



EDCTP

The power of sharing science

EDCTP2 portfolio: Collaborative research and development



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 medicinal products 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. Cofunding from the Agence nationale de recherche sur le sida et les hépatites virales (ANRS, France), the Bundesministerium für Bildung und Forschung (BMBF, Germany), the Department of Health and Social Care (DHSC, United Kingdom), the Fonds National de la Recherche (FNR, Luxembourg), the Foreign, Commonwealth & Development Office (FCDO, United Kingdom), the Foundation for Science & Technology (FCT, Portugal), the Fundación Mundo Sano (FMS, Argentina/Spain), the Institut national de la santé et de la recherche médicale (Inserm, France), the Instituto de Salud Carlos III (ISCIII, Spain), the Joint Global Health Trials (JGHT, United Kingdom), the Leprosy Research Initiative (LRI, Netherlands), the Medical Research Council (MRC, United Kingdom), the NWO-WOTRO Science for Global Development (NWO-WOTRO, Netherlands), and the Swedish International Development Cooperation Agency (Sida, Sweden) for the projects highlighted in this publication is gratefully acknowledged.

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EDCTP2: International partnerships against infectious disease

Dear EDCTP stakeholders,

The seventh year of implementation of the second programme of the European & Developing Countries Clinical Trials Partnership (EDCTP2) presents an opportune time to share with you the progress and achievements so far. This programme is advancing the development of diagnostics, drugs and vaccines against the most important infectious diseases affecting sub-Saharan Africa, particularly benefiting vulnerable groups such as infants, children, adolescents and pregnant women.

The challenge

Infectious diseases remain a major cause of death and disability in sub-Saharan Africa. Despite much progress, diseases such as HIV/AIDS, malaria and tuberculosis (TB) still kill millions every year. As well as their effects on individuals, infectious diseases have a huge economic impact, in treatment costs and lost productivity.

Controlling infectious disease will therefore be core to achieving Sustainable Development Goal 3 – ensuring healthy lives and promoting wellbeing for all at all ages. Furthermore, ensuring healthy populations through effective infectious disease control will be central to achieving many other SDGs.



EDCTP2 at a glance

Duration: 2014-2024

Funding to date: €752.74 M*

Membership and reach: 16 sub-Saharan African countries are a member of EDCTP Association; 41 African countries and 244 African institutions are participating in EDCTP projects

Studies: Funded 274 clinical studies, including 124 clinical trials

Capacity-building: We are supporting 196 African researchers through fellowships; 39 ethics and regulatory projects involving 35 African countries

*As of December 2020

Control of infectious diseases requires diagnostics to detect them, drugs to treat them and vaccines to prevent them. As pathogens inevitably develop resistance to drugs, the world relies on an ongoing supply of new treatments. However, new product development is costly and risky – failure rates are high – and it is often not commercially viable for companies to develop new products for infections mainly affecting low-income countries. Innovative partnerships are therefore required to advance new product development.

To determine their safety and efficacy, new products undergo extensive evaluation, in phase I, II and III trials of increasing size. However, the results of trials in high-income countries are only a partial guide to how well products perform in other settings. Genetic differences and past history of infections, for example, can influence how people respond to drugs and vaccines. Ideally, therefore, studies need to be conducted in sub-Saharan Africa to generate locally relevant evidence.

In addition, trials undertaken to secure regulatory approval often exclude certain populations, such as children, pregnant women or people with other

Advancing early clinical testing	Generating key data on safety, efficacy and performance	Adapting for key populations
> Innovative HIV, malaria and TB vaccines	> Typhoid conjugate vaccine	> Novel antiretroviral drugs for children, adolescents and pregnant women
> New drugs to shorten TB treatment	> Ebola vaccine use in children	> Antimalarial drugs for malaria prevention in pregnant woman
> Broadly neutralising antibodies to prevent HIV	> Novel drug combinations for malaria	> Extending use of drugs against neglected infectious diseases, inc. parasitic worm infections
> Single-dose cures for malaria	> New TB diagnostics	> Adapting pre-exposure prophylaxis for adolescents
> Transmission-blocking vaccines for malaria	> Simplified treatment of cryptococcal meningitis in HIV patients	> Second-line antiretroviral therapy for children
> Preparations for testing of Lassa fever vaccine	> Optimising treatment of severe pneumonia in children	

infections. Further studies are needed to ensure that new products are safe, effective and can be delivered in suitable formulations to these special groups.

The response

A partnership of equals between European and sub-Saharan Africa countries, and supported by the European Union, EDCTP2 invests in international research collaborations carrying out clinical trials of new interventions against poverty-related infectious diseases in sub-Saharan Africa. It aims to provide the evidence to guide informed decision-making on the introduction of new interventions, and also to build the capacity of African countries to plan, undertake and lead clinical studies of local priority infections.

EDCTP2 targets

EDCTP2 focuses on the key poverty-related infectious diseases affecting sub-Saharan Africa – HIV/AIDS, TB, malaria, lower respiratory tract infections, diarrhoeal diseases and neglected tropical diseases. As infections are rarely experienced on their own, co-infections and co-existing health conditions (including interaction with non-communicable diseases) are a further important priority.

EDCTP2 also has a focus on infectious diseases of epidemic potential, including Ebola and COVID-19. It supports international consortia that are developing the capacity of countries to prepare for and respond promptly to infectious disease outbreaks, and to undertake clinical research in outbreak situations.

The EDCTP2 niche

EDCTP2 occupies a distinct global niche. Concerted global efforts have seen much

progress made in early-stage drug discovery and intervention development. Increasingly, a bottleneck is the later-stage evaluation of interventions among target populations (phase II and III clinical trials) and post-licensing implementation studies (phase IV trials) to ensure smooth introduction of new interventions and to generate evidence on their performance in real-life settings – essential information for local policymakers.

EDCTP2 also has a strong emphasis on building the capacity for clinical research in sub-Saharan Africa, by supporting the development of up-and-coming researchers and scientific leaders, and by providing funds for laboratory equipment and other clinical research essentials. As well as being an integral part of clinical trial funding, support for capacity building is also provided through specific fellowships and capacity-building grants. EDCTP2 also aims to build an enabling environment for clinical research, by strengthening national regulatory and ethical review capabilities and promoting harmonisation of approaches across the region.

As well as partnerships between EU and sub-Saharan researchers and institutions, EDCTP2 also encourages global networking, with active involvement of teams from third countries such as the USA, other high-income countries and the global South. It also supports regional networks within Africa to promote the local dissemination of knowledge and expertise. EDCTP2 also works with an extensive range of global partners to coordinate efforts, align priorities and maximise impact.

We are very appreciative of the efforts of many of you who are associated with the EDCTP journey.

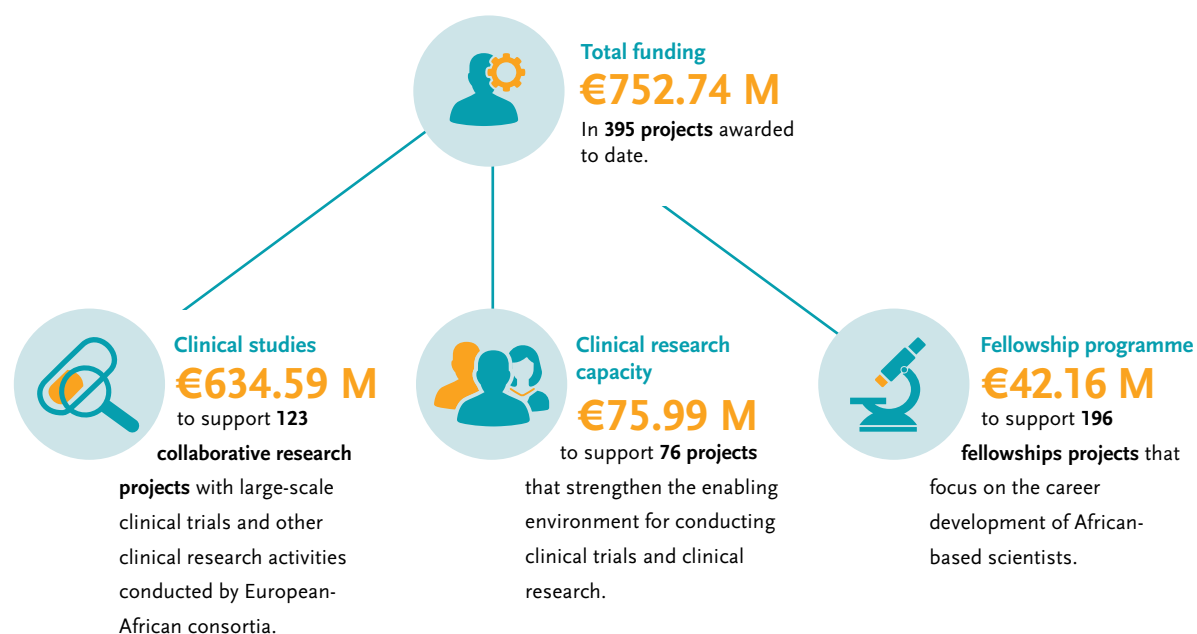
Kind regards,

Dr Michael Makanga
Executive Director



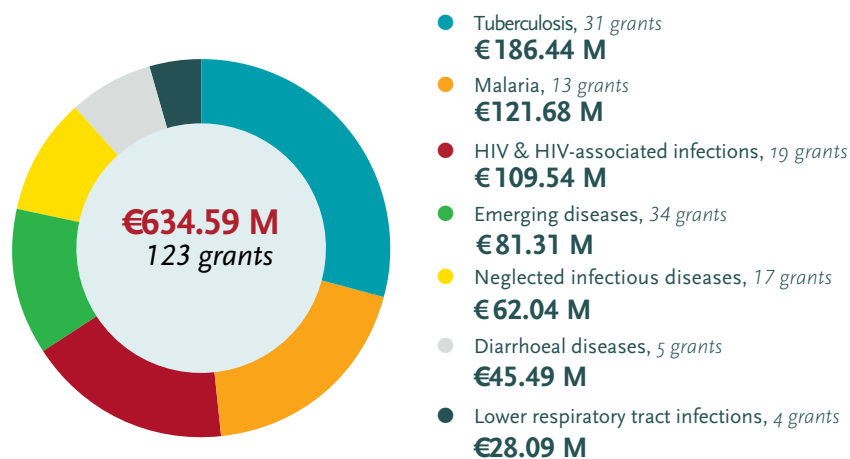
EDCTP's investment in research & development

2014-2020



Collaborative clinical trials and clinical studies

By disease



By intervention

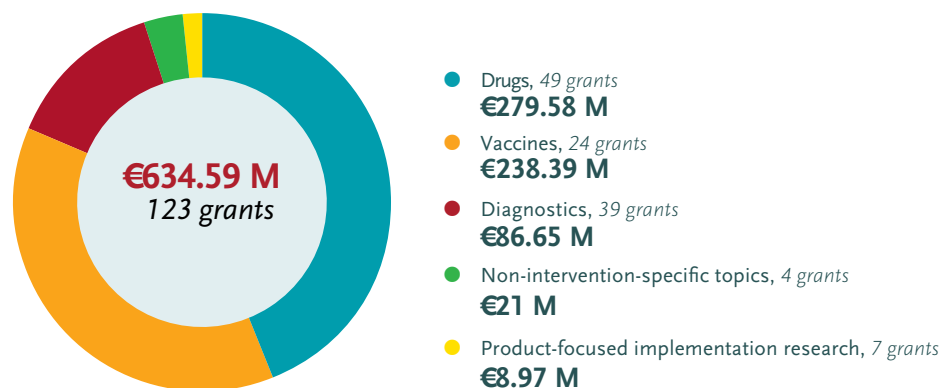




Photo:
A resident of the Kangemi community in Kenya

€109.54 M













€64.10 M



€35.59 M



€9.86 M

Caption	Study phase	Population
Project name	 Phase I	 Adults (18yr and above)
<i>Site(s) in sub-Saharan Africa</i>	 Phase II	 Adolescents (10yr-17yr)
	 Phase III	 Children (2yr-9yr)
	 Phase IV	 Infants (above 1mo-1yr)
	 Observational study	 Pregnant women and/or newborns (birth to 1mo)



Better tools for HIV prevention in women

The CAPRISA 018 study is developing an antiretroviral implant to protect women against HIV infection.

The challenge

Young women are twice as likely as young men to acquire HIV. Every year since 2010, they have accounted for two thirds of new infections among adolescents. In some parts of sub-Saharan Africa, women are up to eight times more vulnerable to HIV than young men.

Pre-emptive use of antiretroviral drugs – pre-exposure prophylaxis (PrEP) – can be a highly effective way to prevent HIV infection. However, results with women have been inconsistent, mainly because of a lack of adherence to the daily drug-taking that PrEP requires.

The project

To provide women with an improved option for PrEP, the CAPRISA 018 study is evaluating an innovative sustained-release antiretroviral implant. A new implant is being developed incorporating tenofovir alafenamide (TAF), a highly potent antiretroviral with fewer unwanted side effects than earlier drugs.

The CAPRISA 018 team is evaluating an implant that would last six months. It will carry out preparatory studies to examine the safety, acceptability and pharmacokinetics of the TAF implant, and to gather initial data on its efficacy for HIV prevention. A randomised controlled trial will then be carried out on nearly 500 at-risk women.

Impact

The CAPRISA 018 study will create a safe intervention that enables women to take control of HIV prevention. Positive results in the initial trial would pave the way to a large-scale phase III trial that would provide definitive evidence of the ability of a TAF implant to prevent HIV infection. As sub-dermal implants are already widely available through family planning service in several sub-Saharan African countries, implementation could be relatively straightforward.

Project at a glance

Project: CAPRISA 018 study

Project lead: Professor Salim Abdool Karim, Centre for the AIDS Programme of Research in South Africa, South Africa

Countries involved: France, The Netherlands, South Africa

Target population(s): Women

Year funded: 2016

EDCTP funding: €9.8 M

Total project funding: €11.4 M plus donation of study drugs

Project website: www.caprisa.org/Pages/EDCTP-funded%20studies

Clinical trial registration: <https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=3584>

Back-up treatment for children with HIV

The CHAPAS 4 study aims to identify a suitable second-line therapy for children with HIV who are not responding to first-line drugs.

The challenge

WHO now recommends that all children with HIV infections should be given antiretroviral drugs. A projected 2.3 million children are likely to be taking antiretroviral drugs by 2020.

Although antiretroviral therapy is highly effective in children, not all children respond as well as others. In addition, as more children take antiretroviral drugs for longer periods, drug-resistant infections will inevitably emerge. Documented levels of treatment failure vary widely in Africa, but can be as high as 50%. Treatment failure requires a shift to second-line antiretroviral therapy. However, current formulations for second-line treatments have significant drawbacks, being based on whole pills, mini-pill pellets, or unpleasant liquids, and limited data are available on their use in children.

The project

For more than a decade, the CHAPAS Consortium has organised clinical trials to improve the treatment options available for children with HIV in sub-Saharan Africa. Data from EDCTP-funded CHAPAS 1 and CHAPAS 3 projects supported licensing applications for children-specific formulations and provided evidence in support of WHO recommendations on updated treatment options, opening the door to more extensive use of antiretroviral therapy in African children.

The CHAPAS 4 study is designed to identify an optimal second-line treatment for children with HIV infections. The study, being carried out in three sub-Saharan countries, will use an innovative trial design to compare a range of possible options. These include formulations incorporating dolutegravir, a relatively new drug with significant advantages over existing treatments; atazanavir/ritonavir (ATV/r), which is now available in a single pill suitable for children; and tenofovir–alafenamide (TAF), a tenofovir pro-drug that may be particularly suitable for use in children, co-formulated with

Project at a glance

Project: CHAPAS-4 study

Project lead: Dr Mutsa Bwakura-Dangarembizi, University of Zimbabwe College of Health Sciences

Countries involved: the Netherlands, South Africa, Uganda, United Kingdom, Zambia, Zimbabwe

Target population(s): Children with HIV (3–15 years) failing first-line treatment

Year funded: 2017

EDCTP funding: €7.6 M

Clinical trial registration: www.isrctn.com/ISRCTN22964075

emtricitabine. These agents will be tested in different combination regimens against the current standard of care for children.

The project will also explore interactions between antiretroviral drugs and anti-TB medications, and their impact on the effectiveness of treatment and toxicity. It will also examine the cost implications of the new treatments.

Impact

CHAPAS 4 will generate key data on multiple second-line options for children in whom first-line antiretroviral therapy is failing – a vulnerable group that is destined to grow as use of antiretroviral drugs increases. In particular, the innovative trial design will enable comparisons to be made between multiple treatment options in a single clinical trial. The study will also provide important evidence on treatment options for children who are infected with TB as well as HIV.





Improving treatment of HIV-associated meningitis

The AMBITION-cm trial will confirm whether a simple treatment for a potentially lethal fungal infection is suitable for use in Africa.

The challenge

Early mortality from HIV is much higher in Africa than in high-income countries. Up to one in five HIV-related deaths in Africa are attributable to an opportunistic fungal infection, *Cryptococcus*, which can cause a lethal meningitis. Cryptococcal meningitis is responsible for around 500,000 deaths a year in sub-Saharan Africa.

The most widely used treatment in Africa, fluconazole, is of limited effectiveness – mortality is still higher than 50%. A superior alternative treatment, amphotericin B, is rarely used in African settings because it has to be given over two weeks and can trigger severe toxic reactions so patients require specialist monitoring.

The project

The AMBITION-cm team has been evaluating an alternative formulation of amphotericin B, delivered in tiny lipid-based packages (liposomes), which would be more suitable for resource-poor settings. A phase II study showed that a single high dose of liposomal amphotericin B was safe and early antifungal responses were as good as those seen with the traditional two-week course.

Building on these promising findings, the phase III AMBITION-cm trial is comparing a one-week course of amphotericin B with single high-dose liposomal amphotericin B. The trial, taking place in five African countries, will determine whether single-dose liposomal amphotericin B is as good as the traditional two-week course at reducing mortality at 10 weeks.

Impact

The AMBITION-cm trial is the largest HIV-associated cryptococcal meningitis treatment trial ever undertaken. If the encouraging phase II results are confirmed, a simple amphotericin B-based therapy could transform treatment

Project at a glance

Project: AMBITION-cm trial

Project lead: Professor Joseph Jarvis, London School of Hygiene and Tropical Medicine, United Kingdom

Countries involved: Botswana, France, Malawi, South Africa, Uganda, the UK, Zimbabwe

Target population(s): Adults with HIV infection

Sample size: 850 (target)

Year funded: 2017

EDCTP funding: €10 M

of one of the most important causes of HIV-associated mortality in Africa.

Key reference

Jarvis JN et al. Short course high-dose liposomal amphotericin B for HIV-associated cryptococcal meningitis: A phase-II randomized controlled trial. *Clin Infect Dis*. 2018. [Epub ahead of print]

Molloy SF et al. Cryptococcal meningitis: A neglected NTD? *PLoS Negl Trop Dis*. 2017;11(6):e0005575.

Rajasingham R et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet Infect Dis*. 2017;17(8):873–881.

Reducing HIV infections in adolescents

The CHAPS study is evaluating novel approaches for preventing HIV infection, tailored to the needs of African adolescents.

The challenge

HIV/AIDS is the leading cause of death of young people aged 10–24 in Africa. Between 2000 and 2015, the number of adolescents dying from AIDS-related illness tripled – the only age group in which the number of deaths rose. Young people account for 37% of all new HIV infections, and in 2016 nearly three-quarters of all new HIV infections in adolescents occurred in Africa.

These figures suggest that prevention strategies that have proven effective in other populations are not working in this age group, and alternatives are required.

The project

The CHAPS project is evaluating a range of strategies adapted to the characteristics of adolescents. These include a modified version of pre-exposure prophylaxis (PrEP) – pre-emptive use of antiretroviral drugs to prevent infection. Although daily PrEP has been clearly shown to reduce the risk of HIV infection, it is costly, has some side effects, and adherence is less good in adolescents.

The CHAPS project aims to overcome these challenges by evaluating the impact of an alternative, less toxic drug combination (tenofovir alafenamide and emtricitabine) as well as ‘on-demand’ PrEP – use of PrEP just around the time of sexual activity.

The project is consulting with adolescents to determine attitudes to on-demand PrEP and its likely acceptability. Laboratory-based studies are being used to optimise dose levels and dosing schedules for the novel antiretroviral drug combination. The CHAPS team is also undertaking laboratory studies to explore whether the drug combination could provide protection for longer periods after exposure to HIV, allowing more flexible use of post-exposure prophylaxis.

Project at a glance

Project: CHAPS study

Project lead: Dr Julie Fox, King's College London, United Kingdom

Countries involved: South Africa, Sweden, Uganda, United Kingdom, Zimbabwe

Target population(s): Adolescents

Year funded: 2018

EDCTP funding: €3 M

Project website: www.chaps.uct.ac.za

Clinical trial registration: <https://clinicaltrials.gov/ct2/show/NCT03986970>

Impact

The CHAPS study is the first to undertake research into attitudes to on-demand PrEP among adolescents in sub-Saharan Africa and the first multi-country study to investigate optimal dosing for on-demand PrEP. Its findings will play a key role in shaping the design of trials of on-demand PrEP in a group where more effective prevention is urgently required.





Finding ‘hidden’ HIV-infected infants

The PROMISE-EPI study is evaluating a novel strategy for identifying infants who, despite big drops in mother-to-child transmission, have still been infected with HIV.

The challenge

WHO now recommends that all pregnant and breastfeeding women with HIV should be offered antiretroviral therapy and all infants at risk of contracting HIV should be given antiretrovirals for 6 weeks. This so-called option B+ strategy has been implemented across most of sub-Saharan Africa. However, significant numbers of infants are falling through the net – in 2015, residual transmission rates were still about 14% at one year, well above the WHO target of 5%.

The project

The PROMISE-EPI study is assessing whether a ‘rescue’ package can be integrated into routine immunisation services (generally known as the expanded programme on immunisation, EPI). Its goal is to identify and treat the hidden infant HIV cases, and to prevent transmission from previously undiagnosed HIV-infected mothers.

In countries such as Burkina Faso and Zambia, nearly all newborn babies receive vaccinations through the EPI at 4–6 weeks. The PROMISE-EPI study will assess whether it is possible to use the EPI platform to examine mothers’ experience of prevention services at birth; to detect missed HIV infections through point-of-care testing, so antiretroviral therapy can be started; and to measure virus levels in mothers, to identify infants at risk of infection, so mothers can be treated and preventive measures initiated.

Impact

For more than a decade, the PROMISE consortium, set up with EDCTP funding, has developed a portfolio of studies addressing mother-to-child transmission of HIV in Africa. Having generated vital evidence on the importance of pre-emptively treating infants to prevent transmission of HIV, the latest study could identify a readily implementable strategy for reducing still further infant infection rates, and for identifying those who nonetheless have been infected.

Project at a glance

Project: PROMISE-EPI study

Project lead: Professor Philippe van de Perre, Montpellier University, France

Countries involved: Burkina Faso, France, Norway, Zambia

Target population(s): Mothers, infants

Sample size: 2000 mothers and infants (target)

Year funded: 2018

EDCTP funding: €3 M

Key reference

Nagot N et al. Extended pre-exposure prophylaxis with lopinavir-ritonavir versus lamivudine to prevent HIV-1 transmission through breastfeeding up to 50 weeks in infants in Africa (ANRS 12174): a randomised controlled trial. *Lancet*. 2016;387(10018):566–73.

Improving the quality of life of adolescents living with HIV

The BREATHER Plus study is evaluating whether simpler treatments maintain control of HIV but are easier for adolescents to manage.

The challenge

Adolescents who acquire HIV or were infected at birth are currently obliged to take antiretroviral drugs every day for the rest of their lives. This daily routine can be challenging for young people to stick to.

International trials have identified alternative approaches that simplify treatment schedules. These include a 'weekends off' approach, in which young people take a two-day break from treatment, and monthly use of a long-acting injectable antiretroviral.

The project

The BREATHER Plus trial will compare these two new approaches – weekends off and a monthly injectable – with standard treatment in adolescents in four African countries. The oral regimens will be based on dolutegravir, an increasingly used antiretroviral. Importantly, the trial will take place in settings where viral load is monitored annually, as recommended by WHO, so any resurgence of HIV can be detected.

The trial will last 96 weeks and will assess control of HIV replication, the side effects of treatment, impacts on quality of life, and acceptability of the new approaches.

Impact

The BREATHER Plus trial will generate evidence that could influence the treatment, and improve the quality of life, of more than 2 million adolescents living with HIV – most of whom are in sub-Saharan Africa.

Project at a glance

Project: BREATHER Plus study

Project lead: Dr Adeodata Kekitiinwa-Rukyalekere, Baylor College of Medicine Children's Foundation, Uganda

Countries involved: Italy, Kenya, The Netherlands, South Africa, Uganda, United Kingdom, Zimbabwe

Target population(s): Adolescents

Year funded: 2018

EDCTP funding: €7.4 M





Improving treatment of HIV in pregnant women

The PREGART study is evaluating two new first-line antiretroviral treatment regimens in pregnant women living with HIV.

The challenge

New treatment regimens are typically first tested in clinical trials that exclude groups such as pregnant women. Without further trials, pregnant women may therefore not benefit from advances in treatment.

In 2016, almost 750,000 women of reproductive age became HIV-positive, most of them in sub-Saharan Africa. Effective treatment is important not just for the health of mothers but also to prevent mother-to-child transmission of HIV.

The project

The PREGART trial is evaluating two possible enhancements to antiretroviral therapy in pregnant women. The first is use of dolutegravir, which has shown greater inhibition of viral replication than other first-line treatments and is less likely to be discontinued by patients. The second is a lowering of the dose of efavirenz, as standard-dose efavirenz may be associated with greater toxicity in pregnancy.

