



EDCTP

The power of sharing science

Tackling infectious disease in sub- Saharan Africa



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 by 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.

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EDCTP: Research & development partnerships to tackle infectious disease in Africa

Dear EDCTP stakeholders,

It is with pleasure that I share with you the European & Developing Countries Clinical Trials Partnership's success stories through R&D partnerships to tackle infectious disease in Africa.

To date, EDCTP has achieved significant success in bringing together researchers and institutions in Europe and Africa to advance interventions for infectious diseases that blight the lives of millions.

The challenge

Poverty-related infectious diseases such as HIV, tuberculosis, malaria and the neglected infectious diseases affect millions of people across sub-Saharan Africa. As well as their devastating impact on individuals, families and communities, infectious diseases have a profound economic impact on countries, in terms of healthcare costs and lost productivity. Tackling infectious diseases is therefore central to most if not all Sustainable Development Goals.



Developing new interventions – diagnostics, vaccines and drugs – is a long, complex and expensive process. For infections that mainly affect low-income countries, the lack of a significant market is a major disincentive to commercial investment in new product development.

Furthermore, apart from diseases that are endemic to Africa, the safety and efficacy of new products is generally determined on populations in high-income countries. It cannot be taken as read that the safety and efficacy of products will be the same when used in Africa. In addition, very little safety and efficacy data are available for some vulnerable populations – such as children and pregnant women.

More positively, recent years have seen tremendous progress in drug discovery and new product development, through the work of researchers in academia, industry and product-development partnerships. However, clinical evaluation of these products – determining their safety and efficacy in target populations – is a significant bottleneck.

The response

Set up in 2003 as a key EU contribution to the Millennium Development Goals, EDCTP fills this vital niche in intervention development. It brings together researchers and institutions in Europe with those in sub-Saharan Africa to carry out clinical trials on new interventions and improved formulations for the most important infectious diseases affecting the continent.

Clinical trials to international standards require high-specification facilities and scientific expertise. As many African countries lack the human and infrastructure capacity to conduct high-quality clinical trials, capacity development has been fundamental to EDCTP's work.

A complementary aim has been to build a supportive environment for research, through projects that build the regulatory and ethical

review capacity of countries in sub-Saharan Africa, so that they can evaluate research proposals and oversee clinical research in compliance with ethical principles and international regulatory standards.

The first EDCTP programme focused on HIV, tuberculosis and malaria. EDCTP2 has the same overall aims but its scope has expanded to include neglected infectious diseases – which collectively affect a billion people – as well as emerging and re-emerging infections such as Ebola and yellow fever, and antimicrobial resistance, which is eroding the power of drugs to control infections.

The impact

EDCTP has had a major impact across all its target diseases and has catalysed the creation of international partnerships of lasting value in the battle against infectious disease.

For **HIV**, EDCTP-funded studies made vital contributions to the development of antiretroviral drug formulations tailored to children – facilitating their widespread introduction in Africa. Other landmark studies were carried out in prevention of mother-to-child transmission of HIV and in detection and treatment of opportunistic fungal infections – responsible for one in five HIV-related deaths.

For **tuberculosis (TB)**, EDCTP-funded research played a pivotal role in the evaluation of the Xpert MTB/RIF diagnostic technology, now recommended by WHO and widely implemented globally. Other studies have advanced the development of diagnostics for use in special groups, such as children and people with HIV infections. Landmark drug trials have identified possible ways to shorten TB drug treatment and have also been hugely influential in shaping how TB drug trials should be carried out.

For **malaria**, EDCTP-funded trials have generated key evidence on antimalarial use in pregnant women – who are particularly susceptible to malaria, which can harm both mothers and their developing babies. Other trials have had a significant influence on the choice of antimalarial drugs for children.

Across all these areas, EDCTP funding has had a major impact on the development of clinical research capacity. Researchers at all career stages

have been supported, including more than 100 fellows many of whom have gone on to secure leadership positions in African science and are mentoring the next generation of clinical researchers. Institutions across sub-Saharan Africa have been helped to establish facilities able to carry out international standard trials. Regional Networks of Excellence have been created enabling countries to share expertise, coordinate activities and undertake major multicentre international trials.

The future

Building on EDCTP1's successes, newly funded EDCTP2 projects are continuing to address the key infectious disease challenges in sub-Saharan Africa, with infants, children, women and other vulnerable groups an important focus. Innovative vaccine development projects have been launched in malaria, TB and HIV. A globally important platform for TB drug evaluation is being strengthened, and new international networks established to facilitate research on emerging infections in emergency situations. New medical interventions are being evaluated for neglected infectious diseases such as schistosomiasis and leishmaniasis.

Importantly, EDCTP's work is leaving a lasting legacy – not just in accelerating access to new interventions but in the people and facilities now in place to lead clinical research in Africa in the future. The third EDCTP programme, part of the Horizon Europe initiative and due to launch in 2021, will build on this foundation to drive forward an African-led clinical research agenda addressing its key infectious disease challenges.

We are extremely grateful for the efforts of many of you who have been associated with the EDCTP journey.

Kind regards,

Michael Makanga
Executive Director



EDCTP1 at a glance



Established in 2003 as the **European Union's contribution to the Millennium Development Goals.**



EDCTP was the first Article 185 initiative and the **largest programme on clinical trials targeted to Africa.**



Focused on **HIV, tuberculosis and malaria.**



Awarded **254 grants** with a total funding of **€208 million**



Supported **521 African researchers**, including 51 senior fellows and 400 PhD and master's students



Supported consortia spanning **30 African countries and 16 European countries**



Funded **102 clinical trials and 13 diagnostics studies** in 24 countries



Generated more than **700 peer-reviewed publications**



Supported studies influencing **national policies and WHO treatment guidelines**



Supported **ethics-related activities in 23 countries** (including an African research ethics manual)



Established **four regional Networks of Excellence**



Created a **Pan-African Clinical Trials Registry**

Towards EDCTP2's objectives

1. Medical interventions

88% of total EDCTP2 project funding is invested into grants supporting **82 large-scale clinical studies** on diagnosis, prevention and treatment of PRDs in sub-Saharan Africa.



22% of EDCTP2 large-scale clinical studies include pregnant women and newborn populations,

36% include children and

43% include adolescent populations in sub-Saharan Africa.



2. Capacity development

EDCTP 2 is supporting **research ethics review and regulatory affairs** for medical interventions against PRDs in **24 sub-Saharan African** countries.



In order to foster **sub-Saharan African leadership in scientific research**, EDCTP is offering a comprehensive fellowship programme, with currently **90 fellows** enrolled from all regions of sub-Saharan Africa.



4. Partnerships

16 sub-Saharan African countries are full members of the **EDCTP Association**. In 2017, Nigeria and Ethiopia joined EDCTP as full members and Angola became an aspirant member.



Currently, **36 project partners from sub-Saharan Africa** benefit from **EDCTP-funded grants**, in comparison to 30 in the first EDCTP programme. Coverage of recruitment sites for clinical studies expanded also with the involvement of **32 sub-Saharan African countries**, in comparison to 24 sub-Saharan African countries in the first programme.

EDCTP expects to leverage over **€80 million in external project funding through its strategic grant schemes** to maximize the benefits of its PRDs research. In addition, **several partnerships have been signed between EDCTP and third parties**, e.g. the Mundo Sano Foundation and the Leprosy Research Initiative, bringing contributions to EDCTP calls for proposals.



54% of EDCTP2 large-scale clinical studies are **phase II and phase III clinical trials** aiming to deliver key **evidence on safety and efficacy of medical interventions** against poverty-related infectious in sub-Saharan Africa.



12% of EDCTP2 large-scale clinical studies involve **post-licensing (phase IV) studies**, in order to effectively **deliver medical interventions** for the wide range of sub-Saharan African health systems and diverse populations.



3. EU coordination

EDCTP holds joint calls with its **European member countries** to encourage **strategic research alignment across the EU**. For example, in 2017 EDCTP formed a partnership between Germany, Sweden and the UK to launch the 'Joint WHO-AFRO/TDR/EDCTP Small Grants Scheme for implementation research on infectious diseases of poverty'. Furthermore, the EDCTP General Assembly set up a working group to improve 'strategic alignment of national research activities with EDCTP-managed activities'.



5. Development cooperation

In efforts to bring **development partners** on board, an EDCTP call on 'Strategic actions supporting health systems/services optimisation research capacities in cooperation with development assistance' was launched. It resulted in **3 grant consortia established and funding from development cooperation agencies**: U.S. Agency for International Development and the Swedish International Development Cooperation Agency.



Joint calls in collaboration with WHO initiatives have been pursued such as the 'Research and capacity development in support of the EVD response' (2015), the 'EDCTP-TDR Clinical Research and Development Fellowships' (2014-2016), the 'WHO-AFRO/TDR/EDCTP small grants scheme for implementation research on infectious diseases of poverty' (2017).

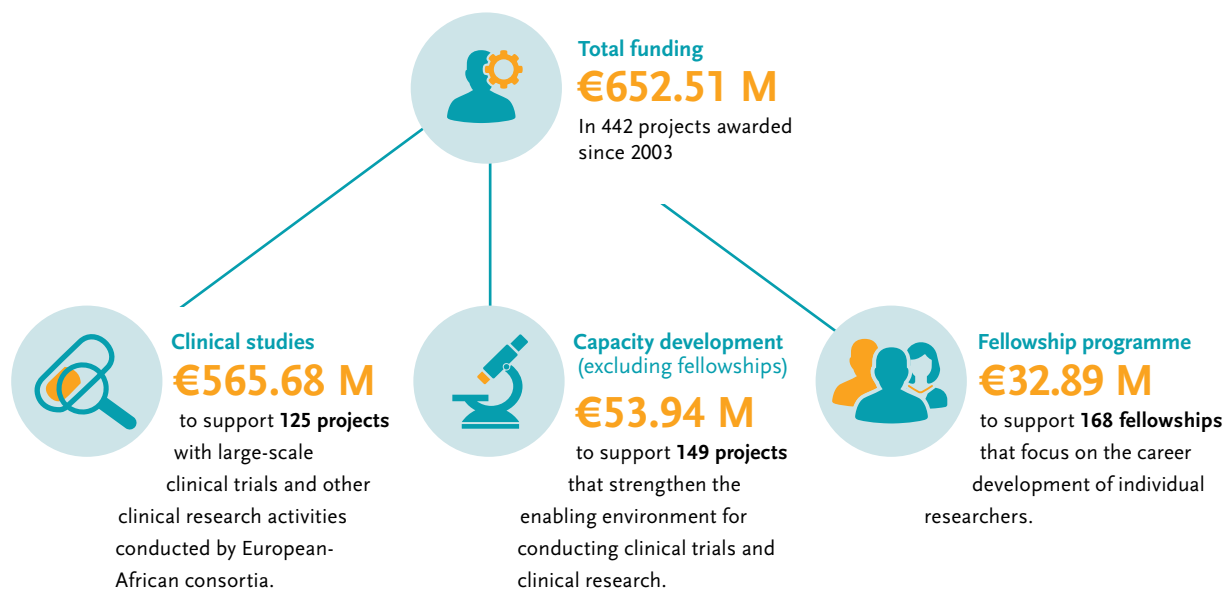


Jointly with WHO-AFRO, EDCTP is **assessing the national health research systems capacities** in 17 sub-Saharan African countries. The survey will **inform the development of a strategic policy plan** for strengthening health research systems capacities of countries in sub-Saharan Africa.



