levels of the candidate biomarker proteins in these samples, Charles Sande will select the three that are most discriminative of pneumonia aetiology for further testing in a prospective cohort.

Impact

If successful, the results of this study will contribute to the fight against AMR by providing clinicians with a robust tool for guiding decisions to administer antibiotics, specifically in cases of acute pneumonia in children.



Dr Charles Sande
Kenya

Monitoring use and safety of vaccines and medicines

Dr Dan Kajungu conducts the VXMedSSurv project which utilises demographic and health care data and monitoring to understand the risk of adverse reactions and treatment outcomes in health facilities.

The challenge

Developing countries receive immense volumes of drugs and vaccines because of the huge disease burden. However, the burden of adverse reactions/effect of these efficacious drugs and vaccines at the population level has not been fully explored in the African context. This is in addition to medication errors, irrational drug use, poor drug quality and counterfeits which undermine patient safety as well as put the health system's credibility in jeopardy.

The VXMedSSurv project will utilise the health and demographic surveillance system (HDSS) to monitor the safety and use of vaccines and medicines (pharmacovigilance) in both public and private health facilities.

The project

Dr Kajungu and his team use will utilise the health and demographic surveillance system (HDSS) in Uganda to monitor the safety and use of vaccines and medicines (pharmacovigilance) in both public and private health facilities.

The VXMedSSurv project will actively and passively track adverse drug and vaccine reactions and/or events, within the Iganga Mayuge health and demographic surveillance site in Uganda. Using the system, the study link demographic HDSS data with health facility data like immunisation, diagnosis, prescriptions and antenatal-care outcomes. In this way, the project will study drug utilisation and diagnostics to understand their contribution to the risk of adverse reactions and treatment outcomes. Beyond the project lifespan, the team will establish a reproductive and pregnancy registry to capture treatment seeking patterns, maternal immunisation and lifestyle during pregnancy as well as pregnancy outcomes in women of reproductive age. Data mining of spontaneous

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Dan Kajungu, Makerere University Centre for Health and Population Research, Uganda

Year funded: 2018

EDCTP funding: €149,750

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/7645973c-b40f-4e25-befe-3de270d34c9c>

reporting systems data and electronic health records for pharmacovigilance purposes using various machine learning methods will be used to identify potential adverse drug reactions and detection of drug safety signals.

Impact

The outputs and findings of the project and its follow-up will be used directly by regulators, pharmaceutical companies, academia, and researchers to improve pharmacovigilance policies in Africa. The study will also hone the expertise of the fellow in pharmacoepidemiology and pharmacovigilance in African settings. Moreover, it will add to his experience in research leadership and project management. Capacity building and mentorship activities in the project will empower junior African researchers in Africa with an interest in pharmacovigilance.



Dr Dan Kajungu
Uganda



Environmental impact on immune responses relevant to vaccine development

Dr Moustapha Mbow aims to identify geographical footprints (rural to urban gradient) of the immune system for improving vaccine development.

The challenge

Critical to vaccine efficacy is the induction of a strong and long-lasting immune response. The vaccine development pipeline needs to involve testing in African populations because of differences not only in the genetic background but importantly because of their very diverse environmental exposures, including chronic infections. Recent indications are that geographical differences may define immunological footprints. The challenge is to evaluate the impact of these difference as an integral part of vaccine development.



Dr Moustapha Mbow
Senegal

The project

In studies comparing immune responses of rural and urban Africans as well as matched Europeans, Dr Mbow has shown that there are major differences in the immune response that cannot be accounted for by genetic variation alone. These findings so far form the basis of Dr Mbow proposal to investigate the role of environmental differences in immune responses relevant for vaccine development. This study also serves to strengthen research skills in West Africa to conduct in-depth immunological, molecular and bioinformatics analysis for vaccine responses.

At the Immunology Department of the Laboratory of Bacteriology and Virology of Cheikh Anta Diop University Hospital of Dakar, Senegal, a platform of resources is being used to conduct immunological investigations for various studies, including vaccine trials. The Parasitology Department of the Leiden University Medical Centre (LUMC), with which we are collaborating, has developed a mass cytometry (CyTOF®) panel able to analyse over 36 immune markers simultaneously and possesses Illumina technology for analysis of gene transcriptional signatures of immune cells. In addition to

Project at a glance

Project: EDCTP Career Development Fellowship

Project lead: Dr Moustapha Mbow, Université Cheikh Anta Diop de Dakar, Senegal

Year funded: 2018

EDCTP funding: €148,924

Fellow profile: <https://edctp.alumninetwork.org/fe/profiles/view/c4963040-ecb3-4e9b-9223-2eb4909875c5>

methods of characterisation of cell subsets and immune responses already implemented in Senegal, the candidate will be trained to use CyTOF® and Illumina technologies (including the important step of data analysis) to enable him and his institute to participate in the global effort for vaccine development.

Impact

The study will improve understanding of the role of environmental differences as a factor in determining differences in immune response relevant to vaccine development. The study aims also to show the feasibility of technologically demanding laboratory assays in a way that is applicable in field settings. The study topic underlines the need for the research capacity development in West Africa which is part of the study.





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to offer researchers and key members of clinical research teams the opportunity to acquire technical and project skills in clinical R&D through placement in pharmaceutical companies, PDPs and CROs.



Surveilling and managing disease comorbidities

Dr Alice Matimba broadened her skills in epidemiology and clinical research at Merck KGaA, with a focus on comorbidities of infectious and non-communicable diseases in Zimbabwe.

The challenge

The main goal of the placement at Merck KGaA was to acquire proficiency in clinical trial design and operations.

The project

First, Dr Matimba was mentored by the Director Early Stage Clinical Operations, and the Head of Financial Performance, Planning & Analysis who provided her with many opportunities to learn about clinical trial management, clinical trials operations and study implementation, finance and forecasting, KPIs and benchmarking, and project management systems.

Then, under the guidance of a Senior Clinical Research Manager, she was given specific tasks on the study ENCORE, an observational trial for recurrent metastatic head and neck cancer and the use of Erbitux® (cetuximab) which is being conducted in five countries. Dr Matimba had the opportunity to oversee some activities including protocol amendments, drug safety and SAE reporting, data management, risk assessment, SAP, interim snapshot analysis and conference abstract preparation. This involved regular interactions with the Medical Affairs, Drug Safety and Data Management departments as well as the CROs. After the introduction to the trial and the team, she was given team leadership for an interim analysis of this trial.

Discussions at Merck also showed agreement that there is a need to increase awareness of diabetes and conduct observational and clinical trials on this disease. In future, partnerships could be developed with local health authorities and NGOs to support screening programmes and to include African populations in future observational trials which could expand the market for current drugs.

Project at a glance

Project: EDCTP Clinical R&D Fellowship

Project lead: Dr Alice Matimba, University of Zimbabwe, College of Health Sciences, Zimbabwe

Year funded: 2016

EDCTP funding: €106,000

Impact

This fellowship was not completed as expected. The reintegration plans to be implemented at her home institution were not executed as Dr Matimba intended. Her fellowship and placement at Merck provided her with a platform for her being recognised by other organisations. She was able to pursue other opportunities which were better aligned with her career development goals. Currently, she is an Overseas Courses Development Officer for Wellcome Genome Campus Advanced Courses and Scientific Conferences.