Lack of safety and efficacy data on the use of dolutegravir and low-dose efavirenz in pregnant and breastfeeding women has been identified as a priority evidence gap by WHO. Preliminary observational data from Botswana suggested that dolutegravir might be associated with an increased risk of neural tube defects if used during the first trimester of pregnancy. However, the numbers are small, and it is difficult to draw firm conclusions in advance of the final results. Nevertheless, WHO has updated its recommendation on the use of dolutegravir among pregnant women during the first trimester of pregnancy, and women in the first trimester of pregnancy will not be recruited into the trial.

Project at a glance

Project: PREGART study

Project lead: Dr Birkneh Tadesse, Hawassa University, Ethiopia

Countries involved: Ethiopia, Italy, Sweden, Uganda

Target population(s): Pregnant women

Year funded: 2018

EDCTP funding: €3.9 M

The PREGART trial will compare triple therapy regimens containing dolutegravir and low-dose efavirenz with standard efavirenz-containing regimens, and with each other. It aims to enroll nearly 2,000 women in Ethiopia and Uganda.

The trial will also undertake pharmacokinetic and pharmacogenetic studies to see how genetic variation affecting the enzymes that metabolise dolutegravir and efavirenz influence the distribution of the drugs in the body. These studies will be important for determining the most appropriate dosing of dolutegravir in women in sub-Saharan Africa.

Impact

The PREGART trial will provide key safety and efficacy data on two potentially superior antiretroviral drugs for pregnant and breastfeeding women, and on the appropriate dosing for women living in sub-Saharan Africa.

Extending flucytosine use for HIV-associated meningitis

The 5FC HIV-Crypto study is evaluating a new formulation of flucytosine that could encourage its greater use to treat cryptococcal meningitis in people living with HIV.

The challenge

Infection with the fungal pathogen *Cryptococcus* is one of the main causes of death of people living with HIV in sub-Saharan Africa. Cryptococcal meningitis is responsible for an estimated 180,000 deaths a year, with mortality rates as high as 60%.

Flucytosine, originally developed as an anti-cancer drug, is part of the WHO-recommended treatment for cryptococcal meningitis. In 2018, it was shown to reduce the risk of death by 40% compared to an alternative widely used drug. However, it remains underutilised because of low availability in sub-Saharan Africa and because the recommended dosing schedule – four times daily – is difficult to implement.

The project

The 5FC HIV-Crypto study aims to increase use of flucytosine by developing a more convenient formulation and promoting its wider implementation in sub-Saharan African countries.

The study has twin aims. The first is to develop an improved and affordable sustained-release formulation of flucytosine, allowing for twice-daily administration. The second is to encourage wider adoption of both the sustained-release and original immediate-release formulations.

Clinical research activities will initially compare the bioavailability of the sustained-release and immediate-release formulations, in fed and fasting states. If they are comparable, a phase II study will be undertaken to assess the fungicidal properties of the new formulation and its impact on clinical outcomes in patients with HIV-associated cryptococcal meningitis.

Project at a glance

Project: 5FC HIV-Crypto study

Project lead: Dr Isabela Ribeiro, Drugs for Neglected Diseases Initiative, Geneva, Switzerland

Countries involved: Luxembourg, South Africa, Switzerland, Tanzania, UK

Target population(s): People living with HIV

Year funded: 2020

EDCTP funding: €3.5 M

Total project funding: €3.7 M

In parallel, the project team will develop locally appropriate educational tools and engage with ministries of health to raise awareness of cryptococcal meningitis and WHO treatment guidelines. Economic analyses will also be carried out, alongside estimation of national treatment needs. The plan is to promote the implementation of flucytosine in selected 'trailblazer' countries in sub-Saharan Africa.

Impact

The project will generate the data necessary for submissions for WHO prequalification and for licensing approvals in sub-Saharan African countries. It has the potential to increase use of an effective but underutilised treatment for one of the most serious infections affecting people living with HIV. As part of coordinated efforts to improve timely detection and treatment of cryptococcal infections, the project could significantly reduce mortality in this vulnerable group.





Diabetes prevention in people with HIV

The META TRIAL study will establish whether metformin reduces the risk of type 2 diabetes in people living with HIV.

The challenge

Type 2 diabetes is a growing challenge in sub-Saharan Africa. Almost 20 million people in the region are currently affected, with numbers projected to rise to nearly 50 million by 2045. Even more alarmingly, an estimated 45 million people have early signs of diabetes – a number that could rise to 110 million by 2045. Even though many of those affected are unaware of their condition, treatment costs already amount to US\$9.5 BN a year.

There is now substantial evidence that metformin, an affordable drug widely used to treat diabetes, is also effective at preventing the development of diabetes in those at increased risk of the condition (such as those with pre-diabetes, increased blood glucose levels). Its use is highly cost-effective. However, metformin remains underutilised for diabetes prevention and its effectiveness has not been assessed in all populations, such as those living with HIV.

The project

The META TRIAL team is already running a phase II trial in Tanzania assessing the impact of metformin on diabetes prevention in people living with HIV who are on antiretroviral therapy and have been diagnosed with pre-diabetes. This follow-on project will take advantage of the infrastructure established in Tanzania in order to organise a larger phase III study in the same target population.

The project aims to recruit 2,000 patients on antiretroviral therapy – making it the largest trial of its kind in Africa. Patients will be followed for three years and, as well as progression to diabetes, data will be gathered on financial impacts, health-related quality of life and cost-effectiveness.

Project at a glance

Project: META TRIAL study

Project lead: Professor Shabbar Jaffar, Liverpool School of Tropical Medicine, UK

Countries involved: Norway, Spain, Tanzania, UK

Target population(s): People living with HIV

Year funded: 2020

EDCTP funding: €4 M

Impact

Antiretroviral therapy is becoming more widely available – 14 million people in the region are currently receiving antiretroviral therapy. With improved survival, increasing numbers of people in the region will be living to ages at which the risk of non-communicable diseases such as diabetes begins to increase sharply. Furthermore, there is evidence that HIV-infected individuals are at higher risk of diabetes. Without action, these conditions will have a major impact on the health, quality of life and financial wellbeing of households and countries. Increasingly, care for people with HIV will therefore need to encompass prevention and treatment of co-morbidities such as diabetes.

Data from the META TRIAL study will reveal whether metformin is an effective drug for diabetes prevention in people living with HIV, as well as its likely cost-effectiveness – evidence that will be of global as well as regional importance.

Protecting bone growth in children living with HIV

The VITALITY project is assessing whether high-dose vitamin D and calcium carbonate supplements can protect bone and muscle development in children living with HIV.

The challenge

Globally, 2 million children are living with HIV, 90% of them in sub-Saharan Africa. As access to antiretroviral therapy improves, more of these children are surviving to adolescence and adulthood.

One of the consequences of HIV infection is a shift in the balance between bone resorption and new bone formation, leading to loss of bone mass and bone weakening. Some HIV medications also lead to reduced bone mass. These effects are typically worse in young people from sub-Saharan Africa owing to high rates of past infections and malnutrition.

The project

The VITALITY project aims to determine whether supplementation with vitamin D3 and calcium carbonate, key factors contributing to bone growth, can improve musculoskeletal health in young people aged 8–16 years with HIV infection. In addition, vitamin D supplementation may have beneficial effects on the immune system and on the development of healthy microbial communities in the gut (the microbiome).

This age group is critical, as puberty is the time when bone mass reaches its maximum (peak bone mass). During adulthood, bone mass gradually declines, so low peak bone mass increases vulnerability to bone fractures and conditions such as osteoporosis in later life.

The VITALITY project is conducting a randomised controlled trial of high-dose vitamin D3 and calcium carbonate supplementation in 800 children living with HIV in Zambia and Zimbabwe. Children will be treated for a year and followed for a further year. Although small trials

Project at a glance

Project: VITALITY

Project lead: Professor Rashida Ferrand, London School of Hygiene and Tropical Medicine

Countries involved: Germany, UK, Zambia, Zimbabwe

Target population(s): Children, adolescents

Year funded: 2020

EDCTP funding: €3.9 M

of vitamin D supplementation have been run, the VITALITY study is the first large-scale trial to investigate this combination in sub-Saharan Africa.

Impact

The VITALITY project will generate data on a simple, safe and affordable intervention that could have significant benefits for people living with HIV. Vitamin D3 has the potential to provide short-term benefits, with strengthened bones and the associated improvements in muscle mass helping to improve social participation and wellbeing. Over the longer term, greater peak bone mass in adolescence would reduce the risk of fractures and osteoporosis in adulthood and later life, safeguarding health and the risk of financial hardship due to loss of employment or treatment costs.





Progressing a second-generation HIV vaccine

The GREAT project will test an improved prototype HIV vaccine in high-risk and vulnerable African populations.

The challenge

An HIV vaccine is likely to be central to global efforts to eradicate the virus. However, developing an effective HIV vaccine has been highly challenging. One major issue is the extreme diversity of HIV – meaning that protection against one strain may not afford protection against another. In addition, the virus rapidly evolves within individual patients, generating variants that may evade vaccine-induced protection.

The project

Over many years, a group led by Professor Tomáš Hanke has been developing an HIV vaccine capable of targeting a wide range of HIV variants. HIV control is likely to depend on different vaccines that elicit either T cell- or antibody-based protection, and his group's focus has been a vaccine that generates protective T cells. His team has been aiming to identify highly conserved HIV structures that are shared across different HIV variants and are thought to be critical to its ability to multiply and spread. These structural antigens are delivered via commonly used DNA-based vectors.

Recently, Professor Hanke's team has developed a second-generation vaccine, tHIVconsvX, that builds on this promising platform but adds new features. The new vaccine is a 'mosaic': as well as several widely shared antigens, it also includes multiple variants of antigens known to stimulate strong T-cell responses. In addition, it incorporates antigens that, in patients, are associated with relatively good control of HIV replication. This extensive combination of antigens in a single vaccine, partnered with a potent delivery system, has generated encouraging results in animal models and initial human studies.

The GREAT project will test the safety of tHIVconsvX, as well as its ability to generate HIV-specific immune responses. The project team will work with a range of marginalised communities,

Project at a glance

Project: The Globally Relevant AIDS Vaccine Europe–Africa Trials (GREAT) Partnership

Project lead: Professor Tomáš Hanke, University of Oxford, UK

Countries involved: Kenya, the Netherlands, Uganda, the UK, the US, Zambia

Target population(s): HIV-negative adults

Sample size: 88

Year funded: 2017

EDCTP funding: €7.1 M

Total project funding: €16.8 M

Project website: www.great-partnership.eu

including fishing communities around Lake Victoria, male and female sex workers, and men who have sex with men.

Impact

The GREAT trial will generate evidence that will indicate whether tHIVconsvX is sufficiently potent to justify a phase III efficacy trial. Moreover, the consortium's capacity building and extensive community engagement will provide a platform for a pivotal phase III study, should one be merited.

Key reference

Ondondo B et al. Novel conserved-region T-cell mosaic vaccine with high global HIV-1 coverage is recognized by protective responses in untreated Infection. *Mol Ther.* 2016;24(4):832–42.

Combining drugs and vaccines to prevent HIV infection

The PrEPVacc trial is the first to test whether a combination of pre-exposure prophylaxis and an experimental vaccine can prevent HIV infection.

The challenge

An effective HIV vaccine is likely to be key to controlling the HIV epidemic. Unfortunately, HIV is very difficult to target with vaccines and past trials have had limited success. However, the RV144 trial in Thailand did find that a DNA vaccine 'prime' followed by a protein vaccine 'boost' appeared to offer modest levels of protection.

Nevertheless, more innovative approaches may be needed. One possibility is pre-exposure prophylaxis (PrEP), in which high-risk populations receive antiretroviral drugs to prevent HIV infection.

The project

The PrEPVacc trial is combining these two approaches to HIV prevention in a large-scale phase II trial. It will assess the impact of two experimental HIV vaccine regimens, already tested and shown to be safe in people, when used alongside antiretroviral-based PrEP. The vaccine regimens both combine DNA-based and protein-based elements, as used in the RV144 trial.

The trial will be carried out in high-risk populations in four sub-Saharan African countries. It also includes an innovative design feature: PrEPVacc will be an 'adaptive' trial, so that combinations can be halted mid-trial if they are turning out to be ineffective – the first time this approach has been adopted in an HIV vaccine trial.

Project at a glance

Project: PrEPVacc

Project lead: Professor Jonathan Weber, Imperial College, UK

Countries involved: Germany, Mozambique, Netherlands, South Africa, Sweden, Switzerland, Tanzania, Uganda, United Kingdom, and the United States

Target population(s): High-risk, marginalised communities

Sample size: 1668 (target)

Year funded: 2017

EDCTP funding: €15 M

Total project funding: €22.2 M

Clinical trial registration: <https://clinicaltrials.gov/ct2/show/NCT04066881>

Impact

PrEPVacc will generate the first evidence of the ability of vaccine plus PrEP combinations to prevent HIV infections – information that would have major public health importance. It will also provide key data on the ability of the experimental vaccines to stimulate protective immune responses, and the likely success of DNA plus protein prime–boost vaccine strategies. Data on the nature of the immune responses triggered by the vaccines may also reveal which are key to prevention of HIV infection.





Using antibodies to prevent HIV transmission to babies

The Neo bnAb study is evaluating whether emerging ‘broadly neutralising antibody’ approaches can protect newborns against HIV infection.

The challenge

Despite much progress in reducing mother-to-child transmission of HIV – more than 1.4 million infections have been averted since 2010 – 180,000 infants acquired HIV in 2017. With current approaches, global elimination goals are unlikely to be achieved.

Broadly neutralising antibodies are an exciting new option in HIV control. On very rare occasions, people generate antibodies to HIV that recognise multiple HIV strains. Mass production of these antibodies could provide a new weapon in the anti-HIV armoury.

The project

Most studies on broadly neutralising antibodies to date have focused on adults. The Neo bnAb will explore their potential use in newborns to prevent mother-to-child transmission.

The study is focused on one specific broadly neutralising antibody known as VRC01. Minor modifications have created a slightly different version, VRC01LS, that survives longer in the bloodstream, so could potentially provide protection for longer periods and require less frequent administration. Initial studies have shown that VRC01LS is safe to give to newborns.

The Neo bnAb trial will compare standard approaches used to prevent mother-to-child transmission with an enhanced programme in which babies also receive four doses of VRC01LS – at birth and at 12, 24 and 36 weeks. A total of 2,000 babies will be studied in two countries. As well as gathering data on efficacy, the study will also analyse cases of infection to determine how HIV evaded antibody protection, to inform the design of preventive antibody strategies.

Project at a glance

Project: Neo bnAb study

Project lead: Dr Arne Kroidl, Ludwig Maximilian University of Munich, Germany

Countries involved: Germany, Mozambique, Tanzania, UK

Target population(s): Newborns

Year funded: 2019

EDCTP funding: €4.2 M

Total project funding: €4.8 M

Impact

The Neo bnAb study will provide proof-of-concept evidence on the safety and efficacy of broadly neutralising antibody use for HIV prevention in newborns. It will also examine the operational feasibility and affordability of the intervention in the African context. Evidence of the effectiveness of broadly neutralising antibody could offer a novel way to prevent mother-to-child transmission of HIV and achieve global elimination targets.

A new approach to HIV prevention

Passive immunisation with broadly neutralising antibodies could offer a novel way to block HIV infection.

The challenge

HIV is a highly diverse and rapidly evolving pathogen. Despite much effort, a vaccine that would protect against multiple HIV variants has yet to be developed, threatening global efforts to bring the HIV/AIDS epidemic under control by 2030.

However, a small number of individuals worldwide have been found to produce ‘broadly neutralising antibodies’ – antibodies that recognise structures common across many HIV strains. There are hopes that these antibodies could be mass produced and used in passive immunisation – given to people periodically to protect against infection.

The project

The CAP012 SAMBA project builds on the discovery of a broadly neutralising antibody, known as CAP2456-VRC26.25, in a woman from KwaZulu Natal. Excitingly, this antibody, and two others, have been found to protect monkeys from infection with the monkey version of HIV.

The CAP012 SAMBA project is extending this work by analysing the safety of the antibodies in people, exploring their acceptability to potential recipients, and monitoring their metabolism in the body. On the basis of these studies, the most promising combinations of antibodies will be taken forward to a phase II trial to assess safety and efficacy at preventing HIV infection.

Impact

The CAP012 SAMBA project could advance the development of a radically new approach to HIV prevention. It offers the prospect of HIV protection delivered through injections every four to six months. Notably, it is envisaged as an approach of particular benefit to women – the antibodies are being evaluated in groups of women, and the intervention is one that places HIV control in the hands of women, who are currently experiencing the brunt of the HIV epidemic in Africa.

Project at a glance

Project: CAP012 SAMBA project

Project lead: Professor Salim Abdool Karim, Centre for the AIDS Programme of Research in South Africa, South Africa

Countries involved: France, the Netherlands, South Africa, Zambia

Target population(s): Women

Year funded: 2018

EDCTP funding: €9.3 M

Total project funding: €18.7 M

Project website: www.caprisa.org/Pages/EDCTP-funded%20studies

Clinical trial registration: <https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=3553>





Improving management of meningitis in HIV-infected adults

The DREAMM project aims to embed innovative meningitis diagnostic practices into routine health care.

The challenge

Infections of the central nervous system (CNS) are responsible for 25–30% of HIV-related deaths, with cryptococcal fungal infections alone accounting for up to 20% of such deaths. There is growing evidence, from EDCTP-funded and other trials, that early screening for cryptococcal infections and prompt treatment can save lives, but take-up of diagnostics has so far been limited, in part because of the practical difficulties of implementing new procedures in existing healthcare systems.

The project

The DREAMM project is a product-based implementation study aiming to demonstrate how screening for CNS infections can be introduced into routine care of people with HIV, and the likely benefits this would deliver.

One key aim of the project is to generate data on an upgraded version of a dipstick diagnostic for cryptococcal infections, the CrAG LFA test, a diagnostic dipstick test that is heat-stable, inexpensive, requires minimal training and has been shown to be cost-effective in resource-limited settings. The test provides an indication of the severity of infection and the need for more intensive care.

In collaboration with healthcare staff, the DREAMM team will develop new clinical pathways and decision-making procedures that incorporate use of an upgraded CrAG LFA test and assessment of other possible causes of meningitis. This should facilitate more rapid use of lumbar punctures to confirm infection and faster initiation of treatment.

Once these new procedures have been finalised, staff will be given training in their use. The project will then evaluate whether they reduce the delays in assessment and treatment, and lead to improved survival.

Project at a glance

Project: DREAMM

Project lead: Dr Angela Loyse, St George's University of London, UK

Countries involved: Cameroon, France, Malawi, Tanzania, the United Kingdom

Target population(s): Adults with HIV

Sample size: 450 (target)

Year funded: 2016

EDCTP funding: €1.9 M

Impact

DREAMM has been designed to generate both evidence and resources directly relevant to health policymakers. It will provide a measure of the added value of the upgraded CrAG LFA test used in conjunction with specific patient management algorithms designed for low-resource settings. The study will also produce training and other materials to support implementation elsewhere, enabling the new procedures and diagnostics tools to be readily introduced in other settings.

More generally, the study illustrates how product-based implementation research can provide a stepping stone between clinical trials and routine clinical use, accelerating the introduction of new interventions.

Speeding up HIV treatment in infants

The LIFE study is assessing whether use of new rapid diagnostic tests for HIV leads to quicker and better treatment of infants with HIV.

The challenge

Less than half of infants exposed to HIV are tested for HIV, less than half of those tested receive early infant diagnostic test results, and less than half of those found to be infected receive antiretroviral therapy. The need to send samples away to central facilities for testing is a key barrier to timely diagnosis and initiation of therapy.

There are hopes that a new generation of easy-to-use rapid diagnostic tests could overcome these hurdles, so more infants receive an early diagnosis and start to receive antiretroviral therapy. Point-of-care testing has been recommended by WHO, but implementation presents practical challenges and is likely to have significant financial implications.

The project

Members of the LIFE consortium carried out a pilot trial in Mozambique, evaluating point-of-care testing administered by nurses. Compared with usual practices, point-of-care testing led to nearly all infants receiving results within 60 days, compared to 12% in the control group, and 90% of HIV-infected babies were put on antiretroviral therapy within 60 days, compared to 13% in the control group.

Following up these encouraging results, the LIFE consortium has begun a larger trial spanning 24 sites in two countries. The trial will follow infants for 18 months to assess initial antiretroviral therapy initiation rates as well as longer-term impacts on child mortality and illness. The team will also measure virus levels in mothers at delivery, as a way of identifying infants at high risk of mother-to-child transmission.

Impact

The LIFE study will fill important gaps in the evidence base. It will reveal whether use of rapid point-of-care HIV diagnostics at birth increases antiretroviral therapy coverage and benefits infant survival; whether measurement

Project at a glance

Project: LIFE study

Project lead: Dr Ilesh Jani, Instituto Nacional de Saude, Mozambique

Countries involved: Germany, Mozambique, Portugal, Tanzania, the United States

Target population(s): Infants of mothers with HIV

Sample size: 5040 women and their HIV-exposed babies (144 HIV-infected infants)

Year funded: 2018

EDCTP funding: €3 M

Project website: <https://hivlifestudy.org>

Clinical trial registration: <https://clinicaltrials.gov/ct2/show/NCT04032522>

of virus levels in mothers at delivery leads to the adoption of special measures to prevent mother-to-child transmission; and what the financial and practical implications are of rapid diagnostic use. The study will therefore provide key data for decision makers on the cost-effectiveness and practicalities of implementing the new technology and new models of care.

Key reference

Jani IV et al. Effect of point-of-care early infant diagnosis on antiretroviral therapy initiation and retention of patients. *AIDS*. 2018;32(11):1453–1463.



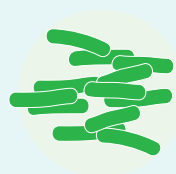


SINGLE USE ONLY

MTBVAC-202
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Apr 1, 2019
11:10 (24hr)
NORMAL USE

Tuberculosis

2014-2020



31 grants

€186.44 M



Drugs
10 grants

€66.76 M



Vaccines
4 grants

€51.20 M



Diagnostics
17 grants

€68.48 M

EDCTP portfolio: Tuberculosis

Drugs	Vaccines	Diagnostics	
PanACEA Ethiopia, Malawi, Mali, Mozambique, Nigeria, Rwanda South Africa, Senegal, Tanzania	POR TB South Africa, Tanzania	Stop TB/HIV at one Ethiopia, Nigeria	TB TRIAGE+ Lesotho, South Africa
VirTUAL Uganda, South Africa	MTBVAC-Newborns South Africa	Screen TB Ethiopia, The Gambia, Namibia, South Africa, Uganda	SeroSelectTB Ethiopia, Tanzania, South Africa
TREATS South Africa, Zambia	priMe Gabon, Kenya, South Africa, Tanzania, Uganda	DIAMA Benin, Cameroon, DR Congo, Ethiopia, Guinea, Mali, Nigeria, Rwanda, Senegal	STool4TB Eswatini, Mozambique, Uganda
Simplici-TB Gabon, Malawi, Mozambique, South Africa, Tanzania, Uganda	MTBVACN3 Madagascar, Senegal, South Africa	Predict TB South Africa	ERASE-TB Mozambique, Tanzania, Zimbabwe
CLICK-TB South Africa		RaPaed Malawi, South Africa, Tanzania	TriageTB The Gambia, South Africa, Uganda
StatinTB South Africa		TBCAPT Tanzania, Mozambique	CUT TB Lesotho, South Africa, Tanzania
INTENSE-TBM Cote d'Ivoire, Madagascar, South Africa, Uganda		PreFIT Mozambique, South Africa, Uganda	TRiAD study Ethiopia, Nigeria, South Africa
PROTID Tanzania, Uganda		XACT III Mozambique, South Africa, Zimbabwe	
DATURA Cameroon, Guinea, Uganda, Tanzania			
PanTB-HM South Africa			
BETH-TB South Africa			

Caption	Study phase	Population
Project name <i>Site(s) in sub-Saharan Africa</i>	Phase I	Adults (18yr and above) Pregnant women and/or newborns (birth to 1mo)
	Phase II	Adolescents (10yr-17yr)
	Phase III	Children (2yr-9yr)
	Phase IV	Infants (above 1mo-1yr)
	Observational study	

Caption

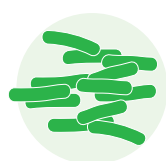
Project name
Site(s) in sub-Saharan Africa

Study phase

Phase I
 Phase II
 Phase III
 Phase IV
 Observational study

Population

Adults (18yr and above)
 Adolescents (10yr-17yr)
 Children (2yr-9yr)
 Infants (above 1mo-1yr)
 Pregnant women and/or newborns (birth to 1mo)



Advancing a suite of TB drug treatments

Building on its past successes, the PanACEA2 Consortium is continuing its innovative programme of work on shorter, simpler and better treatments for TB.

The challenge

TB is one of the most difficult infections to treat, and presents major challenges to drug development. Current treatment regimes last six months and require patients to take multiple medications. Shorter and simpler regimens would improve adherence, reduce side effects and lower costs.

Unfortunately, evaluation of new TB drugs, and new combinations and doses of existing drugs, is highly challenging. In particular, methods for determining the impact of drugs on TB bacteria are imperfect, making it harder to determine whether drug treatments should be progressed. In addition, long and costly phase III trials are required, and several promising treatments have failed at this stage. As a result, there are many possible improvements to TB treatment, and a key challenge is to determine as efficiently as possible which are most likely to succeed so they can be rigorously evaluated in large-scale trials.

The project

The PanACEA Consortium, funded in the first EDCTP programme, was set up not just to evaluate novel TB drugs and combinations, but also to build capacity for TB drug trials in Africa and, importantly, to advance clinical trial methodology to improve the efficiency of drug development and enhance the likelihood of success. It carried out landmark trials aiming to shorten TB treatment and introduced novel clinical trial designs never before used in infectious disease research.

PanACEA2 will build on this foundation. With higher doses of rifampicin showing promise in trials, it will carry out studies to identify the maximum tolerated dose that could be evaluated in future trials. In addition, it plans to assess the safety of promising new drugs entering the TB drug development pipeline, using a novel design that will allow determination of slow-acting effects and evaluation of multiple combinations in one study.