EDCTP's investment in research & development

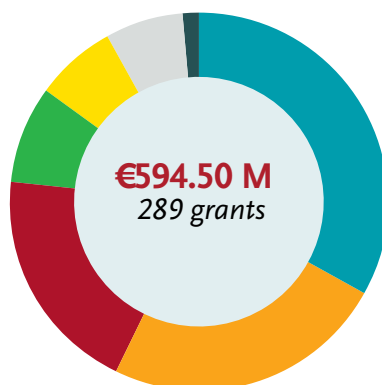
2003-2018



By disease

Note:

A further €58.01M for 153 grants was awarded to projects on non-disease-specific topics.
*EDCTP1 grants only
**EDCTP2 grants only

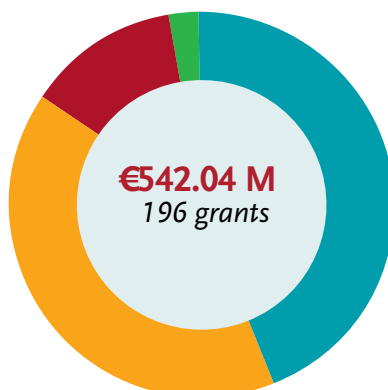


- Tuberculosis, 76 grants
€198.44 M
- HIV & HIV-associated infections, 96 grants
€145.16 M
- Malaria, 64 grants
€114.83 M
- Neglected infectious diseases**, 21 grants
€48.36 M
- Emerging diseases**, 12 grants
€40.35 M
- Diarrhoeal diseases and lower respiratory tract infections**, 8 grants
€40.23 M
- HIV/TB*, 12 grants
€7.13 M

By intervention

Note:

A further €110.47M for 246 grants was awarded to projects on non-intervention-specific topics.
*EDCTP1 grants only



- Drugs, 109 grants
€297.05 M
- Vaccines, 48 grants
€187.63 M
- Diagnostics, 34 grants
€47.98 M
- Microbicides*, 5 grants
€9.38 M



Vacuum
Collection
Plate

KANGAROO BRAND

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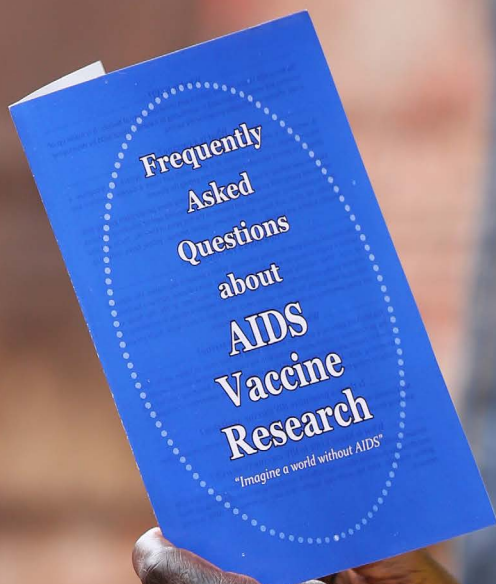


Photo:
A resident of the Kangemi community in Kenya

EDCTP portfolio: HIV & HIV-associated infections

2003-2018



96 grants

€153.16 M



Drugs
35 grants

€84.62 M



Vaccines
15 grants

€45.03 M



Diagnostics
3 grants

€5.14 M



Microbicides
5 grants

€9.39 M

Note:

A further €8.98M for 38 grants was awarded to projects on non-intervention-specific.



“
crucial in
widening African
children's access
to antiretrovirals
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Bringing antiretroviral drugs to children

The CHAPAS trials have ensured that many more children with HIV have benefited from life-saving antiretrovirals.

The challenge

More than 3 million HIV-infected children live in Africa. Initially, treatment of these children relied on antiretroviral-containing syrups, which were costly, difficult to transport, awkward to administer, and each drug had to be administered separately. Low-cost, scored, dispersible fixed-dose combinations (multiple drugs in a single tablet) developed specifically for children potentially provided major advantages.

The project

The CHAPAS-1 trial evaluated a new fixed-dose combination containing three antiretroviral drugs – stavudine, lamivudine and nevirapine – in a formulation designed specifically for children. Its key aim was to analyse how the active ingredients in the new tablets were metabolised by children, to ensure that drug concentrations in the body would be high enough to control HIV but not so high that they would cause serious side effects.

The later CHAPAS-3 trial compared the efficacy and safety of three fixed-dose combinations, including two without stavudine (found to have some long-term side effects in adults, leading to a recommendation that its use be discontinued in children). The trial, the first of its kind in Africa, studied nearly 500 children at four sites in two African countries.

Impact

The CHAPAS studies have been highly influential. CHAPAS-1 data contributed to the approval of specific HIV medicines (Triomune Baby/Junior) by the US Food and Drug Administration in 2007. The development of fixed-dose combinations was crucial in widening African children's access to antiretrovirals, provided through initiatives such as the US President's Emergency Plan for HIV/AIDS Relief (PEPFAR) and the Clinton HIV/AIDS Initiative. The study also informed WHO recommendations on optimal drug ratios for fixed-dose combinations and on appropriate dosage according to weight.

Project at a glance

Projects: Children with HIV in Africa Pharmacokinetics and Adherence of Simple Antiretroviral Regimens (CHAPAS): CHAPAS-1 and -3

Project lead: Professor Chifumbe Chintu, University Teaching Hospital, Zambia (CHAPAS-1); Dr Veronica Mulenga, University Teaching Hospital, Zambia (CHAPAS-3)

Target population(s): Children with HIV

Sample size: 71 (CHAPAS-1); 480 (CHAPAS-3)

Countries involved: Ireland, the Netherlands, the UK, the USA, Zambia (CHAPAS-1); Uganda, Zambia (CHAPAS-3)

Project duration: 2005–2009 (CHAPAS-1); 2010–2011 (CHAPAS-3)

EDCTP funding: €1.2M (CHAPAS-1); €4.6M (CHAPAS-3)

Total project funding: €1.2M (CHAPAS-1); €5.0M

The CHAPAS-3 trial confirmed the effectiveness of fixed-dose combinations, providing further impetus to the rollout of antiretrovirals to children. Its evidence on abacavir informed the WHO recommendation of abacavir-containing combinations for first-line therapy in children. Trial data have also been used to support applications for regulatory approval for new scored efavirenz tablets.

Key references

L'homme RF et al. Nevirapine, stavudine and lamivudine pharmacokinetics in African children on paediatric fixed-dose combination tablets. *AIDS*. 2008;22(5):557–65.

Mulenga V et al. Abacavir, zidovudine, or stavudine as paediatric tablets for African HIV-infected children (CHAPAS-3): an open-label, parallel-group, randomised controlled trial. *Lancet Infect Dis*. 2016;16(2):169–79.

WHO. Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2010.

WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach (second edition). 2016

Video: The CHAPAS Clinical Trials. Available at: www.youtube.com/watch?v=dSPjCxSfYU



Photo:
Staff member and volunteer at the Charles De Gaulle University
Hospital, part of the MONOD project (led by Dr Valérie Leroy)



“
key data
on optimal
treatments for
HIV infections in
children
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New back-up treatments for children with HIV

The CHAPAS-4 study is evaluating a suite of new therapies for children with drug-resistant HIV infections.

The challenge

In 2016, an estimated 740,000 children and adolescents with HIV were receiving antiretroviral therapy in low- and middle-income countries. Although the numbers of children becoming infected with HIV is dropping as mother-to-child transmission of HIV has been markedly cut, improving access to antiretroviral therapy will increase the number of young people on anti-HIV medication.

Antiretroviral therapy works well in children, but HIV inevitably develops resistance in some, necessitating a switch to back-up or second-line therapy. However, the WHO-recommended second-line therapy has significant drawbacks – it has to be taken as whole non-crushed pills, mini-pellets or in unpleasant liquid form. Furthermore, components of some second-line therapies interact with anti-TB drugs. Recently, new drugs have been developed that could offer more suitable alternatives, but there is limited data on their effectiveness in African children.

The project

The long-standing CHAPAS consortium has developed world-leading expertise in HIV-related clinical trials in African children. Its previous studies (CHAPAS 1, 2 and 3) have been instrumental in enhancing children's access to antiretroviral therapy in Africa. Its latest trial, CHAPAS-4, is evaluating a range of new drug combinations for second-line HIV therapy. These include two variants of one of the components used in current second-line therapy, as well as a highly promising new drug, dolutegravir.

The trial will also assess another new drug, tenofovir alafenamide (TAF), as a replacement for a different component of current second-line therapy. TAF is a 'gentler' treatment and likely to have fewer long-term side effects. The trial will recruit nearly 700 children who are failing first-line treatment in three countries.

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, Uganda, the UK, Zambia, Zimbabwe

Target population(s): Children with HIV (aged 3–13)

Sample size: 690 (target)

Year funded: 2017

EDCTP funding: €7.6M

Impact

The CHAPAS-4 trial is a highly efficient design testing multiple new combinations of antiretroviral drugs. It will provide key data on optimal treatments for HIV infections in children. The trial will also investigate how metabolism of the drugs is affected by anti-TB therapies – many children in sub-Saharan Africa are likely to be infected with both HIV and TB. In the absence of third-line therapies, it is essential that second-line therapies are used as wisely as possible to prevent the emergence of essentially untreatable HIV infections in individuals who will need lifelong treatment.

Key reference

Study protocol: www.isrctn.com/ISRCTN22964075



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highlighted the
achievability of
elimination of
mother-to-child
transmission
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Preventing mother-to-child transmission of HIV

The landmark Kesho Bora trial generated compelling evidence of the power of antiretrovirals to prevent mother-to-child transmission of HIV during breastfeeding.

The challenge

Breastfeeding makes a critical contribution to infant health and development. Unfortunately, it also provides a route by which HIV can be transmitted from HIV-infected mothers to their babies. In addition, many families in Africa cannot afford the main alternative, formula milk.

The study

The Kesho Bora study ('Kesho Bora' is Swahili for 'a better future') examined whether triple antiretroviral therapy was more effective than the current WHO-recommended regime for preventing mother-to-child transmission of HIV. More than 800 women were studied at five sites in three African countries.

The results

The study found that triple therapy was markedly better than the recommended regime, cutting the risk of mother-to-child transmission by 43% at 12 months. Triple therapy was not associated with any serious adverse effects on either mothers or their offspring.

Impact

The Kesho Bora study provided some of the earliest and strongest evidence that triple therapy could have a major impact on mother-to-child transmission of HIV during breastfeeding. It informed the development of revised WHO guidelines, which recommended more extensive use of antiretrovirals in pregnant and breastfeeding women. More generally, the results highlighted the potential achievability of elimination of mother-to-child transmission, now a key global goal.

Project at a glance

Projects: Kesho Bora study

Project lead: Professor Marie Louise Newell, University of KwaZulu Natal, South Africa

Target population(s): Mothers with HIV

Sample size: 882

Countries involved: Belgium, Burkina Faso, France, Kenya, South Africa

Project duration: 2006–2010

EDCTP funding: €1.1M

Total project funding: €2.7M

Key reference

Kesho Bora Study Group, de Vincenzi I. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. *Lancet Infect Dis.* 2011;11(3):171–80.

WHO. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: recommendations for a public health approach. 2010.



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preventing
mother-to-child
transmission
of HIV through
a full year of
breastfeeding
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Preventing HIV transmission throughout breastfeeding

The PROMISE-PEP trial showed that prophylactic use of antiretroviral drugs in babies during a year of breastfeeding almost completely eliminated HIV transmission.

The challenge

Babies are at risk of acquiring HIV from infected mothers while in the womb but also via breastfeeding. In 2015, around 150,000 children were infected with HIV, almost half of them in the period between 6 months of age and the end of breastfeeding.

The study

The PROMISE-PEP trial evaluated a form of 'pre-exposure prophylaxis' (PrEP), in which antiretroviral drugs are given to at-risk individuals to prevent infection. The trial compared two liquid formulations suitable for babies (lopinavir/ritonavir and lamivudine), which were given to the babies of HIV-infected mothers who, based on guidelines in place at the time, were not eligible for antiretroviral therapy. Importantly, unlike most previous studies, it examined mother-to-child transmission through the full first year of life – in line with breastfeeding practices in sub-Saharan Africa.

The results

Both treatments were safe and highly effective at preventing mother-to-child transmission. Among more than 1200 infants studied, only 17 infections were detected. Notably, around half the infections occurred after 6 months of breastfeeding. Later follow-up work suggested that these infections reflected breaks in drug use rather than a failure of the drugs to prevent infection.