Dr Alice Matimba
Zimbabwe

Advancing international standards in clinical research in Burkina Faso



Dr Isidore Traore acquired advanced skills in clinical trial management at Merck KGaA, Germany, and back at the Centre Muraz contributed to improving the quality of clinical research of its new Department of Clinical Research.

The challenge

Centre Muraz is a biomedical research centre located at Bobo-Dioulasso (Burkina Faso) with experience in conducting clinical trials in HIV, malaria, tuberculosis, Ebola, etc. Its new Department of Clinical Research needs to continue to strengthen its capacities and retain young scientists in Burkina Faso. Therefore, the fellowship offered an opportunity to acquire advanced knowledge and skills in clinical trial design and operations at Merck in Germany.

The project

The first six months at Merck allowed Dr Traore to rotate through different departments, in order to update his competencies and have a good understanding of Merck's activities and organisation. These activities included a tour of the Merck headquarters, immersion in the Department of Global Clinical Operations, attendance of the clinical trial management and governance meetings, and the completion of 194 training modules in Security, ICH-GCP, GPVP as well as Merck's Policies, SOPs and Work Instructions.

To become proficient in clinical trials operations and study implementation, he was involved in the management of phase I/II trials. In order to build a future strategic partnership with Merck for conducting clinical trials at Centre MURAZ, he adapted a site assessment checklist which was shared with Centre MURAZ. He also familiarised himself with the Merck development pipeline. At Merck, he was mentored by the Director of Early Stage Clinical Operations, Global Clinical Operations and the Head of Financial & Performance Planning & Analysis.

Impact

The impact of his placement at Merck Global Clinical Operations will be both individual and

Project at a glance

Project: EDCTP Clinical R&D Fellowship

Project lead: Dr Isidore Traore, Centre MURAZ, Burkina Faso

Year funded: 2016

EDCTP funding: €97,875

Fellow profile: <https://edctp.alumninetwork.org/fe/profiles/view/91e89a67-aa4b-42f2-b472-9770fa9c1085>

institutional. The advanced knowledge and skills he acquired will further his career development. These will help him to increase the quality of his research protocols and his publications in peer-reviewed journals.

His capabilities and activities will also sustain Centre MURAZ's research platform. Dr Traore has shared with his home institution, Centre MURAZ, best practices identified at Merck which could be implemented to strengthen the ongoing capacity development, such as the administrative management of the Department of Clinical Research, which he has been appointed to lead. He has conducted training workshops using the training module developed at Merck. During the reintegration phase after his return to Burkina Faso, he and others planned statistical analysis and publication of the data collected during previous studies at Centre MURAZ. Moreover, a specific epidemiological study protocol is to be developed to identify potential participants who could be enrolled in future HIV and malaria clinical trials in Burkina Faso. A long-term partnership with Merck may be established.



Dr Isidore Traore
Burkina Faso



Upgrading postgraduate clinical research curricula of the Center for Innovative Drug Development and Therapeutic Trials for Africa

Dr Solomon Mequanente Abay broadened his knowledge of clinical trial operations, ethics review and regulatory aspects at the Novartis Institute of Biomedical Research.

The challenge

This fellowship aimed to support the fellow to acquire skills in clinical research and development through placement at the Novartis Institutes for Biomedical Research (NIBR).

The project

To improve his theoretical and practical capabilities in clinical trials, Dr Abay completed advanced training organised by NIBR. The assigned courses included advanced GCP, clinical trial monitoring, pharmacokinetic analysis, data management, clinical trials project management, and working practices and SOPs.

Dr Abay was also engaged in phase I and phase II clinical trials. The work included reviewing clinical trials protocols and preparation of clinical study reports. He also conducted remote monitoring and site co-monitoring of company-sponsored studies.

During the reintegration phase of the fellowship at Addis Ababa University, a clinical research protocol template was developed to support researchers in developing protocols with the appropriate content and correct format for submission to the institutional review board and the regulatory authority. Similarly, he supported faculties at the University of Addis Ababa in their efforts to strengthen the phase I clinical trial centre and its side laboratory. He also organised a two-day national training workshop on medicine development and regulation. At the same time, Dr Abay was assigned to be a member and the secretary of the institutional review board of the College of Health Sciences at the Addis Ababa University.

Project at a glance

Project: EDCTP Clinical R&D Fellowship

Project lead: Dr Solomon Mequanente Abay, Addis Ababa University, Ethiopia

Year funded: 2016

EDCTP funding: €72,087

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/cc7d40c6-c5a0-4797-90a3-316c1cbc81d5>

Impact

At Novartis, Dr Abay broadened his knowledge of clinical trial operations, ethics review processes and regulatory authority functions. In his home institution at Addis Ababa University, he shared his clinical research skills by training postgraduate students and collaborated with the university and other national institutions to improve clinical research management. As a member and secretary of the institutional review board, he reviews clinical research protocols and is involved in the follow-up of clinical studies. Furthermore, Dr Abay contributed to reviewing curricula of postgraduate programs involving clinical research which will be hosted at the Center for Innovative Drug Development & Therapeutic Trials for Africa (CDT-Africa).



Dr Solomon Mequanente Abay
Ethiopia

Maintaining trial safety and quality control

Dr Mwaka Kakolwa pursued an advanced technical training in all aspects of clinical research across the product development timeline at GSK, United Kingdom.



The challenge

For several years Dr Kakolwa has been involved in clinical trials at the Ifakara Health Institute in Tanzania. Her fellowship at the pharmaceutical company GSK gave her the opportunity to develop her technical and practical skills in clinical trial management. The challenge integral to the clinical R&D Fellowships is for the fellows to then apply and share these advanced skills at their home institutions.

The project

Dr Kakolwa's career in research started when she joined the Ifakara Health Institute in Tanzania as a study coordinator of a malaria-in-pregnancy clinical trial (2010-2013). After the MiP study, she joined a second trial which assessed the clinical safety of the dihydroartemisinin-piperazine (Euratersim®) in the general population (2013-2014). In both trials, she had similar roles of coordinating clinical activities and many other tasks including such as data quality control, making sure lab procedures and sample collection followed GCP, SAE assessment and reporting, and attending investigators meetings. In 2014, she was involved in the therapeutic and efficacy studies of antimalarials as a sub-PI. In 2016, she joined a Focal Screening and Treatment (FSAT) group (Entomology) as a supervisor of the clinical team, a study which aimed at reducing malaria transmission in the Coastal region of Tanzania.

At GSK, her activities have immersed her in all aspects of clinical R&D across the product development timeline. Topics explored during the training were many, including:

- Clinical product development: understanding clinical product development plans (including life cycle management activities such as post-market activities, regulatory aspects and pathways of drug registrations) and preparation of such a plan (phases I-IV, with focus on phase I) as well as evaluation of pre-clinical information (pharmacology,

Project at a glance

Project: EDCTP Clinical R&D Fellowship

Project lead: Dr Mwaka Kakolwa, Ifakara Health Institute Trust (IHI), Tanzania

Year funded: 2017

EDCTP funding: €55,100

Fellow profile: <https://edctp.alumninetwork.org/fe/profiles/view/4baf41cb-008b-4e24-be46-1e480aa39100>

pharmacokinetics, toxicology, quality) relating to small molecule and biological investigational medicinal products (IMPs). This also includes identifying risks in the preclinical package of new small molecules or biological IMPs and devising a risk mitigation plan, its application in the protocol development, trial design and procedures and choosing suitable facilities to carry out such studies with minimal risks.