Project at a glance

Project: PanACEA2 Consortium

Project lead: Professor Martin Boeree, Radboud University Nijmegen Medical Centre, The Netherlands

Countries involved: Germany, Gabon, Malawi, Mozambique, the Netherlands, South Africa, Switzerland, Tanzania, Uganda, the United Kingdom

Target population(s): Adults with TB

Year funded: 2018

EDCTP funding: €11.4 M

Project website: <http://panacea-tb.net>

In a third strand of work, multiple combinations will be assessed in an adaptive trial, allowing for discontinuation of poorly performing therapies. Long-term follow-up will be undertaken – addressing the issue that early responses to drugs do not necessarily provide an accurate indicator of long-term treatment success. This will provide a key step towards reducing the risk of failure in phase III trials.

Impact

PanACEA2 will generate key data on TB drug treatments, pilot innovative methodologies for drug evaluation that could greatly accelerate drug development and reduce the risk of failure, and build capacity for trials of the highest international regulatory standard. Furthermore, by operating as an open partnership, it can carry out studies in partnership with multiple drug developers, and also coordinate activities with other international TB drug consortia, minimising duplication of efforts.

Treating TB and HIV in neglected groups

The VirTUAL study is combining modelling and clinical research to identify the optimal drug treatments for pregnant women, children and adolescents with HIV and TB.

The challenge

As more people gain access to antiretroviral therapy, new challenges are arising in the management of HIV, and more tailored approaches to treatment are required.

For example, every year around one in ten people being treated for HIV transfer to second-line antiretroviral therapy, because of drug resistance or other factors. Second-line therapy includes drugs known as boosted protease inhibitors, which interact with a key anti-TB drug, rifampicin. Determining the most appropriate dose of boosted protease inhibitors is therefore challenging, particularly in groups such as pregnant women, children and adolescents who are generally excluded from clinical trials.

The project

The VirTUAL project is drawing on existing data, conducting new clinical studies and using modelling to determine and test the most appropriate dosing of boosted protease inhibitors in second-line treatment of HIV.

It will use an approach known as physiologically based pharmacokinetic modelling to explore how rifampicin affects the metabolism and excretion of boosted protease inhibitors and their distribution around the body. These analyses will reveal the drug doses likely to be necessary for antiretroviral concentrations to be high enough to effectively suppress HIV replication.

The results of the modelling will be tested in clinical pharmacokinetic studies, with gradually increasing levels of boosted protease inhibitors being given to patients receiving high-dose rifampicin. Pharmacokinetic modelling will also be used to determine appropriate antiretroviral doses for special populations, such as pregnant women, children and adolescents.

Project at a glance

Project: VirTUAL study

Project lead: Dr Catriona Waitt, University of Liverpool, United Kingdom

Countries involved: Italy, South Africa, Uganda, United Kingdom

Target population(s): Pregnant women, children and adolescents

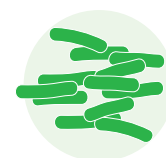
Year funded: 2018

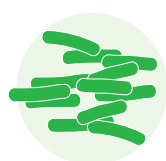
EDCTP funding: €2.1 M

Project website: <https://virtualconsortium.org>

Impact

The VirTUAL project will provide much-needed data on complex but increasingly common clinical scenarios in HIV management, including antiretroviral use in vulnerable and neglected populations. In addition, it will build the capacity of African scientists in pharmacokinetic modelling, increasingly used to identify dosing strategies for evaluation in clinical trials.





Tackling TB and HIV together

The TREATS study will reveal whether combined HIV and TB interventions targeting entire populations have an impact on the prevalence of TB.

The challenge

TB is responsible for around 40% of the deaths of people living with HIV. Hence there is great interest in interventions that address both infections.

Control of HIV is increasingly moving towards 'test and treat' strategies, screening as many people as possible and starting antiretroviral therapy in all those found to be infected with HIV. Potentially, approaches to TB detection and prevention could be integrated into population-based initiatives to identify HIV infections.

The project

The HPTN 071 (PopART) trial, the largest trial ever of combined HIV and TB prevention, involving around one million people, found that targeting entire populations cut the number of new HIV infections by 30%. The TREATS study is using the PopART trial infrastructure to determine whether population screening for active TB, piggybacking universal HIV testing and treatment, leads to a reduction in the community burden of TB.

The trial is taking place in 21 communities in South Africa and Zambia. A trial on the scale of PopART is unlikely ever to be repeated, so it provides a unique opportunity to collect data on population-based approaches for detecting TB.

TREATS will also use a range of methods for detecting TB infections and cases of active TB (most cases of TB are inactive, or latent; people with latent TB infections cannot spread the disease). These studies will provide a wealth of data on the best ways of measuring the number of new cases of TB each year and the prevalence of TB infection and disease.

Project at a glance

Project: TREATS study

Project lead: Professor Helen Ayles, London School of Hygiene & Tropical Medicine, UK

Countries involved: France, Germany, the Netherlands, South Africa, United Kingdom, Zambia

Target population(s): All ages

Year funded: 2018

EDCTP funding: €12.9 M

Total project funding: €26.3 M

Project website: <https://treatsproject.org>

Impact

The TREATS trial is a unique opportunity to gather information from large numbers of people on the impact of a combined HIV and TB control intervention on the TB disease burden. As countries move to more population-based HIV control strategies, its findings will help policymakers decide whether to combine large-scale TB and HIV screening.

Facilitating implementation of TB testing

The CAP-TB study will provide crucial information on the performance and impact of new TB diagnostics in real-life settings.

The challenge

Introduction of Xpert technology was a major step forward in the molecular diagnosis of TB as an alternative to culturing TB bacteria. However, although offering several significant advantages – notably, much faster results – its impact has been less than expected. This reflected some drawbacks in the Xpert technology, but also the fact that, in practice, clinicians do not rely solely on diagnostic test results when deciding on treatment.

As new generations of molecular diagnostic tests for TB become available, therefore, it will be important to consider not just their technical performance but also how they would contribute to clinical decision-making and working practices in existing healthcare systems.

The project

The CAP-TB project is examining practical implementation issues for an updated version of Xpert, known as Cepheid Omni. The Omni platform enables high sensitivity testing for TB (Omni/Ultra) and detection of a greater range of drug resistance genes (Omni/XDR).

The CAP-TB team is evaluating the performance of these new tools at a range of sites in sub-Saharan Africa. One aim of the project is to gather data on health outcomes and HIV-related mortality when the new tools are used. But the study will also examine how Omni technology, including its internet connectivity, can improve care and logistical processes – from linking patients to care pathways to stock management.

It will also explore implications for staff training and practical matters such as stock management and maintenance, when the technology is used outside specialist laboratory facilities.

Project at a glance

Project: CAP-TB study

Project lead: Dr Samuel Schumacher, Foundation for Innovative New Diagnostics, Switzerland

Countries involved: Ethiopia, Germany, Italy, Mozambique, Spain, South Africa, Switzerland, Tanzania

Target population(s): All age groups

Year funded: 2018

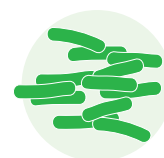
EDCTP funding: €6 M

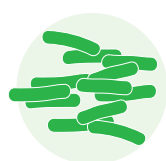
Total project funding: €10.6 M

Project website: www.cap-tb.org

Impact

The CAP-TB study will provide insight into the clinical benefits the Omni platform might offer, based on its use in realistic contexts, and into the financial implications of its introduction. It will provide policymakers with much clearer evidence of the most impactful implementation strategies based on local patterns of disease and healthcare infrastructure, enabling them to make more informed decisions on introduction of the new technology.





Shorter treatment for drug-resistant TB

The Simplici-TB study is evaluating a new combination of drugs that could significantly shorten treatment times for both drug-sensitive and drug-resistant TB.

The challenge

TB kills more than 1.5 million people every year. Standard treatment involves six months' use of multiple antibiotics. In addition, multidrug-resistant TB is on the rise – nearly half a million cases were reported in 2016 – and requires even longer and more arduous treatment, with only a 50% chance of cure.

Shortening and simplifying TB drug treatments are major goals in TB research. Shorter regimens would cost less, be easier to implement and easier for patients to manage.

The project

The development of highly effective new drugs – particularly bedaquiline and pretomanid – is raising hopes that shorter duration treatments are a realistic possibility.

A recent trial which showed that bedaquiline and pretomanid, combined with two potent currently used drugs (moxifloxacin and pyrazinamide), cleared TB bacteria from the lungs of patients with multidrug-resistant TB up to three times faster than the standard regimen cleared bacteria from patients with drug-sensitive TB – the fastest rate of clearance ever seen in a clinical trial. Following up these positive findings, the Simplici-TB trial is now comparing a four-month course of the new combination to treat drug-sensitive TB and a six-month course to treat multidrug-resistant TB.

The study is being run in partnership with the TB Alliance, a US-based not-for profit organisation, with the African studies forming part of a wider global trial evaluating the new combination.

Project at a glance

Project: Simplici-TB study

Project lead: Professor Stephen Gillespie, University of St Andrews, UK

Countries involved: Gabon, Germany, Malawi, Mozambique, the Netherlands, South Africa, Switzerland, Tanzania, Uganda, United Kingdom, and the United States

Target population(s): All age groups

Year funded: 2018

EDCTP funding: €12 M

Total project funding: €32.4 M

Clinical trial registration: <https://clinicaltrials.gov/ct2/show/NCT03338621>

Impact

The Simplici-TB will provide key data on a highly promising new combination treatment for TB. It could accelerate the introduction of a treatment that has a major impact on treatment of both drug-sensitive and drug-resistant TB in sub-Saharan Africa.

Advancing new options for treatment of TB

The CLICK-TB study is adopting a novel approach to identify the most likely promising new treatment options for TB.

The challenge

The rise of drug resistance is making treatment of TB even more difficult. Treatment of multidrug-resistant TB typically lasts at least a year, involves up to 10 drugs, and cures only around half of all patients. Hence new drugs are urgently required.

Phase III clinical trials of TB treatments are large, lengthy and expensive. It is therefore critical that resources are focused on drugs with the greatest likelihood of success.

The project

The CLICK-TB study aims to identify the most promising combinations of TB drugs from a pool of early-stage candidates from new chemical classes. It is focusing on three novel compounds, two of which have already completed early-stage clinical trials: sanfetrinem cilexetil, a broad-spectrum antibiotic with potential for repurposing for TB; GSK3036656, an inhibitor of an enzyme pivotal to mycobacterial protein synthesis (LeuRS); and two inhibitors of DprE1, an enzyme involved in cell wall synthesis, which are in late pre-clinical development.

The CLICK-TB team will assess each of these drugs in combination with newly approved anti-TB drugs, delamanid or pretomanid and bedaquiline. Up to 10 combinations will be evaluated in rapid (two-week) assays examining early potency against TB bacteria. As well as bacterial culture results, the team will also collect radiological and immunological data, providing an additional readout of treatment responses.

The team will then develop a statistical model to compare results across the different combinations and to determine the relative contributions of each drug component. This model will be used to identify the likely most potent combinations, which will be evaluated in a four-week trial using the same response readouts alongside traditional phase IIb trial endpoints.

Project at a glance

Project: CLICK-TB study

Project lead: Dr David Barros, GSK I+D, Spain

Countries involved: Germany, Spain, South Africa

Target population(s): All age groups

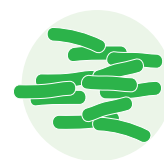
Year funded: 2018

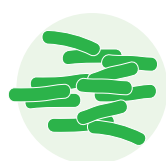
EDCTP funding: €6.9 M

Total project funding: €11 M

Impact

The CLICK-TB study has adopted a novel trial methodology that will rapidly generate a wealth of data on a suite of candidate TB drugs, efficiently identifying the most promising combination for a definitive phase III trial.





Statin use to boost anti-TB therapies

The StatinTB proof-of-concept study is exploring whether statins can reduce lung damage and lower the risk of recurrence of TB.

The challenge

Mycobacterium tuberculosis (Mtb) causes 1.8 million deaths every year. Treatment is based on use of multiple antibiotics over six months, but disease recurs in 3–5% of patients after they have supposedly been cured. Patients may also continue to experience a deterioration in lung function due to persistent inflammation.

There is growing evidence that statins, drugs widely used to lower cholesterol levels, could be beneficial in treatment of TB. Mtb relies on host cholesterol for survival. As well as lowering cholesterol levels, statins also have anti-inflammatory properties, which may limit the damage caused to the lungs during TB infections. Notably, several studies have found that people who are taking statins have a decreased risk of active TB disease.

The project

The StatinTB team is carrying out a rigorous proof-of-concept trial to determine whether use of statins, in addition to antibiotic therapy, reduces the risk of relapse and lessens damage to the lung.

HIV-infected and -uninfected adults will be given a statin, atorvastatin, for 12 weeks at the end of their antibiotic treatment. They will undergo PET/CT (positron emission tomography/computed tomography) scans, which will provide insight into whether active TB disease is still present and the extent of inflammatory damage to the lungs.

Impact

If the StatinTB trial shows that statins have a beneficial impact on lung health as judged by PET/CT measures, it would open the door to large-scale trials to investigate their impact on TB relapse rates and long-term lung function.

Project at a glance

Project: StatinTB study

Project lead: Dr Reto Guler, University of Cape Town, South Africa

Countries involved: Germany, Namibia, South Africa, and the United Kingdom

Target population(s): Adults, with and without HIV infection

Year funded: 2019

EDCTP funding: €4.9 M

Improving treatments for TB-associated meningitis

The INTENSE-TBM study will provide the first data on whether intensified treatment of tuberculous meningitis – TB infection of the brain – reduces mortality and long-term disability.

The challenge

Although the TB bacterium is mainly found in the lungs, it can also invade the central nervous system, causing a potentially lethal form of meningitis in the brain. Tuberculous meningitis is particularly common in young children, and has a high mortality rate (30%). Mortality is much higher in patients with HIV, particularly when they are infected with drug-resistant strains of TB. In addition, around half of survivors are affected by long-term disabilities.

Treatment of tuberculous meningitis is complicated as the blood–brain barrier restricts access of anti-TB drugs to infected tissues. In addition, despite its severity, there is relatively little evidence on the optimum treatment of tuberculous meningitis.

The project

The INTENSE-TBM study is evaluating a revised, more intensive treatment of patients with tuberculous meningitis, including those with HIV infections. The first week's treatment will include high-dose intravenous rifampicin, which does not cross the blood–brain barrier well, and linezolid, an anti-TB drug that shows good uptake into the brain, plus other anti-TB drugs and corticosteroids. For the next two months, treatment switches to an oral regime, followed by a simplified antibiotic regime up to seven months. The trial will also test whether daily aspirin is beneficial, by reducing tissue-damaging inflammation.

For patients with HIV infections, triple antiretroviral therapy will begin four weeks after the start of treatment for tuberculous meningitis. Dexamethasone will also be given during the first four weeks of antiretroviral treatment, to reduce the risk of immune reconstitution inflammatory syndrome (IRIS) – when a recovering immune system launches a powerful response against TB infections.

Project at a glance

Project: INTENSE-TBM study

Project lead: Professor Fabrice Bonnet, University of Bordeaux, France

Countries involved: Côte d'Ivoire, France, Madagascar, South Africa, Spain, Switzerland, Uganda

Target population(s): Adults and children >15 years old, including those with HIV infections

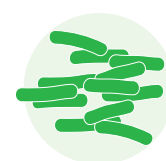
Year funded: 2018

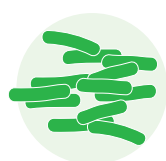
EDCTP funding: €9.3 M

The study will also examine how combined use of antiretroviral and anti-TB medicines affects their metabolism in the body.

Impact

The INTENSE-TBM study will answer key questions in treatment of tuberculous meningitis, which has scarcely changed in decades. It will assess the impact of more intensive treatment on mortality and the likelihood of longer-term disability, and generate data on a tailored regimen specific for those infected with HIV.





Prevention of TB in people with diabetes

The PROTID project is assessing the potential benefits of preventive treatment of TB in people with diabetes.

The challenge

Globally, one in four people are infected with the TB bacterium. Of these, 10% go on to develop active TB disease. One key TB control strategy is to target groups at high risk of progression to active TB disease, and highly effective preventive treatments have been developed.

Vulnerable groups include people with diabetes, who are nearly four times more likely to develop TB, especially if their diabetes is uncontrolled. They also suffer worse symptoms, more treatment failures, and a higher risk of death. An estimated 629 million people are likely to develop diabetes by 2045, 90% of them in low- and middle-income countries. Around 7% of people in sub-Saharan Africa currently have diabetes, although 70% of cases are undiagnosed. The numbers affected in the region could reach 41 million by 2045, a 156% increase (compared with a global increase of 48%).

The project

The PROTID project aims to determine whether preventive treatment of TB in people with diabetes is beneficial and cost-effective. It is the first ever large-scale randomised controlled trial of preventive treatment of TB in people with diabetes.

A total of 6,000 people will be recruited in Tanzania and Uganda, countries with high TB burdens, and randomised to placebo or a 12-week course of a standard preventive regimen, rifapentine and isoniazid. They will then be followed for two years to examine progression to active TB disease and the severity of symptoms.

The project will also investigate different approaches for screening for TB in people with diabetes, ways to better improve the care pathway, including coordination of TB and diabetes care, and the cost-effectiveness of preventive TB treatment in this group.

Project at a glance

Project: PROTID

Project lead: Professor Reinout van Crevel, Stichting Katholieke Universiteit Radboudumc, The Netherlands

Countries involved: The Netherlands, New Zealand, Tanzania, Uganda, UK

Target population(s): Adults living with diabetes

Year funded: 2020

EDCTP funding: €4.8 M

Clinical trial registration: <https://clinicaltrials.gov/ct2/show/NCT04600167>

Impact

The PROTID project will generate evidence that could have a major influence on global policy and practice. People with diabetes are already thought to account for more than 10% of the spread of TB, a figure that is projected to rise as the number of cases of diabetes increases. Overall, 15–30% of the global TB disease burden may be attributable to diabetes. If preventive treatment is found to be effective in people with diabetes, this would benefit large numbers of people with a chronic health condition but also reduce the transmission of TB – the PROTID project team estimates that preventive treatment in people with diabetes could prevent 11% of cases and 13% of TB-associated morbidity.

Intensified TB treatment for people living with HIV

The DATURA trial is evaluating whether an intensified treatment regimen can reduce the disturbingly high risk of death from TB in people living with HIV.

The challenge

Although care for people living with HIV has improved markedly in recent years, around a quarter only start treatment when their CD4 white blood cell numbers have been severely depleted. This places them at greatly increased risk of other infections, including TB. As many as 30% of people living with HIV succumb to TB, accounting for 19% of global TB mortality.

HIV infections increase the risk of active TB disease, and also lead to reduced concentrations of TB drugs in the bloodstream, owing to abnormalities in the adsorption of TB drugs. Antiretroviral therapy can also interfere with the action of TB drugs. Conversely, antiretroviral therapy can also trigger a potentially deadly exaggerated immune response to TB (immune reconstitution inflammatory syndrome, IRIS).

The project

The DATURA trial is evaluating an intensified TB treatment regimen designed to address these challenges in people living with HIV and with low CD4 cell counts.

Recent trials have confirmed the safety of high doses of the key TB drug rifampicin. The DATURA trial is combining high-dose rifampicin with a higher than usual dose of isoniazid. The trial team will liaise with the EDCTP-funded INTENSE TBM project, which is using high-dose rifampicin to reduce mortality associated with tuberculosis meningitis.

The trial regimen will also incorporate a corticosteroid (prednisone), shown in the EDCTP-funded PREDART trial to reduce the risk of IRIS reactions in patients starting antiretroviral treatment.

The trial will compare the intensified approach – 8 weeks of high-dose anti-TB drugs followed by 16 weeks of classical treatment, plus 6 weeks of prednisone – with the standard 24-week TB

Project at a glance

Project: DATURA

Project lead: Dr Didier Laureillard, Institut National de la Santé et de la Recherche Médicale, Montpellier, France

Countries involved: Cameroon, France, Guinea, Norway, Uganda, Zambia

Target population(s): Adults and adolescents

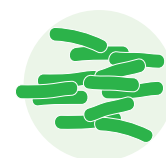
Year funded: 2020

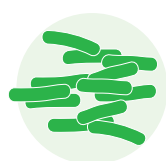
EDCTP funding: €4.6 M

treatment regime. The trial will include nearly 1,000 patients from all four regions of sub-Saharan Africa, generating definitive evidence on the efficacy and safety of this new approach.

Impact

The DATURA trial is addressing a critical health issue in sub-Saharan Africa. If intensified treatment is shown to be more effective, it would have the potential to save the lives of a very vulnerable group of patients and also to reduce transmission of TB. The new regimen is based on existing widely used drugs so could be readily implemented in sub-Saharan Africa. The trial team is also maintaining close links with policymakers in the region, as well as global bodies involved in TB control, to ensure that findings are rapidly communicated to decision-makers and inform policy and practice.





A new approach for TB vaccination

The POR TB trial is evaluating a novel strategy for protecting against TB – preventing latent infections from springing back to life.

The challenge

Most TB vaccines aim to prevent new infections. However, an estimated 2 billion people are already infected with *Mycobacterium tuberculosis*. Although 1.5 million lives are lost to TB every year, not everyone with an *M. tuberculosis* infection develops clinical disease. Hence an alternative goal for vaccination is to promote immune responses that keep an existing infection in check – which is likely to require a different type of vaccine from one designed to prevent initial infection.

The POR TB team has developed a candidate vaccine, known as H56:IC31, that has been specifically designed to protect people already exposed to *M. tuberculosis*. It is based on a fusion protein (known as H56) containing antigens made by *M. tuberculosis* at different stages of its life cycle, combined with an adjuvant (IC31). Preliminary clinical trials have shown that H56:IC31 is safe and stimulates good immune responses of the kind thought likely to be protective.

The project

The POR TB consortium is now carrying out a larger phase II trial, to assess the safety and efficacy of H56:IC31 using a 'prevention of recurrence' approach not previously applied to TB. Even after successful treatment of TB, up to 10% of patients experience a relapse – their TB returns, following reinfection or reawakening of dormant bacteria that survived initial treatments. Preventing recurrence would improve the success of treatments and reduce the spread of TB.

In the placebo-controlled POR TB trial, H56:IC31 will be given to TB patients who have successfully completed 6 months of standard TB treatment. Patients will be monitored for 2 years for recurrence of their TB.

Project at a glance

Project: POR TB Consortium

Project lead: Professor Peter Andersen, Statens Serum Institute, Copenhagen, Denmark

Countries involved: Denmark, Italy, South Africa, Tanzania

Target population(s): Adults treated for TB

Sample size: 900 (target)

Year funded: 2018

EDCTP funding: €13.8 M

Project website: www.porconsortium.org

Clinical Trial registration: <https://clinicaltrials.gov/ct2/show/NCT03512249?term=H56%3AIC31&rank=1>

Impact

Complementing preventive vaccines such as BCG, H56:IC31 could enhance the long-term success rates of TB drug treatments. Potentially, by stimulating host responses to infection, it could also provide a route to shortened drug treatments.

The POR TB consortium is also piloting a novel clinical trial approach and measures of success that could be adopted for evaluation of similar products. Finally, the trial will also generate data on the elements of the immune response and features of *M. tuberculosis* that are associated with recurrence or the success of vaccination to prevent recurrence.

Key reference

Luabeya AK et al. First-in-human trial of the post-exposure tuberculosis vaccine H56:IC31 in *Mycobacterium tuberculosis* infected and non-infected healthy adults. *Vaccine*. 2015;33(33):4130–40.

Better TB protection for newborns

The MTBVAC-Newborns study will determine whether a weakened form of the TB bacterium is suitable for large-scale trials – potentially offering a better alternative to BCG.

The challenge

BCG (Bacillus Calmette-Guérin) has been used to protect newborn infants against TB for nearly 100 years. It is a weakened (attenuated) form of the bacterium that causes TB in cattle, *Mycobacterium bovis*. It was developed by repeated culturing of *M. bovis* and selection for strains that stimulated anti-TB immune responses but did not cause disease.

Although BCG offers generally good protection to newborn infants, it has many drawbacks and is significantly less effective in older age groups. In part, this reflects the fact that attenuation led to the loss not just of genes that trigger disease but also of others that stimulate strong immune responses. Using this knowledge, the MTBVAC team has developed a new vaccine based on *M. tuberculosis* which has been precisely engineered to eliminate genes central to disease while maintaining those lost in BCG that provoke strong immune responses.

The project

MTBVAC has been shown to be safe in healthy adult volunteers and in a small number of newborn infants in South Africa; it appears to stimulate an immune response as least as strong as BCG. In a new trial, the MTBVAC team is carrying out a larger trial in newborn infants in South Africa to evaluate the safety of increasing doses of MTBVAC and the strength of anti-TB immune responses, in comparison with BCG. In parallel, the consortium is building capacity for future large-scale trials in Senegal and Madagascar, which have a high burden of TB.

Impact

In theory, MTBVAC should provide better protection in older age groups, but it is also important to determine whether it is a suitable alternative to BCG. Positive results would pave the way to a pivotal phase III trial that would

Project at a glance

Project: MTBVAC-Newborns trial

Project lead: Ms Ingrid Murillo, Biofabri SL, Spain

Countries involved: Madagascar, the Netherlands, Senegal, South Africa, Spain

Target population(s): Newborns

Sample size: 99 (target)

Year funded: 2018

EDCTP funding: €5.5 M

Project website: www.tbvi.eu/for-partners/mtbvac-in-newborns-2/mtbvac-in-newborns

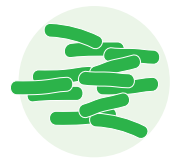
Clinical trial registration: <https://clinicaltrials.gov/ct2/show/NCT03536117>

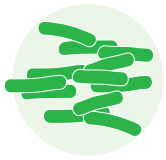
provide definitive evidence of MTBVAC's efficacy in newborn infants compared with BCG.

Key reference

Spertini F et al. Safety of human immunisation with a live-attenuated *Mycobacterium tuberculosis* vaccine: a randomised, double-blind, controlled phase I trial. *Lancet Respir Med*. 2015;3(12):953–62.