Impact

The WHO now recommends treatment of all HIV-infected pregnant and breastfeeding women, as well as antiretroviral therapy of babies for 6 weeks. However, treatment of mothers does not entirely prevent mother-to-child transmission, mothers' adherence to treatment is far from

Project at a glance

Project: PROMISE-PEP/ANRS 12174

Project lead: Professor Philippe Van de Perre, INSERM, Montpellier, France

Countries involved: Burkina Faso, France, Norway, South Africa, Sweden, Uganda, Zambia

Target population(s): Infants of mothers with HIV

Sample size: 1273

Project duration: 2008–2014

EDCTP funding: €2.8M

Total project funding: €12.2M

complete, and infants remain at risk throughout breastfeeding. This study showed that PrEP in infants is highly effective at preventing mother-to-child transmission of HIV through a full year of breastfeeding. Hence PrEP throughout breastfeeding beyond WHO's 6-week recommendation is a viable strategy and could make a significant contribution to the elimination of mother-to-child transmission.

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.



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a readily
implementable
strategy for
reducing further
infant infection
rates
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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: €3.0M

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



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”

Effective therapies for drug-resistant HIV

The EARNEST and 2LADY trials have generated crucial findings on the best treatments to use in people with drug-resistant HIV.

The challenge

HIV treatment in Africa is based on the rollout of standardised and simple treatment regimes suitable for low-resource settings. Even with combination therapies, HIV infections can become resistant to standard treatments, at which point patients are switched from first-line drugs to an alternative or second-line therapy. Because standard second-line therapy contains a drug from the same class as is used in first-line therapies, there have been concerns that resistance might also affect the potency of second-line therapy. There is also very little evidence from Africa on which specific drugs should be included in second-line combinations.

The studies

The EARNEST trial was based on the reasoning that a second-line therapy would be more effective if it included a drug from a class of antiretroviral not included in first-line therapy*. It therefore compared the standard second-line therapy (two NRTIs plus a PI) with a new regime (PI plus raltegravir, a non-NRTI drug), as well as to a PI on its own. The trial was carried out in five countries, in conditions mirroring usual treatment settings.

The 2LADY trial, carried out in three countries, compared three different PI–NRTI combinations, including the then-recommended WHO standard.

The results

The new regime, PI plus raltegravir, was found to be safe and effective. Surprisingly, though, it was not better than PI plus NRTIs, even though patients showed high levels of resistance to first-line NRTIs. Thus, development of resistance to an NRTI does not seem to affect responses to subsequent NRTIs. PI on its own was markedly less effective than the other two options. A four-year follow up confirmed that PI plus NRTIs retains its effectiveness over the long term, and actually appears to out-perform PI plus raltegravir.

Project at a glance

Projects: Europe Africa Research Network for Evaluation of Second Line Therapy (EARNEST); 2LADY

Project lead: Professor Peter Mugenyi, Joint Clinical Research Centre, Uganda (EARNEST); Professor Eric Delaporte, University of Montpellier, France (2LADY)

Countries involved: Belgium, Ireland, Italy, Kenya, Malawi, Spain, Uganda, , the UK, Zambia, Zimbabwe (EARNEST); Belgium, Cameroon, France, Germany, Senegal, Switzerland (2LADY)

Target population(s): Adults with drug-resistant HIV

Sample size: 1277 (EARNEST); 454 (2LADY)

Project duration: 2009–2014 (EARNEST); 2009–2015 (2LADY)

EDCTP funding: €4.3M (EARNEST); €1.1m (2LADY)

Total project funding: €4.9M (EARNEST); €3.7M (2LADY)

The 2LADY study found that all three combinations were equally safe and effective, confirming the appropriateness of the WHO recommendation.

Impact

The initial EARNEST findings confirmed that, despite concerns about cross-resistance, the current WHO-recommended second-line treatment of NRTIs plus PI was still appropriate. Although WHO now suggests that PI plus raltegravir is a possible second-line therapy, the long-term follow up – the only such evidence available for second-line therapy in Africa – suggests not only that the additional cost of PI plus raltegravir is not justified but also that the combination may actually be less effective than the current standard. The study also suggests that there is no benefit to be gained from expensive genotyping to identify NRTI mutations, since they do not seem to affect clinical responses to second-line therapy.

Key publications

Paton NI et al. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. *N Engl J Med*. 2014;371(3):234–47.

Hakim JG et al. Lopinavir plus nucleoside reverse-transcriptase inhibitors, lopinavir plus raltegravir, or lopinavir monotherapy for second-line treatment of HIV (EARNEST): 144-week follow-up results from a randomised controlled trial. *Lancet Infect Dis*. 2018;18(1):47–57.

Ciaffi L et al. Efficacy and safety of three second-line antiretroviral regimens in HIV-infected patients in Africa. *AIDS*. 2015;29(12):1473–81.

*Antiretroviral classes: NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor.



Photo:
Researchers of the DREAMM project (Malawi)



“
**cryptococcal
screening adds a
further survival
benefit at
minimal cost**
”

Cutting early HIV mortality due to fungal infections

In the REMSTART trial, a combination of screening for fungal infections and community support reduced HIV-associated deaths by 28%.

The challenge

Some 10 million people in Africa are being treated with antiretroviral drugs. However, mortality is higher in Africans than in people from high-income countries during the first year of antiretroviral treatment, especially in the early months of treatment. One particular challenge is infection with *Cryptococcus*, a fungal pathogen that can cause fatal meningitis and is responsible for 15–20% of HIV-associated deaths.

The study

The REMSTART trial evaluated a new approach to early management of people diagnosed with HIV. It had two key elements: screening for *Cryptococcus* infection with an antigen test and prompt initiation of antifungal therapy in those testing positive; and use of trained lay workers to provide support in the community, in addition to the usual clinic-based care. The lay workers undertook four home visits to promote adherence to antiretroviral treatment. This new approach was compared with usual clinic-based care in urban centres in Tanzania and Zambia.

The results

Mortality after 12 months was 28% lower in the intervention group (18% in the usual care group and 13% in the intervention group). It is likely that cryptococcal screening and community support contributed equally to these survival gains.

Impact

The REMSTART study, carried out in a ‘real life’ setting, showed that relatively straightforward measures implemented at the community level could have a significant impact on mortality in vulnerable people newly diagnosed with HIV. Use of lay workers addresses a key challenge in African healthcare, the shortage of trained healthcare professionals. On its own it improves survival, while addition of cryptococcal screening

Project at a glance

Project: The REMSTART trial

Project lead: Dr Saida Egwaga, Tanzanian Ministry of Health and Social Welfare

Countries involved: South Africa, Sweden, Switzerland, Tanzania, the UK, Zambia

Target population(s): Adults with HIV

Sample size: 1999

Project duration: 2011–2015

EDCTP funding: €2.2M

Total project funding: €3.8M

adds a further survival benefit at minimal additional cost over the lifetime of treatment.

To map out a route to implementation, the follow-on Translating Research into Practice (TRIP) study is exploring use of cryptococcal screening and mobile phone-based patient engagement embedded within the Tanzanian health system.

Key reference

Mfinanga S et al. Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial. *Lancet*. 2015;385(9983):2173–82.



“
largest HIV-associated cryptococcal meningitis trial ever
”

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 Jo Jarvis, London School of Hygiene and Tropical Medicine, UK

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

Target population(s): Adults with HIV

Sample size: 850 (target)

Year funded: 2017

EDCTP funding: €10.0M

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.



“
work with
a range of
marginalised
communities
”

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): High-risk and marginalised communities

Sample size: 168 (target)

Year funded: 2017

EDCTP funding: €7.1M

Total project funding: €16.8M

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.



“
*evidence of
the ability of
vaccine plus PrEP
combinations
to prevent HIV
infections*
”

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 III 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.

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

Project at a glance

Project: PrEPVacc

Project lead: Professor Jonathan Weber, Imperial College, UK

Countries involved: Germany, Mozambique, South Africa, Switzerland, Tanzania, Uganda, the US

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

Sample size: 1668 (target)

Year funded: 2018

EDCTP funding: €15.0M

Total project funding: €22.2M

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.



“
*a stepping stone
between clinical
trials and routine
clinical use*
”

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 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: €1.9M

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.



“
revealing whether
point-of-care HIV
diagnostics do
benefit infants
”

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 US

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: €3.0M

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

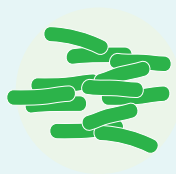
Jani IV et al. Effect of point-of-care early infant diagnosis on antiretroviral therapy initiation and retention of patients. *AIDS*. 2018;32(11):1453–1463.



Photo:
Clinic staff and volunteer at the Ubuntu Clinic in Khayelitsha, South Africa, part of the PredART project (led by Dr Graeme Meintjes)

EDCTP portfolio: Tuberculosis

2003-2018



76 grants

€198.44 M



Drugs
20 grants

€83.30 M



Vaccines
12 grants

€56.15 M

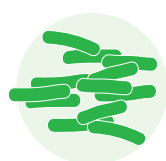


Diagnostics
20 grants

€32.93 M

Note:

A further €26.06M for 24 grants was awarded to projects on non-intervention-specific .



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*demonstrated
the capacity of
African centres
to carry out trials
to the highest
regulatory
standards*
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Building capacity for TB drug trials in Africa

Although the REMoxTB trial found that a novel TB drug regimen could not shorten the duration of treatment, it showed that drug trials could be carried out to the highest international standards in Africa.

The challenge

TB patients must take a combination of pills for six months. Shorter and simpler treatments are highly desirable, as they would lead to greater adherence, fewer side effects and lower costs. Studies in mice and preliminary studies in humans suggested that moxifloxacin, an antibiotic not previously used in TB, might be sufficiently potent to allow treatment schedules to be reduced from six months to four months.

The study: The REMoxTB trial was carried out by the EDCTP-funded PanACEA Consortium in nine countries, including four in Africa. Of the 1931 patients involved, 1323 were recruited in Africa. It compared standard treatment with two alternatives in which moxifloxacin replaced either ethambutol or isoniazid.

The results

The moxifloxacin regimes led to more rapid clearance of TB bacteria, but survival was lower at 18 months because more patients relapsed after the end of treatment.

Impact

The results do not support the use of shortened moxifloxacin-containing regimes for TB. Although disappointing from the point of view of treatment shortening, the trial nevertheless provided important lessons. Notably, it highlighted that the results of studies in animals and short-term trials in humans may not be a good guide to long-term success of treatments, with important implications for the way new TB drugs are developed and evaluated. It also demonstrated the capacity of African centres to carry out clinical trials to the highest possible regulatory standards, establishing a sustainable infrastructure able to host future TB drug trials.

Project at a glance

Project: The PanACEA Rapid Evaluation of Moxifloxacin in Tuberculosis (REMoxTB) study

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

Countries involved: Kenya, South Africa, Tanzania, South Africa (China, India, Malaysia, Mexico, Thailand), the UK, the US, Zambia

Target population(s): Adults with drug-sensitive TB infections

Sample size: 1931 (1323 in Africa)

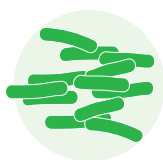
Project duration: 2005–2014

EDCTP funding: €9.7M

Total project funding: €28M

Key reference

Gillespie SH et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med.* 2014;371(17):1577–87.



“
the MAMS
trial has shown
that high-dose
rifampicin has
great promise

”

Accelerating TB drug development

As well as identifying a possible way to shorten TB treatment, the PanACEA Consortium's groundbreaking MAMS trial has also piloted a clinical trial approach that could greatly accelerate evaluation of future treatments.

The challenge

TB is responsible for more deaths than any other infection – more than 400,000 in Africa alone every year. *Mycobacterium tuberculosis* is hard to kill; current treatments typically last six months and require patients to take multiple medicines. Hence there is an urgent need for shorter and simpler treatments. In addition, large-scale trials are hugely expensive and a major bottleneck in the evaluation of promising new treatments.