- Clinical trial management with topics such as study designs, concepts, protocols development and case report form design, study implementation, data management and financial management. The fellowship offered opportunities to participate in or observe meetings of safety review teams for on-going clinical studies and participate in phase I/II clinical trials.

Impact

The activities Dr Kakolwa is involved in after the training phase at GSK, are targeted to transfer clinical trial management skills and knowledge. She will also contribute to maintaining trial safety and quality control and be involved in writing systematic reviews and grant proposals.



Dr Mwaka Kakolwa
Tanzania



Broadening the scope of an institutional clinical trials unit

Dr Stephen Ian Walimbwa was hosted for one year at the Novartis Institutes for Biomedical Research in Basel, Switzerland. focusing on early phase clinical research.

The challenge

The EDCTP clinical R&D Fellowships support researchers and key members of clinical trial research teams from low- and middle-income countries for them to acquire specific skills in clinical research and development through placements in pharmaceutical companies, product development partnerships (PDPs) and research institutions. Dr Walimba aimed to acquire experience and expertise in early-phase clinical trials especially.



Dr Stephen Ian Walimbwa
Uganda

The project

Dr Walimbwa was hosted for one year at the Novartis Institutes for Biomedical Research (NIBR) in Basel, Switzerland. Under the mentorship of NIBR scientists within translational medicine, he participated in clinical trials that provided early proof of efficacy in humans, and in clinical trials that profiled the safety, tolerability, pharmacokinetics and pharmacodynamics of novel compounds. Some of these novel compounds will be key in the management of autoimmune diseases, neglected tropical diseases, malaria and rare diseases.

The fellowship allowed Dr Walimbwa to receive training and acquire skills and expertise in the design, set-up, operationalisation and follow-up of phase I-IIa clinical trials. Furthermore, he was able to establish a network of contacts within Swiss academia and pharmaceutical industry which will provide opportunities for collaboration, career progression and development of strategies for addressing poverty-related diseases.

Impact

Dr Walimba's experience and expertise in early-phase clinical trials will be a vital contribution to the capacity of the Clinical Trials Unit at the Infectious Diseases Institute (IDI) of the Makerere University College of Health Sciences.

Project at a glance

Project: EDCTP Clinical R&D Fellowship

Project lead: Dr Stephen Ian Walimbwa, Infectious Diseases Institute Ltd, Uganda

Year funded: 2017

EDCTP funding: €97,393

Fellow profile: <https://edctpalumnetwork.org/fe/profiles/view/87b80988-8ff6-4547-85a9-6ac6e6648d15>

Getting to quality clinical trial services

Dr Suzanne Staples pursued expertise in advanced phase clinical trials at Julius Clinical, the Netherlands, then conducting an intensive quality and training project at the THINK organisation in South Africa.

The challenge

The challenge for many early-career researchers is to hone their skills and experience in clinical product R&D. The EDCTP clinical R&D fellowships allow fellows to do just that through a placement in a clinical research organisation. Dr Staples aimed especially to familiarise herself with all the requirements for phase III/IV clinical trials and other study designs such as pragmatic trials and real-world observational studies.

The project

Dr Staples has a background in medicine and started to work as a research clinician in 2012; she completed a Master's in Transdisciplinary Health and Development Studies from Stellenbosch University. Since 2012, she participated in several TB and HIV clinical trials. Working at THINK (TB and HIV Investigative Network, Durban, KwaZulu-Natal, South Africa) she was promoted to Principal investigator in 2013 and conducted multiple phase II and III trials, which were conducted in collaboration with sponsors such as TB Alliance, MRC UK, and pharmaceutical industry.

Her placement at Julius Clinical, the Netherlands immersed her in the operation of this scientific clinical research organisation. She was able to train on all aspects of phase III/IV clinical trials, from proposal writing to reporting and manuscript preparation, from design and protocol development, site selection and initiation, trial management (including GCP and data-management) to monitoring and pharmacovigilance.

Impact

Besides preparing her for the next step in her career as a researcher (developing her own research project and successfully apply for funding), the immediate impact at THINK, her home institution, will be an extensive

Project at a glance

Project: EDCTP Clinical R&D Fellowship

Project lead: Dr Suzanne Staples, THINK TB & HIV Investigative Network (RF) NPC, South Africa

Year funded: 2017

EDCTP funding: €97,800

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/411ef147-e7bb-4db1-9e65-2efd185c47fa>

training and role development programme for all staff in combination with revisiting and developing guidelines and standard operating procedures and reviewing the conditions and key requirements of quality service. She also envisages developing an African research network.



Dr Suzanne Staples
South Africa



Transferring knowledge to junior researchers

Dr Armel Martin Zemsi Kala pursued a training at Janssen Pharmaceutical NV, Beerse, Belgium, with a view to training and mentoring students and junior researchers in Cameroon.

The challenge

As pertains to this type of fellowship, Dr Zemsi Kala aims to acquire knowledge and practical expertise in many aspects of the setup and conduct of clinical trials in sub-Saharan Africa, e.g. with a view to identifying gaps in regulatory and clinical capacities.

The project

In addition to his routine clinical activities as a general practitioner, Dr Kala has been contributing as a sub-investigator in various research programs and health promotion activities in the fields of HIV and tuberculosis at his institution in Cameroon. He has also been involved at site level in the planning, set-up and conduct of a GSK-funded Ebola vaccine trial.

The aim of the project is to complement his experience in implementing health and research projects in resource-constrained settings, with better knowledge of study design, regulatory requirements and trial reporting.

He seeks to learn how to proactively identify gaps and corresponding investments to be made in terms of the regulatory framework, capacity building (infrastructure/resources) and evaluate the operational readiness of investigational sites in different countries. He wants to gain expertise in the management of complex multi-country trials and learn various aspects of a clinical trial from protocol design to clinical study reporting.

Impact

After the placement period, for six months Dr Kala focused on the so-called reintegration activities of the clinical R&D fellowships at his home institution. He organised a 4 days training workshop on research methodology for 60 medical students. Furthermore, he designed and implemented two research projects in collaboration with two medical students as mentees. Finally, he set up an online forum on

Project at a glance

Project: EDCTP Clinical R&D Fellowship

Project lead: Dr Armel Martin Zemsi Kala, The Bamenda Center for Health Promotion and Research, Cameroon

Year funded: 2017

EDCTP funding: €63,579

Fellow profile: <https://edctp.alumninetwork.org/fe/profiles/view/450f927b-5916-4c39-b641-c384a0f5bd41>

which junior researchers can discuss issues they face in their projects with more experienced researchers.



Dr Armel Martin Zemsi Kala
Cameroon

Forging an institute of pharmaceutical research and biotechnology

Dr Ahmed Zeynudin Kasim aims to use new clinical research and product development skills to support the research capacity development at Jimma University.

The challenge

In line with the Ethiopian national strategic plan for research and development, Jimma University is investing heavily in human resource development, physical infrastructure and material resources that will enable the university to conduct rigorous clinical research and policy analyses. This will provide knowledge-based input for policymaking and policy implementation. The university is currently creating an Institute of Pharmaceutical Research and Biotechnology by merging its laboratory for drug quality with the laboratory of molecular biology.

The challenge for the fellow is to support this strategic push by Jimma University to establish, conduct, and support clinical and pharmaceutical research in medicines and biotechnology.