Tamaris et al. Live-attenuated *Mycobacterium tuberculosis* vaccine MTBVAC versus BCG in adults and neonates: a randomised controlled, double-blind dose-escalation trial. *Lancet Respir Med*. 2019 Sep;7(9):757-770.





Building a successor to BCG

The priMe study will reveal whether a promising alternative to BCG is safe and effective for use in newborn infants.

The challenge

The BCG (Bacillus Calmette-Guérin) vaccine has been used to vaccinate against TB since the 1920s. It is reasonably effective at preventing serious disease, but many vaccinated infants still develop TB meningitis and it appears to have little impact on the spread of pulmonary TB. Modelling studies suggest that, despite BCG, around 7.5 million children were infected with *Mycobacterium tuberculosis* in 2010 and 650,000 developed TB disease.

BCG is a weakened or attenuated version of *Mycobacterium bovis*, a relative of *M. tuberculosis* that causes TB in cattle. Researchers have recently revisited *M. bovis* and introduced precise genetic changes that cause it to stimulate stronger immune responses and make it safer for use in individuals with HIV, who sometimes suffer reactions to conventional BCG.

The project

The large-scale phase III priMe study will build on promising preliminary trials, in adults and children, of this updated version of BCG, known as VPM1002. Aiming to recruit around 7000 newborns, it will provide definitive evidence of the safety and efficacy of VPM1002 in both HIV-free and HIV-infected newborn infants.

Impact

Positive findings would indicate that VPM1002 is a suitable alternative to BCG, widely recognised to be an imperfect vaccine but included in most countries' routine immunisation programmes. Furthermore, production methods for VPM1002 are relatively simple and straightforward to scale up, so the vaccine could meet global demand and overcome some of the supply difficulties recently experienced with BCG. The priMe study will also generate important data on the immune responses associated with good protection against *M. tuberculosis*, to enhance the design of future vaccines.

Project at a glance

Project: priMe trial

Project lead: Dr Leander Grode, Vakzine Projekt Management GmbH, Germany

Countries involved: Gabon, Germany, India, Kenya, the Netherlands, South Africa, Tanzania, Uganda

Target population(s): Newborn infants (HIV-free and HIV-infected)

Sample size: 6940

Year funded: 2018

EDCTP funding: €12.5 M

Total project funding: €25 M

Project website: www.pri-me-vaccine.eu

Key reference

Loxton AG et al. Safety and immunogenicity of the recombinant *Mycobacterium bovis* BCG vaccine VPM1002 in HIV-unexposed newborn infants in South Africa. *Clin Vaccine Immunol.* 2017;24(2). pii: e00439-16.

Efficient diagnosis of HIV and TB

The Stop TB/HIV at One study is assessing technologies to allow diagnosis of HIV and TB in a single visit.

The challenge

HIV infections greatly accelerate progression from latent TB to active TB disease. Globally, around 10% of new TB cases are among people living with HIV, and in 2016, 374,000 people with HIV and TB co-infections died – 86% of them in Africa. TB remains the leading cause of death of people with HIV.

Diagnosis of HIV is relatively straightforward, as simple and affordable point-of-care tests are available. Detection of TB is more challenging – national surveillance programmes are thought to miss a third of new cases. In particular, TB can be difficult to detect in people living with HIV, leading to delayed diagnosis and initiation of treatment.

The project

The Stop TB/HIV at One study aims to develop new approaches for diagnosing HIV and TB rapidly and cost-effectively. Current approaches for TB detection are not suitable for rapid and large-scale screening. Smear microscopy is time-consuming and misses a significant number of cases, and is particularly poor at identifying TB in people with HIV, who may not be able to generate a sputum sample for analysis. Molecular tests and X rays require equipment that may not be available at clinics.

To overcome these shortcomings, new point-of-care diagnostic tools are being developed. The Stop TB/HIV at One study is evaluating a range of tools for diagnosing HIV and TB. Based on the performance of these tests, it will then develop new approaches for use of these tests, or diagnostic algorithms, to enable health care workers to detect TB and HIV in the shortest possible time and at the lowest possible cost.

The performance of these new diagnostic algorithms will then be evaluated in real-life settings in Nigeria and Ethiopia.

Project at a glance

Project: Stop TB/HIV at One study

Project lead: Professor Luis Cuevas, Liverpool School of Tropical Medicine, UK

Countries involved: Ethiopia, Moldova, Nigeria, Spain, and the United Kingdom

Target population(s): All age groups

Year funded: 2016

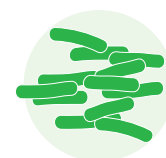
EDCTP funding: €1.4 M

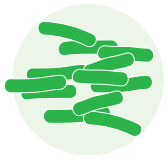
Impact

Rapid detection of TB is essential to ensure rapid initiation of treatment, which improves patient outcomes and reduces the risk of disease transmission. Earlier identification of TB and prompt treatment could prevent most TB-related deaths in people with HIV infections. However, detection of TB is challenging, particularly in people with HIV. New tests, and careful design of testing strategies, could provide diagnostic algorithms that are practical for use in health centres with limited facilities and cost-effectively improve timely detection of both HIV and TB.

Key reference

Santos VS et al. Acute phase proteins and IP-10 as triage tests for the diagnosis of tuberculosis: systematic review and meta-analysis. *Clin Microbiol Infect.* 2019;25(2):169–177.





Developing a point-of-care test to detect active TB

The ScreenTB study is developing a rapid, point-of-care test to identify active TB using just a fingerprint blood sample.

The challenge

Screening for active TB in remote populations is problematic. Sputum samples need to be transported to suitable facilities for analysis, leading to delays that may mean patients never start treatment.

This challenge could be overcome by point-of-care diagnostics suitable for use with minimal training. Implementation would also be easier if blood samples rather than sputum could be analysed.

The project

In an earlier EDCTP-funded project, the ScreenTB team identified a set of six biomarkers in blood that were strongly associated with active TB. Building on this discovery, the team is now developing a simple-to-use 'dipstick' test (lateral flow assay) that would detect these biomarkers, allowing rapid initiation of anti-TB treatment.

The project is making use of novel nanoparticle-based detection methods, which are both highly sensitive and robust enough to be used in environmentally challenging settings. Using this technology, the team is developing a tool that can simultaneously detect all six biomarkers in a finger-prick blood sample. The performance of the test is being compared with that of gold-standard methods in 800 adults with suspected active TB.

Impact

A rapid, reliable and user-friendly TB screening test could streamline diagnostic processes in resource-limited settings, reducing unnecessary referrals for molecular testing and ensuring more patients immediately start treatment.

Project at a glance

Project: ScreenTB study

Project lead: Professor Gerhard Walzl, Stellenbosch University, South Africa

Countries involved: Ethiopia, The Gambia, Germany, Namibia, the Netherlands, South Africa, Uganda, and the United Kingdom

Target population(s): Adults

Year funded: 2016

EDCTP funding: €3 M

Key reference

Chegou NN et al. Diagnostic performance of a seven-marker serum protein biosignature for the diagnosis of active TB disease in African primary healthcare clinic attendees with signs and symptoms suggestive of TB. *Thorax*. 2016;71(9):785–94.

Awoniyi DO et al. Evaluation of cytokine responses against novel Mtb antigens as diagnostic markers for TB disease. *J Infect*. 2016;73(3):219–30.

Better detection of multidrug-resistant TB

The DIAMA study is evaluating new diagnostics that could provide a faster and more complete picture of drug resistance in TB.

The challenge

Multidrug-resistant TB infections are becoming more common. A failure to identify drug resistance is bad for individual patients, and facilitates the wider spread of drug-resistant bacteria.

Culturing TB bacteria to assess resistance is technically difficult and can take up to four months. Molecular diagnostics are increasingly being used, but do not necessarily identify all resistance mutations.

The project

The DIAMA study is evaluating new options that could provide more rapid results on drug resistance than culturing. It builds on previous EDCTP funding and an infrastructure that undertakes continuous monitoring of TB patients for resistance to rifampicin.

Benin and Rwanda have established reference laboratories that can use the 'Deeplex' assay, which generates sequence information on genes conferring resistance to 14 key anti-TB drugs. In the first phase of the study, sputum samples will be shipped to the reference labs for Deeplex analysis and results compared with those obtained by the traditional culturing method.

In the second phase of the study, all participating countries will begin using two lower-tech tools – Molbio Diagnostics' TrueNat test and the latest version of the Xpert molecular diagnostic platform – which do not require samples to be sent to a reference laboratory. Results will be compared with those obtained by Deeplex analysis. Newly developed software will be used to transmit results immediately to national TB programmes. Use of the new tools in patient management will be evaluated at two pilot sites. The project will also explore use of two faster alternatives to culture to monitor responses to treatment.

Project at a glance

Project: DIAMA study

Project lead: Dr Dissou Affolabi, Centre National Hospitalier de Pneumo-Phtisiologie, Benin

Countries involved: Belgium, Benin, Cameroon, Democratic Republic of the Congo, Ethiopia, France, Guinea, Mali, Nigeria, Rwanda, Senegal, Switzerland, and the United Kingdom

Target population(s): All age groups

Year funded: 2016

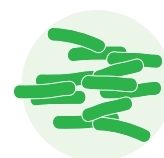
EDCTP funding: €3 M

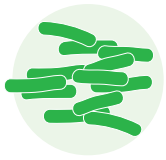
Project website: www.diama-project.com

Clinical trial registration: <https://clinicaltrials.gov/ct2/show/NCT03303963>

Impact

Use of the new approaches could lead to more rapid identification of multidrug-resistant TB, and dramatically improve treatment in resource-poor settings, where treatment outcomes are typically much worse than in high-income countries.





Identifying TB patients suitable for shortened treatment

The PredictTB study is investigating whether a combination of biomarkers can identify TB patients who are responding well to antibiotics so their treatment can be halted early.

The challenge

Reducing treatment times from six to four months is a major goal in TB research. Shorter treatment times would reduce costs, increase compliance and reduce the risk of drug resistance.

In clinical trials, four-month regimens have generally not been as successful as standard six-month treatments. However, 80–85% of participants are cured at four months. If these patients could be identified reliably, their treatment could safely be stopped early.

The project

The PredictTB team has identified a combination of markers, based on radiographic examination of lungs and detection of *Mycobacterium tuberculosis* by Xpert molecular diagnostic technology, that are good predictors of individuals who respond well to therapy and whose treatment could be stopped at four months.

To evaluate these markers, the team is running a phase IIb clinical trial on more than 600 patients with drug-sensitive pulmonary TB. All patients are receiving standard TB treatment for 16 weeks; at this point, radiographic and Xpert results are being used to distinguish 'poor responders', who will continue with the full six-month course, and 'good responders', who will be randomised to continued therapy or early completion. Cure rates will then be compared at 18 months.

The PredictTB project has received support from a range of funders, including the Bill & Melinda Gates Foundation, and is recruiting patients at multiple sites in China as well as South Africa.

The sophisticated radiographic tools used to identify good responders would not be suitable for routine use in low-resource settings. The project is therefore also investigating other

Project at a glance

Project: PredictTB study

Project lead: Professor Gerhard Walzl, Stellenbosch University, South Africa

Countries involved: Germany, The Netherlands, South Africa, UK

Target population(s): All age groups

Year funded: 2017

EDCTP funding: €7.7 M

Total project funding: €24.7 M

Project website: <https://predict-tb.com>

possible biomarkers that are associated with good response to treatment, which could be used as alternatives to radiographic screening. This is informing the development of a more practical point-of-care test that could be used to identify patients suitable for early completion of therapy. The project is also developing a biobank of samples for future biomarker research.

Impact

The PredictTB study could provide the tools to enable large numbers of TB patients to finish TB therapy early, even with currently used drugs. This would benefit patients, reducing their exposure to powerful drugs and a daily drug-taking routine, as well as health systems, by reducing costs of treatment.

Key reference

Chen RY et al. Using biomarkers to predict TB treatment duration (Predict TB): a prospective, randomized, noninferiority, treatment shortening clinical trial. *Gates Open Res.* 2017;1:9.

Improving TB diagnosis in children

The RaPaed TB study is exploring a range of new tools for diagnosing TB in children – one of the biggest obstacles to control of TB disease.

The challenge

More than 200,000 children die from TB every year, and 1 million new cases are reported. However, TB in childhood can be treated effectively – mortality rates are just 1% – suggesting that many children are dying because their TB is never diagnosed.

Unfortunately, TB is hard to diagnose in children. Clinical symptoms are similar to those for other respiratory infections and young children may find it hard to generate a sputum sample for analysis. Furthermore, because of the way that the TB bacterium infects children, sputum samples may contain few bacteria. Reliable new diagnostics suitable for children are thus urgently needed.

The project

The RaPaed TB project has brought together a consortium of experts from different fields to evaluate eight promising new diagnostic approaches for childhood TB. These include TAM-TB, a blood test that showed promise in the EDCTP-funded TB-CHILD project, as well as a version of the Xpert MTB/RIF molecular diagnostic adapted for stool samples. The RaPaed team will also evaluate two LAM-based tests, which detect a component of *Mycobacterium tuberculosis* in urine known as lipoarabinomannan (LAM); a LAM-based urine test is now recommended by WHO for detection of TB in HIV-infected adults.

Impact

The RaPaed TB team anticipates that at least two of these innovative new approaches will prove sufficiently sensitive to attract WHO endorsement. The team's make-up and project partners are designed to ensure rapid capture of field-relevant results, encompassing experts in child TB clinical research, industry partners developing point-of-care tests, the Foundation for Innovative New Diagnostics (FIND), and national TB control programmes. FIND,

Project at a glance

Project: RaPaed TB project

Project lead: Norbert Heinrich, Ludwig Maximilians Universität, Munich, Germany

Countries involved: Australia, Germany, Malawi, Mozambique, South Africa, Sweden, Switzerland, Tanzania

Target population(s): Children

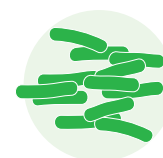
Sample size: 800 suspected TB cases (minimum 200 confirmed cases)

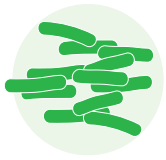
Year funded: 2018

EDCTP funding: €3 M

Clinical trial registration: <https://clinicaltrials.gov/ct2/show/NCT03734172>

which has developed a portfolio of possible technologies, would be well-placed to take forward the WHO submission process for diagnostics achieving sensitive and specific detection of TB in children.





Early detection of TB

The ERASE-TB study will assess the potential of innovative approaches to detect early signs of active TB disease.

The challenge

TB is responsible for almost 1.5 million deaths every year, with sub-Saharan Africa accounting for around a third of them. A major challenge globally is the detection of infection – an estimated 4 million cases go undiagnosed each year, hampering control efforts.

Late diagnosis can lead to additional lung damage, with long-term consequences for patients' respiratory health, and creates further opportunities for the spread of infection. However, it is becoming increasingly clear that TB infection occurs along a clinical continuum, as low-level sub-clinical infection gradually develops into a more clinically serious and infectious state. Being able to track this transition would provide more opportunities for early intervention.

The project

The ERASE-TB study aims to explore the potential of new molecular approaches to detect early signs of clinical TB. Distinctive gene activity signatures have been identified that correlate with the transition to active disease. However, they are not yet specific enough to be used in clinical practice, as they generate too many false positives.

The ERASE-TB study is simultaneously assessing ten of the most promising candidate tests for identifying incipient TB. The tests encompass a range of detection technologies, assessing immunological, gene transcription and protein markers, as well as automated image processing and analysis of metabolites in urine.

Their performance will be evaluated and compared in more than 2,000 heavily exposed household contacts of people living with TB, who are at high risk of contracting a TB infection and progressing to TB disease. This approach will ensure that the precise timing of TB infection can be determined, so that the precision of diagnostic validation can be enhanced. A biobank

Project at a glance

Project: ERASE-TB study

Project lead: Dr Norbert Heinrich, Ludwig Maximilian University, Germany

Countries involved: Germany, Mozambique, Sweden, Tanzania, UK, Zimbabwe

Target population(s): All age groups

Year funded: 2020

EDCTP funding: €3.3 M

of samples will also be created to support the evaluation of future tests.

Based on the data collected, the study team will also develop algorithms to identify the combination of tests that provide the best performance.

Impact

The ERASE-TB project will generate, in a single study, key evidence on multiple potential TB biomarker technologies – a highly efficient way of generating high-quality comparative data. It will also enable the performance of combinations of tests to be assessed. By including commercial and academic test developers in the project team, the study will also have rapid impact on test development. Ultimately, it should accelerate the development of tests filling a key gap in TB diagnosis and facilitate regional and global TB control efforts.

Detecting TB in children

The Stool4TB study will test an innovative new method for identifying TB infections in children and people living with HIV.

The challenge

Mycobacterium tuberculosis (Mtb) is the most common pathogen on the planet, causing 10 million new infections and almost 1.5 million deaths every year, around a third of them in sub-Saharan Africa.

Diagnosis of TB generally relies on analysis of sputum samples, which may be difficult to obtain from children and people with HIV. As a result, confirmation of infection is rare in these groups. This can lead to under-diagnosis and delayed treatment or mis-diagnosis, wasting resources and exposing patients unnecessarily to powerful drugs.

The project

The Stool4TB study team has developed a method for identifying Mtb in stool samples. As Mtb bacteria are transported up the airways in the lungs and enter the gastrointestinal tract, stool samples have long been seen as a potential alternative source of samples for diagnosis, but results to date have been mixed.

The Stool4TB study aims to validate an innovative new approach to diagnosis based on novel methods of stool preparation, DNA extraction and quantification of Mtb numbers using DNA amplification (polymerase chain reaction, PCR) methods. Preliminary findings suggest that this approach has advantages over other diagnostic methods and increases the number of cases detected.

Importantly, repeated use of the test would provide a way to track responses to treatment, which is highly challenging in these groups of patients.

The Stool4TB study will generate more data on the PCR-based approach in areas with a high burden of TB and HIV in three African countries, assessing its ability to improve confirmation rates and its usefulness for monitoring treatment responses.

Project at a glance

Project: Stool4TB study

Project lead: Dr Alberto García-Basteiro, Fundación Privada Instituto de Salud Global Barcelona (ISGlobal), Spain

Countries involved: Eswatini, Germany, Mozambique, The Netherlands, Spain, Uganda

Target population(s): Children, people living with HIV

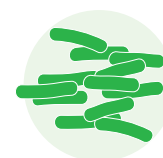
Year funded: 2020

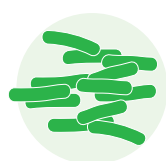
EDCTP funding: €3 M

Impact

The project will assess the feasibility, usability and acceptability of stool collection from both the patient and the health system perspective. Increasing numbers of peripheral health facilities in sub-Saharan Africa are developing PCR capabilities, so the approach is likely to be technologically feasible. There is also the potential to develop it into a more convenient point-of-care test.

The project will also create a biobank of samples to support additional studies of TB diagnosis or detection of drug resistance in these groups. In addition, it will establish a TB diagnostic network among African countries with a high TB burden, boosting the capacity of sites to carry out clinical studies on children and people living with HIV.





Triage testing for TB

The SeroSelectTB project is evaluating a new tool for rapid testing of possible TB cases, to improve the efficiency of TB detection.

The challenge

Although a large proportion of the populations of low-resource countries are infected with the TB bacterium, *Mycobacterium tuberculosis* (Mtb), most infections are 'latent' or inactive and are not treated. A key challenge in TB control is to identify those who develop active TB disease and require treatment.

Unfortunately, the clinical symptoms of TB are not specific and currently used diagnostic tools have multiple drawbacks. A molecular platform, Xpert MTB/RIF, offers relatively good performance and speedy results, but at a cost. A key priority is therefore a cheap and easy-to-use 'triage test' that could be used at the frontline to identify those most likely to have active TB, who could then be referred for confirmatory testing.

The project

The SeroSelectTB project team has investigated the presence of antigens in patients with active TB and in controls, identifying a range of potential molecular markers indicative of active TB. Importantly, these markers also differentiate active TB infections in people living with HIV – a key consideration, as half of TB cases in sub-Saharan Africa are also HIV-positive.

Drawing on these findings, the project team plans to develop a simple dipstick-type diagnostic (a lateral flow assay), based on an established technology platform available in South Africa. After a trial to evaluate the new test's performance, the project will organise a larger study to assess its impact in real-life settings – in particular, whether use of the new tool reduces diagnostic delays and leads to speedier initiation of treatment. The trial will be run in three countries with different health system settings to examine the potential impact of contextual health system factors. Cost-effectiveness will also be explored.

The goal is to develop a tool with comparable sensitivity to molecular diagnostics that could

Project at a glance

Project: SeroSelectTB

Project lead: Professor Carol Holm-Hansen, Norwegian Institute of Public Health, Norway

Countries involved: Austria, Ethiopia, France, Germany, The Netherlands, South Africa, Tanzania

Target population(s): Adults

Year funded: 2020

EDCTP funding: €3 M

be used in initial assessments to guide further investigation. The project team includes members with expertise in regulatory approvals and, if results are positive, a dossier would be put together to support regulatory submissions and applications for WHO prequalification.

Impact

The SeroSelectTB project aims to develop a simple, easy-to-use and affordable triage test for TB that could be manufactured in South Africa for as little as US\$1. Modelling suggests that its introduction could reduce the costs of TB diagnosis by 40%, generating savings to national TB programmes of US\$36m a year, while also ensuring more rapid initiation of treatment of people with active TB and reducing transmission due to missed cases.

Tools for TB triage

The TB TRIAGE + project is assessing whether two tests – an innovative digital chest X-ray analysis system and a simple-to-use blood test – can provide a rapid indication of the likelihood of TB disease.

The challenge

It is estimated that around 3.6 million cases of active TB disease are not detected every year. This means that people fail to get the treatment they need, and also continue to transmit TB to others.

WHO recommends that active attempts are made to identify TB cases in the community, focusing on high-risk groups such as household contacts, those likely to be exposed, and hard-to-reach groups with less access to healthcare facilities. Implementing and expanding this active case-finding strategy requires sensitive and rapid tests to identify potential cases.

The project

The TB TRIAGE + project team is comparing two possible technologies for active case-finding. The first is an innovative X-ray analysis system, based on machine learning, that has proven highly effective at detecting TB in chest X-rays. The portable platform, CAD4TB, rapidly generates accurate results.

The second approach is based on readily available tests that detect C-reactive protein (CRP), a marker of infection. These are affordable and easy to use at point-of-care.

The project team is organising two studies to evaluate these options. The first, TB TRIAGE + -ACCURACY, aims to evaluate the performance of CAD4TB and CRP testing in sub-Saharan African settings, with tests on 1,400 presumptive TB patients in Lesotho and KwaZulu Natal. The study will also determine appropriate cut-offs for diagnosis of TB in these groups.

The second study, TB TRIAGE + -RCT, is a very large, community-based clinical trial involving 35,000 participants. Its three arms will compare CAD4TB, CRP testing and standard diagnostic pathways as a control. The aim is to determine the impact of CAD4TB- and CRP-based screening

Project at a glance

Project: TB TRIAGE +

Project lead: Dr Klaus Reither, Swiss Tropical and Public Health Institute, Switzerland

Countries involved: Belgium, Germany, Lesotho, The Netherlands, South Africa, Switzerland

Target population(s): All

Year funded: 2020

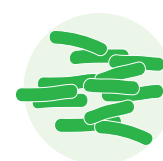
EDCTP funding: €3.2 M

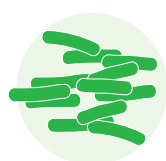
on notification rates, diagnosis and treatment delays, and patient outcomes. Health economic and equity analyses will also be carried out.

The infrastructure established for the project will also support a range of sub-studies, for example to refine the CAD4TB software for diagnosis of other conditions, evaluation of a point-of-care test for CD4 cell counts in people living with HIV, and mapping of risk factors such as diabetes and alcohol use in targeted populations.

Impact

The TB TRIAGE + project will determine the feasibility of using CAD4TB or CRP testing, after clinical screening but before molecular testing with the Xpert system. It has the potential to increase the numbers of people with TB receiving care, but could also lower costs by reducing unnecessary treatment, decreasing demand for molecular testing, and reducing the numbers of drug-resistant infections requiring longer and more intensive treatment.





New tools for TB triage

The Triage TB project is building on past EDCTP-funded research to develop and evaluate a simple dipstick test for identifying patients with active TB disease.

The challenge

TB kills more people than any other single microorganism. However, an estimated one in three cases worldwide are never identified, meaning individuals do not get the treatment they need and can continue to pass on infection to others.

Unfortunately, it is difficult to diagnose TB on the basis of symptoms. Other diagnostic methods are often time-consuming or unreliable. Molecular tests show good performance but are expensive. As a result, WHO has prioritised development of 'triage tests' that would rapidly identify individuals most likely to have active TB, who could then be referred for confirmatory molecular testing.

The project

With funding from the EDCTP, the Triage TB project team has been searching for host biomarkers that could act as signatures of active TB infections. Its goal is to identify a combination of markers that could form the basis of an easy-to-use dipstick-type point-of-care diagnostic.

In its first EDCTP-funded project, the team identified a six-marker signature that was highly predictive of active TB disease. This was used to develop a potential point-of-care diagnostic with the ability to deliver results within 30 minutes using fingerprick blood samples. Prototype devices achieved a sensitivity of more than 90% and a specificity of 75%. This Multi-Biomarker Test (MBT) is being evaluated in the EDCTP-funded ScreenTB project.

The team's results also suggested that a smaller number of markers, three or four, might give similarly high levels of performance. This would make a test easier to produce – particularly three-marker systems, which could use standard lateral flow assay strips (which can accommodate a maximum of three markers).

Project at a glance

Project: Triage TB

Project lead: Professor Gerhard Walzl, Stellenbosch University, South Africa

Countries involved: Germany, The Netherlands, South Africa, Switzerland, Uganda, UK

Target population(s): Adults

Year funded: 2020

EDCTP funding: €3.3 M

The Triage TB project is validating the new tool on a collection of samples from around the world, which is necessary if the test is to have global use. The best performing combination will then be tested on 100 patients from sub-Saharan Africa. Once the design has been finalised, a validation study will be carried out on samples from 600 adult participants from Southern, East and West Africa.