The study: The PanACEA Consortium has established a platform for TB drug trials across Africa. This has enabled it to carry out a 'multi-arm, multi-stage' (MAMS) clinical trial, which simultaneously compared four new treatment regimens against the currently used approach. This enabled evidence on multiple treatments to be gathered in one trial, and reduced the number of patients needed to be recruited (the single standard-treatment arm could act as a control for all the other interventions). In addition, treatments showing disappointing results could be discontinued mid-trial.

The results

A key aim of MAMS was to test whether high doses of a currently used drug, rifampicin, cleared infections quicker, which would allow shorter treatment schedules. Indeed, the highest dose of rifampicin tested was associated with the best inhibition of *M. tuberculosis* growth ever seen in a clinical trial. By contrast, evaluation of an experimental drug, SQ109, was terminated early because of its limited impact on *M. tuberculosis*.

Impact

The MAMS trial has shown that high-dose rifampicin has great promise as part of a shorter TB treatment regimen. It also suggested that further investment in SQ109 for drug-sensitive TB infections may not be warranted. Importantly,

Project at a glance

Project: PanACEA Consortium, Multi-Arm, Multi-Stage (MAMS) study

Project leads: Professor Martin Boeree, Radboud University Nijmegen Medical Centre, The Netherlands, Professor Stephen Gillespie, University of St Andrews, UK, Professor Michael Hoelscher, Ludwig-Maximilians University Munich, Germany

Countries involved: Germany, the Netherlands, Tanzania, South Africa, the UK

Target population(s): Adults with drug-sensitive TB infections

Sample size: 365

Project duration: 2012–2015

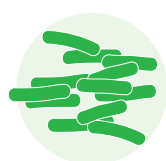
EDCTP funding: €6.3M

Total project funding: €48.3M (PanACEA Consortium)

it showed that the MAMS design – previously used only in cancer drug studies – could be applied in multicentre TB trials in Africa, offering a cost-effective way to generate efficacy and safety data on multiple experimental new treatment regimens.

Key reference

Boeree MJ et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. *Lancet Infect Dis.* 2017;17(1):39–49.



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to improve the
efficiency of drug
development
and enhance
the likelihood of
success
”

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 UK

Target population(s): Adults with TB

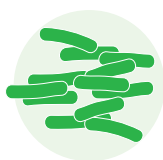
Year funded: 2018

EDCTP funding: €11.4M

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.



“
a 30% reduction
in the incidence
of TB-IRIS
”

Reducing the risk of TB ‘flare ups’ during HIV therapy

The PredART trial has shown that an affordable steroid drug, prednisone, reduces the risk of damaging inflammatory responses in TB-infected HIV patients.

The challenge

Up to 42% of people with HIV in sub-Saharan Africa are also infected with TB. Early initiation of antiretroviral therapy in HIV patients with TB infections and low levels of CD4 cells (the immune cells infected by HIV) saves lives. However, around one in five such patients experience an inflammatory reaction known as TB-IRIS, as their immune system recovers and responds too vigorously to the TB infection. TB-IRIS may require hospitalisation and can lead patients to question the effectiveness of their HIV treatment.

The project

The PredART trial tested whether prednisone, a steroid drug used to treat TB-IRIS, could also prevent the reaction when used prophylactically. TB-infected HIV patients in South Africa who had not yet begun antiretroviral therapy, but had recently started TB treatment, were enrolled in a randomised double-blind placebo-controlled trial. Patients received either oral prednisone or placebo during the first 4 weeks of antiretroviral therapy and patients developing TB-IRIS were treated with corticosteroids as required.

The results

Prophylactic use of prednisone at the start of antiretroviral therapy resulted in a 30% reduction in the incidence of TB-IRIS, from 47% to 30%. It also more than halved the need for steroids to treat those who developed TB-IRIS. In the prednisone-treated patients, there were fewer adverse events overall and no evidence of any increased risk of severe infections or malignancy.

Impact

The PredART trial has generated the first evidence that a simple and affordable drug given during the initial weeks of antiretroviral therapy can significantly reduce the risk of TB-IRIS, a

Project at a glance

Project: PredART trial

Project lead: Dr Graham Meintjes, University of Cape Town, South Africa

Countries involved: Belgium, South Africa, the UK

Target population(s): Adults with HIV and TB infections

Sample size: 240

Project duration: 2012–2015

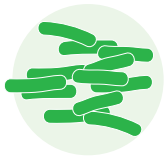
EDCTP funding: €0.59M

Total project funding: €0.89M

common complication of HIV treatment in sub-Saharan Africa. Prednisone could be readily integrated into HIV treatment guidelines.

Key reference

Meintjes G et al. Randomized controlled trial of prednisone for prevention of paradoxical TB-IRIS. Conference on Retroviruses and Opportunistic Infections, Seattle, Washington, USA, 13–16 February 2017. Abstract no. 81LB



“
specifically
designed
to protect
people already
exposed to *M. tuberculosis*
”

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: €13.8M

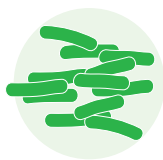
Impact

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.



“
Positive results
would pave
the way for a
pivotal phase III
trial

”

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)

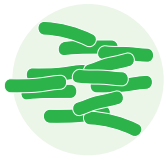
Year funded: 2018

EDCTP funding: €5.5M

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.



“
**Positive findings
would indicate
that VPM1002
is a suitable
alternative to
BCG**
”

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 more than 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; it would also provide a suitable vaccine for infants with HIV. 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: 10,000 (target)

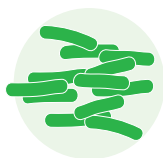
Year funded: 2018

EDCTP funding: €12.5M

Total project funding: €25M

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.



“
key data on
real-world use of
Xpert MTB/RIF
”

Making the case for Xpert MTB/RIF

EDCTP Senior Fellow Professor Mark Nicol made a key contribution to a landmark global study confirming the power of the Xpert MTB/RIF test to diagnose TB.

The challenge

Diagnosis of TB is a major challenge. Culturing of *Mycobacterium tuberculosis* is the most accurate method, but takes several weeks and requires specialist facilities. Microscopy is quicker but misses many cases, particularly in people with HIV infections. The absence of a rapid and reliable test has led to delays in the initiation of treatment, increasing the risk of serious disease and death and providing more opportunity for TB to spread.

The project

In the early 2000s, a new molecular diagnostic test for TB was developed, Xpert MTB/RIF, which could also detect a common form of drug resistance (to rifampicin). In trials, Xpert MTB/RIF was shown to be a rapid and reliable TB diagnostic. However, highly controlled trials in specialist centres may not give a true indication of test performance in more challenging real life settings. A global trial was therefore organised, in six countries, to assess the performance of Xpert MTB/RIF in routine healthcare facilities in resource-poor settings. EDCTP Senior Fellow Professor Mark Nicol made key contributions to this trial, with South Africa accounting for more than a third of the total number of participants.

The results

The trial showed that Xpert MTB/RIF could rapidly and reliably detect TB in district health facilities when used by routine staff with minimal training.

Impact

The study's findings provided key data on real-world use of Xpert MTB/RIF. They formed a major part of a report submitted to the WHO Strategic and Technical Advisory Group for Tuberculosis which endorsed use of Xpert MTB/RIF in 2010. Following the WHO recommendation, by the end of 2016, 28 out

Project at a glance

Project: EDCTP Senior Fellowship

Project lead: Professor Mark Nicol, University of Cape Town, South Africa

Countries involved: South Africa

Target population(s): Adults

Sample size: 2522 (out of 6648)

Year funded: 2008

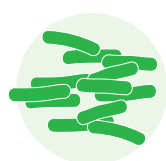
EDCTP funding: €0.2M

of 48 high-burden countries have adopted Xpert MTB/RIF as the initial diagnostic test for pulmonary TB.

Key references

Boehme CC et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet*. 2011;377(9776):1495–505.

WHO. *Global Tuberculosis Report 2017*. 2017. Geneva: WHO



“
leading to
recommendation
for LAM testing
in immunocom-
promised HIV
patients
”

New tools for rapid diagnosis of TB

The TB-NEAT consortium has generated key evidence on methods of TB diagnosis – including the first evidence that use of a new diagnostic saves lives.

The challenge

Traditional methods of TB diagnosis rely on culturing of bacteria from sputum samples, which takes several weeks and requires specialist facilities. Rapid and accurate TB diagnosis could provide huge benefits, allowing rapid initiation of treatment. The Xpert MTB/RIF test has proven to be a sensitive and specific rapid test, and its use has been recommended by WHO. However, there may also be a role for alternative tests, including the LAM-TB test, a dipstick test that detects lipoarabinomannan (LAM), a molecule derived from *Mycobacterium tuberculosis*, in urine.

The project

The TB-NEAT consortium has generated important data on how TB diagnostics function in real-life settings – the most valuable evidence for decision makers. It has examined how use of the Xpert MTB/RIF test affects clinical outcomes in primary care in Africa, its use to detect TB in children in primary care, and the impact of LAM-TB use on survival in patients with HIV and TB.

The results

Use of Xpert MTB/RIF test by nurses in primary care was found to be feasible, more patients started treatment the same day, and overall treatment was started quicker. However, these advantages did not translate into survival benefits, largely because, in practice, doctors do not solely rely on the results of diagnostic tests when deciding on treatment.

Diagnosis of TB in children is even more challenging, as symptoms are typically very non-specific. The TB-NEAT team found that use of Xpert MTB/RIF was feasible in primary care, where most children with pulmonary TB are treated, using washings from the back of the nose. The test was more sensitive than culture methods and results were available much more rapidly.

The LAM-TB study showed that adding the dipstick test to existing diagnostics reduced the risk of death by 17% at 8 weeks – making it the first trial to show survival benefits following

Project at a glance

Project: TB-NEAT study

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

Countries involved: Germany, the Netherlands, South Africa, Sweden, Tanzania, the UK, Zambia, Zimbabwe

Target population(s): Adults; children; HIV-positive adults

Sample size: 1502 (adults); 384 (children); 2659 (HIV-positive adults)

Project duration: 2010–2014

EDCTP funding: €4.3M

Total project funding: €7.2M

introduction of a new TB diagnostic. Survival benefits were greatest in patients whose immune systems were most badly affected.

Impact

The Xpert MTB/RIF studies have shown that this technology could be used to detect TB in children in primary care settings. The findings in adults, however, indicate that quicker diagnosis may not in practice deliver the anticipated clinical benefits, emphasising that the impact of the technology will depend fundamentally on the health service context in which it is introduced. Finally, the LAM-TB study informed the deliberations of a WHO expert panel, leading to recommendation for LAM testing to be used in immunocompromised HIV patients.