The project

Personally, Dr Kasim, an associate professor of infectious disease engaged in research, teaching, community service and other forms of scholarly activity for more than 10 years at Jimma University, aims to establish himself as an independent investigator and potential leader in the field of infectious disease clinical research with a special emphasis on neglected infectious diseases.

From the fellowship and the placement at Julius Clinical Research BV, the Netherlands, he expects to gain new skills and experience, especially in the design, implementation and management of multidisciplinary trials with a focus on neglected infectious diseases. An important part of every EDCTP Clinical R&D Fellowship is the translation of skills and knowledge to the home institution of the fellow. Dr Kasim developed a plan to apply and disseminate his knowledge by training staff and students in the fields of tropical and infectious disease, medical parasitology

Project at a glance

Project: EDCTP Clinical R&D Fellowship

Project lead: Dr Ahmed Zeynudin Kasim, Jimma University (JU), Ethiopia

Year funded: 2018

EDCTP funding: €108,725

Fellow profile: <https://edctpalumnetwork.org/fe/profiles/view/12a657be-ff5c-423c-945e-3b5ed19b7297>

and medical microbiology. He aims also to accelerate existing clinical research and plan new collaborative multidisciplinary research targeting the health and wellbeing of the community in Ethiopia. In this way, he will contribute to the establishment of an expanded clinical trial centre as well as contribute to the transformation of the university laboratory to an institute of pharmaceutical research and biotechnology. One of the projects is to improve the quality of the performance of the laboratory for malaria and experimental entomology.

Impact

The expected impact of this fellowship is a substantial contribution to the strategic project of Jimma University to create and develop an institute of Pharmaceutical Research and Biotechnology with a clinical research centre.



Dr Ahmed Zeynudin Kasim
Ethiopia



Advocating a national fellowship programme

Dr Alphonce Liyoyo aims to specialise as an infectious disease clinical researcher with a view to further research in Tanzania.

The challenge

Dr Liyoyo is active as a researcher and clinician at the Kibong'oto Infectious Diseases Hospital in Tanzania and the challenge he has set for himself is to become a specialist in clinical research on infectious diseases. His objective and the fellowship reflect the wider challenge in sub-Saharan Africa, the relatively low rate of trained researchers that are able to compete for funding, inform policy-making and address national infectious disease challenges.



Dr Alphonce Liyoyo
Tanzania

The project

Through the fellowship Dr Liyoyo seeks to boost hands-on skills and experience in the following areas: pharmacology, pharmacokinetics, and pharmacodynamics of old and new antibiotics for TB, TB/HIV and MDR-TB including those in early clinical phases and their interaction with other drugs. Secondly, he expanded his skills in designing a clinical research protocol, including developing the hypothesis, perform a literature review and submitting a proposal to regulatory and ethical review committees. To that end he also studies regulations of the Food and Drug Administration as well as Institutional Review Board policies.

After his placement at Novartis (Switzerland), he will return to the Kibong'oto Infectious Diseases Hospital and continue his career as a clinical researcher at the hospital. Besides further pursuing his own specialisation, he will teach, train, support and mentor junior scientists. He aims to mobilise research funding through teamwork and networking, nationally, regionally and internationally. Interestingly, he plans to disseminate his experience during the fellowship with a view to promoting fellowships as an instrument of capacity development. His approach comprises a peer-reviewed manuscript for publication; a short manuscript on capacity building and lessons learnt in an appropriate open access journal; a policy brief with recommendations specific to the Ministry of Health and Ministry of Science &

Project at a glance

Project: EDCTP Clinical R&D Fellowship

Project lead: Dr Alphonce Liyoyo, Kibong'oto Infectious Diseases Hospital, Tanzania

Year funded: 2018

EDCTP funding: €98,700

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/20b4d97e-30d7-4715-b0e8-a3103cf1bd0f>

Technology in Tanzania promoting a fellowship programme in the country; a press release for a general audience; and presentations at scientific conferences.

Impact

Dr Liyoyo expects his fellowship will have impact at various levels: individually, at his home institution, the Kibong'oto Infectious Diseases Hospital, in a wider academic circle of students and colleagues, and perhaps at the level of national policymaking, through both the research supporting disease control and advocacy for a national fellowship programme.

Becoming an expert clinical research pharmacologist



Dr Workineh Shibeshi Alemayehu aims to acquire high-level expertise in clinical infectious diseases pharmacology through a placement at Merck KGaA.

The challenge

Ethiopia has a high disease burden for HIV/AIDS, tuberculosis, malaria and human African trypanosomiasis. However, there are very few people in Ethiopia who are highly skilled in clinical research and product development. The main goal of the placement at Merck for Dr Alemayehu, who has already extensive experience as a pharmacologist and university teacher, is to acquire expert knowledge and advanced skills which will enable him to contribute to the structural development of the clinical research and teaching capacity at the University of Addis Ababa, Ethiopia.

The project

The EDCTP R&D Fellowship is to boost an already distinguished career as a pharmacologist, university teacher and mentor of young researchers. Dr Alemayehu graduated with honours from Addis Ababa University and received a PhD in veterinary molecular pharmacology from the University of Leipzig, Germany. He has eighteen years of experience in higher education teaching, research and administration. From 2010 to 2016, he was head of his department. He published over 48 articles in peer-reviewed scientific journals.

In 2014, the University of Addis Ababa awarded him the title of “Emerging Researcher” in recognition of his participation in the research of the College of Health Sciences. In 2016, he received a Mid-Career Track NIH-Fogarty Fellowship for research training. Also in 2016, he was one of twenty globally selected Novartis Next Generation Scientists and successfully completed a three months research internship with certification by the University of Basel, Switzerland.

The EDCTP R&D Fellowship and placement at Merck will enable him to acquire experience in all elements of clinical research including trial design, operation, implementation, project management, regulation, clinical trial data

Project at a glance

Project: EDCTP Clinical R&D Fellowship

Project lead: Dr Workineh Shibeshi Alemayehu, Addis Ababa University (AAU), Ethiopia

Year funded: 2018

EDCTP funding: €109,375

Fellow profile: <https://edctpalumnnetwork.org/fe/profiles/view/79f2458a-f1e2-4199-9571-ce7129cf1727>

reporting, medicines development, etc, which will establish him as full-fledged principal investigator for the conduct of clinical trials on infectious diseases in Ethiopia.

Impact

The expected immediate impact of this fellowship will consist of training workshops at the University of Addis Ababa for junior staff members and postgraduate students. Moreover, Dr Alemayehu will be in an excellent position to strongly contribute to the development of the recently established Clinical Trial Unit (CTU), and the Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa) at the College of Health Sciences. The fellowship at Merck will also be conducive to developing international collaborations.

Regarding his personal career, Dr Alemayehu is interested in the development of better medicinal products for malaria, tuberculosis, HIV/AIDS, and human African trypanosomiasis. He will be qualified to compete for international and national research grants such as the Thematic Research Grants awarded by the University, the Ministry of Science and Technology, and the Ministry of Health (Grand Challenge Ethiopia). He will lead team formation for the Infectious Disease Pharmacology Research Group and supervise several PhD and MSc graduate students. He intends also to lend his support to the growing pharmaceutical sector in Ethiopia.



Dr Workineh Shibeshi Alemayehu
Ethiopia



Determining actual drug exposure

Dr Ezenwa James Onyemata aims to apply therapeutic drug monitoring as a tool for improving HIV case management and monitor viral load suppression.