Impact

The Triage TB project will determine whether MBT use offers a practical additional step in the TB diagnostic pathway. It has the potential to rationalise use of expensive molecular testing, greatly reducing unnecessary testing of those without TB. Moreover, with the chances of TB diagnosis being much higher, and with results available immediately, it is more likely that healthcare workers and patients will adhere to referral procedures following a positive MBT result.

Community-based detection of TB

The XACT III study is assessing whether a new portable molecular diagnostic can underpin active searches for TB cases in the community.

The challenge

Globally, around 40% of cases of TB are being missed, leading to unnecessary loss of life and providing opportunities for the spread of infection.

Many of these cases are in urban and peri-urban settlements in resource-poor settings. Reducing the numbers of missed TB cases will require a shift from 'passive' case finding, waiting for people with symptoms of TB to visit health facilities, to 'active' case finding – going out into communities to search for likely cases.

The project

Active case finding is reliant on efficient approaches to diagnose TB infections. In the EDCTP-funded XACT I project, the XACT team showed that Xpert molecular diagnostic technology could provide the foundation for active case-finding programmes. However, the recently developed Xpert Omni system provides additional advantages – notably, portable equipment ideally suited to active case finding.

In the XACT II study, funded by the US National Institutes of Health, the XACT team demonstrated that community-based point-of-care testing for TB was feasible. This approach was based on use of the Xpert Omni system in low-cost panel vans, a highly practical and scalable approach to case finding within communities.

In the XACT III study, the team aims to collect confirmatory data from a larger population – with 17,000 people projected to be screened – in a range of settings in sub-Saharan Africa. The trial will compare Omni-based community testing with Xpert-based laboratory testing of samples; laboratory testing has the advantage that it does not require any new infrastructure, but typically leads to relatively high loss to follow up. The project team will also compare the cost-effectiveness of the two approaches.

The project will also characterise patients with few or no symptoms, for example by genome sequencing of TB isolates and cough aerosol sampling, to provide insights into how such patients contribute to the transmission of TB. This will inform the development of more

Project at a glance

Project: XACT III and IIIB

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

Countries involved: Italy, Mozambique, The Netherlands, South Africa, UK, Zambia, Zimbabwe

Target population(s): All

Year funded: 2020

EDCTP funding: €0.74 M

JGHT funding: €2.92 M*

Clinical trial registration: <https://clinicaltrials.gov/ct2/show/NCT04303104>

*The XACT III study is co-funded by EDCTP and the UK Joint Global Health Trials (JGHT) initiative through the XACT III and IIIB grants.

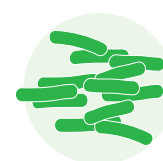
accurate models of transmission for assessing the impact of case-finding interventions.

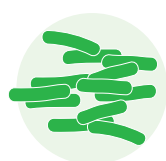
Impact

Omni-based diagnosis could transform active case finding for TB. The approach being trialled has already been shown to be feasible, practical and low cost, and could readily be introduced in other low-resource settings in sub-Saharan African. Given the enormous financial impact of TB – projected to cost 2.5% of GDP over 15 years, or US\$130bn – there is a high likelihood that improved disease control through active case finding will be cost-effective. The project team has already established close links with national and global policymakers, including the Foundation for Innovative New Diagnostics (FIND) and the STOP-TB Partnership, which are awaiting the results of the trial with great interest.

Key references

- Calligaro GL *et al.* Effect of new tuberculosis diagnostic technologies on community-based intensified case finding: a multicentre randomised controlled trial. *Lancet Infect Dis.* 2017;17(4):441-450. doi: 10.1016/S1473-3099(16)30384-X.





Predicting TB progression

The PreFIT project is evaluating a suite of tools that may be able to predict which people with TB infections are likely to go on to develop active TB disease.

The challenge

Across sub-Saharan Africa, 200 million people are infected with the bacterium causing TB. Globally, in 2017, an estimated 1.6 million people (300,000 of them with HIV infections) died of TB.

It is not practical to treat all those with TB infections. Unfortunately, it is not easy to identify those likely to develop active TB disease. With current methods, 25–50 people would need to be treated to prevent one case, which would not be a good use of resources. However, new biomarkers are emerging that may allow those on the pathway to active disease to be identified and treated.

The project

The PreFIT project is evaluating a range of tests that individually or collectively hold promise as potential tools to identify those destined to develop active TB. The project team has analysed the product pipeline and selected the most promising products with potential to be introduced in the region. These include a version of the widely used Xpert diagnostic platform, Predict3, based on a three-gene signature associated with transition to active TB disease.

Alongside Predict3, two other simple tests are being assessed – a cheap test for C-reactive protein (CRP) based on fingerprick blood samples and a point-of-care test for haemoglobin. By evaluating the devices in the same study, the project will be able to determine if combinations of tests offer improved performance, generating cost-optimised algorithms for diagnosis.

The project team includes representatives from the Foundation for Innovative New Diagnostics (FIND), who bring wide-ranging expertise in diagnostic development and are advising on the generation of ‘admissible evidence’ for WHO endorsement. Also involved in the project are two EDCTP-funded Regional Networks of Excellence, TESA (Southern Africa) and EACCR

Project at a glance
Project: PreFIT
Project lead: Professor Frank Cobelens, Stichting Amsterdam Institute for Global Health and Development, The Netherlands
Countries involved: Mozambique, South Africa, Spain, Switzerland, Uganda
Target population(s): Adults and children aged 12 and above
Year funded: 2020
EDCTP funding: €3.3 M

(East Africa), which will provide connections to local policymakers and offer the potential of accelerated translation into practice.

Impact

The PreFIT project will provide key data on the use of urgently needed new diagnostic tools for TB. Based on the performance of the tools, the project team suggests that the number needed to be tested to prevent a case of TB could be as low as five, which would likely make introduction highly cost-effective. Use of the tools would support more targeted treatment, reducing unnecessary use of drugs, and improve the efficiency of preventive treatment. It is estimated that active case finding and preventive treatment could reduce the incidence of TB by 40–90%. A 40% cut would reduce the number of TB patients by 1 million and deaths by 265,000 a year.





Malaria

2014-2020



13 grants
€121.68 M



Drugs
9 grants
€73.77 M



Vaccines
3 grants
€44.91 M



Diagnostics
1 grant
€3 M

EDCTP portfolio: Malaria

Drugs	Vaccines	Diagnostics
IMPROVE Kenya, Malawi, Tanzania	MMVC Burkina Faso, Sierra Leone, Tanzania	DIAGMAL Burkina Faso, Ethiopia, Kenya, Namibia
IMPROVE II Kenya, Malawi	PfTBV Burkina Faso, Guinea, Liberia, Mali	
MAMAH Gabon, Mozambique	MIMVac-Africa Burkina Faso, Gabon, Mozambique, Tanzania	
ASAAP Benin, Burkina Faso, Ghana, Gabon, Mali		
PYRAPREG Burkina Faso, Democratic Republic of Congo, The Gambia, Mali, Mozambique		
WANECAM II Burkina Faso, Gabon, Mali, Niger		
PAMAFRICA Burkina Faso, Gabon, Mozambique, Uganda		
SINDOFO Burkina Faso, Kenya, Mozambique		
DPP Ethiopia		

Caption	Study phase	Population
Project name	Phase I	Adults (18yr and above)
Site(s) in sub-Saharan Africa	Phase II	Adolescents (10yr-17yr)
	Phase III	Children (2yr-9yr)
	Phase IV	Infants (above 1mo-1yr)
	Observational study	Pregnant women and/or newborns (birth to 1mo)



Protecting pregnant women from malaria

The IMPROVE trials should reveal whether a recently developed drug can protect pregnant women from malaria.

The challenge

Some 30 million pregnant women are at risk of malaria in Africa, and 10,000 die from malaria each year. In addition, malaria is responsible for the deaths of 100,000 infants, and 900,000 are born underweight because of malaria infections.

To prevent infections, pregnant women receive a series of preventive treatments with sulfadoxine-pyrimethamine (SP), as well as insecticide-treated bednets. However, resistance to SP is growing, and the hunt is on for safe and effective alternatives. Unfortunately, several possible options have been ruled out because, although they prevent malaria infections, many women experience side effects such as dizziness and vomiting.

The project

The IMPROVE team has been exploring the use of a recently developed antimalarial drug, dihydroartemisinin–piperaquine (DP), to replace SP in areas where resistance to SP is high. Small-scale trials in Kenya and Uganda have shown that DP is better than SP at preventing malaria infections and is well-tolerated, but were not large enough to judge the effect of DP on pregnancy outcomes. Trial data were reported to WHO in 2015, which stated that supportive evidence from a large-scale trial was required before DP could be recommended in pregnancy.

In two new larger-scale trials in ten sites in three countries, involving more than 4500 women, the IMPROVE team is aiming to generate confirmatory evidence of DP's efficacy against malaria infection, as compared with SP, and new data on birth outcomes – such as fetal loss, premature birth and low birthweight. As well as comparing SP and DP, the phase III IMPROVE-1 study has a third arm, which includes the antibiotic azithromycin as well as DP. Azithromycin is used to prevent sexually transmitted and reproductive tract infections, which are common in East Africa and can also affect birth outcomes.

Project at a glance

Project: IMPROVE-1 and IMPROVE-2 trials

Project lead: Professor Feiko ter Kuile, Liverpool School of Tropical Medicine, United Kingdom

Countries involved: Denmark, Finland, Kenya, Malawi, Norway, Tanzania, and the United Kingdom

Target population(s): Pregnant women (with and without HIV) and their newborn infants

Sample size: 4680 (IMPROVE-1); 1335 (IMPROVE-2)

Year funded: 2016

EDCTP funding: €10.6 M

Total project funding: €10.6 M

Furthermore, the team is running a complementary phase III trial (IMPROVE-2) in pregnant women with HIV, who cannot receive SP because of its interactions with co-trimoxazole, an antibiotic used prophylactically to prevent infection. A previous small-scale study suggested that DP is safe and well-tolerated, but this larger study will show whether it also protects against negative birth outcomes and whether azithromycin provides any further benefits to mother or offspring.

Impact

The trials should provide definitive evidence on the suitability of DP as a preventive treatment against malaria in pregnancy. They will also reveal whether azithromycin provides any additional benefits.

Key reference

Desai M et al. Intermittent screening and treatment or intermittent preventive treatment with dihydroartemisinin–piperaquine versus intermittent preventive treatment with sulfadoxine–pyrimethamine for the control of malaria during pregnancy in western Kenya: an open-label, three-group, randomised controlled superiority trial. *Lancet*. 2015;386(10012):2507–19.

Preventing malaria in pregnant women with HIV

The MAMAH study is evaluating a new drug combination for preventing malaria infections in pregnant women with HIV.

The challenge

In Africa, at least a million pregnant women are affected by both HIV and malaria infections. The two infections have mutually reinforcing effects, leading to higher parasite loads and greater viral replication. This is harmful to mothers, but also to the developing fetus, including an increased risk of mother-to-child transmission of HIV.

Because of the risks of malaria in pregnancy, WHO recommends that pregnant women receive preventive treatment with antimalarial drugs, generally sulphadoxine–pyrimethamine (SP). However, this is not recommended for women with HIV, because of the risk of side effects when women are also taking cotrimoxazole, an antibiotic used to prevent HIV-related infections.

The project

A previous EDCTP-funded study found that an alternative to SP, mefloquine, used alongside insecticide-treated bednets and cotrimoxazole, offered good protection against malaria. However, it caused unpleasant symptoms in women, and was also associated with elevated viral replication and an increased risk of mother-to-child transmission of HIV.

The MAMAH study is assessing whether a different antimalarial drug, dihydroartemisinin–piperaquine (DP), may be a more suitable alternative. It has proven safe and effective in pregnant women without HIV infections, but there are limited data on its use in HIV-infected pregnant women.

Working in two African countries, the MAMAH team is running a placebo-controlled trial of DP for malaria prevention in HIV-infected pregnant women who are receiving antiretroviral therapy and cotrimoxazole. As well as impacts on malaria in mothers, the project will explore whether DP affects the pharmacokinetics of antiretroviral drugs and cotrimoxazole, and infants will be followed up to the age of one year to assess any impacts on mother-to-child transmission of HIV.

Project at a glance

Project: MAMAH study

Project lead: Professor Clara Menendez, ISGlobal, Spain

Countries involved: Austria, Gabon, Germany, Mozambique, Spain

Target population(s): Pregnant women with HIV

Year funded: 2016

EDCTP funding: €3 M

Impact

The MAMAH study will provide data on a possible approach to malaria prevention in a highly disadvantaged group – pregnant women with HIV. Effective malaria prevention in this group would benefit the health not only of mothers but also their offspring – improving maternal health, reducing infant mortality, and increasing birthweight, with long-term benefits for child health and development.





A fallback therapy for malaria

The ASAAP study is evaluating a novel triple combination to protect current antimalarial drugs and to provide an alternative if artemisinin resistance spreads to Africa.

The challenge

After several years of progress, malaria control has stalled. An estimated 435,000 deaths occurred in 2017, with Africa accounting for 93% of deaths.

Malaria control is undermined by the development of drug resistance in malaria parasites. Although resistance to the mainstay of malaria treatment, artemisinin-based combination therapies, has not yet been widely seen in Africa, there are concerns that it could be introduced from South-East Asia and threaten the use of highly effective antimalarial therapies.

The project

The ASAAP project is evaluating the safety and efficacy of a novel triple therapy – combining artemether+lumefantrine (AL) and atovaquone–proguanil (AP, also known as Malarone). The AL combination is already widely used and is highly effective, but it is important that it is protected against the

development of resistance. Adding AP, another antimalarial with proven efficacy, will reduce the risk of resistance and have additional benefits. AP targets multiple stages of the malaria parasite life cycle, and may contribute to continuing protection after treatment and prevent the transmission of parasites to others.

The ASAAP project is organising primarily a pilot phase III study (in adults and adolescents) and a main phase III trial (in your children) in four African countries, comparing the AL–AP combination with AL on its own. The main trial will involve more than 1,500 children aged 6–59 months.

As well as cure rates at 42 days and safety, the trial will also look for any effects on re-infections, to assess post-treatment protection, and investigate the novel drug combination's ability to block transmission of malaria parasites from blood samples to mosquitoes.

Project at a glance

Project: ASAAP study

Project lead: Dr Oumou Maïga-Ascofaré, Kwame Nkrumah University of Science and Technology, Ghana

Countries involved: Benin, Burkina Faso, France, Gabon, Ghana, Germany, Mali

Target population(s): Adults (pilot study), Young children (main trial)

Year funded: 2018

EDCTP funding: €7.6 M

Impact

The ASAAP project will contribute to preparedness in Africa for the emergence of artemisinin-resistant malaria parasites. It will determine whether AL–AP is a suitable alternative in such a situation, and whether it provides additional benefits by reducing human-to-mosquito transmission of malaria parasites.

Expanding the options for malaria control in pregnancy

The PYRAPREG study is exploring whether pregnant women can benefit from a newly developed safe and effective antimalarial drug.

The challenge

Malaria in pregnancy can be harmful to both mother and child, causing maternal anaemia and low birth weight. In 2015, it was the third most common cause of death of women of reproductive age in Africa. Malaria in pregnancy is responsible for around 400,000 cases of maternal anaemia and 15% of maternal deaths globally.

Several artemisinin-based combination therapies are recommended for treatment of malaria in the second and third trimesters of pregnancy, but they vary in their efficacy, safety and tolerability. Pyronaridine–artesunate (PA) is a relatively new artemisinin-based combination therapy that could be a suitable alternative but it has yet to be evaluated in pregnancy.

The project

The PYRAPREG study is carrying out a large-scale evaluation of PA use in pregnant women in five African countries. The safety and efficacy of PA will be compared with those of two other commonly used artemisinin-based combination therapies, dihydroartemisinin–piperaquine and artemether–lumefantrine.

The main aim of the trial is to determine if PA is as good as the comparator treatments, with acceptable safety and tolerability. The pharmacokinetics of PA are also being monitored, and any influence of antiretroviral medications examined in a subset of women with HIV infections.

Impact

The PYRAPREG study will determine whether a relatively new drug with some attractive features – for example, it only needs to be taken once a day, does not need to be eaten with fatty food, and has a relatively long half-life – is suitable for use in pregnant women.

Project at a glance

Project: PYRAPREG study

Project lead: Dr Kassoum Kayentao, Université des Sciences, des Techniques et des Technologies de Bamako, Mali

Countries involved: Burkina Faso, Democratic Republic of the Congo, The Gambia, Mozambique, Mali, the Netherlands, Spain, and the United Kingdom

Target population(s): Pregnant women, including HIV-positive women

Year funded: 2018

EDCTP funding: €7.1 M





Advancing a new class of antimalarial drug

The WANECAM II study is accelerating the development of a new class of antimalarial drug that may have significant advantages over existing treatments.

The challenge

Despite much progress, malaria control has stalled in recent years, with deaths still in excess of 400,000 a year in Africa, most of them young children.

In addition, the emergence in South-East Asia of resistance to the mainstay of malaria treatment, artemisinin combination therapy (ACT), is of grave concern and emphasises the need to identify possible alternative treatments.

The project

With EDCTP funding, the WANECAM consortium played a key role in the evaluation of new antimalarial formulations suitable for use in children. With additional funding through the EDCTP2 programme, the WANECAM II is now a pivotal partner in a global collaboration advancing a novel antimalarial treatment that does not include artemisinin-based drugs. The collaboration includes the not-for-profit Medicines for Malaria Venture and the Novartis pharmaceutical company.

WANECAM II is focusing on a new antimalarial drug, KAF156 (ganaplacide), from an entirely novel chemical class. Its mode of action appears to be different to that of artemisinin-based drugs, and it is highly active against several stages of the malaria parasite and against *Plasmodium vivax* as well as *P. falciparum*. It is being teamed up with a new formulation of an existing antimalarial, lumefantrine, that is less affected by food intake and would allow the new combination to be given as a single dose.

The WANECAM II team is carrying out a phase IIb trial with groups of children from 12 years down to six months of age. A phase III trial will then be conducted in adults and infants of six months of age and older.

Project at a glance

Project: WANECAM II study

Project lead: Professor Abdoulaye Djimdé, Université des Sciences, des Techniques et des Technologies de Bamako, Mali

Countries involved: Burkina Faso, France, Gabon, Germany, Mali, the Netherlands, Niger, Sweden, Switzerland, and the United Kingdom

Target population(s): All age groups, including children

Year funded: 2018

EDCTP funding: €10 M

Impact

WANECAM II will provide key evidence on the safety and efficacy of KAF156–lumefantrine in Africans, including children, who are most at risk from malaria. Positive data would support submissions to regulatory authorities for approval of the new combination. KAF156–lumefantrine would be an alternative to artemisinin-based combination therapies, but would also have advantages, including the need for just a single dose and the possibility of blocking parasite transmission to mosquitoes, which would prevent the spread of the infection to others.

In addition, the project is further strengthening research capacity across the WANECAM network, including in Niger, which to date has not had a strong medical research base.

Advancing a portfolio of malaria drugs

The PAMAFRICA project is advancing the development of a suite of drugs to address unmet needs in malaria treatment.

The challenge

Between 2000 and 2015, malaria deaths were more than halved, mainly through use of artemisinin-based combination therapies (ACTs). However, progress has slowed markedly, and may even have gone into reverse. The rise of resistance to ACTs in South-East Asia is also greatly concerning. To achieve ambitious malaria control and elimination goals, new tools are urgently required to close treatment gaps and to provide new impetus.

The project

Since its launch in 1999, the Medicines for Malaria Venture (MMV) and its partners have developed the most extensive portfolio of candidate malaria drugs ever seen. As many drugs do not make it through the development pipeline, a portfolio approach is essential. In addition, a portfolio approach is required so that treatments can be tailored to the needs of specific groups, including vulnerable populations such as young infants.

The PAMAFRICA project will draw on MMV resources – drug candidates and reformulations of licensed medicines – to address significant unmet needs in malaria treatment. One priority is a single-dose cure for malaria. The project is likely to focus on two promising compounds: M5717, which is active against all stages of the parasite life cycle; and SAR121, a potent and long-lasting agent that the malaria parasite is unable to develop resistance to. However, with additional clinical data due to be released shortly, other compounds in the MMV portfolio could be considered. A final decision will be made on the basis of all available clinical data.

PAMAFRICA will also undertake a specific study to develop and test a new formulation of artemether–lumefantrine for children less than 5 kg in weight. Drug metabolism changes significantly in the first two years of life, so current formulations may not be appropriate for newborns and young infants. Previous studies

Project at a glance

Project: PAMAFRICA

Project lead: Dr Timothy Wells, Medicines for Malaria Venture, Switzerland

Countries involved: Burkina Faso, Gabon, Germany, Mozambique, Spain, Switzerland and Uganda

Target population(s): Adults and children

Year funded: 2019

EDCTP funding: €22 M

Total project funding: €41.9 M

have identified a suitable dose combination, which will be tested in a phase II trial.

A further strand of work will advance a new injectable formulation of cipargamin, a highly potent antimalarial being developed as a back-up treatment for severe malaria caused by ACT-resistant parasites. A phase I study is planned to determine a suitable dose of the new formulation for a phase II trial in patients.

MMV has previously partnered with EDCTP-funded consortia such as WANECAM on highly successful projects and will again work with African and international partners, helping to build African research capacity.

Impact

The PAMAFRICA project will continue the successful relationship between EDCTP and MMV, which has already led to the licensing of new antimalarial treatments. It will be a joint funding venture, with MMV providing 50% of funding. The project will generate key data that will feed into licensing applications for treatments focused on some of the most urgent needs in malaria treatment – simple and effective treatments for deadly severe malaria and a treatment for the youngest and most vulnerable patients.





A four-strike vaccine against malaria

With encouraging progress in malaria vaccine development, the Multi-Stage Malaria Vaccine Consortium (MMVC) will test a novel vaccine combination targeting four stages of the malaria parasite life cycle.

The challenge

The malaria parasite has a complex life cycle, spanning mosquitoes and humans. When injected into the bloodstream following the bite of an infected mosquito, it first invades and multiplies within liver cells, before seeking refuge and multiplying again in red blood cells. When these burst, parasites circulating in the bloodstream can be taken up by a feeding mosquito.

Although only a single cell, the parasite is a master of disguise, adopting entirely different forms at different stages of its life cycle. Malaria vaccine developers typically focus on one specific stage of the life cycle. The only licensed malaria vaccine, RTS,S, targets the initial human stage, to prevent liver infection. However, a vaccine targeting the final bloodstream stage could block transmission to mosquitoes.

The project

With exciting progress being made in vaccine development at all stages of the life cycle – pre-liver, liver, red blood cell and bloodstream stages – MMVC has ambitious plans to combine them in a single formulation, maximising the benefits of the individual vaccines.

The four-stage vaccine will include a next-generation version of RTS,S, known as R21; a liver-stage vaccine that has shown positive results in EDCTP-funded trials; a promising vaccine targeting a key protein involved in red blood cell invasion, PfrH5; and a vaccine targeting a key protein in the final bloodstream form, Pfs25.

Results from a series of controlled human infection studies – using new capacity in Africa – and pilot trials will inform the design of an appropriate vaccination strategy. This will be tested in a phase II trial in infants in sites of different levels of malaria transmission. The project will also build capacity to test

Project at a glance

Project: Multi-Stage Malaria Vaccine Consortium

Project lead: Professor Adrian Hill, University of Oxford, United Kingdom

Countries involved: Burkina Faso, France, India, Kenya, the Netherlands, Sierra Leone, Sweden, Tanzania, and the United Kingdom

Target population(s): Adults, children and infants

Sample size: 1493 (estimated for four trials)

Year funded: 2018

EDCTP funding: €15 M

Total project funding: €20 M

Project website: www.jenner.ac.uk/mmvc

the vaccine in adults as a possible way of blocking transmission to mosquitoes in malaria elimination campaigns.

Impact

The project will generate key evidence on the efficacy of the four-stage vaccine, with the aim of achieving the WHO Roadmap's target of 75% efficacy. Such a vaccine could make a major contribution to reducing the incidence of an infection that still kills more than 1000 children every day.

Prevention of malaria transmission

The PfTBV study is accelerating the development of vaccines that interfere with the transmission of malaria via mosquitoes.

The challenge

Blood-sucking mosquitoes are responsible for transmitting malaria parasites from an infected individual to a new host. Parasites are taken up by mosquitoes at a particular stage in their life cycle, the gametocyte, and develop further in the mosquito into a form that can re-infect people. Vaccination against gametocyte antigens could prevent parasites completing their life cycle in the mosquito.

Hence, although transmission-blocking vaccines would not protect an individual from being infected, they could prevent parasites being transmitted to others.

The project

Some progress has been made in the development of transmission-blocking malaria vaccines. However, progress has been slow, in part because most studies investigate single vaccine options in a step-wise fashion. The PfTBV study aims to accelerate development by comparing multiple options, and multiple adjuvants, and focusing on those showing most promise.

It will focus on three gametocyte antigens: Pfs230D1M, a well-advanced candidate; R0.6C (a fusion of two antigens, GLURP and Pfs48/45), which has yet to be tested in humans; and Pfs230-6C, a novel fusion antigen combining Pfs230 and Pfs48/45. Initial studies will focus on how well these candidates elicit transmission-blocking antibodies, when used with a range of different adjuvants. The safety and efficacy of Pfs230D1M will also be assessed in children over the age of 5 years.

The project will also make use of 'controlled human malaria infection' facilities established in Africa, to determine whether vaccination reduces the ability of mosquitoes to transmit parasites. Following these preparatory studies, the most suitable candidate will be evaluated in a phase II field trial in adults.