Key references

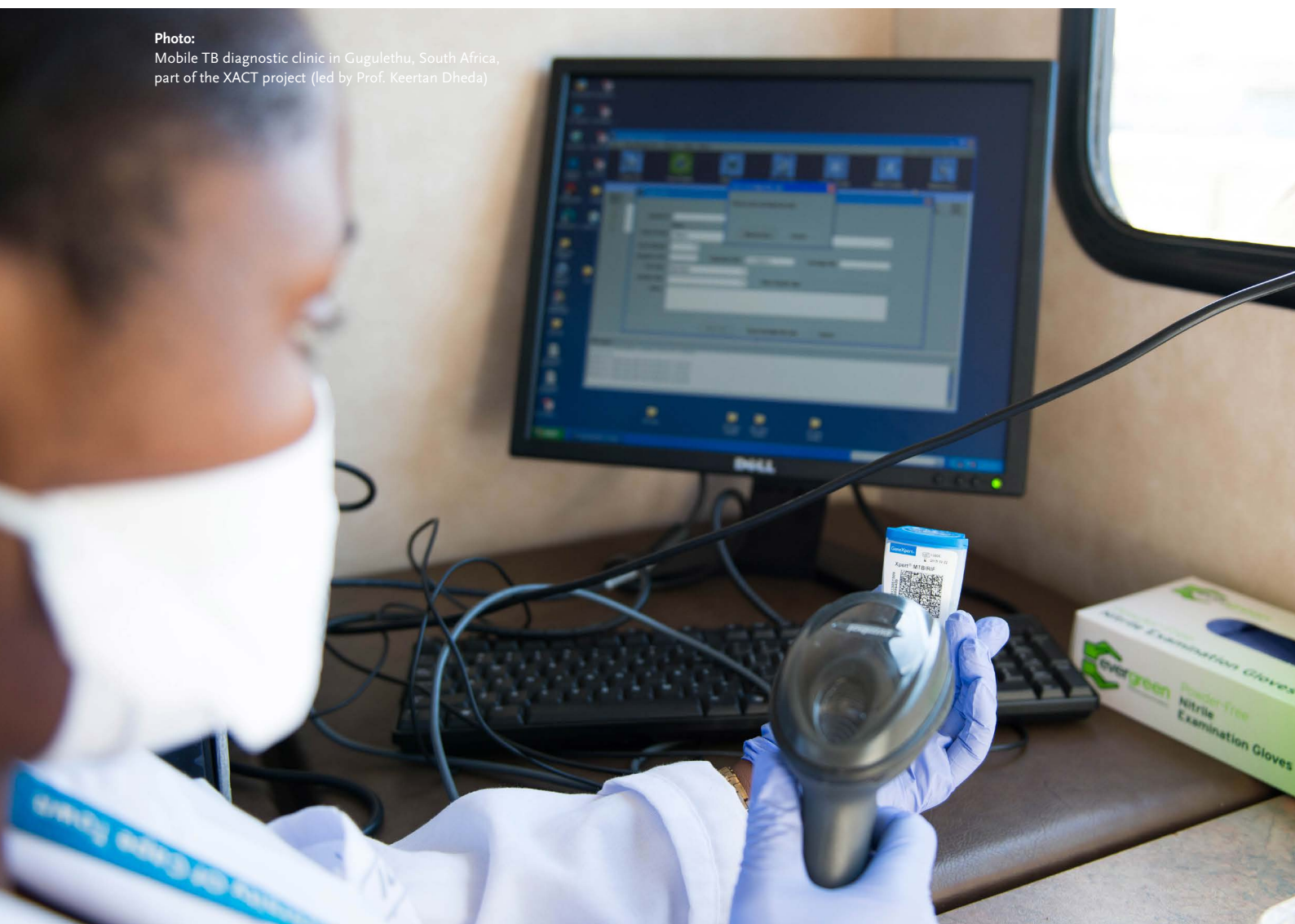
Theron G et al. Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. *Lancet*. 2014;383(9915):424–35.

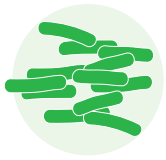
Zar HJ et al. Rapid diagnosis of pulmonary tuberculosis in African children in a primary care setting by use of Xpert MTB/RIF on respiratory specimens: a prospective study. *Lancet Glob Health*. 2013;1(2):e97–e104.

Peter JG et al. Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group, multicountry, open-label, randomised controlled trial. *Lancet*. 2016;387(10024):1187–97.

WHO. *The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV*. 2015. Geneva: WHO

Photo:
Mobile TB diagnostic clinic in Gugulethu, South Africa,
part of the XACT project (led by Prof. Keertan Dheda)





“
**findings
support WHO's
conditional
recommendation
of Xpert MTB/
RIF in children**

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Detecting TB in children

The TB-CHILD Consortium has generated much-needed evidence on tools to diagnose TB in children.

The challenge

Identifying active TB disease in children is one of the most difficult and important challenges in TB. Culturing of *Mycobacterium tuberculosis* from sputum is the 'gold standard', but takes weeks and requires specialist facilities, and children may not be able to generate the necessary samples. Furthermore, sputum samples from young children may contain very few culturable bacteria.

The project

The TB-CHILD Consortium has evaluated a range of possible diagnostics for TB in children. A study of the mostly commonly used molecular diagnostic, Xpert MTB/RIF, performed well, identifying 1.7 times as many confirmed cases as another rapid method, microscopic examination of sputum samples. However, the difficulties of obtaining sputum samples remained a significant obstacle.

A sputum-independent diagnostic method would therefore have many advantages. In a proof-of-concept study, the TB-CHILD Consortium has obtained encouraging data on one possible approach. The TAM-TB assay is a rapid blood test that detects changes in the numbers of a particular type of immune cell, seen in active TB infections. TAM-TB showed good specificity and excellent sensitivity, and provided results from a simple blood sample within a day. Importantly, the test could distinguish between latent TB (quiescent infections with no clinical symptoms) and active TB disease.

Impact

The TB-CHILD Consortium's findings support the WHO's conditional recommendation of Xpert MTB/RIF in children and open up the potential for a new simpler and more convenient blood-based test. The TAM-TB results are promising, although the test is currently expensive and requires sophisticated laboratory procedures. Work is ongoing to develop a more affordable

Project at a glance

Project: TB-CHILD Consortium

Project lead: Professor Fred Lwilla, Ifakara Health Institute, Tanzania

Countries involved: Germany, Italy, South Africa, Switzerland, Tanzania, Uganda, the UK

Target population(s): Children

Sample size: 451 (Xpert MTB/RIF); 130 (TAM-TB)

Project duration: 2010–2013

EDCTP funding: €1.9M

Total project funding: €3.3M

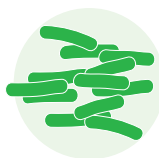
version compatible with the equipment used in laboratories in low- and middle-income countries.

Key references

Reither K et al. Xpert MTB/RIF assay for diagnosis of pulmonary tuberculosis in children: a prospective, multi-centre evaluation. *J Infect.* 2015;70(4):392–9.

Portevin D et al. Assessment of the novel T-cell activation marker-tuberculosis assay for diagnosis of active tuberculosis in children: a prospective proof-of-concept study. *Lancet Infect Dis.* 2014;14(10):931–8.

WHO. *Xpert MTB/RIF: WHO policy update and implementation manual.* 2013. Geneva: WHO



“
*many children
are dying because
their TB is never
diagnosed*
”

Improving TB diagnosis in children

The RaPaed 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 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 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

Project at a glance

Project: RaPaed project

Project lead: Norbert Heinrich, Ludwig Maximilians University, 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: €3.0M

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, 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.



Photo:
Medical staff and research volunteer at the Regional Hospital of Banfora, Burkina Faso, part
of the WANECAM project (led by Prof. Abdoulaye Djimdé)

EDCTP portfolio: Malaria

2003-2018



64 grants

€114.83 M



Drugs
34 grants

€76.70 M



Vaccines
10 grants

€33.69 M



Diagnostics
3 grants

€0.73 M

Note:

A further €3.71M for 17 grants was awarded to projects on non-intervention-specific.



“
successful
applications
to the EMA to
extend use of PA
to treatment of
multiple episodes
of malaria
”

New options for repeat use of antimalarials

The WANECAM trial has shown that two newly developed antimalarials remain safe and efficacious in West Africa even when used repeatedly.

The challenge

In West Africa, which accounts for half the world's malaria deaths, malaria infections are commonplace. It is therefore important to determine whether treatments remain safe and effective when used repeatedly in the same patient. AL and ASAQ are the main artemisinin-based combination therapies (ACTs) used in West Africa*, but use of ASAQ in seasonal chemoprevention campaigns means that countries are relying almost entirely on AL – a risky strategy given the danger that resistance will develop.

The study

The WANECAM study, carried out by the EDCTP-funded West African Network for Clinical Trials of Antimalarial Drugs, compared the efficacy and safety of two new antimalarial drug combinations – PA and DP – with those of AL and ASAQ. More than 4700 patients, adults and children over 6 months, were treated during the course of two years, at seven sites in three countries. Most patients had at least two infections over this period, and children had up to 13.

The results

All the drug combinations were highly efficacious. DP had the added advantage of reducing the incidence of disease, probably because it persisted longer in the bloodstream of patients (the downside of this being a potentially increased risk of resistance as parasites are exposed to lower drug doses for longer). There was no evidence that PA was associated with liver toxicity, an earlier concern, or that repeated use of DP worsened its known sub-clinical impact on heart function.

Impact

The study provided high-quality evidence that PA and DP are safe and effective in West Africa even when used repeatedly, and provided

Project at a glance

Project: The WANECAM trial

Project lead: Professor Abdoulaye Djimdé, University of Science, Techniques and Technologies of Bamako, Mali

Countries involved: Burkina Faso, France, the Gambia, Germany, Guinea, Mali, Sweden, the UK

Target population(s): Children over 6 months; adults

Sample size: 4710

Project duration: 2009–2014

EDCTP funding: €4.8M

Total project funding: €9.3M

a new option for national malaria control programmes, to reduce the concerning reliance on a single ACT in the region. Trial results were used to support successful applications to the European Medicines Agency to extend use of PA to treatment of multiple episodes of malaria, and for use of a granular paediatric formulation suitable for children from 5 to 20 kg; both formulations are now on the list of WHO-prequalified medicines.

Key reference

West African Network for Clinical Trials of Antimalarial Drugs (WANECAM). Pyronaridine-artesunate or dihydroartemisinin-piperaquine versus current first-line therapies for repeated treatment of uncomplicated malaria: a randomised, multicentre, open-label, longitudinal, controlled, phase 3b/4 trial. *Lancet*. 2018;391(10128):1378–1390.

*AL: artemether–lumefantrine (Coartem®); ASAQ: amodiaquine–artesunate; DP: dihydroartemisinin–piperaquine (Eurartesim®); PA: pyronaridine–artesunate (Pyramax®).



“
the largest
clinical trial of
artesunate–
mefloquine in
young African
children
”

Expanding the drug arsenal for childhood malaria

The ASMQ trial showed that a new formulation of artesunate–mefloquine is effective and well-tolerated in young children, and should be considered for use in Africa.

The challenge

Artemisinin-based combination therapies (ACTs) are the mainstay of treatments for malaria, responsible for the deaths of around 300,000 children in Africa every year. Several ACTs are used in Africa, but it is important to maintain a diversity of combinations to reduce the selection pressures that drive drug resistance. Artesunate–mefloquine is extensively used globally, but has not been widely introduced in Africa, in part because of the availability of affordable alternatives, including a combination known as AL*, and in part due to concerns about its side effects in young children – particularly vomiting, which can lead to treatment failure.

The study

The Drugs for Neglected Diseases Initiative has worked with a Brazilian pharmaceutical company, Farmanguinhos, to develop a fixed-dose combination for artesunate–mefloquine – single tablets containing both active ingredients. Several global studies have shown that this fixed-dose combination is effective and well-tolerated. The ASMQ trial compared the artesunate–mefloquine fixed-dose combination with AL, the most commonly used ACT in Africa, for treatment of uncomplicated malaria in children under 5 at six sites in three African countries.

The results

Artesunate–mefloquine was as effective as AL in treating malaria, and no more likely to cause vomiting. As mefloquine persists in the bloodstream longer than lumefantrine, it may also have the additional advantage of reducing the risk of early re-infection.

Project at a glance

Project: The Artesunate–Mefloquine (ASMQ) study

Project lead: Dr Nathalie Strub-Wourgaft, Drugs for Neglected Diseases Initiative, Switzerland

Countries involved: Burkina Faso, France, Kenya, Luxembourg, Switzerland, Tanzania

Target population(s): Children (6 months to 5 years)

Sample size: 945

Project duration: 2010–2014

EDCTP funding: €381,000

Total project funding: €2M

Impact

The ASMQ trial was the largest randomised controlled trial of artesunate–mefloquine in young African children. It confirmed that artesunate–mefloquine is a suitable treatment in Africa, providing an additional option for health policymakers and enabling them to follow the WHO recommendation to use multiple ACTs to reduce the risk of resistance.

Key references

Sirima SB et al. Comparison of artesunate–mefloquine and artemether–lumefantrine fixed-dose combinations for treatment of uncomplicated *Plasmodium falciparum* malaria in children younger than 5 years in sub-Saharan Africa: a randomised, multicentre, phase 4 trial. *Lancet Infect Dis*. 2016;16(10):1123–1133.

WHO. *Guidelines for the Treatment of Malaria* (3rd edn). 2015. Geneva: WHO

*AL: artemether–lumefantrine (Coartem®).