The challenge

The massive global increase in the number of HIV-infected patients on antiretroviral therapy (ART) has resulted in improved quality of life and reduced death rate. The UN aims to achieve 90% viral load (VL) suppression levels among patients on ART by the year 2020.

VL is affected by the level of antiretrovirals (ARVs) within the biological system (among other factors). This can be assessed through therapeutic drug monitoring (TDM). TDM allows for actual drug exposure to be determined, patient compliance gleaned, and provides opportunities for dose adjustment, thus increasing ART efficacy among some populations while avoiding drug-related toxicity. TDM thus could trigger early interventions to address non-adherence or correct low pharmacokinetic levels



**Dr Ezenwa James
Onyemata**
Nigeria

The project

The aim of the project is foremost the individual research capacity development of the fellow but with a view to applying therapeutic drug monitoring to support the ambitious global goals for HIV control, in particular, viral load suppression.

The fellowship will support Dr Onyemata to become proficient in skills regarding drug profile safety, tolerability, pharmacokinetics and pharmacodynamics for novel compounds. These skills are useful for future involvement in clinical trials phase I and II, one of the goals his institution, the Institute of Human Virology in Nigeria, is pursuing. In addition, TDM can be applied to estimating ARV levels in HIV patients to understand the contribution of ARV bioavailability and dosing to treatment failure. Developing

TDM also requires that the science behind the extraction of ARVs from plasma, peripheral blood mononuclear cells (PBMCs), and hair be understood. Furthermore, the science behind small molecule separation such as choosing

Project at a glance

Project: EDCTP Clinical R&D Fellowship

Project lead: Dr Ezenwa James Onyemata, Institute of Human Virology, Nigeria

Year funded: 2019

EDCTP funding: €99,259

mobile phase and chromatographic matrix needs to be understood and optimised for the particular application. Skill in the use of High-Performance Liquid Chromatography and Mass spectrometry is required for detection and quantification of ARV, and associated data processing and interpretation.

Impact

The expected impact of the fellowship is the advanced professional development of the fellow who will also contribute to the clinical research capacity of the Nigerian Institute of Human Virology. In future, the availability of personal and institutional expertise in therapeutic drug monitoring may contribute to the inclusion of ARV level monitoring in the HIV treatment guidelines in Nigeria.

Building a clinical trial support unit

Dr Nneka Onyejebu aims to become proficient in clinical trial design and management with a view to build a clinical trial support unit at the Nigerian Institute of Medical Research.

The challenge

Sub-Saharan Africa bears a disproportionate burden of tuberculosis (TB), multidrug (MDR)/extensively drug (XDR) TB, human immunodeficiency virus (HIV) and other poverty-related diseases.

Intervention efforts for poverty-related diseases are focused on research and development of new drug regimens, vaccines and diagnostics, some presently undergoing clinical trials in various continents including Africa. Most African researchers, however, are rarely involved in the early stages of product development and the design of clinical trials. They are more likely to be involved in the implementation phase of effectiveness trials.

In order to develop a mutually beneficial research partnership, African researchers must develop the capacity to design clinical trials, develop protocols and implement all phases of clinical trials.

The project

Dr Onyejebu is confident that the Clinical Research and Product Development Fellowship will offer her the opportunity to increase her competencies and prepare her for assuming leading roles in clinical trial processes from design to protocol development, implementation and manuscript writing.

After the placement, the so-called re-integration period at the Nigerian Institute of Medical Research will focus on the development of human resources through training and mentorship. Moreover, advocacy for institutional management buy-in will be pursued, involving various interest groups such as co-researchers the home institution and other tertiary institutions of tertiary education and networks of non-governmental and civil society organisations.

Project at a glance

Project: EDCTP Clinical R&D Fellowship

Project lead: Dr Nneka Onyejebu, Nigerian Institute of Medical Research, Nigeria

Year funded: 2019

EDCTP funding: €99,875

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/a589325f-7e2b-43aa-bddd-02b9bd545cfb>

Impact

One anticipated outcome is the formation of a Clinical Trial Unit that will offer support for future trials and research within and outside the Nigerian Institute of Medical Research, following international standards. Over time, this will also create career paths for the fellow and other young researchers in Nigeria.



Dr Nneka Onyejebu
Nigeria



Advanced laboratory skills at IAVI

Dr Micah Ongeru aims to acquire essential clinical research skills including advanced laboratory skills and train laboratory scientists and technicians at the University of Nairobi.

The challenge

Through a 12-month placement at the International Aids Vaccine Initiative (IAVI), Dr Ongeru challenges himself to learn the process of developing and implementing new laboratory tests (diagnostics) and acquire practical experience in clinical trial design and implementation.

The project

The specific objectives of Dr Ongeru's fellowship are several. First, he will contribute to increasing laboratory capacity in clinical trial research through his training in advanced laboratory skills. These will include hands-on training on viral inhibition assay, viral neutralisation assay and ELISPOT assay, validation of diagnostics, and implementing quality systems (GCLP compliance, quality control and quality control safety), laboratory data management and other laboratory protocols important for product (vaccine/drug) evaluation. Secondly, he will acquire practical experience in the conduct of a clinical trial in a multi-country, multi-cultural environment.

In the reintegration period at the University of Nairobi, he will share the acquired skills and knowledge through training initiatives, mentorship and supervision activities, as well as through scientific workshops and seminars at his home organisation. He will develop training materials and training certificates for the participants who attended and completed the courses offered in the context of his reintegration activities.

Impact

The fellowship will boost the technical laboratory and clinical trial expertise of Dr Ongeru. At least 40 laboratory scientists and technicians will be trained in the relevant clinical trials skills and knowledge acquired during the fellowship.

Project at a glance

Project: EDCTP Clinical R&D Fellowship

Project lead: Dr Micah Ongeru, University of Nairobi, Kenya

Year funded: 2019

EDCTP funding: €93,700

Fellow profile: <https://edctpalumninetwork.org/fe/profiles/view/e7043916-88db-47de-9be1-5e1f0a8b9a71>



Dr Micah Ongeru
Kenya

Supporting the next generation of researchers in Burkina Faso



Mr Aboubakar Soma is trained in comprehensive clinical trial competencies and skills at IDDO/WWARN (United Kingdom) to train young researchers at the Centre Muraz.

The challenge

Sub-Saharan African countries urgently need to further develop their clinical research capabilities on poverty-related diseases such as malaria, HIV, tuberculosis and neglected tropical diseases. To lead research projects on diagnostics, drugs and vaccines for these diseases, African researchers need to develop their skills even more.

The project

Mr Aboubakar Soma will train at the Infectious Diseases Data Observatory/the Worldwide Antimalarial Resistance Network (IDDO/WWARN); afterwards, he will return to the Centre Muraz in Burkina Faso to share and implement his new knowledge.

After English language training, he will start with his placement activities to gain skills in clinical trial competencies, covering: clinical trial design (protocol development); statistics (sample size calculation and data analysis); protocol development and systematic reviews) ethical considerations and patient safety (GCP and GCLP), study and site management, and data management and informatics (CRF and source data, quality control and data correction and clinical trial databases). He will also enhance his skills in using clinical trial toolkits for antimalarial drugs. Moreover, he will acquire skills in geospatial analysis using ArcGIS.