Project at a glance

Project: PfTBV study

Project lead: Dr Issaka Sagara, Université des Sciences, des Techniques et des Technologies de Bamako, Mali

Countries involved: Burkina Faso, Denmark, Guinea, Liberia, Mali, the Netherlands, and the United States

Target population(s): All age groups

Year funded: 2019

EDCTP funding: €18 M

Total project funding: €32.3 M

The PfTBV project also aims to identify features of immune responses associated with vaccine efficacy. In addition, it will build malaria vaccine research capacity in Africa and establish a biobank of African samples for future study.

Impact

Transmission-blocking vaccines have the potential to break the cycle of malaria transmission. They could be used in combination with existing malaria vaccines, such as RTS,S/AS01 or its successors, which would provide protection against infection. In particular, by reducing the 'reservoir' of infective parasites, transmission-blocking vaccines have been identified as critical to malaria elimination and eradication.





Accelerating malaria vaccine development

The MIMVaC-Africa study is bringing together a global consortium to rapidly identify the most promising malaria vaccines for large-scale trials.

The challenge

The RTS,S/AS01 vaccine shows significant protective efficacy against malaria and is undergoing pilot implementation studies in three African countries. However, it does not provide complete protection and the search continues for vaccines with a higher degree of efficacy.

Globally, recent years have seen significant progress made in the development of candidate malaria vaccines. However a major bottleneck is the clinical evaluation of these new vaccines. In particular, there is a need to efficiently identify the most promising vaccines to increase the chances of success in long and expensive phase III trials.

The project

Controlled human infection model (CHIM) studies have emerged as a hugely valuable approach for rapidly assessing the efficacy of developmental vaccines. In such models, volunteers are deliberately infected with pathogens, under highly controlled situations, and are treated before serious disease develops. Crucially, they enable the efficacy of vaccines to be rapidly tested in relatively small numbers of people who are closely monitored. By testing multiple candidates, researchers can quickly identify the most promising for testing in large-scale field trials.

CHIM platforms for malaria have been introduced into several African countries, so studies can be carried out on populations actually affected by malaria. The MIMVaC-Africa consortium is taking advantage of this new capacity to evaluate multiple new promising malaria vaccine candidates. It has drawn together leading academic researchers involved in vaccine development from Europe and Japan, as well as multiple African centres with extensive experience in vaccine clinical trials and use of the malaria CHIM platform.

Project at a glance

Project: MIMVaC-Africa study

Project lead: Dr Sodiomon Bienvenu Sirima, Group de Recherche Action en Santé, Burkina Faso

Countries involved: Burkina Faso, Gabon, Germany, Japan, Luxembourg, Mozambique, The Netherlands, Tanzania, UK

Target population(s): Adults, children and infants

Year funded: 2020

EDCTP funding: €11.9 M

Total project funding: €21.5 M

The consortium plans to use CHIM platforms to evaluate five vaccine candidates. Three are pre-erythrocytic vaccines – designed to prevent infection progressing to clinically serious disease – and two are blood-stage vaccines; they target a later stage in the malaria parasite life-cycle and, as well as protecting individuals, they interrupt transmission to mosquitoes.

Based on the data collected in the CHIM studies, the consortium will then test one or more candidate vaccines in phase II trials to assess their safety, immunogenicity and protective efficacy in infants and young children – those most at risk of serious infections – in endemic countries.

Impact

The MIMVaC-Africa project will accelerate clinical evaluation of five of the most promising experimental malaria vaccines, identifying which are sufficiently effective to warrant progression to a phase III trial. The consortium will maintain contact with all key regional stakeholders to advise them on progress. The project will also build capacity, by expanding the range of sites able to carry out CHIM studies, strengthening clinical trial infrastructures and transferring the latest laboratory assays to participating African centres.

Towards elimination-grade malaria detection

The DIAGMAL project is evaluating a highly sensitive rapid diagnostic for malaria, an essential component of strategies to eliminate malaria.



The challenge

Malaria still kills more than 400,000 people a year, with 92% of deaths occurring in sub-Saharan Africa. However, with effective treatment and control measures already available, there is great potential to reduce these numbers and even to consider the possibility of elimination.

Rapid diagnostic tests have become a mainstay of malaria control. However, current tests, mostly based on detection of two key parasite antigens (known as HRP2 and LDH), have some drawbacks. For example, persistence of HRP2 after infection leads to false positives, while loss of the corresponding *pfhrp2* gene in some areas can generate false negatives. Molecular testing would be more accurate but typically requires laboratory facilities.

The project

The DIAGMAL project is evaluating a new point-of-care molecular test for malaria. Known as Mini-db-PCR-NALFIA, the diagnostic platform is battery operated, controlled by a mobile phone, has a simple readout, requires no cold chain, provides results within an hour, and can be used following limited training. Compared with other molecular tests, it has the advantage of not requiring a DNA extraction step, making it cheaper and easier to use.

The performance of the new diagnostic is being evaluated in five settings with different malaria transmission characteristics. These include areas with high malaria incidence, seasonal malaria transmission, high levels of *pfhrp2* deletions, and low malaria transmission where elimination might be feasible. The diagnostic is also being tested at a range of sites in Kenya with different patterns of malaria transmission.

Mini-db-PCR-NALFIA is around 100 times more sensitive than currently used rapid diagnostic tests. Its performance will be compared with gold standard polymerase chain reaction (PCR) testing at central facilities. The project will also

Project at a glance

Project: DIAGMAL

Project lead: Dr Henk Schallig, Academisch Medisch Centrum bij de Universiteit van Amsterdam, The Netherlands

Countries involved: Burkina Faso, Ethiopia, Kenya, Namibia, Sudan, UK

Target population(s): All

Year funded: 2019

EDCTP funding: €3 M

examine the costs of introduction, as well as practical factors affecting its implementation within national control programmes in the different settings. The project team also includes members with expertise in product registration, to facilitate the development of a dossier for regulatory approvals and WHO prequalification.

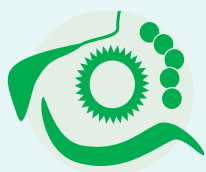
Impact

The DIAGMAL project will provide data on a highly sensitive tool for malaria detection. It is likely to be of most value in situations where high sensitivity is important, for example when the number of cases is low, as in areas targeted for elimination. It could also be used in locations where other tools have been compromised, for example because of *pfhrp2* deletions. With 18 countries already having plans for malaria elimination, it could therefore be a critical tool in future malaria control efforts.



Neglected infectious diseases

2014-2020



17 grants
€62.04 M



Drugs
12 grants
€43.25 M



Vaccines
1 grant
€8 M



Diagnostics
4 grants
€10.79 M

EDCTP portfolio: Neglected infectious diseases

Drugs		Vaccines		Diagnostics	
AfriKADIA Ethiopia, Kenya, Sudan, Uganda		MiniMox Ghana		PREV-PKDL Ethiopia, Kenya, Sudan, Uganda	
PZQ4PSAC Cote d'Ivoire, Kenya		ACOZI-KIDS DR Congo, Ghana		AfriKADIA Ethiopia, Kenya, Sudan, Uganda	
MoxiMultiDoseMod DR Congo, Ghana		ADOPT Cote d'Ivoire, Kenya		DTECT-HAT Cote d'Ivoire, Burkina Faso, DR Congo, Guinea	
STOP Ethiopia, Kenya, Mozambique				FREEBILY Madagascar, Gabon	
HAT-r-ACC Malawi, Uganda				SOLID Tanzania, Zambia	
PEP4LEP Ethiopia, Mozambique, Tanzania				LAMP4Yaws Cameroon, Cote d'Ivoire, Ghana	
FibroScHot Uganda					
PEOPLE Comoros, Madagascar					

Caption	Study phase	Population
Project name	Phase I	Adults (18yr and above)
Site(s) in sub-Saharan Africa	Phase II	Adolescents (10yr-17yr)
	Phase III	Children (2yr-9yr)
	Phase IV	Infants (above 1mo-1yr)
	Observational study	Pregnant women and/or newborns (birth to 1mo)



Improving diagnosis and treatment of visceral leishmaniasis

The AfriKADIA project is developing treatments for visceral leishmaniasis (kala azar) and testing diagnostic tools better suited to challenging African settings.

The challenge

Leishmania infections of body tissues (visceral leishmaniasis or kala azar) can be fatal if untreated. East Africa is particularly badly affected by visceral leishmaniasis, and up to 70% of infections occur in children.

Treatment of visceral leishmaniasis has typically relied on drugs that have unpleasant side effects and are difficult to administer, requiring daily injections for 17 days. Diagnosis is also difficult, and some methods are associated with a significant risk of harm.

The project

The AfriKADIA project aims to improve management of visceral leishmaniasis, by developing safer and easier to administer treatments and by evaluating new tools for rapid diagnosis of infections. It has a particular focus on approaches that are suitable for the remote rural populations characteristic of affected East African countries.

The project is developing a combination therapy, based on oral miltefosine and paromomycin, that is more suitable for use in remote settings with limited access to healthcare facilities. Following studies of the metabolism of this combination in patients, it will be tested in a large phase III trial comparing its safety and efficacy with the standard 17-day treatment.

The project will also evaluate possible tests to determine whether patients have been cured or are at risk of relapse, as well as rapid point-of-care tests for detecting new infections.

Impact

The AfriKADIA project will generate key evidence on the efficacy of the miltefosine and paromomycin combination, to inform decision-making on its introduction in East Africa. In addition, it will identify tools that

Project at a glance

Project: AfriKADIA study

Project lead: Dr Jorge Alvar, Drugs for Neglected Diseases initiative, Switzerland

Countries involved: Ethiopia, Kenya, The Netherlands, Spain, Sudan, Switzerland, Uganda

Target population(s): All age groups

Year funded: 2018

EDCTP funding: €5.6 M

Total project funding: €11.6 M

Project website: www.afrikadia.org

could be adopted to improve control of visceral leishmaniasis and ultimately drive forward elimination of the disease in the region.

Partnering up in the battle against parasitic infections

EDCTP has joined forces with a Japanese funding agency to progress a young children's version of a drug treatment for schistosomiasis, a common and debilitating parasitic disease.

The challenge

Schistosomiasis, a neglected infectious disease caused by parasitic flatworms, affects around 250,000 people a year, most of them in Africa. It causes a variety of symptoms, including abdominal pain and diarrhoea, and may lead to more serious organ damage and even death. In children, infections interfere with growth and development, and therefore have lifelong impact.

Schistosomiasis can be treated with a drug known as praziquantel. However, currently used praziquantel pills are difficult for young children to swallow, cannot be crushed, and have an unpleasant bitter taste.

The project

The Pediatric Praziquantel Consortium, funded primarily by the Japan-based Global Health Innovative Technology Fund (GHIT), has developed a new praziquantel pill that dissolves in the mouth, making it easier to give to young children. In partnership with EDCTP, the Consortium will undertake one clinical trial to test the safety and efficacy of this new formulation in young children in Cote d'Ivoire and Kenya. The trial will be carried out to international regulatory standards, so that their results can feed directly into submissions to regulatory agencies and the new pills can rapidly be made available to young children.

Impact

The new formulation will enable more young children to gain the benefits of praziquantel – potentially both for treatment and in mass drug administration campaigns to prevent infections. More generally, the project is the first outcome of an ongoing partnership between EDCTP and GHIT, organisations with common interests in HIV/AIDS, malaria, TB and poverty-related infectious diseases.

Project at a glance

Project: Praziquantel for Pre-School-Age Children (PZQ4PSAC) trial

Project lead: Dr Remco de Vroeh, Stichting Lygature, Netherlands

Countries involved: Cote d'Ivoire, Germany, Kenya, Netherlands, Switzerland, and the United Kingdom

Target population(s): Children aged 3 months to 6 years

Sample size: 311

Year funded: 2018

EDCTP funding: €2.0 M

Total project funding: €12.1 M

Project website: www.pediatricpraziquantelconsortium.org





Accelerating elimination of river blindness

The MoxiMultiDoseMod study is evaluating the suitability of a new river blindness drug for use in mass drug administration campaigns and disease elimination.

The challenge

The tissue-dwelling parasitic worm *Onchocerca volvulus* produces millions of tiny larvae (microfilariae), which live in the skin but can also invade the eye. Inflammatory reactions cause skin conditions and, in the eye, loss of sight – ‘river blindness’. Around 200 million people are at risk of infection, nearly all of them in 31 African countries.

Use of ivermectin in mass drug administration campaigns has had a major impact on disease burden. However, better treatments are required to support full elimination.

The project

In 2018, the US Food and Drug Administration (FDA) approved moxidectin – the first new treatment for river blindness in 20 years. In trials in Africa, moxidectin was much better than ivermectin at clearing microfilariae from the skin and had longer-lasting effects, owing to its significantly longer half-life in the body.

FDA approval of moxidectin was for single-dose use in people 12 years old and older. However, for use in mass drug administration campaigns, moxidectin would have to be used repeatedly and in children under the age of 12 years. The MoxiMultidoseMod study is comparing the safety and efficacy of moxidectin and ivermectin given annually or every six months over three years. Additionally, the study is gathering more safety data on the use of a single dose of moxidectin.

It will also undertake safety and pharmacokinetic studies to assess moxidectin usage in 4–11-year-olds. And it will carry out modelling analyses to compare the time to disease elimination and cost-effectiveness of campaigns based on use of either moxidectin or ivermectin.

Project at a glance

Project: MoxiMultiDoseMod study

Project lead: Dr Michel Vaillant, Luxembourg Institute of Health

Countries involved: Belgium, Democratic Republic of the Congo, Ghana, Luxembourg, the Netherlands, and the United Kingdom

Target population(s): Adults; children

Year funded: 2019

EDCTP funding: €4.8 M

Total project funding: €6.4 M

Impact

Moxidectin could accelerate *Onchocerca* elimination in countries that have lagged behind in parasite control and in fragile settings where regular mass drug administration campaigns are difficult to organise. The project will provide policymakers with key evidence on the comparative advantage of moxidectin, which could be introduced using existing mass drug administration infrastructures.

Better tools for control of parasitic worm infections

The STOP study is developing a convenient pill to improve control of parasitic worm infections in Africa.

The challenge

One in four of the world's population have parasitic worm infections, with the most deprived communities particularly badly affected. Worm infections affect children's physical and mental development, and can have long-lasting impact on their success in life.

Control of parasitic worms is based on mass drug administration campaigns with albendazole and mebendazole, targeting pre-school and school-aged children. However, these drugs do not work against threadworm (*Strongyloides stercoralis*) and are losing their ability to kill whipworm (*Trichuris trichiura*). In addition, use of drugs individually increases the risk that parasites will develop resistance.

The project

The STOP study is exploring whether adding ivermectin will improve the effectiveness of mass drug administration campaigns. Ivermectin is effective against *S. stercoralis* and its activity against *T. trichiura* is enhanced when it is used in combination with albendazole. A combination approach would also reduce the risk of resistance development.

The STOP team has extensive experience of drug development and formulation for parasitic diseases. It will carry out a large-scale phase III trial comparing the parasite-clearance performance of a single tablet combining albendazole and ivermectin, given either as a single dose or in a three-dose regime, with the usual treatment with albendazole.

Project at a glance

Project: STOP study

Project lead: Dr Jose Muñoz Gutierrez, Instituto de Salud Global (ISGlobal), Spain

Countries involved: Ethiopia, Kenya, Mozambique, the Netherlands, Spain, and the United Kingdom

Target population(s): Children

Year funded: 2018

EDCTP funding: €4.9 M

Project website: <http://stoptheworm.org>

Clinical trial registration: <https://clinicaltrials.gov/ct2/show/NCT03845140>

Impact

The STOP study will generate key evidence to support a licensing decision on the albendazole–ivermectin co-formulation. The combination could improve the effectiveness of mass drug administration campaigns against common but neglected parasitic worm infections, and protect a vital drug against the development of resistance.





Treating East African sleeping sickness

The HAT-R-ACC study is assessing whether a new treatment is effective against a type of sleeping sickness mainly found in East Africa.

The challenge

Sleeping sickness (human African trypanosomiasis, HAT) is a parasitic disease that can be fatal without effective treatment. It is usually caused by a single-celled parasite, *Trypanosoma brucei gambiense*, but a relative, *T. b. rhodesiense*, can cause a similar but more acute disease (r-HAT). r-HAT is found mainly in East Africa, with Malawi and Uganda accounting for 88% of global infections.

Treatment of r-HAT has traditionally relied on either a toxic arsenic-based drug, melarsoprol, or a less toxic but difficult-to-administer drug, suramin, depending on how far disease has progressed.

The project

Recently, a highly effective, safe oral treatment – fexinidazole – has been developed for HAT caused by *T.b. gambiense*. The HAT-R-ACC study will determine whether fexinidazole could also be adopted for treatment and control of r-HAT.

The HAT-R-ACC project will carry out a clinical trial to determine whether fexinidazole is a suitable alternative to replace both melarsoprol and suramin at different stages of disease. The project will also work with local communities to raise awareness of the condition and treatment, and build local capacity to undertake scientific studies.

Impact

The study will fill a major gap in knowledge on a rare but deadly disease having a significant regional impact, addressing an urgent WHO request for information on methods of r-HAT control in East Africa. Fexinidazole could also provide a key tool in the ultimate elimination of r-HAT in Africa.

Project at a glance

Project: HAT-R-ACC study

Project lead: Dr Olaf Valverde Mordt, Drugs for Neglected Diseases initiative, Switzerland

Countries involved: France, Malawi, Portugal, Switzerland, Uganda

Target population(s): All age groups

Year funded: 2018

EDCTP funding: €3.8 M

Project website: www.dndi.org/diseases-projects/portfolio/fexinidazole-tb-rhodesiense/

Clinical trial registration: <https://clinicaltrials.gov/ct2/show/NCT03974178?term=fexinidazole&rank=2>

Limiting the spread of leprosy

The PEP4LEP study is comparing two possible approaches for screening and pre-emptively treating those at risk of leprosy infections.

The challenge

Leprosy is a chronic infection affecting the skin and nerves, and loss of sensation can lead to tissue damage in areas such as the hands and feet. Affecting much of Africa, it is associated with considerable social stigmatisation.

Single-dose rifampicin is used to prevent infection in those exposed to people with leprosy infections. A major challenge is to identify the best way to deliver preventive treatments.

The project

The PEP4LEP project is a highly practical implementation study comparing two possible approaches for screening and identifying people at risk of developing leprosy.

It will carry out a randomised implementation trial comparing two possible strategies. One will be community based: 'skin camps' will be set up to screen around 100 people likely to have been in contact with a leprosy patient. The second approach will be focused on health facilities, with contacts invited to attend screening sessions. Both approaches will include wider dermatological assessments to identify common skin conditions and neglected infectious diseases affecting the skin.

The study will determine which is the better model for detecting new infections and reducing delays in detection. It will also explore community acceptability and cost-effectiveness.

Impact

The PEP4LEP project will provide policymakers with highly relevant information on the effectiveness and cost-effectiveness of two methods for improved leprosy control, ultimately ensuring that more people benefit from an intervention of proven efficacy.

Project at a glance

Project: PEP4LEP study

Project lead: Ms Liesbeth Mieras, Nederlandse Stichting voor Leprabestrijding, the Netherlands

Countries involved: Ethiopia, Germany, Mozambique, the Netherlands, Tanzania

Target population(s): All age groups

Year funded: 2018

EDCTP funding: €3.2 M

Project website: www.leprosyrelief.org/pep4lep





Intensified prevention of schistosomiasis

The FibroScHot study is assessing whether a more intensive preventive drug treatment programme can reduce the incidence of liver damage caused by parasitic flatworm infections.

The challenge

Infections with schistosomes, parasitic flatworms, affect hundreds of millions of people globally – schistosomiasis is the second most socioeconomically impactful parasitic disease after malaria. Africa accounts for 90% of cases, with children and young adults bearing the brunt of disease.

Mass drug administration programmes with praziquantel have been the cornerstone of schistosome control efforts. However, in badly affected countries such as Uganda, despite good coverage, many children are still being infected and developing debilitating symptoms. In particular, inflammatory responses to schistosome parasites can cause the build up of fibrous tissue (fibrosis) in blood vessels in the liver, which can lead to dangerously high blood pressure.

The project

The FibroScHot study is evaluating whether increasing the frequency of mass drug administration reduces the prevalence of liver fibrosis in hotspots of persistent schistosomiasis.

In areas where schistosomiasis is less common, mass drug administration campaigns target school children. The FibroScHot study will carry out a controlled trial in areas of high transmission, comparing usual community campaigns with an intensified campaign that includes treatment in schools, to see if this reduces the prevalence of liver fibrosis.

The project will also explore community attitudes to mass drug administration campaigns, immune responses associated with liver fibrosis, and genetic features of parasites associated with fibrosis and poor responses to drug treatment.

Project at a glance

Project: FibroScHot study

Project lead: Dr Shona Wilson, University of Cambridge, United Kingdom

Countries involved: Denmark, Uganda, and the United Kingdom

Target population(s): Children

Year funded: 2018

EDCTP funding: €3 M

Project website: www.fibroschot.eu

Impact

The study will determine whether a readily implementable intervention, building on existing approaches to schistosomiasis control, protects more children against a common, debilitating and potentially deadly neglected infectious disease. The approach would be practical to adopt in Uganda and other countries in which childhood schistosomiasis persists.

It will also establish an integrated trial platform spanning Makerere University and the Ministry of Health in Uganda, increasing capacity for clinical trials on neglected infectious disease, and build research capacity in a range of areas, including parasite genomics, immunology and anthropology.

Protecting against leprosy infection

The PEOPLE study is exploring a new way to prevent the spread of leprosy, an ancient but neglected tropical disease.

The challenge

Leprosy, caused by infection with *Mycobacterium leprae*, is a disfiguring and disabling disease associated with considerable social stigma. Although it can be treated, efforts to eliminate the disease have stalled and new approaches are needed.

One promising option is post-exposure prophylaxis. In this approach, the contacts of people diagnosed with leprosy are pre-emptively treated with anti-leprosy drugs to protect them against infection.

The project

The PEOPLE trial is evaluating a range of approaches to post-exposure prophylaxis in Madagascar and the Comoros, two island states in which leprosy is endemic and current control programmes have not succeeded in reducing the numbers of infections.

The trial will compare the impact of three models of post-exposure prophylaxis using rifampicin, a highly effective leprosy drug. Rifampicin will be provided either to household contacts of a person newly diagnosed with leprosy, to all contacts within 100 metres, and to household contacts and nearby contacts with immunologic evidence of *M. leprae* infection.

The study will start with a consultative phase to assess the best way to implement the study. It will also carry out a molecular genotyping study of *M. leprae* infections and analyse social networks, to shed light on leprosy transmission patterns and factors affecting them.

Project at a glance

Project: PEOPLE study

Project lead: Professor Bouke de Jong, Institute of Tropical Medicine, Belgium

Countries involved: Belgium, Comoros, France, Madagascar, the Netherlands

Target population(s): All age groups

Year funded: 2018

EDCTP funding: €3 M

Project website: www.people-project.be

Impact

The study will reveal whether post-exposure prophylaxis is an effective approach for controlling the spread of leprosy. If it is, policymakers in Madagascar, the Comoros and other African countries in which leprosy is endemic would have a new tool for reinvigorating national leprosy control programmes.





Preventing a life-changing skin disease

A new vaccine, being evaluated in the PREV_PKDL study, could prevent a disfiguring parasitic skin condition that blights the lives of hundreds of thousands of people.

The challenge

Some 350 million worldwide, mostly society's poorest, are at risk of the single-celled parasite *Leishmania*. In the most severe cases, *Leishmania* migrates deep within the body, causing a potentially fatal condition known as visceral leishmaniasis or kala azar. Effective drugs are now available to treat kala azar, but patients may respond by developing a disfiguring chronic skin condition, post-kala azar dermal leishmaniasis (PKDL).

PKDL can have a dramatic effect on quality of life, particularly of women and children. In addition, it may provide a reservoir of *Leishmania* that can be transmitted to others, thwarting attempts at eradication.

The studies

The PREV_PKDL study will determine whether a newly developed vaccine, which stimulates immune responses known to be lacking in PKDL patients, is able to clear PKDL infections. The team will carry out a trial in Sudan on people who have been cured of visceral leishmaniasis by drug treatment. They will test the safety and efficacy of a single dose vaccination in preventing PKDL.

In addition, the team will work with an East African network, the Leishmaniasis East African Platform, to characterise the immune response to *Leishmania* and in response to drug treatments. Such studies should reveal why some patients are at risk at developing PKDL, and whether any immune responses can be used as markers to detect those at risk so they can be vaccinated.

Impact

The PREV_PKDL trial will provide data on the safety and efficacy of the new vaccine, and whether a large phase III trial would be justified – a key step in its clinical evaluation. The study will also help to develop the capacity of East African countries in immunology research, enhancing their ability to carry out research on poverty-related neglected infectious diseases.

Project at a glance

Project: PREV_PKDL study

Project lead: Dr Sophie Houard, European Vaccine Initiative, Germany

Countries involved: Germany, Ethiopia, Kenya, Sudan, Uganda, and the United Kingdom

Target population(s): Adults, children

Sample size: 300

Year funded: 2018

EDCTP funding: €8 M

Project website: www.prevpkdl.eu

Key reference

Osman M et al. A third generation vaccine for human visceral leishmaniasis and post kala azar dermal leishmaniasis: First-in-human trial of ChAd63-KH. *PLoS Negl Trop Dis*. 2017;11(5):e0005527.

Better detection of sleeping sickness

The DiTECT-HAT study is evaluating a range of tools that will make it easier to detect, treat and ultimately eradicate sleeping sickness.

The challenge

The numbers of cases of sleeping sickness (human African trypanosomiasis, HAT) have fallen markedly in the past decade, raising hopes that the disease can be eliminated entirely. Efficient methods of detecting the cause of sleeping sickness, the parasite *Trypanosoma brucei gambiense*, will be pivotal to eradication, enabling monitoring of at-risk populations for infections, and would also provide valuable tools for evaluating new treatments in clinical trials.

The project

The DiTECT-HAT study will evaluate three different approaches for detecting trypanosome infections. The first is based on new rapid diagnostic tests, which could be used to screen for infections in people visiting clinics, who could then immediately be started on treatment. This approach is being evaluated in three countries.