“
data on the
safety of DP in
young children, a
key evidence gap
”

Optimising antimalarial dosing in children

The ADJusT project is combining data gathering and modelling to provide guidance on the appropriate dosage of antimalarials for children.

The challenge

Appropriate dosing of antimalarial drugs is critical – if drug concentrations are too low, malaria parasites may not be killed but if they are too high they may cause side effects. Determining the right dose for young children is particularly challenging, as at the same mg/kg dose the achieved drug concentrations may differ considerably from those in older children and adults. In addition, as many treatment sites in Africa do not have weighing scales, dosing decisions are often based on age rather than weight, resulting in a much larger variation in drug concentrations in children in practice.

One specific challenge relates to dosing of dihydroartemisinin–piperaquine (DP) in children. The recommended DP range in target dose and drug concentrations is narrower than for the other WHO-recommended malaria treatments. An analysis of DP studies done to date suggested that young children were receiving sub-optimal dosing, putting them at risk of treatment failures. However, as DP can also influence heart rhythms, use of higher doses might have clinically important safety implications.

The project

The ADJusT project was carefully designed to safely explore the pharmacokinetic profile (drug concentrations over time) of step wise increases towards higher doses that had been proposed from pharmacometric modelling. The higher DP dose was evaluated in over 100 children with uncomplicated malaria to evaluate dosing, tolerability and safety, particularly any impact on heart rhythms. The ADJusT study provides valuable supportive data to optimise antimalarial dosing in children, designed to ensure that the smallest number of patients with malaria receive doses above or below the target therapeutic range. This was the first study to use the higher dose in young children and was the only clinical data available to the World Health Organization (WHO) when they decided to adjust the dose recommendation for young children for the 3rd

Project at a glance

Project: ADJusT

Project lead: Dr D J (Anja) Terlouw, Malawi–Liverpool–Wellcome Trust Clinical Research Programme

Countries involved: Austria, Malawi, the UK

Target population(s): Children

Sample size: 106

Project duration: 2013–2015

EDCTP funding: €535,064.55

Total project funding: €535,064.55

edition of WHO Guidelines for the Treatment of Malaria.

Pharmacometric Modelling was then used to systematically evaluate the impact of factors that cannot be tested in clinical trials, such as variation in adherence or drug resistance.

The results

The study in children with uncomplicated malaria confirmed that the evaluated higher dose of DP was safe. However, while DP was associated with a concentration-related change in heart rhythms, no clear dose–response relationship was observed with the assessed dose range.

The modelling work showed how programmatic use of artemether–lumefantrine (AL) or DP would be affected by age-based regimens and various factors such as adherence and drug resistance. Notably, age-based dosing for DP was associated with a much higher projected failure rate, suggesting that AL would be more appropriate when age-based dosing is used, highlighting the risk of under-dosing of the dihydroartemisinin component in currently available DP formulations.

Impact

The models have the potential to shape the design of malaria control programme policies on malaria treatment, preventive treatment and mass drug administration. The field study generated important data on the safety of DP in young children, a key evidence gap. Preliminary data were presented to the dosing workgroup of the WHO Technical Expert Group on Malaria Chemotherapy, which directly informed the revised DP dose recommended in the WHO Guidelines for the treatment of malaria in 2015 and likely contributed to the WHO Malaria Policy Advisory Committee decision to review the evidence on cardiac safety of malaria drugs in 2016. Based on the recommendations from this review an EDCTP-funded follow-up study was initiated. In partnership with the WorldWide Antimalarial Resistance Network (WWARN), the ADJusT data were then pooled with other individual patient data on the relationships between dose, drug concentrations and treatment response (efficacy, safety and tolerability) to help inform the optimal dosing and use of both DP and artemether-lumefantrine (AL) in vulnerable populations to address remaining evidence gaps.

Key references

Hodel EM et al. Optimizing the programmatic deployment of the anti-malarials artemether-lumefantrine and dihydroartemisinin-piperaquine using pharmacological modelling. *Malar J.* 2014;13:138.

Guidelines for the treatment of malaria - third edition. 15 May 2015. World Health Organization.

The cardiotoxicity of antimalarials. Report of the WHO Evidence Review Group Meeting, 13–14 October 2016 Varembe Conference Centre, Geneva, Switzerland



Photo:
Medical staff and volunteers, part of the
PfSPZ Challenge study (Kenya)



“
largest head-to-head comparison of ACTs in children ever undertaken in Africa
”

New treatment options for children with malaria

The 4ABC trial identified the most effective antimalarial drug combinations for treating uncomplicated malaria in young African children.

The challenge

In 2005, malaria was responsible for the deaths of an estimated one million people in sub-Saharan Africa every year, most of them children. At that time, highly effective combination therapies based on artemisinin or one of its derivatives (artemisinin-based combination therapies, ACTs) were beginning to be introduced globally. However, there was little evidence from Africa on the safety and efficacy of these treatments in children to guide national drug policies.

The study

The 4ABC study directly compared four ACTs – two already in use in Africa (known as AL and ASAQ), a recently developed combination (DP) and a promising combination in development (CD+A)*. The combinations were evaluated in a range of head-to-head comparisons at 12 sites in seven west, east and southern Africa countries.

The results

AL, ASAQ and DP were all safe and highly effective treatments for uncomplicated malaria in children. CD+A was less efficacious, and its development was halted during the trial when a separate study identified an increased risk of anaemia in some patients. Notably, in follow-up, DP was found to reduce the number of re-infections, probably because it persists in the bloodstream longer than the other combinations.

Impact

The 4ABC trial was the largest head-to-head comparison of ACTs in children ever undertaken in Africa, and proved to be a very important and high-impact study. It showed that AL, ASAQ and DP were all highly efficacious, and that DP had the additional benefit of significantly reducing re-infection rates.

Project at a glance

Project: The Four Artemisinin-Based Combinations (4ABC) study

Project lead: Professor Umberto D'Alessandro, Institute for Tropical Medicine, Antwerp, Belgium (now Medical Research Council, The Gambia)

Countries involved: Belgium, Burkina Faso, Gabon, Germany, Mozambique, Nigeria, Rwanda, Spain, Uganda, the UK, Zambia

Target population(s): Children (6 months to 5 years)

Sample size: 4116

Project duration: 2005–2010

EDCTP funding: €2.4M

Total project funding: €5.6M

The trial data contributed to the approval of DP by the European Medicines Agency and to the WHO recommendation for use of DP to treat uncomplicated malaria. The trial also provided evidence to guide the decision making of national malaria control agencies based on the local characteristics of malaria transmission and patterns of drug resistance. Widespread use of ACTs has contributed to a dramatic reduction in malaria cases, with deaths in Africa falling by 37% between 2010 and 2016.

Key references

Four Artemisinin-Based Combinations (4ABC) Study Group. A head-to-head comparison of four artemisinin-based combinations for treating uncomplicated malaria in African children: a randomized trial. *PLoS Med.* 2011;8(11):e1001119.

WHO. *Guidelines for the Treatment of Malaria* (3rd edn). 2015. Geneva: WHO

*AL: artemether–lumefantrine (Coartem®); ASAQ: amodiaquine–artesunate; DP: dihydroartemisinin–piperaquine (Eurartesim®); CD+A: chlorproguanil–dapsone–artesunate.



“
Positive results
would pave
the way for a
pivotal phase III
trial

”

Safe antimalarials for pregnant women

The PREGACT trial confirmed that four artemisinin-based combination therapies are safe and effective in pregnant women.

The challenge

Malaria in pregnancy, and asymptomatic infections with the Plasmodium parasite, are harmful to both mother and child. Infections increase a mother's risk of anaemia and can affect a baby's birthweight, increasing the risk of death in early infancy. Although the WHO recommends the use of ACTs in the second and third trimester of pregnancy, there is very little evidence on their safety and efficacy in pregnant women, who are routinely excluded from clinical trials.

The study

The PREGACT study compared four ACTs – AL, ASAQ, DP and mefloquine–artesunate* – in 3400 pregnant women with malaria in four African countries.

The results

All of the treatments were highly effective, although cure rates were slightly lower for AL. No significant differences were seen in serious side effects and birth outcomes, while fewest minor side effects were seen with AL use. DP had the highest efficacy and also offered best protection from re-infection, probably because of its longer persistence in the bloodstream.

Impact

Performing studies in vulnerable populations such as pregnant women is extremely challenging but may be of major medical importance. This study, still the largest ever carried out on malaria treatment in pregnant women in Africa, confirmed that the four ACTs are all safe and effective in this vulnerable group of patients.

Furthermore, the findings provide guidance on the most appropriate choice of ACT in different settings – where malaria transmission is intense, for example, and women are at risk of multiple infections during pregnancy, the longer-term

Project at a glance

Project: The PREGACT study

Project lead: Professor Umberto D'Alessandro, Institute for Tropical Medicine, Antwerp, Belgium (now Medical Research Council, The Gambia)

Countries involved: Austria, Belgium, Burkina Faso, Ghana, Malawi, the Netherlands, Rwanda, Tanzania, Zambia

Target population(s): Pregnant women (second and third trimester)

Sample size: 3428

Project duration: 2009–2014

EDCTP funding: €3M

Total project funding: €6.5M

protection offered by DP would be an advantage. The results are already informing national malaria treatment policies and are likely to influence revisions of WHO treatment guidelines.

Key reference

PREGACT Study Group et al. Four artemisinin-based treatments in African pregnant women with malaria. *N Engl J Med.* 2016;374(10):913–27

*AL: artemether–lumefantrine (Coartem®);
ASAQ: amodiaquine–artesunate;
DP: dihydroartemisinin–piperaquine (Eurartesim®).



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increased
preventive use of
SP in pregnant
women could
have a major
beneficial impact
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Protecting pregnant women from malaria

The ISTp-A and -B trials have provided valuable information on ways to protect pregnant women from malaria.

The challenge

Malaria poses a particular threat to pregnant women, potentially affecting both their health and that of their baby: malaria infection in pregnancy can lead to low birthweight, which increases the risk of death in the first year of life. Pregnant women are routinely given a drug combination known as SP to prevent malaria*, but the effectiveness of SP is threatened by growing levels of drug resistance. A ‘test-and-treat’ model has been suggested as an alternative approach, with pregnant women being screened for malaria infection using rapid diagnostic tests and those testing positive being given artemisinin combination therapy (ACT).

The project

The ISTp-A and -B trials compared two novel ACT-based test-and-treat approaches – using either AL or DP – and conventional SP-based prevention in pregnant women. The research team also explored how local levels of SP resistance impacted on the effectiveness of existing SP-based programmes.

The results

The ISTp team found that an AL-based test-and-treat approach was as good as the SP-based preventive strategy. However, modelling suggested that, given the additional cost of ACT, it would be unlikely to be cost-effective (although it did estimate levels of SP resistance at which the test-and-treat approach would become cost-effective). In addition, in an area of high SP resistance, the DP-based test-and-treat strategy was actually less effective than the conventional SP-based approach.

Furthermore, the team also found that, in areas of very high SP resistance, although SP is less effective at curing malaria, it was still associated with less maternal anaemia and higher birthweight. Indeed, a modelling study suggested that increased preventive use of SP in pregnant women could have a major beneficial impact, despite the spread of SP resistance.

Project at a glance

Project: The Intermittent Screening and Treatment in Pregnancy studies (ISTp-A and -B)

Project lead: Professor Feiko Ter Kuile, Liverpool School of Tropical Medicine, UK

Countries involved: Austria, Burkina Faso, Denmark, The Gambia, Ghana, Mali, Mozambique, the UK (ISTp-A); Austria, Malawi, Mozambique, the UK (ISTp-B)

Target population(s): Pregnant women

Sample size: 5354 (ISTp-A); 1873 (ISTp-B)

Project duration: 2008–2013

EDCTP funding: €3.6M

Total project funding: €6.2M

Impact

The findings have provided important input to decision-makers considering how best to protect pregnant women from malaria. In particular, as well as highlighting the shortcomings of current test-and-treat alternatives, the findings have identified the benefits of even compromised SP strategies.