Centre MURAZ is a biomedical centre dedicated to research and control of tropical diseases and malaria. It is experienced in evaluating strategies for the prevention of malaria, HIV, and meningococcal disease through clinical trials. Centre MURAZ is also conducting a phase II trial on an Ebola vaccine. In July 2018, Centre MURAZ merged with two other research centres to form the National Institute of Public Health (INSP) of Burkina Faso. The INSP's mission comprises research, disease prevention & control and training.

Project at a glance

Project: EDCTP Clinical R&D Fellowship

Project lead: Mr Aboubakar Soma, Institut National de Santé Publique, Burkina Faso

Year funded: 2020

EDCTP funding: €98,500

After this placement at WARRN, Mr Soma will conduct several projects at Centre MURAZ. He will organise three comprehensive dissemination workshops. The training modules for the workshops will be developed during his placement under the supervision of mentors from both organisations.

He will also develop a specific efficacy study protocol on malaria listing several research questions on malaria that could be addressed by the specific protocol.

Impact

An IDDO/WARRN team will visit the Centre MURAZ to build a strategic partnership. Moreover, Mr Soma will aim to strengthen partnerships with other research centres in Burkina Faso and West Africa. To that end, the training workshops and his methodological support will be open to applicants from other research centres in Burkina Faso whenever possible.

His future role will be to give continuous methodological support to the young researchers involved in MSc or PhD programmes. This methodological support to young researchers and the strengthening of the strategic relationships will have a long-term impact on research capacity in Burkina Faso and centres in West Africa.



Mr Aboubakar Soma
Burkina Faso



Expanding the malaria research scope in Mali

Dr Nouhoum Diallo will acquire skills for malaria clinical development studies (early-stage drug discovery and diagnostics) at Novartis Pharma AG (Switzerland) to strengthen the capacity of the MRTC in Mali.

The challenge

The Malaria Research and Training Centre (MRTC) in Bamako, Mali, has developed an integrated approach to the study of malaria using clinical and molecular biology as a basis of addressing field epidemiological and entomological problems at the community level. The MRTC has conducted numerous, longitudinal cohort studies, case-control studies, drug efficacy trials and malaria vaccine trials. However, the centre has little experience in early-stage drug discovery and diagnostic tools development. Consequently, there are very few well-trained researchers in these areas.



Dr Nouhoum Diallo
Mali

The project

To strengthen the capacity of MRTC, Dr Nouhoum Diallo will acquire experience working on malaria clinical development projects during a placement at Novartis Pharma AG - Global Drug Development in Basel, Switzerland.

The work plan for the placement comprises 1) acquiring advanced laboratory skills, 2) gain hands-on knowledge of and insight in drug discovery and the path of diagnostic test development, and 3) all aspects of clinical trials.

The programme will focus on scientific concepts and (malaria) research design (clinical trial design, statistics, clinical pharmacology and protocol development); 2) ethical considerations and patient safety; 3) drug development and regulation (clinical development pipeline and regulatory pathway to medicines approval); 4) clinical trials operations and study implementation (obtaining ethical and regulatory approval, study participant recruitment, adverse event identification and reporting, post-marketing surveillance and pharmacovigilance, quality control and clinical trial monitoring, including adherence and maintaining trial master and investigator files);

Project at a glance

Project: EDCTP Clinical R&D Fellowship

Project lead: Dr Nouhoum Diallo, Université des Sciences, des Techniques et des Technologies de Bamako, Mali

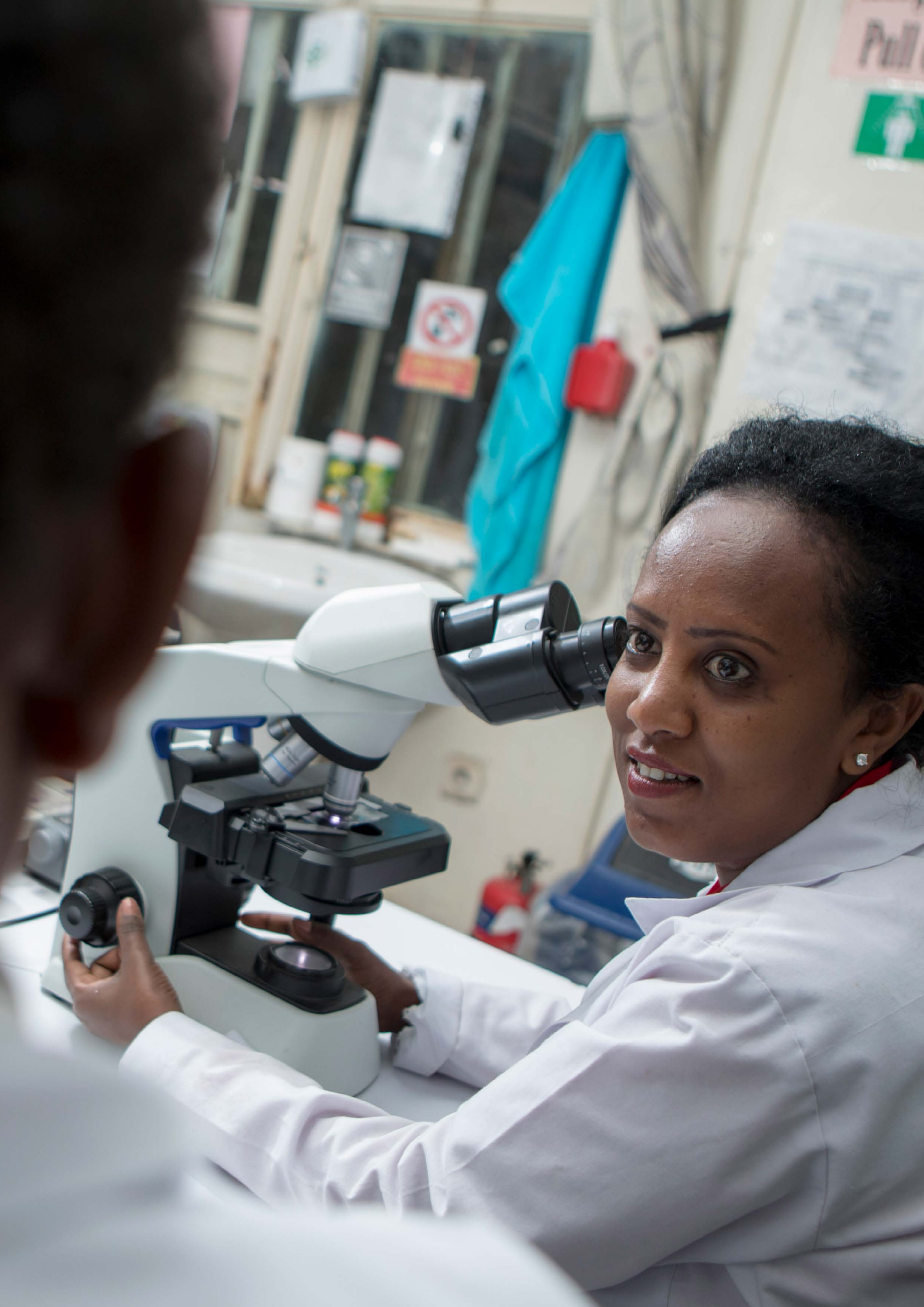
Year funded: 2020

EDCTP funding: €99,999

5) data management and informatics; 6) clinical trial reporting; 7) networking with clinical trial stakeholders.