The second approach is designed for large-scale monitoring of populations at risk to assess the effectiveness of elimination campaigns. Blood samples will be collected on filter paper by health workers travelling door to door, and then sent to central laboratories for analysis. This method is being tested in three countries where sleeping sickness is now rare.

In the third strand of the project, the DiTECT-HAT team will see whether sophisticated molecular tests can provide a rapid indication that drug treatments are killing parasites, which could help to speed up the development of new drugs. This work will take advantage of an ongoing clinical trial in the Democratic Republic of the Congo.

Project at a glance

Project: DiTECT-HAT study

Project lead: Dr Veerle Lejon, Institute of Research for Development, France

Countries involved: Belgium, Burkina Faso, the Democratic Republic of the Congo, Cote d'Ivoire, Guinea, and the United Kingdom

Target population(s): All age groups

Year funded: 2016

EDCTP funding: €3 M

Project website: www.ditect-hat.eu

Impact

The different scenarios require slightly different methods for detecting trypanosome infections. By evaluating different tools and pathways of analysis, the DiTECT-HAT could identify how the range of diagnostic tools could be deployed most effectively to treat infection in routine care, to support eradication campaigns, and to facilitate the development of new drugs.





Better detection of tapeworm infection and brain cysts

The SOLID study is field testing a new point-of-care diagnostic that can detect both adult tapeworm infections and larval cysts in the brain.

The challenge

The tapeworm *Taenia solium* is the leading food-borne cause of death and disability, responsible for the loss of 2.8 million years of healthy life every year. One of the most severe consequences of *Taenia* infection is the migration of larvae to body tissues including the brain, where they form cysts known as neurocysticerci. In endemic areas, these cysts are responsible for 30% of cases of epilepsy.

Although accurate diagnostics have been developed for cysticercosis, they are expensive, complex and require specialist skills.

The project

The US Centers for Disease Control and Prevention (CDC) has developed a more practical dipstick diagnostic able to detect antibodies to both adult tapeworms and cysticerci. It holds great promise as a tool for simultaneously detecting tapeworm infections and cysticercosis using finger-prick blood samples.

However, the CDC test has not been evaluated in field settings. The SOLID study is comparing its performance in primary care and community settings in Tanzania and Zambia, comparing results with gold standard tests and radiographic scanning to detect brain cysts.

Impact

The SOLID study will provide key evidence on the field use of the CDC diagnostic. A point-of-care diagnostic for *Taenia* infections and neurocysticercosis would be a major advance, enabling early identification and treatment of neurocysticercosis cases, as well as treatment of tapeworm infections to reduce the risk of transmission. It would also enable more information to be gathered on the distribution, disease burden and dynamics of transmission of *Taenia*, supporting control efforts and advocacy.

Project at a glance

Project: SOLID study

Project lead: Dr Pierre Dorny, Institute of Tropical Medicine, Belgium

Countries involved: Belgium, Denmark, Germany, Tanzania, Zambia

Target population(s): All age groups

Sample size: 3800

Year funded: 2016

EDCTP funding: €1.9 M

Total project funding: €2.9 M

Project website: www.ugent.be/di/vph/en/research/fpz/solid

Clinical trial registration: <https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=2788>

Rapid detection of schistosome infections

The FREEBILY study is accelerating the development of schistosome diagnostics for pregnant women and young children.

The challenge

Among parasites, schistosomes (flatworms) are second only to malaria in terms of their health and socioeconomic impact. Around 700 million people live in countries where schistosomiasis occurs, and 90% of those requiring treatment live in Africa.

Control of schistosomiasis relies mainly on mass drug administration with praziquantel. As the condition becomes less common, there is an increasing need for accurate diagnostics to support more targeted strategies. In particular, diagnostics could ensure that vulnerable groups, such as pregnant women and young children, are not unnecessarily exposed to praziquantel.

The project

Diagnostic tests have been developed to detect schistosome infections. The point-of-care POC-CCA test is good for detecting intestinal schistosomiasis but has lower sensitivity for urinary schistosomiasis. By contrast, the UCP-LF test is highly sensitive and specific but requires laboratory facilities.

The FREEBILY project is evaluating the use of these tests to detect schistosome infections in women and young children in different contexts. One application being assessed is use of the POC-CCA test in routine mother and child clinics, to support 'test and treat' strategies.

The project is also evaluating use of the UCP-LF test to detect *S. haematobium* and provide an accurate measure of praziquantel efficacy in a trial of praziquantel use in pregnant women in Gabon.

Impact

FREEBILY will provide evidence on the effectiveness and cost-effectiveness of test-and-treat strategies for schistosomiasis in pregnant women and young children, as well as additional data on the UCP-LF test. Although the studies

Project at a glance

Project: FREEBILY study

Project lead: Dr Govert van Dam, Leiden University Medical Centre, the Netherlands

Countries involved: Gabon, Germany, Madagascar, the Netherlands, Spain

Target population(s): Pregnant women, young children

Year funded: 2018

EDCTP funding: €3 M

Project website: <https://freebily.eu>

are being conducted in areas of high and low schistosome endemicity in Madagascar and Gabon, the results will be generalisable to other countries affected by schistosomiasis.





Sensitive detection of yaws

The LAMP4YAWS project is evaluating a highly sensitive diagnostic test for yaws, which could accelerate eradication of this highly debilitating neglected tropical disease.

The challenge

Yaws is a neglected tropical disease mostly affecting children. Caused by the bacterium *Treponema pallidum* pertenue, it is characterised by disfiguring skin lesions that can progress to major destruction of muscle and bone tissue.

Control of yaws has been greatly aided by the development of a highly effective treatment, single-dose azithromycin. There are hopes that yaws could be eradicated, but this would require sensitive tests to detect infections. Unfortunately, existing antibody-based tests cannot distinguish current from past infections, or discriminate between infections with *T. pallidum* pertenue and *Haemophilus ducreyi*, which causes similar symptoms.

The project

The LAMP4YAWS project is evaluating a new yaws diagnostic with significant advantages over existing tools. It can be used to identify (and discriminate between) both *T. pallidum* pertenue and *H. ducreyi* and is also able to detect mutations responsible for resistance to azithromycin.

The diagnostic detects the pathogens' genetic material. However, unlike standard molecular testing using the polymerase chain reaction (PCR), it uses a technology known as 'loop-mediated isothermal amplification' (LAMP), which does not require repeated cycles of heating and cooling. This means it is more amenable to near-point-of-care applications.

Laboratory studies have shown that the LAMP-based diagnostic has good sensitivity (85%) and specificity (96%). The LAMP4YAWS project will compare its performance at district hospitals (where suspected yaws cases are normally investigated) with processing of samples by PCR at national reference laboratories in three countries with the highest burden of yaws cases – Cote d'Ivoire, Ghana and Cameroon, which

Project at a glance

Project: LAMP4YAWS

Project lead: Dr Michael Marks, London School of Hygiene and Tropical Medicine, UK

Countries involved: Cameroon, Cote d'Ivoire, Germany, Ghana, Spain, UK

Target population(s): All

Year funded: 2020

EDCTP funding: €2.9 M

collectively see 15,000 cases a year.

Impact

The LAMP4YAWS project will provide key data on a diagnostic tool that could support more effective control of yaws and accelerate its eventual eradication. It will provide data on its use in programmatic settings in three of the countries in the region most badly affected by the disease. By engaging closely with local policymakers, researchers and national control programmes, the project has ensured that its results will generate the evidence required to support national decision-making on use of the new approach to testing.





Emerging diseases

2014-2020



34 grants

€81.31 M



Drugs
2 grants

€0.69 M



Vaccines
7 grants

€49.21 M



Diagnostics
15 grants

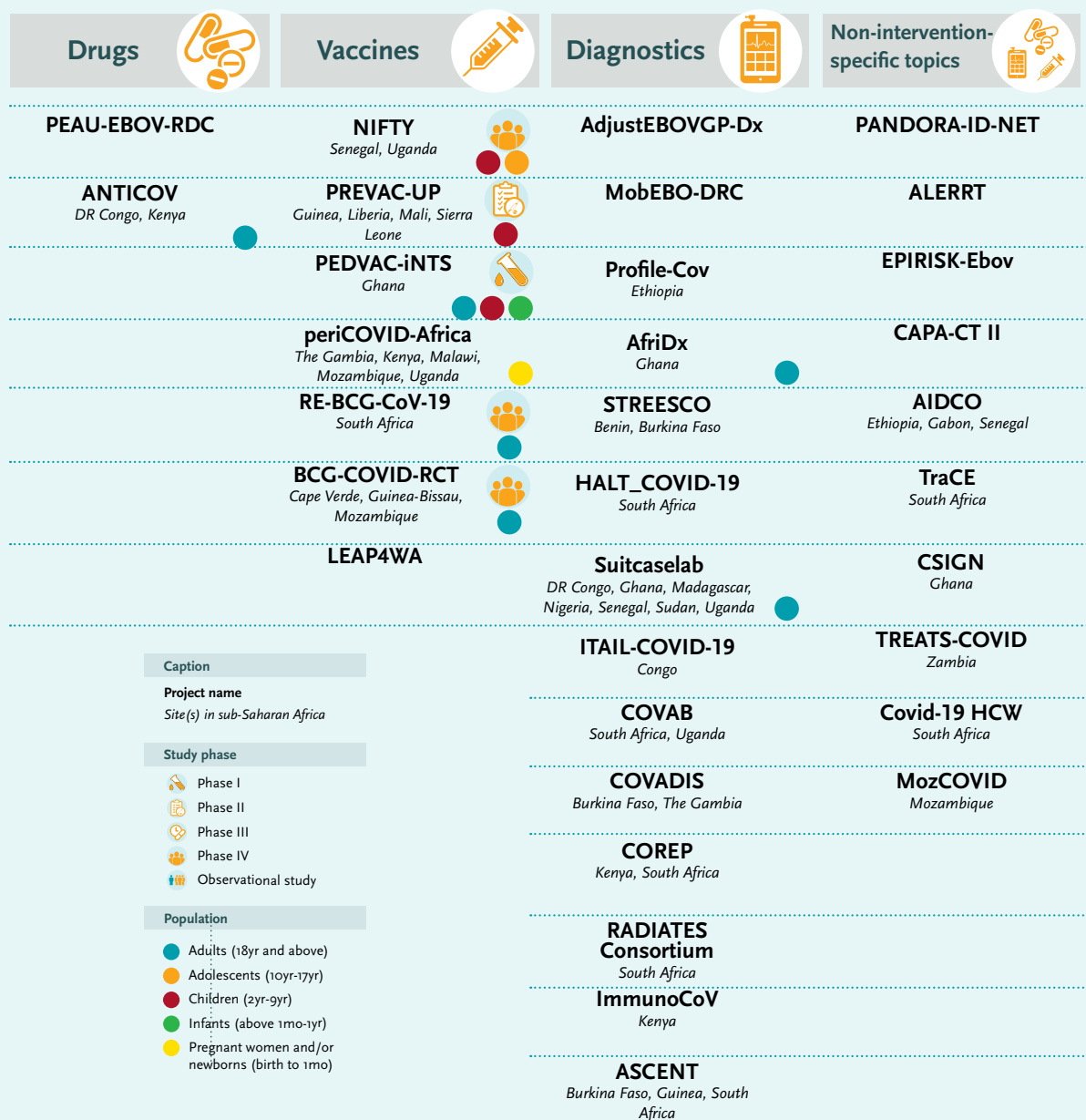
€7.42 M



Non-intervention-
specific topics,
10 grants

€23.99 M

EDCTP portfolio: Emerging diseases





Improving care of Ebola patients

The PEAU-EBOV-RDC study is building the capacity of the Democratic Republic of the Congo to evaluate new diagnostics and treatments for Ebola, to reduce very high fatality rates.

The challenge

Fatality rates in Ebola outbreaks in the Democratic Republic of the Congo (DRC) have been very high – two-thirds of people with infections have died. There is some evidence that early diagnosis and high-quality patient management can improve survival rates.

In addition, a range of new diagnostics and treatments have been developed since the West Africa Ebola outbreak. They may aid survival, but their performance and effectiveness can only be truly tested in outbreak situations.

The project

The PEAU-EBOV-RDC project is carrying out a range of activities to improve the care of patients with Ebola infections, by enhancing the quality of supportive care and by evaluating new diagnostics and treatments.

The DRC's national public health laboratory, l'Institut National de Recherche Biomédicale, has the responsibility for coordinating research on experimental emergency interventions for Ebola, and has developed an Ebola viral disease research plan. The PEAU-EBOV-RDC project will support a key aim of this plan, strengthening national capacities to undertake trials of experimental treatments and to collect and use high-quality safety data. It will also support the national priority of strengthening capacity to handle suspected Ebola samples and diagnose infections.

The project has been developed in partnership with an existing EDCTP-funded network building epidemic preparedness capacities in sub-Saharan Africa, the African Coalition for Epidemic Research, Response and Training (ALERTT).

Impact

The PEAU-EBOV-RDC project will play a key role in supporting the development of research capacities

Project at a glance

Project: PEAU-EBOV-RDC study

Project lead: Professor Jean-Jacques Muyembe-Tamfum, Institut National de Recherche Biomédicale, Democratic Republic of the Congo

Countries involved: Belgium, Democratic Republic of the Congo, France, and the United Kingdom

Target population(s): All age groups

Year funded: 2018

EDCTP funding: €0.5 M

This project was funded through an emergency funding mechanism launched in response to the 2018 Ebola outbreak in the Democratic Republic of the Congo.

in the DRC, ultimately identifying approaches that enhance the survival of patients with Ebola infections.

Making yellow fever vaccine go further

The NIFTY trial will determine whether smaller doses of yellow fever vaccine stimulate protective immune responses – which could enable more people to benefit from a vaccine in limited supply.

The challenge

Yellow fever has shown a resurgence in recent years. It affects 34 countries in Africa, causing up to 170,000 cases and 60,000 deaths a year. A safe and highly effective vaccine is available, but it is difficult to manufacture and shortages in supply contribute to limited routine immunisation and inadequate stockpiles to deal with major outbreaks.

To address supply shortage, WHO recently recommended the use of ‘fractional dosing’ – using one fifth of the standard vaccine dose – in emergency outbreak situations. This is thought to be appropriate as studies have shown that even fractional doses stimulate immune responses in excess of those thought to provide protection from infection. However, the shortage of data (including the absence of data from Africa) prevented WHO from recommending wider use of fractional dosing.

The study

The NIFTY trial will generate key data on fractional dosing of yellow fever vaccine in adults and children to guide policymaking. Immune responses will be monitored in nearly 2000 adults vaccinated with the full dose and three fractional doses of decreasing volume. The lowest fractional dose generating protective responses in adults will then be compared with the full dose in 700 children. Immune responses will be evaluated after a month and a year.

Impact

In 2015, UNICEF estimated that global demand for yellow fever vaccine was more than 40% higher than supply. Fractional dosing could enable more individuals to receive a potentially life-saving vaccine but it will be important to ensure that this does not compromise vaccine effectiveness – and the NIFTY trial will generate key data to answer this question.

Project at a glance

Project: Non-inferiority of Fractional Doses Trial for Yellow Fever Vaccine (NIFTY)

Project lead: Professor Philip Bejon, Wellcome–KEMRI– Oxford Collaborative Research Programme, Kenya

Countries involved: France, Kenya, Senegal, Uganda, and the United Kingdom

Target population(s): Adults; children

Sample size: 1935 adults; 700 children (targets)

Year funded: 2018

EDCTP funding: €3.2 M

Key references:

Trial protocol: <https://clinicaltrials.gov/ct2/show/NCT02991495>

WHO. Yellow fever vaccine: WHO position on the use of fractional doses – June 2017. *Weekly Epidemiological Record*. 2017;92; 345–356





Long-term data on Ebola vaccines

The PREVAC-UP study is ensuring that additional years' data are obtained on a range of important experimental Ebola vaccines.

The challenge

Effective vaccines will be central to the control of future Ebola outbreaks. Following the devastating West Africa Ebola outbreak of 2014–16, Ebola vaccine development has been accelerated globally and several promising vaccines are in the pipeline.

The rVSVΔG-ZEBOV-GP vaccine was initially deployed in the 2018/19 Ebola outbreak in the Democratic Republic of the Congo, and a second vaccine, Ad26.ZEBOV, was introduced later. Nevertheless, there are limited data on their effectiveness.

The project

The global PREVAC consortium has been running a phase IIb trial assessing the anti-Ebola immune responses generated by rVSVΔG-ZEBOV-GP (as a single dose and with a 'boost' from the same vaccine) and by Ad26.ZEBOV, with a boost from a second vaccine, MVA-BN-Filo. The trial is taking place in three African countries.

The PREVAC-UP study is enabling the team to extend data collection from one year to five years. A total of 1,400 adults and 1,400 children are being followed to determine the long-term safety of the vaccine regimens and the persistence of protective antibody and cell-mediated immune responses to vaccination.

Impact

The PREVAC-UP study will generate long-term data on immune responses generated by two of the most advanced Ebola vaccines, in children as well as adults. It will provide key evidence on the likelihood that individuals remain protected against Ebola infection in the years after vaccination. In particular, the study will provide data on responses in children, who were particularly vulnerable to Ebola in the 2014–16 outbreak and for whom little evidence on vaccine responses currently exists.

Project at a glance

Project: PREVAC-UP study

Project lead: Professor Yazdan Yazdanpanah, Institut National de la Santé et de la Recherche Médicale, France

Countries involved: France, Guinea, Mali, Sierra Leone, and the United Kingdom

Target population(s): All age groups, including children

Year funded: 2018

EDCTP funding: €15.9 M

Total project funding: €29.7 M

Rapid detection of Ebola infection

The AdjustEBOVGP-Dx project is developing and testing a rapid point-of-care diagnostic to detect Ebola virus and to distinguish Ebola from a close relative, Marburg virus.

The challenge

Ebola and Marburg viruses cause severe viral haemorrhagic fevers with a high fatality rate. However, during the early stages of infection, symptoms are similar to other tropical infectious diseases.

Current diagnostic tools for Ebola and its relatives are costly, require laboratory facilities, and are too slow to support effective clinical care and disease control. Point-of-care tests have recently been developed for Ebola but these do not detect its relatives such as Marburg virus.

The project

Monoclonal antibodies have been developed that recognise a structure, known as filovirus glycoprotein (GP), which is common to a range of viruses in the Ebola family. However, these antibodies have not been able to detect GP in samples from infected patients, probably because GP is biochemically modified after it is made.

The AdjustEBOVGP-Dx project is exploring whether a range of biochemical treatments can strip away these modifications, enabling monoclonal antibodies to access GP. It is developing a prototype point-of-care diagnostic that will combine this biochemical pretreatment with monoclonal antibody-based detection of GP.

The prototype will then be tested in the ongoing Ebola outbreak in the Democratic Republic of the Congo.

Impact

The AdjustEBOVGP-Dx project could provide a new tool to support the early detection of and rapid response to Ebola virus infections. Importantly, it would also be the first diagnostic able to identify infections with both Ebola and Marburg virus, another lethal viral infection with epidemic potential.

Project at a glance

Project: AdjustEBOVGP-Dx study

Project lead: Dr Misaki Wayengera, Makerere University, Uganda

Countries involved: France, Greece, Poland, South Africa, Sweden, Uganda

Target population(s): All age groups

Year funded: 2018

EDCTP funding: €0.5 M

This project was funded through an emergency funding mechanism launched in response to the 2018 Ebola outbreak in the Democratic Republic of the Congo.





Onsite detection of Ebola

The MobEBO-DRC project is enabling teams in the Democratic Republic of the Congo to use a mobile 'laboratory in a suitcase' successfully deployed in Guinea in the 2014–16 West Africa Ebola outbreak.

The challenge

Rapid diagnosis of Ebola infection is essential for effective control. However, standard methods of diagnosis require laboratory facilities, and even field-based tent laboratories take time to generate results and are not truly mobile.

To speed diagnosis, a mobile suitcase laboratory was developed and successfully in Guinea in 2014. It provides the tools for safe on-site extraction of DNA and molecular identification of Ebola virus. It delivered the first on-site detection of Ebola virus in Guinea, and proved able to diagnose infections in less than an hour.

The project

The aim of the MobEBO-DRC project is to enable use of the mobile suitcase laboratory, a proven diagnostic technology, in the Democratic Republic of the Congo (DRC).

The team behind the development of the technology will work with groups in the DRC to train teams on field use of the mobile suitcase laboratory in outbreak settings.

Impact

The MobEBO-DRC project is ensuring that the DRC can benefit from a proven mobile diagnostic technology. It has brought together the existing development team with the leading Ebola research group in the DRC, strengthening the group's capacity to respond to outbreaks. A wide international network has also been established to explore use of point-of-care tests. Ultimately, rapid and accurate detection of Ebola infections will be an essential tool in the swift control of potential outbreaks.

Project at a glance

Project: MobEBO-DRC study

Project lead: Dr Manfred William Weidmann, University of Stirling, and the United Kingdom

Countries involved: Canada, Democratic Republic of the Congo, Germany, Senegal, and the United Kingdom

Target population(s): All age groups

Year funded: 2018

EDCTP funding: €0.5 M

This project was funded through an emergency funding mechanism launched in response to the 2018 Ebola outbreak in the Democratic Republic of the Congo.

Accelerating research in emergency situations

The ALERRT consortium will ensure that African countries are better prepared to carry out research during emergency infectious disease outbreaks.

The challenge

Africa is at risk of a multitude of emerging and re-emerging infections, including Ebola and other viral haemorrhagic fevers, yellow fever and plague. If not controlled effectively, outbreaks can have a catastrophic human and economic impact – the 2014–16 Ebola epidemic claimed 11,000 lives and cost the three countries affected an estimated US\$2.2 B in lost GDP in 2015 alone.

Clinical evaluation of new interventions for emerging infections is particularly challenging as new vaccines, drugs and diagnostics can only be tested during emergency outbreak situations. At these times, public health responses are naturally focused on treatment and prevention of spread, but outbreaks also provide an opportunity when much can be learned that could improve treatment and prevention of future outbreaks. It is therefore vital that research is embedded in these responses.

The project

ALERRT is a multidisciplinary consortium building a patient-centered clinical research network to respond to epidemics across sub-Saharan Africa. It aims to reduce the public health and socio-economic impact of disease outbreaks by building a sustainable clinical and laboratory research preparedness and response network.

Since speed of response is critical in emergency situations, capacity for clinical research and response procedures must be established in advance and maintained at an appropriate level of readiness to allow rapid mobilisation when needed. The network will enable high-quality and ethical clinical research studies to be designed and launched rapidly in response to outbreaks.

Its work will span development of laboratory infrastructure and IT platforms to support research, as well as training to ensure rapid initiation of operations. Extensive community engagement will be undertaken to ensure that

Project at a glance

Project: African Coalition for Epidemic Research, Response and Training (ALERRT)

Project lead: Professor Peter Horby, University of Oxford, and the United Kingdom

Countries involved: Belgium, Cameroon, Central African Republic, the Democratic Republic of the Congo, Cote d'Ivoire, France, Germany, Ghana, Madagascar, Senegal, Uganda, and the United Kingdom

Year funded: 2018

EDCTP funding: €10 M

its activities are accepted and welcomed by local communities.

Impact

ALERRT has already been called into action, following a formal request from the Republic of Congo for help with control of an Ebola outbreak in 2018. The consortium provided advice on local surveillance activities and diagnostic tools, and organised training on the rapid and rigorous review of research proposals for emergency situations.

The 2014–16 Ebola epidemic illustrated that the world was poorly prepared to organise and coordinate clinical research during outbreak situations, when vital information could have been obtained on new vaccines and drug treatments. Alongside global initiatives to coordinate research during emergency situations, and together with a complementary EDCTP-funded initiative, PANDORA-ID-NET, ALERRT will ensure that African countries are better prepared to prevent, respond to and minimise the impact of infectious disease outbreaks.





Boosting preparedness for infectious disease outbreaks

The PANDORA-ID-NET Consortium is enhancing the capacity of African regions to detect and respond to infectious disease outbreaks through a 'one health' approach encompassing human and animal medicine.

The challenge

The 2014–16 Ebola outbreak, which claimed the lives of at least 11,000 people, illustrated the devastating impact of emerging infections. Recently, Africa has experienced multiple other outbreaks, including yellow fever, plague and Ebola-related viral infections. In addition, given the growth in international air travel, Africa is at risk of importing emerging infections from other regions, such as Middle East respiratory syndrome coronavirus (MERS-CoV). Finally, there is an ongoing risk that entirely new infections will jump species from animals to humans, with potentially devastating consequences.

Central to the control of emerging and re-emerging infections is early detection and rapid response, to treat those affected and to initiate measures to halt further spread of infection. Countries therefore need to be prepared for outbreaks, with effective epidemiologic surveillance for infections and mechanisms in place for rapid responses when new outbreaks are detected. As infectious diseases are no respecters of national borders, international cooperation is essential.

The project

PANDORA-ID-NET is a major new international consortium that is strengthening outbreak response capabilities across Africa, in partnership with national governments and other key stakeholders in Africa and Europe. Given the intimate relationship between humans, livestock and wild animals, and the potential for transmission through animal and environmental reservoirs, the consortium has adopted a 'one health' approach, with key input from both human medicine and veterinary science.

Its work with national governments and public health bodies will promote a wider awareness of the importance of infectious disease control and

Project at a glance

Project: Pan-African Network for Rapid Research, Response, Relief and Preparedness for Infectious Disease Epidemics (PANDORA-ID-NET)

Project lead: Professor Francine Ntoumi, Fondation Congolaise pour la Recherche Médicale, Republic of the Congo

Countries involved: Republic of Congo, France, Gabon, Germany, Ghana, Italy, Nigeria, Sierra Leone, Sudan, Tanzania, Uganda, United Kingdom, and Zambia

Year funded: 2018

EDCTP funding: €10 M

outbreak preparedness. It is establishing rapid response teams that can be mobilised within days in all four African regions. It is also developing capacity for research on emerging infections, before and during outbreaks.