Key references

Tagbor H et al. A non-inferiority, individually randomized trial of intermittent screening and treatment versus intermittent preventive treatment in the control of malaria in pregnancy. *PLoS One*. 2015;10(8):e0132247.

Fernandes S et al. Cost effectiveness of intermittent screening followed by treatment versus intermittent preventive treatment during pregnancy in West Africa: analysis and modelling of results from a non-inferiority trial. *Malar J*. 2016;15(1):493.

Desai M et al. Impact of sulfadoxine-pyrimethamine resistance on effectiveness of intermittent preventive therapy for malaria in pregnancy at clearing infections and preventing low birth weight. *Clin Infect Dis*. 2016;62(3):323–333.

Madanitsa M et al. Scheduled intermittent screening with rapid diagnostic tests and treatment with dihydroartemisinin-piperaquine versus intermittent preventive therapy with sulfadoxine-pyrimethamine for malaria in pregnancy in Malawi: An open-label randomized controlled trial. *PLoS Med*. 2016;13(9):e1002124.

Desai M et al. Prevention of malaria in pregnancy. *Lancet Infect Dis*. 2018;18(4):e119–e132

Walker PG et al. Estimated impact on birth weight of scaling up intermittent preventive treatment of malaria in pregnancy given sulphadoxine-pyrimethamine resistance in Africa: A mathematical model. *PLoS Med*. 2017;14(2):e1002243.

*AL: artemether–lumefantrine (Coartem®);
DP: dihydroartemisinin–piperaquine (Eurartesim®); SP: sulfadoxine–pyrimethamine.



Photo:
Laboratory staff at the Ahero Sub-district Hospital
in Nyanza, Kenya, part of the PfSPZ Challenge study (led by
Dr Bernhards Ogutu)



“
**Although
mefloquine
could not be
recommended,
the results have
provided valuable
input to WHO**
”

The case against mefloquine use in pregnancy

The MiPPAD trial has found that mefloquine-containing antimalarial treatments are not suitable for use in pregnant women.

The challenge

Pregnant women are particularly badly affected by malaria infections. In addition, fetal growth may be impaired, leading to low birthweight – a significant risk for infant death in the first year of life. Nearly 30 million pregnancies occur every year in areas where women are at significant risk of malaria. Because of this vulnerability, WHO recommends protective measures including insecticide-treated bednets and courses of preventive antimalarial drug treatment with sulfadoxine–pyrimethamine (SP).

However, resistance to SP is growing and it cannot be used in women with HIV who are also given co-trimoxazole to prevent infections – at least one million pregnancies in sub-Saharan Africa are complicated by both HIV and malaria infections, and in some locations as many as 40% of pregnant women are infected with HIV.

The study

Mefloquine has been identified as a promising alternative to SP. It is safe for use in pregnancy, has long-lasting effects and can be given as a single dose. It is also suitable for use with co-trimoxazole, so offers a potential option for pregnant women with HIV infections. The MiPPAD trial evaluated mefloquine-containing preventive treatment in nearly 5000 HIV-free pregnant women and more than 1000 HIV-infected pregnant women.

The results

In HIV-free women, mefloquine was as effective as SP in preventing low birth weight. There were no differences in birth complications, and mothers on mefloquine had fewer episodes of clinical malaria. However, mefloquine was poorly tolerated, with mothers experiencing high levels of dizziness and vomiting.

Project at a glance

Project: MiPPAD study

Project lead: Professor Clara Menéndez Santos, Barcelona Institute for Global Health, Spain

Countries involved: Austria, Benin, France, Gabon, Germany, Kenya, Mozambique, Spain, Tanzania

Target population(s): Pregnant women with or without HIV infections

Sample size: 4749 (HIV-uninfected); 1071 (HIV-infected)

Project duration: 2008–2014

EDCTP funding: €3.6M

Total project funding: €8.7M

In HIV-infected women, mefloquine use was again associated with some clinical benefits in mothers, including fewer infections and hospital admissions. However, it was again poorly tolerated. In addition, in mefloquine-treated women, HIV replicated more and the incidence of mother-to-child transmission was increased, suggesting that the drug might be interfering with the effectiveness of antiretrovirals.

Impact

The MiPPAD study provided a large body of high-quality evidence on the efficacy, safety and, importantly, the tolerability of mefloquine as a possible alternative to SP for prevention of malaria in pregnancy. The extent of this data allowed a comprehensive assessment of the benefits and risks of using mefloquine in this vulnerable patient population. Although mefloquine could not be recommended, the results have provided valuable input to the WHO Malaria Policy Advisory Committee and WHO malaria policy brief, and is ensuring that resources are now devoted to investigating better alternatives.



Photo:
Research team at the Regional Hospital of Banfora,
Burkina Faso, part of the WANECAM project (project led by
Prof. Abdoulaye Djimde)

Indeed, in the follow-on MAMAH trial, launched in 2018, the MiPPAD team is investigating preventive treatment with a relatively new antimalarial combination, dihydroartemisinin–piperaquine (DP), in HIV-infected pregnant women receiving antiretroviral drugs and cotrimoxazole. As well as impacts on malaria, the trial will also look to see if DP has any impact on metabolism of antiretroviral drugs or affects mother-to-child transmission of HIV.

Key references

González R et al. Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-negative women: A multicentre randomized controlled trial. *PLoS Medicine*. 2014;11(9): e1001733.

González R et al. Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV Infected women receiving cotrimoxazole prophylaxis: A multicenter randomized placebo-controlled trial. *PLoS Medicine*. 2014;11(9): e1001735.

WHO. WHO policy brief for the implementation of intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP) April 2013 (revised January 2014). 2014. Geneva: WHO



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two larger trials
in ten sites in
three countries,
involving more
than 45,000
women
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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, UK

Countries involved: Denmark, Finland, Kenya, Malawi, Norway, Tanzania, the UK

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: €10.6M

Total project funding: €10.6M

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.



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the aim of
achieving the
WHO Roadmap's
target of 75%
efficacy
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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, PfPRH5; 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, UK

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

Target population(s): Infants

Sample size: 1493 (estimated for four trials)

Year funded: 2018

EDCTP funding: €15M

Total project funding: €20M

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.



Photo:
Researcher at the Regional Hospital of
Banfora, Burkina Faso, part of the WANECAM project
(led by Prof. Abdoulaye Djimdé)

8 EDCTP portfolio: Neglected infectious diseases

2014-2018



21 grants
€48.36 M



Drugs
10 grants
€30.85 M



Vaccines
1 grants
€8 M



Diagnostics
6 grants
€8.7 M

Note:

A further €0.81M for 4 grants was awarded to projects on non-intervention-specific .



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test the safety
and efficacy of
this new
formulation in
young children
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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: Stichting Lygature, Utrecht, The Netherlands

Countries involved: Cote d'Ivoire, Germany, Kenya, the Netherlands, Switzerland, the UK

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

Sample size: 295 (target)

Year funded: 2018

EDCTP funding: €2.0M

Total project funding: €12.1M



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two trials in
Sudan on people
cured of visceral
leishmaniasis
by drug
treatment
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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 two trials in Sudan on people who have been cured of visceral leishmaniasis by drug treatment. The first will test the safety of increasing doses of the vaccine and its use in children. The second study will gather data on safety and preliminary evidence of efficacy 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

Project at a glance

Project: PREV_PKDL study

Project lead: Dr Odile Leroy, European Vaccine Initiative

Countries involved: Germany, Ethiopia, Kenya, Sudan, Uganda, the UK

Target population(s): Adults, children

Sample size: 288 (target)

Year funded: 2018

EDCTP funding: €8.0M

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.

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.



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the second
approach is
designed for
large-scale
monitoring of
populations at
risk

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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 DR 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, the UK

Target population(s): All age groups

Year funded: 2016

EDCTP funding: €3.0M

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.



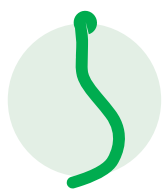
Photo:
Project staff member, part of AMBITION-cm project (Botswana)





Photo:

Researchers at the KAVI-Kenyatta National Hospital in Nairobi, Kenya, part of the HIV-CORE004 project (led by Prof. Tomáš Hanke)



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*new vaccines,
drugs and
diagnostics
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tested during
emergency
outbreaks*
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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\$2.2bn 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, UK

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

Year funded: 2018

EDCTP funding: €10.0M

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.



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PANDORA-ID-NET has already been called into action at the request of the Republic of Congo
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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 Congo

Countries involved: Republic of Congo, France, Gabon, Germany, Ghana, Italy, Nigeria, Sierra Leone, Sudan, Tanzania, Uganda, the UK, Zambia

Year funded: 2018

EDCTP funding: €10.0M

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 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 (ALERT), 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.



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...absence of data
from Africa
prevented
WHO from
recommending
wider use of
fractional dosing
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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, the UK

Target population(s): Adults; children

Sample size: 1935 adults; 700 children (targets)

Year funded: 2018

EDCTP funding: €3.2M

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

CHUMBA CHA MATIBABU





Developing the next generation of scientific leaders

EDCTP senior fellowships have supported emerging scientific leaders from Africa at key stages in their careers.

The challenge

Africa lags behind the rest of the world in terms of numbers of researchers per head of population. This severely limits the amount of research that can be done in Africa, as well as the capacity of African countries to establish and address their own research priorities.

The project

EDCTP senior fellowships fill an important gap, providing a career stepping stone for researchers who have shown outstanding promise in early careers and have the potential to become African research leaders. As well as leading internationally recognised research, EDCTP Senior Fellows mentor junior researchers, helping to build sustainable research capacity in Africa. Fellows funded through the first EDCTP programme have made important contributions to clinical research in Africa. Examples include:

Dr Abdoul Beavogui

In his senior fellowship, Dr Beavogui systematically analysed patterns of malaria, drug resistance, mosquito distribution and insecticide-treated bednet use in different regions of Guinea. He went on to contribute to the landmark WANEAM study on antimalarial use in West Africa, as well as Ebola treatment trials during the West Africa Ebola outbreak and has made important contributions to understanding the wider health impact of the outbreak. He is now Director of Maferinyah Training and Research Center in Rural Health in Guinea.

Professor Mark Nicol

Professor Nicol's fellowship enabled him to make a major contribution to a landmark global evaluation of the GeneXpert MTB/RIF molecular TB diagnostic. Through his work, South Africa contributed most patients to this study, which demonstrated the advantages of

Project at a glance

Project: EDCTP Senior Fellowships

Years funded: 2003–15 (EDCTP1)

EDCTP funding: €10.13M for 51 senior fellowships (EDCTP1)

GeneXpert MTB/RIF in routine clinical settings and underpinned WHO endorsement of the technology. Professor Nicol now works as Head of the Division of Medical Microbiology at the University of Cape Town and the National Health Laboratory Service of South Africa, providing a close link between research and clinical practice.

Dr Cissy Kityo

Dr Kityo has led and contributed to multiple studies on HIV diagnosis, treatment and prevention, particularly in children and highlighting the importance of HIV drug resistance. She has been a driving force behind the introduction of antiretroviral therapy in Uganda. She is now Deputy Executive Director of the Joint Clinical Research Centre in Kampala, Uganda.

Dr Pauline Byakika-Kibwika

In her fellowship, Dr Byakika-Kibwika carried out important studies on antimalarial treatment of severe malaria in Uganda. She is now a prominent researcher at the medical school at Makerere University, active in the mentoring of junior researchers, particularly women – she was instrumental in establishing a Women Scientists' Career Development Programme at Makerere.