Impact

In the second phase of his fellowship, Dr Diallo will transfer the knowledge and experience he acquired through workshops, seminars, round table conferences and by teaching peers, colleagues and students. In collaboration with senior researchers, a multi-module comprehensive workshop on clinical trial research will be held at the MRTC. Generally, the placement will contribute to the expansion of the research scope at MRTC in Mali.





EDCTP/AREF Preparatory Fellowships

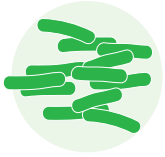
2014-2020



12 grants

€0.77 M

to enhance the competitiveness of up-and-coming post-doctoral sub-Saharan African scientists and clinicians aspiring to receive international/regional/national fellowships or grant support.



Resistance profiling of *Mycobacterium tuberculosis* complex and *Staphylococcus aureus*

Dr Abubakar Shaaban Hoza aims to acquire new technical knowledge and skills in medical microbiology at the University of Leipzig, Germany, and apply these at the Sokoine University, Tanzania.

The challenge

The challenge is to advance research capacity in medical microbiology at the Sokoine University of Agriculture in Tanzania. New technical knowledge and skills will be acquired and then applied in a project while training research staff.

The project

A placement at the University of Leipzig will enable Dr Hoza to acquire the skills (including Next Generation Sequencing) and knowledge to isolate *M. tuberculosis* and *S. aureus* isolates from presumptive TB patients. Dr Hoza will use biological samples and/or data generated during his PhD study.

At his home institute at the Sokoine University of Agriculture, he will then conduct a study on the utility of whole-genome sequencing in the prediction of drug resistance genotypes of *M. tuberculosis* and *S. aureus*. This will give the fellow the opportunity to further train staff in the context of this project.

Impact

In line with the scope and objectives of the EDCTP/AREF Preparatory fellowship, the expected impact of the fellowship is the enhancement of the research capacity in medical microbiology of the fellow and his home institution in Tanzania. Moreover, the planned study aims to address the public health impact of multi-drug resistant tuberculosis (MDR-TB) caused by *M. tuberculosis*, and *S. aureus* resistance in the resource-limited settings of Tanzania.

Project at a glance

Project: EDCTP/AREF Preparatory Fellowship

Project lead: Dr Abubakar Shaaban Hoza, Sokoine University of Agriculture, Tanzania

Year funded: 2019

EDCTP funding: €70,000



**Dr Abubakar Shaaban
Hoza**
Tanzania

How pharmacogenomics affect the pharmacokinetics of first-line TB drugs

Dr Hamdan Abualbasher aims to determine the pharmacokinetics of rifampicin in patients with pulmonary TB and MDR-TB, by training at the University of Cape Town, South Africa, and conducting a study at the Al-Neelain University, Sudan.

The challenge

The challenge is to fight multiple-drug-resistant tuberculosis. *Mycobacterium tuberculosis* can become resistant to multiple drugs resulting in MDR-TB, which complicates the patient's condition and affects the disease course with very poor prognosis.

One of the causes of resistance may be low bioavailability of anti-tuberculosis drugs. Variation of the bioavailability of anti-tuberculosis drugs may be owed to polymorphisms of some drug transporters genes that control drug absorption and secretion. Some of these gene polymorphisms are widely prevalent among Sub-Saharan African populations and some are not investigated.

The project

Dr Abualbasher aims to determine the pharmacokinetics of rifampicin in Sudanese patients with pulmonary tuberculosis and MDR-TB. Additionally, he aims to determine the effect of the transporters' gene polymorphisms on the bioavailability of rifampicin. Thirdly, he wants to determine whether or not rifampicin exposure is associated with a decreased rate of sputum conversion and development of MDR-TB.

The fellow proposed a pilot cohort to follow 70 patients with pulmonary tuberculosis. Sputum will be examined also by GeneXpert assay to rule out any possibility of rifampicin resistance or MDR at the time of diagnosis. DNA sequencing for *M. tuberculosis* will also be done to make sure there are no secondary infections by other MDR-TB bacteria. At 2, 5 and 6 months after starting anti-tuberculosis drugs, sputum microscopy and culture will be done to differentiate those who developed MDR-TB and those who are drug-susceptible. Blood will be collected from the patients to isolate DNA. Genotyping will be done in selected transporters' gene by PCR-RFLP and

Project at a glance

Project: EDCTP/AREF Preparatory Fellowship

Project lead: Dr Hamdan Abualbasher, Al-Neelain University, Sudan

Year funded: 2019

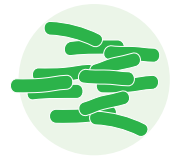
EDCTP funding: €41,720

for others by DNA sequencing. Blood samples will be collected at 1, 3 and 8 hours from taking the drugs just once for rifampicin assay.

Pharmacokinetic analysis and population modelling will be done at the University of Cape Town in collaboration with Professor Helen McIlleron and Dr Paolo Denti. Patients will be recruited from Bashier University hospital which is affiliated to the fellow's home organisation the Al-Neelain University in Sudan.

Impact

The study will have direct clinical and policy implications which will contribute to better clinical and epidemiological outcomes for pulmonary tuberculosis. The findings of this pilot study are expected to lead to a bigger sample size study with the development of a simulation model that tested against higher rifampicin doses for those with alleles that pose a risk.



Dr Hamdan Abualbasher
Sudan



Cardiovascular disease risk in adolescents living with HIV

Dr Edith Majonga studies cardiovascular disease epidemiology in adolescents with perinatal HIV to reduce cardiovascular disease morbidity and mortality.

The challenge

Fortunately, large numbers of HIV-infected children now reach adolescence and then transition to adult HIV services because of the widespread use of ART in sub-Saharan Africa. Unfortunately, longstanding treatment of HIV infection is associated with damage to the heart and vasculature. Currently, there is a high burden of cardiac abnormalities in children and adolescents with perinatal HIV infection in sub-Saharan Africa. Cardiovascular disease risk is also related to alterations in vascular structure and function.

The project

These problems, however, have not been systematically investigated in children and adolescents with a perinatal HIV infection. Moreover, most adolescents in sub-Saharan Africa have had a delayed diagnosis or initiation of ART. The impact of delayed ART on the vascular system is not known.

In this project, Dr Edith Majonga hypothesises that adolescents who have had an early start of ART will have better vascular characteristics compared to those who start ART much later. Therefore, those with a delayed start of ART start will have a higher risk of developing atherosclerosis. The study will cross-sectionally assess vascular characteristics, i.e. carotid intima-media thickness, flow-mediated dilation, pulse wave velocity and endothelial peripheral arterial tonometry, lipid profiles, insulin resistance and systemic inflammatory biomarkers. These characteristics will be compared to those of HIV-uninfected controls.

Impact

A better understanding of cardiovascular disease epidemiology and risk factors in adolescents with perinatal HIV will leverage the extensive investments in the existing HIV care system by

Project at a glance

Project: EDCTP/AREF Preparatory Fellowship

Project lead: Dr Edith Majonga, Biomedical Research and Training Institute, Zimbabwe

Year funded: 2020

EDCTP funding: €38,709

reducing cardiovascular disease morbidity and mortality. At an institutional level, the fellowship would contribute to new research collaborations, capacity building and the establishment of the first Cardiovascular Assessment Centre at the Biomedical Research and Training Institute in Zimbabwe. This will enable clinical assessments and research on cardiovascular disease.



Dr Edith Majonga
Zimbabwe

Maternal antibodies and malaria protection

Dr Hamtandi Natama (Burkina Faso) will train antibody detection at ISGlobal (Spain) for study on maternal antibodies protecting against malaria in early childhood.