Impact

PANDORA-ID-NET has already been called into action, following a formal request from the Republic of the Congo for help with control of an Ebola outbreak in 2018. The consortium provided advice on local surveillance activities and diagnostic tools, and organised training on the rapid and rigorous review of research proposals in emergency situations. In the longer term, together with a complementary EDCTP-funded initiative, the African Coalition for Epidemic Research, Response and Training (ALERRT), PANDORA-ID-NET will help to ensure that African regions are better prepared to prevent, respond to and minimise the impact of infectious disease outbreaks.

Enhancing Ebola preparedness

The EPIRISK-Ebov project is supporting Ebola preparedness in the Republic of the Congo, a neighbour of the Democratic Republic of the Congo that is at risk of importing Ebola infection.

The challenge

The Republic of Congo shares a border with the Democratic Republic of the Congo (DRC), marked by the River Congo. In 2018, Ebola infections were detected along the River Congo, as well as in the major outbreak in the north of the DRC.

Recognising the risk of spillover, the Republic of the Congo adopted a preparedness approach and formally requested international assistance.

The project

The EPIRISK-Ebov project is carrying out a range of activities to support preparedness in the Republic of the Congo. Its main aim is to provide additional epidemiological information of exposure to Ebola virus along the border with the DRC, by identifying individuals carrying antibodies to Ebola and comparing the numbers with a control population in Brazzaville.

The project will also investigate the properties of Ebola-specific antibodies and cell-based immune responses, and explore risk factors for Ebola infection among the local population.

An additional strand of work will focus on identifying the most common viral and bacterial infections in the local population, using state-of-the-art diagnostic technologies.

Impact

The EPIRISK-Ebov project will provide important benchmark data on past exposures to Ebola virus and on current patterns of infection in the Republic of the Congo. Importantly, it will be involved in training of staff from key national research and public health institutions in the Republic of the Congo, building capacity in diagnostics, biosafety, immunological and other laboratory procedures, and social science. The project will maintain regular communication with the Ministry of Public Health, involve key ministry staff and integrate activities fully into national surveillance activities.

Project at a glance

Project: EPIRISK-Ebov study

Project lead: Professor Francine Ntoumi, Fondation Congolaise pour la Recherche Médicale, Republic of the Congo

Countries involved: Republic of the Congo, France, Gabon, Germany, and the United Kingdom

Target population(s): All age groups

Year funded: 2018

EDCTP funding: €0.5 M

This project was funded through an emergency funding mechanism launched in response to the 2018 Ebola outbreak in the Democratic Republic of the Congo.





Boosting Ebola preparedness in Uganda

The CAPA-CT 2 study is building on past EDCTP investments to enhance Ebola preparedness in a country bordering the Democratic Republic of the Congo.

The challenge

The 2018/19 Ebola outbreak in the Democratic Republic of the Congo (DRC) has been concentrated in the north-east of the country, an area that shares a border with Uganda.

With an estimated 8–10,000 people crossing the border on market days, there is a significant risk that the outbreak could spread to Uganda, and several cases have been reported. The country has therefore implemented a range of preparedness measures since 2018.

The project

The CAPA-CT 2 project will carry out multiple activities to support Ebola preparedness in Uganda, building on the capacity developed by previous EDCTP funding (the CAPA-CT and VirTUAL projects and the EDCTP Senior Fellowship awarded to Dr Michael Walimbwa).

One strand of work will focus on pharmacokinetic studies on an unlicensed drug, remdesivir, being used in the Ebola outbreak as an emergency control measure. Metabolism and distribution of the drug will be monitored in healthy volunteers and people with HIV infections taking antiretroviral therapy, and modelling will be used to determine the most appropriate dose for clinical use.

The project will also strengthen surveillance activities in Uganda. A third strand of work will evaluate a novel capacity-building model to rapidly build local skills in laboratory biosafety and infection prevention and control to improve the management of patients with suspected Ebola infections.

Impact

The CAPA-CT 2 project will add to the evidence base on a potentially important new drug therapy for Ebola infections, and contribute to national Ebola preparedness and the development of global health security capacity in Uganda.

Project at a glance

Project: CAPA-CT 2 study

Project lead: Dr Mohammed Lamorde, Infectious Diseases Institute, Uganda

Countries involved: Italy, Uganda, and the United Kingdom

Target population(s): All age groups

Year funded: 2018

EDCTP funding: €0.5 M

This project was funded through an emergency funding mechanism launched in response to the 2018 Ebola outbreak in the Democratic Republic of the Congo.





PATIENT

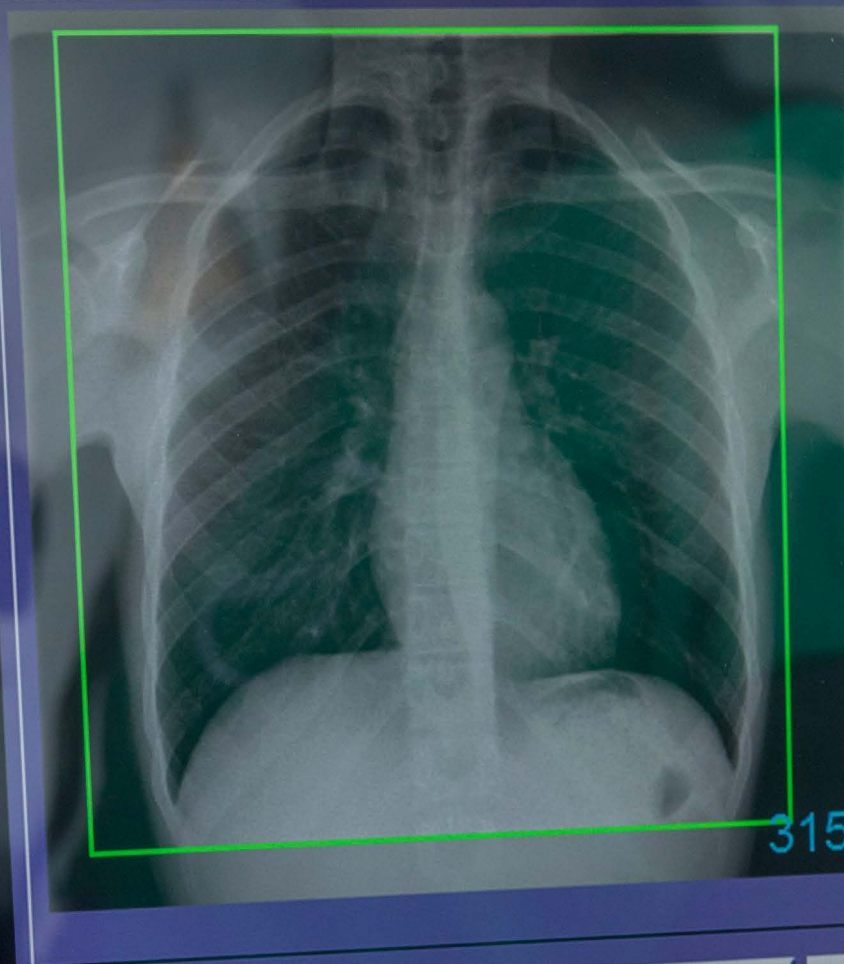
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Diarrhoeal diseases and lower respiratory tract infections

2014-2020



9 grants
€73.59 M



Drugs
3 grants
€18.10 M



Vaccines
5 grants
€49.51 M



Product-focused
implementation research
1 grant
€5.98 M

EDCTP portfolio: Diarrhoeal diseases and lower respiratory tract infections

Drugs	Vaccines	Product-focused implementation research
COAST-Nutrition Kenya, Uganda	ETEC Vaccine Efficacy The Gambia, Zambia	BabyGel
PediCAP South Africa, Uganda, Zambia, Zimbabwe	THECA Burkina Faso, DR Congo, Ghana, Madagascar	
EMPIRICAL Cote d'Ivoire, Malawi, Mozambique, Uganda, Zambia, Zimbabwe	ShigOraVax Burkina Faso, Zambia	
	PREPARE South Africa, Uganda	
	ETEC, ETVAX Zambia	

Caption	Study phase	Population
Project name	Phase I	Adults (18yr and above)
Site(s) in sub-Saharan Africa	Phase II	Adolescents (10yr-17yr)
	Phase III	Children (2yr-9yr)
	Phase IV	Infants (above 1mo-1yr)
Lower respiratory tract infections Diarrhoeal diseases	Observational study	Pregnant women and/or newborns (birth to 1mo)



Reducing deaths from pneumonia

The COAST-Nutrition study is investigating whether nutritional supplements help young children recover from pneumonia.

The challenge

Pneumonia is the leading cause of death in children under the age of five years. Current approaches to hospital care are still associated with relatively high mortality (9–16%). In addition, children are still at risk of dying after they are discharged from hospital, particularly if they are malnourished.

There is considerable scope to improve the treatment of young children with pneumonia. Key questions include when oxygen therapy should be used, and the most effective way it could be delivered, particularly in settings that lack equipment for mechanical ventilation. In addition, there is no formal evidence that supplementary feeding improves survival in under-nourished children.

The project

The COAST-Nutrition team is undertaking a clinical trial, funded by Wellcome and the UK Medical Research Council, which is evaluating different ways to deliver oxygen therapy to children hospitalised with pneumonia. EDCTP funding is being used to take advantage of this platform to assess the benefits of wider use of supplemental feeding, which is currently only given to the most severely under-nourished children.

Children that survive to 48 hours will be enrolled in a further trial to see if supplemental feeding to day 28 improves survival at 90 days. The team will also carry out other studies to see if simple measures or diagnostics are predictive of viral or bacterial pneumonia, to provide tools for improved care of children and targeting of antibiotic therapy in hospitals without microbiology services.

Impact

The COAST-Nutrition trial will reveal whether extending the use of food supplementation beyond the most severely under-nourished children improves longer-term survival after

Project at a glance

Project: COAST-Nutrition

Project lead: Professor Kathryn Maitland, Imperial College, and the United Kingdom

Countries involved: Finland, Kenya, the Netherlands, Uganda, and the United Kingdom

Target population(s): Children

Year funded: 2018

EDCTP funding: €3.4 M

Total project funding: €5.9 M

Project website: <https://coastnutrition.tghn.org>

Clinical trial registration: www.isrctn.com/ISRCTN10829073

hospitalisation for pneumonia. ‘Ready-to-use therapeutic foods’ are safe and widely available, so could be relatively straightforward to implement if evidence suggests that they reduce mortality.

Optimising treatment of childhood pneumonia

The PediCAP study aims to identify the optimal treatment for children hospitalised with severe pneumonia.

The challenge

Pneumonia is the leading cause of death of children under five years of age. Globally, it kills an estimated 1.4 million children every year, and accounts for 18% of deaths of young children. An estimated 500,000–750,000 of these deaths occur in sub-Saharan Africa.

WHO recommends that hospitalised children with severe or very severe pneumonia should be given injectable antibiotics for at least five days. However, this leads to long hospital stays, high costs and an increased risk of hospital-acquired infection.

The project

The PediCAP study is investigating less intensive treatment strategies based on a switch from injected to oral antibiotics, for which little evidence currently exists. Treatment could be switched to amoxicillin, or to a co-amoxiclav, a combination of amoxicillin and a second type of antibiotic; the latter would protect against a wider range of bacteria but could have more side effects and might select for antibiotic resistance. It is also unclear how long oral antibiotics should be given for – courses should be long enough to kill pathogens but not so long that they promote the development of resistance.

The PediCAP team will use an innovative trial design to compare the switch from injected antibiotics to either amoxicillin or to co-amoxiclav, and to assess different durations of treatment. As well as recovery rates, the trial will monitor side effects and the development of resistance. It will also examine whether optimal duration of treatment depends on factors such as age or severity of disease, which could allow treatment regimes to be tailored to particular subsets of patients.

Project at a glance

Project: PediCAP study

Project lead: Professor Carlo Giaquinto, Fondazione PENTA Onlus, Italy

Countries involved: Belgium, Italy, South Africa, Switzerland, Uganda, United Kingdom, Zambia, and Zimbabwe

Target population(s): Children (3 months to 10 years)

Year funded: 2018

EDCTP funding: €7 M

Project website: <https://projectpedicap.org>

Impact

The PediCAP study will fill a large gap in the evidence base for treatment of pneumonia in children. As increasing numbers of children are being treated for pneumonia in hospital, optimised treatments that achieve high cures rates while minimising lengths of hospital stay, side effects and resistance could have a major impact.





Enhancing treatment of respiratory infections in HIV-infected infants

The EMPIRICAL study is exploring whether a greater emphasis on treatment of TB and cytomegalovirus improves survival of young children with HIV.

The challenge

In 2016, around 160,000 children became infected with HIV, and more than 90% of HIV-infected children live in sub-Saharan Africa. Young children are particularly vulnerable to HIV infection – death rates are highest for HIV-infected children less than four years of age.

Respiratory tract infections are the main cause of death of children with HIV. WHO guidelines recommend treatment with antibiotics against common bacteria and the opportunistic pathogen *Pneumocystis jirovecii*, but mortality remains very high.

The project

Evidence has emerged that TB and *cytomegalovirus* – a common virus that only rarely causes disease – are major unrecognised causes of death in children infected with HIV. Each may account for up to 20% of deaths.

As diagnostics for these infections are generally not available in resource-poor settings, the EMPIRICAL trial is evaluating whether empirical treatment against TB and *cytomegalovirus* improves survival of HIV-infected infants with severe pneumonia.

HIV-infected infants aged between one month and 12 months will receive the usual pneumonia treatment of antibiotics, cotrimoxazole and prednisolone. Those thought to have a TB infection will receive anti-TB treatment, and half will also be given an antiviral, valganciclovir. Those not thought to have TB will randomly receive either valganciclovir or anti-TB treatment, on top of the usual pneumonia treatment. Survival will be compared at 15 days and after a year.

Impact

The EMPIRICAL study will determine whether empirical treatment of TB and *cytomegalovirus* reduces pneumonia mortality in young HIV-

Project at a glance

Project: EMPIRICAL study

Project lead: Dr Pablo Rojo, Servicio Madrileña de Salud, Spain

Countries involved: Côte D'Ivoire, France, Italy, Mozambique, The Netherlands, Spain, Uganda, United Kingdom, Zambia, and Zimbabwe

Target population(s): Infants with HIV

Sample size: 624

Year funded: 2018

EDCTP funding: €7.7 M

Clinical trial registration: <https://clinicaltrials.gov/ct2/show/NCT03915366>

infected infants – who currently have the worst survival of all age groups.

Preventing *E. coli* diarrhoea

The ETEC Vaccine Efficacy study is evaluating a vaccine against one of the most common causes of diarrhoeal disease in children.

The challenge

Although *E. coli* is found in all human guts, some strains – known as enterotoxigenic *E. coli* (ETEC) – cause a severe and potentially life-threatening diarrhoea. Around 75 million infections occur each year globally, causing at least 50,000 deaths, mainly in young children. Death rates are highest in Africa.

In addition, ETEC interferes with child growth and development, so it also has longer-term impacts on health and economic wellbeing

The project

The ETVAX® vaccine is the most advanced oral vaccine against ETEC. It is a mix of engineered strains of *E. coli* that produce high levels of four proteins known to stimulate protective immune responses, plus a hybrid protein that combines *E. coli* and cholera toxins. An adjuvant known as dmLT is also used, to stimulate more powerful immune responses.

Following positive results in European adults, the ETEC Vaccine Efficacy study will first conduct a series of safety studies in adults and progressively younger children in Zambia, including children 10–23 months old and infants 6–9 months old.

Assuming no safety issues arise, the project will then progress to a phase IIb study in infants 6–18 months old in The Gambia. The project will also provide a platform for testing of new point-of-care diagnostic tests for ETEC, which would provide a clearer picture of its disease burden.

Impact

The study will provide key data on the efficacy of ETVAX® in African children, and will also strengthen clinical trial and laboratory capabilities in Zambia and The Gambia, which will facilitate further vaccine trials.

Project at a glance

Project: ETEC Vaccine Efficacy study

Project lead: Mr Björn Sjöstrand, Scandinavian Biopharma Holding AB, Sweden

Countries involved: Finland, The Gambia, Sweden, United Kingdom, and Zambia

Target population(s): Young children

Year funded: 2018

EDCTP funding: €7.4 M

Total project funding: €14.9 M





Making the case for typhoid fever vaccination

The THECA study will provide important evidence on the impact of typhoid fever vaccination in Africa.

The challenge

Typhoid fever, caused by infections with *Salmonella Typhi*, affects around 22 million people every year, causing more than 200,000 deaths. African countries are at particular risk of typhoid fever outbreaks.

A typhoid conjugate vaccine, Typbar-TCV®, has been licensed despite limited data on its efficacy. The Bill & Melinda Gates Foundation is supporting three trials – two in Asia and one in Malawi – to generate additional evidence on safety and efficacy.

The project

The THECA study complements the Gates Foundation trials by conducting two additional studies in Ghana and the Democratic Republic of the Congo (DRC).

The Ghana study is a randomised controlled trial that will generate data on safety and efficacy and population-level protection, adding to the pool of African data provided by the Malawi trial.

The DRC study, by contrast, will be embedded within a mass vaccination campaign, with a case-control design used to assess efficacy. This study will provide additional data on protection when the vaccine is used within routine public health systems, as well as valuable insight into feasibility, programmatic barriers and enablers, and cost-effectiveness.

Impact

The THECA study will provide policymakers in Africa with additional data on the safety and efficacy of Typbar-TCV®, but also information on its performance in real-life settings and factors that influence its effectiveness in practice. This will enable them to make much more informed decisions on whether to introduce the vaccine and how to use it.

Project at a glance

Project: THECA study

Project lead: Dr Florian Marks, University of Cambridge, United Kingdom

Countries involved: Bangladesh, Belgium, Burkina Faso, Democratic Republic of the Congo, France, Ghana, Republic of Korea, Madagascar, and the United Kingdom

Target population(s): Children

Year funded: 2019

EDCTP funding: €13 M

Total project funding: €35 M

Preventing dysentery in young children

The ShigOraVax study is collecting essential data to advance the development of vaccines against Shigella, a key cause of diarrhoeal disease in low-income countries.

The challenge

Shigella is the second most common cause of deaths from diarrhoea in children under five years of age. In 2013, *Shigella* infections were responsible for at least 34,000 deaths of children under five years of age, but recent use of more specific diagnostics suggests that the impact of *Shigella* has been significantly underestimated.

Although several *Shigella* vaccines are in development, their evaluation is hampered by a limited understanding of disease burden.

The project

The most common forms of *Shigella* are *S. flexneri* strains 2a, 3a and 6 and *S. sonnei*, all of which are associated with severe diarrhoeal disease. The ShigOraVax project aims to develop a whole-cell inactivated vaccine that is protective against all these strains, can be administered orally, and is cheap and easy to manufacture.

The project will first test the vaccine's safety in European and African adults, before beginning safety studies in children in Burkina Faso. A phase II multicentre trial will be organised in Burkina Faso and Zambia.

Importantly, the project will also collect data on children with moderate to severe diarrhoea at trial sites, to generate a clearer picture of the disease burden attributable to *Shigella* and to provide a foundation for assessing the efficacy of the vaccine.

Impact

The ShigOraVax study will advance the development of a vaccine against one of the most common causes of severe diarrhoea in young children. It will also strengthen the capacity of Burkina Faso and Zambia to carry out vaccine research, and provide much-needed data on the *Shigella* disease burden in Africa.

Project at a glance

Project: The ShigOraVax study

Project lead: Dr Hilde Depraetere, European Vaccine Initiative, Germany

Countries involved: Burkina Faso, Germany, India, the Netherlands, Sweden, Zambia

Target population(s): Young children

Year funded: 2019

EDCTP funding: €8.6 M

Total project funding: €9.8 M





Preventing stillbirths and neonatal meningitis

The PREPARE study is speeding up the development of vaccines that protect women, newborns and young infants against group B streptococci.

The challenge

Group B streptococci are carried by a third of adults and one in five pregnant women, in the digestive system or lower vaginal tract. They usually cause no problems, but they can be transmitted to babies in the womb or during birth. Because of their immature immune systems, babies are at greater risk of invasive disease such as meningitis and septicaemia, and group B streptococci can also cause stillbirth.

There are an estimated 410,000 cases of serious infection each year, leading to 147,000 stillbirths and infant deaths globally. The highest burden is in Africa, which accounts for 64% of stillbirths and infant deaths.

The project

The PREPARE study aims to facilitate the development of vaccines against group B streptococci. Although serious – one in ten babies with an infection are likely to die, and half of those who survive meningitis will have long-term impairments – it is relatively rare, so large-scale phase III trials are difficult to conduct.

The PREPARE study is partnering with manufacturers to test two experimental vaccines, in women with and without HIV. To facilitate trials, the project will collect data on group B streptococcal infections and pregnancy outcomes in 70,000 women attending a hospital in Uganda. A biobank of blood samples will also be created, so links between antibody production and protection against group B streptococci-associated disease in mothers and babies can be investigated.

Impact

The PREPARE study will generate important data on the efficacy of experimental vaccines against group B streptococci, but will also provide additional evidence on disease burden in sub-Saharan Africa and on the immune responses linked to protection. A deeper understanding of

Project at a glance

Project: PREPARE study

Project lead: Dr Kirsty Le Doare, St George's University of London, United Kingdom

Countries involved: Denmark, France, Italy, Malawi, The Netherlands, South Africa, Uganda, United Kingdom, and the United States

Target population(s): Pregnant women (with and without HIV), newborns

Year funded: 2019

EDCTP funding: €10 M

Total project funding: €21 M

the latter could provide a more convenient way to assess the efficacy of vaccines, to inform licensing decision-making and accelerate the introduction of a vaccine.

Diarrhoeal disease prevention in young children

The ETEC ETVAX project is developing and testing a child-adapted formulation of the ETVAX vaccine against enterotoxigenic E. coli.

The challenge

Diarrhoeal diseases account for one in ten deaths of children in sub-Saharan Africa. In 2015, enterotoxigenic E. coli (ETEC) was responsible for an estimated 21,000 deaths in the region (59% of global deaths). In some African countries, ETEC is responsible for more than 10% of deaths from diarrhoeal disease.

Furthermore, although deaths from diarrhoeal diseases have been falling markedly, the incidence of diarrhoeal diseases has not fallen as much. Repeated episodes of diarrhoea increase the risk of death from other infections, and also have a long-term impact on the growth and development of children, affecting their education and later earning potential, as well as their susceptibility to non-communicable diseases in later life.

The project

The ETEC ETVAX study aims to extend use of a highly promising ETEC vaccine, known as ETVAX, to children. ETVAX is a preparation derived from ETEC bacteria that have been engineered to produce high levels of proteins that enable the bacterium to invade the body as well as a hybrid protein based on cholera and ETEC toxins. Delivered with an adjuvant known as dmlT, ETVAX stimulates powerful immune responses against ETEC and is expected to provide protection against 80–85% of ETEC strains in Africa. ETVAX is the only ETEC vaccine in late-stage clinical trials.

ETVAX is being evaluated in phase I and IIb clinical trials (including trials in The Gambia and Zambia supported by the EDCTP). A recent clinical study in Bangladesh has confirmed its safety and immunogenicity in young children, supporting further efficacy trials in this age group. The ETEC ETVAX study is developing a new formulation better suited to young children as well as a user-friendly tool for administering the vaccine. The new all-in-one formulation will then

Project at a glance

Project: ETEC ETVAX project

Project lead: Mr Bjorn Sjöstrand, Scandinavian Biopharma Holding AB, Sweden

Countries involved: Finland, Sweden, Zambia

Target population(s): Young children (6–40 months)

Year funded: 2020

EDCTP funding: €10.6 M

Total project funding: €12 M

be tested in a phase III trial in Zambia in infants 6–22 months in age.

Impact

The ETEC ETVAX study could extend the benefits of ETVAX to young children. As well as its immediate impact on child mortality, ETVAX could also reduce the number of episodes of diarrhoeal disease at a key stage in life, with long-term benefits for health, development, education and economic productivity.

The project aims to generate evidence to support WHO prequalification of an affordable and simple-to-use formulation against a major public health threat in sub-Saharan Africa. It will also strengthen clinical trial and laboratory capabilities in Zambia, particularly expertise in new microbiological and immunological techniques.





Preventing neonatal infection with hand rub

The BabyGel study is examining whether giving mothers an alcohol-based hand rub can reduce severe infections in newborns.

The challenge

Infections account for an estimated 26% of neonatal deaths. Around 750,000 newborns die each year, and neonatal mortality is highest in sub-Saharan Africa, where nearly half of all deaths of children under five years occur. The annual economic burden attributable to severe neonatal infections could be as high as US\$469 B.

Simple water, sanitation and hygiene interventions could dramatically cut infections rates, if widely adopted.

The project

The BabyGel study is exploring whether giving pregnant women alcohol-based hand rub for household use after they have given birth helps to reduce the risk of severe infections in the first three months of life. A pilot study has already shown that BabyGel alcohol-based hand rub could be distributed to women, was widely used and was safe.

The trial is taking place in rural Uganda. Expectant mothers will be given a BabyGel kit including five litres of perfumed alcohol-based hand rub, two dispensers and information about when to use it, emphasising the three key moments of neonatal hand hygiene (before touching baby, for initial cord care and after known risk exposures such as using the toilet).

Expectant mothers will receive the BabyGel kit in addition to a standard birthing kit and antenatal education. The trial will examine if provision of BabyGel has an impact on severe infant illness or death in the first 90 days of life, or on diarrhoeal disease and lower respiratory tract infections.

Impact

The BabyGel study will determine the impact of a simple and widely implementable hygiene intervention that could reduce one of the leading causes of infant death in sub-Saharan Africa. Alcohol-based hand rub is cheap to produce

Project at a glance

Project: BabyGel study

Project lead: Professor Andrew Weeks, University of Liverpool, United Kingdom

Countries involved: Norway, Uganda, and the United Kingdom

Target population(s): Pregnant women, newborns

Year funded: 2019

EDCTP funding: €6 M

locally, active against a wide range of infectious organisms, and easier to use than soap and water.





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The power of sharing science