The challenge

Although infants are thought to be protected against malaria during the first months of life mainly due to maternal antibodies, malaria in early childhood is not uncommon in high-transmission settings. Susceptibility to the infections varies between individuals and, therefore, putting into question the protective effect of maternal antibodies. In such a context, factors that modulate malaria risk/protection in early childhood are not fully understood. Further field studies focusing on the role of maternal antibodies are needed.

The project

A three-month placement at the host institution, the Barcelona Institute for Global Health (ISGlobal), will provide Dr Hamtandi Natama with the necessary training in qSAT multiplex antibody detection using Luminex® platform, immune cell isolation, stimulation, phenotyping and quantification using flow cytometry, data quality control and analysis). ISGlobal also offers the facilities to analyse a set of cord blood samples (n=715) for maternal antibody detection.

The objectives of the project are to 1) generate data on maternal antibodies (IgG/subclasses) relevant for malaria protection during the first months of life, which will guide future studies on malaria immunology in early childhood; 2) acquire skills and competence in immunological techniques and methods, and; 3) develop a compelling proposal for funding after the fellowship.

The placement will be followed by a three-month reintegration period at the home institution. This will be used to train peers on a set of immunological techniques. Moreover, the fellow will complete the statistical analysis, data interpretation and preparation of a publication on the maternal antibodies research and continue the development of Dr Natama's follow-

Project at a glance

Project: EDCTP/AREF Preparatory Fellowship

Project lead: Dr Hamtandi Magloire Natama, Institut de Recherche en Sciences de la Santé / Unité de Recherche Clinique de Nanoro, Burkina Faso

Year funded: 2020

EDCTP funding: €69,700

on project based on the research outputs from the placement.

Impact

The preparatory fellowship will have an impact at several levels. First, it will contribute knowledge of the role of maternal antibodies in malaria protection in infants living in malaria-endemic settings, promote high-quality malaria immunology research and build capacity through the training of colleagues. Secondly, it will prepare the home institution (laboratory development) for future immunological malaria studies and strengthen the relationship with ISGlobal. Thirdly, the fellow will consolidate his skills and competence in malaria immunology research, his competitiveness in attracting grants and establish himself as an independent malaria researcher in his home institution.



Dr Hamtandi Magloire Natama
Burkina Faso



Why certain ARTs work better for some than others

Dr Helena Lamptey will study genetic variations relevant in controlling viral replication by eliciting antibodies.

The challenge

During HIV infection, the immune system plays a role in controlling viral replication by eliciting antibodies that work in collaboration with effector cells such as natural killer (NK) cells. These mechanisms are mediated by Fc receptors for immunoglobulins (Ig). Depending on receptor type, Fc Gamma Receptors (FCGR) can regulate immunity by causing cell activation or inhibition in response to infections. Among different patients, there are differences in progression and treatment outcome. One of the factors hypothesized to be the cause of these differences is FCGR polymorphisms. Furthermore, genetic variations that occur in FCGR genes such as Copy Number Variations (CNV) and Single Nucleotide Polymorphisms (SNPs) have been shown to affect Fc-mediated effector functions. These genetic variations could modify FcR expression and IgG isotype binding, which would affect HIV infection risk and disease progression.

The project

Although the burden of HIV infection in Africa is high, data is lacking on the effect of FCGR polymorphisms on the progression of the infection and the response to antiretroviral therapy (ART) in African populations. Therefore, the project aims to determine this effect in a Ghanaian population. The study will genotype FcγRIIa, FcγRIIb, FcγRIIc, FcγRIIIa and FcγRIIIb small nucleotide polymorphisms (SNPs), copy number variations (CNV), and determine their allelic and haplotype associations with HIV infection progression and ART outcomes.

HIV patients will be recruited and followed up every three months over two years. Baseline viral loads will be determined before ART and pretreatment viral load, CD4 count and FCGR types (using amplicon targeted deep sequencing techniques) will be compared to determine who responds at what rate (through measurement of

Project at a glance

Project: EDCTP/AREF Preparatory Fellowship

Project lead: Dr Helena Lamptey, NMIMR, University of Ghana, Ghana

Year funded: 2020

EDCTP funding: €69,652

drug levels and ART resistance levels) and how that relates to their FC gamma haplotypes.

Impact

The knowledge generated may help explain why certain ARTs work better for some patients but not others. This would also show the need to consider FCGR genotypes before prescribing specific drugs for HIV patients.

As a capacity development project, Dr Lamptey will have the opportunity to use the advanced skills in sequencing acquired during the fellowship, develop her competence in HIV immunology, and support her becoming an independent investigator in HIV translational research at the Noguchi Memorial Institute for Medical Research in Ghana. She will also transfer knowledge and skills to students and colleagues through training and mentorship.



Dr Helena Lamptey
Ghana

Malaria in pregnancy: emerging resistance to SP



Dr Adebajo Adegbola will train at the University of Denmark and conduct an observational study in Nigeria on the prevalence of newly emerging resistance to sulphadoxine-pyrimethamine.

The challenge

Malaria in pregnancy (MiP) continues to be a significant public health issue, particularly in sub-Saharan Africa. The coverage of pregnant women with three or more doses of intermittent preventive treatment using sulphadoxine-pyrimethamine (IPTp-SP) is recommended to prevent risks associated with MiP in moderate-to-high transmission settings. However, the evaluation of malaria prevention strategies during pregnancy relies on the precise diagnosis of parasite and the monitoring of antimalarial resistance using genomic techniques. Recent evidence shows the emergence of a novel Pfdhps-431V mutation in Nigeria. This new mutation may further complicate existing SP-resistance.

The project

Dr Adegbola's project is, first, to advance his expertise in clinical research and malaria parasite genomics by attending a training at the Center for Medical Parasitology of the University of Copenhagen in Denmark. The training will enhance his expertise on techniques such as DNA isolation, PCR amplification and Sanger sequencing.

Secondly, he will conduct a clinical study of resistance to SP, specifically, he will examine to what extent dhps-431V mutation influences the protective efficacy of IPTp-SP. To this end, he will conduct a pilot study based on a small number of samples (100-150) aiming to pinpoint the trends of newly emerging mutations, design qPCR and sequencing methods, and generate a small dataset as the basis for the intended follow-on project.

Impact

The fellow will transfer the acquired skills to his home organization and introduce the skills to

Project at a glance

Project: EDCTP/AREF Preparatory Fellowship

Project lead: Dr Adebajo Adegbola, Obafemi Awolowo University, Nigeria

Year funded: 2020

EDCTP funding: €69,897.72

other colleagues through seminars, workshops and incorporation into a postgraduate training curriculum.

Moreover, an observational study will be done among adult women attending the ante-natal clinic. This follow-on study aims to detect *P. falciparum* positivity at delivery as well as pregnancy outcome in participants who must have received three or more doses of IPTp-SP. The presence of existing and new Pfdhps/Pfdhfr mutations in the samples positive for *P. falciparum* will be determined using a quantitative PCR. The prevalence of novel Pfdhps-431V mutant and other Pfdhps/Pfdhfr resistance alleles among the study population will be estimated. The significance of the resistance genes on the efficacy of SP will be described by looking at its associations with the reported IPTp use, *P. falciparum* infection, maternal anaemia, low birth weight, and preterm delivery.



Dr Adebajo Adegbola
Nigeria



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