Dr Abdoulaye Djimde

Dr Djimde is an internationally recognised expert on genetic diversity in the malaria parasite

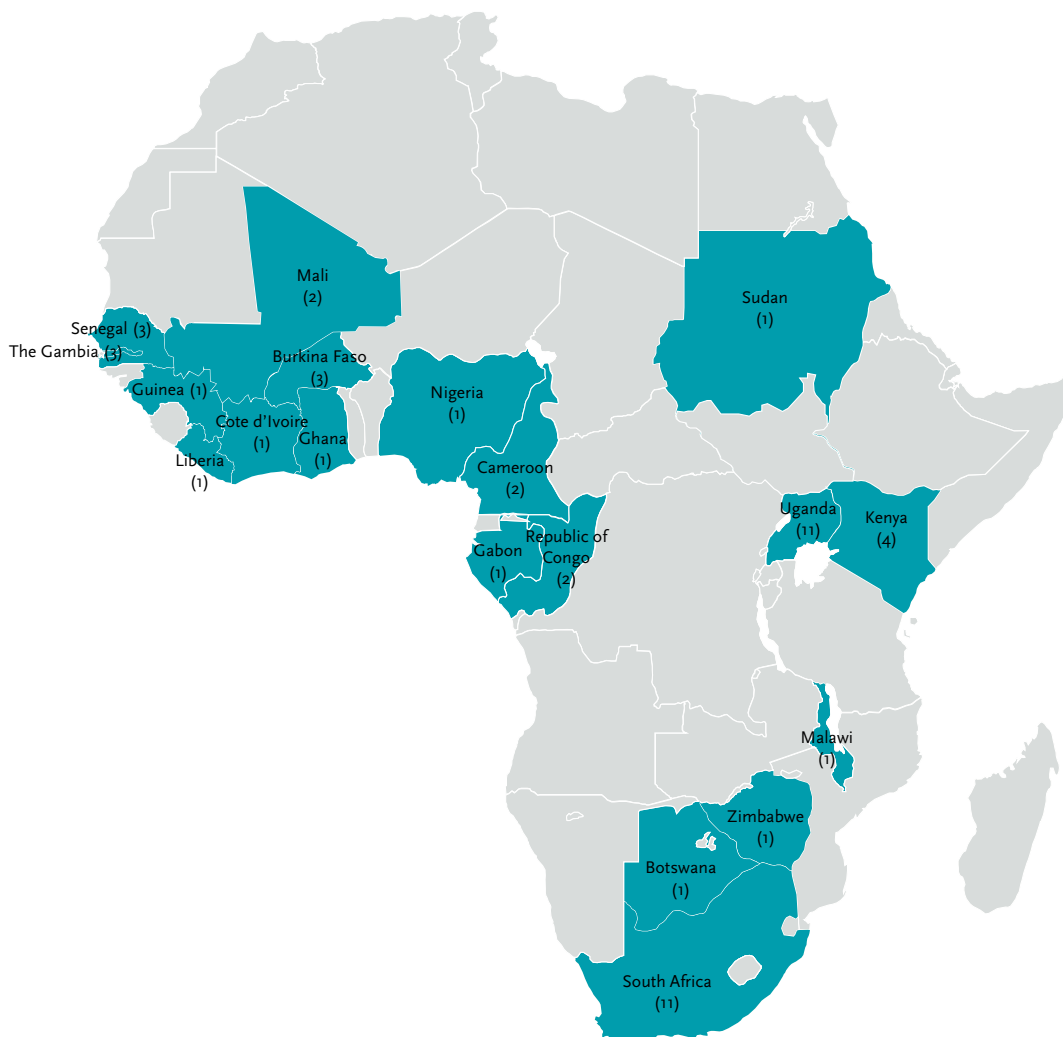
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**Senior
Fellows also
mentor junior
researchers,
building
sustainable
research capacity
in Africa**
”

and mosquito vectors, and their implications for treatment. He played a key role in setting up the international MalariaGEN Consortium, which has carried out groundbreaking work on genetic diversity in the malaria parasite in Africa and elsewhere. His senior fellowship research provided important data on repeat use of antimalarial drugs in West Africa. He now heads a unit at the University of Bamako, Mali, and is coordinator of the EDCTP-funded West African Network for Clinical Trials of Antimalarial Drugs (WANECAM).

Impact

EDCTP Senior Fellows have carried out important research on a number of poverty-related infectious diseases. In addition, their fellowships also provided important career stepping stones enabling them to establish leadership positions within African science and nurture the next generation of African research leaders.

EDCTP Fellowships in sub-Saharan Africa





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strengthened
laboratory
infrastructure
and procedures
across multiple
sites
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Linking scientists across African regions

EDCTP-funded Networks of Excellence (NoEs) in four African regions have created platforms for high-quality clinical studies spanning multiple sites and enabled the sharing of research experience and expertise, to drive sustainable capabilities across 63 institutions in 21 African countries to date.

The challenge

High-quality clinical research depends upon multiple factors, including trained researchers and support staff, suitably equipped laboratory and other facilities, knowledge of regulatory procedures, effective networking between research institutions, and background data on infections so that the impact of interventions can be determined. Many sub-Saharan countries lack capacity in some or all of these areas.

The projects

NoEs were established to strengthen connections between researchers and institutions in regions of Africa. They have focused on TB, HIV/AIDS and malaria, priority infections in the first EDCTP programme. Their mission has been to create sustainable platforms for multicentre trials and a supportive infrastructure for the continued training and development of researchers in Africa.

Central African Network for TB, AIDS and Malaria (CANTAM)

Six African institutions in three countries, with one European partner. CANTAM generated data on the prevalence of TB, HIV and malaria across sites, and on local strains and drug resistance. It supported the training of 34 researchers, while more than 300 support staff took part in 21 training workshops. It also provided a foundation for the work of four EDCTP fellows, strengthening of local ethics capacity, and leveraging of additional funding from third parties.

East African Consortium for Clinical Research (EACCR)

Thirty-five African institutions in five countries, with five European partners and one North American partner. EACCR supported the training of 27 master's students, set up an innovative cross-site mentoring scheme, and provided a

Project at a glance

Projects: EDCTP Networks of Excellence

Project leads: Professor Francine Ntoumi (CANTAM), Professor Pontiano Kaleebu (EACCR), Professor Gerhard Walzl (TESA), Professor Souleymane Mboup (WANETAM)

Countries involved: Congo, Gabon, Germany, Cameroon (CANTAM), Canada, Ethiopia, Germany, Kenya, the Netherlands, Norway, Sudan, Sweden, Tanzania, Uganda, the UK (EACCR), Botswana, Malawi, Mozambique, South Africa, Zambia, Zimbabwe (TESA), Burkina Faso, The Gambia, Ghana, Guinea Bissau, Mali, Nigeria, Senegal (WANETAM)

Years funded: 2008 (CANTAM), 2009 (EACCR, TESA, WANETAM)

EDCTP funding: €2.8M (CANTAM), €3.5M (EACCR), €2.3M (TESA), €3.5M (WANETAM)

platform for the work of four EDCTP fellows, who went on to secure additional funding. Several infrastructure upgrades were achieved and a new e-learning centre was established.

Trials of Excellence in South Africa (TESA)

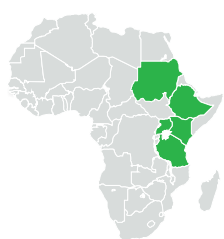
Ten African institutions in six countries. TESA supported the career development of 28 researchers, as well as the work of two EDCTP fellows, while more than 500 support staff attended short training courses. Several baseline studies on HIV and TB were conducted.

West African Network of Excellence for TB, AIDS and Malaria (WANETAM)

Twelve African institutions in seven countries. WANETAM carried out baseline studies in TB, AIDS and malaria, and supported the career development of 19 researchers, while 83 support staff benefited from short-term training opportunities.



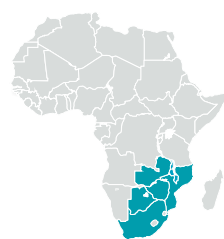
**West African NoE
for TB, AIDS, and
Malaria (WANETAM)**



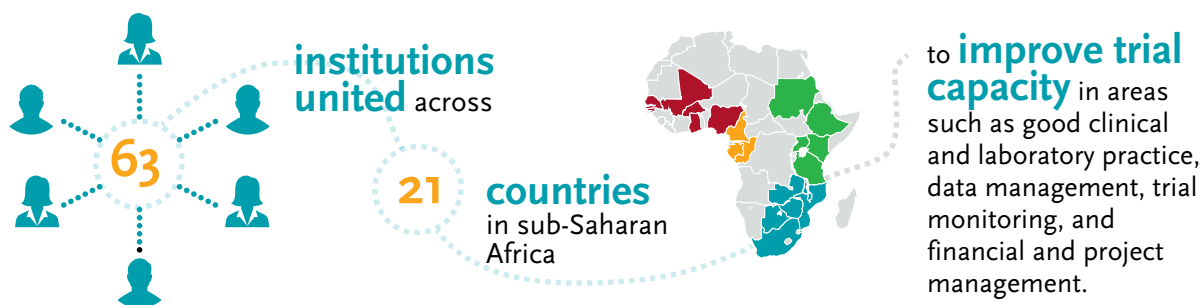
**East African
Consortium for Clinical
Research (EACCR)**



**Central African
Network for TB, AIDS,
and Malaria (CANTAM)**



**Trials of Excellence
in Southern Africa
(TESA)**



Impact

The NoEs have provided a platform for conducting high-quality clinical research and have strengthened laboratory infrastructure and procedures across multiple sites, helping them to achieve international accreditation. They have also established mechanisms for collaboration across multiple sites and generated data to support multicentre trials and new product approvals with stringent regulatory authorities. The NoEs have addressed key research skills gap and supported the development of researchers at all career stages in order to develop a sustainable culture of scientific clinical research. These networks also provide entry points for research initiatives against poverty-related infectious diseases supported by both public and private sources.

The NoEs are building on these achievements in new EDCTP2-funded programmes of work, expanding the range of countries involved and encompassing work on neglected tropical diseases.



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to develop
national
pharmacovigilance
capacity
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Mapping safety and risk–benefit of new treatments

New EDCTP-funded partnerships are enhancing the capacity of African countries to monitor the safety of drugs and other interventions.

The challenge

New interventions – drugs or vaccines – all come with an element of risk. An important role of clinical trials is to assess the safety of new interventions. But once interventions have been licensed, it is important that their use is monitored to evaluate their safety when they are used on a much larger scale, by a wider range of individuals and for longer time periods. This calls for rigorous monitoring, or pharmacovigilance.

Pharmacovigilance is generally the responsibility of national regulatory authorities (NRAs). Responsibilities of NRAs include ensuring that clinical evaluation of new interventions is conducted ethically and responsibly, and assuring the quality and safety of licensed medicines. However, NRAs in many sub-Saharan African countries lack the workforce capacity or national infrastructure to fulfil these responsibilities.

The projects

Three complementary EDCTP-funded partnerships have been established to develop national pharmacovigilance capacity and capabilities in sub-Saharan Africa.

- The **PAVIA consortium** is strengthening links between NRAs, national public health programmes and local medical research institutes. Focusing on multidrug-resistant TB (MDR-TB), it will build links between national TB control programmes and NRAs, and build local capabilities to detect and investigate possible adverse reactions to MDR-TB treatment.
- The **PROFORMA Consortium** aims to build workforce capacity by strengthening links between NRAs and local academic institutions, and using experts from the two sectors to develop a cohort of workers with pharmacovigilance expertise. The project will have a particular focus on clinical trials and mass drug administration and large-scale vaccination programmes.

Project at a glance

Projects: Pharmacovigilance Africa (PAVIA), Pharmacovigilance Infrastructure and Post-Marketing Surveillance System Capacity Building for Regional Medicine Regulatory Harmonization in East Africa (PROFORMA), East African Pharmacovigilance Initiative (EAPI)

Project leads: Professor Frank Cobelens, Stichting Amsterdam Institute for Global Health and Development, The Netherlands (PAVIA), Professor Eleni Aklillu, Karolinska Institute, Sweden (PROFORMA), Dr Kefa Bosire, University of Nairobi, Kenya (EAPI)

Countries involved: Ethiopia, Italy, the Netherlands, Nigeria, Swaziland, Tanzania (PAVIA), Ethiopia, Kenya, the Netherlands, Rwanda, Sweden, Tanzania (PROFORMA), Kenya (EAPI)

Year funded: 2017 (API), 2018 (PAVIA, PROFORMA)

EDCTP funding: €3.0M (PAVIA), €3.0M (PROFORMA)

Total project funding: €12.8M (PAVIA), €6.0M (PROFORMA)

- The **EAPI** project brings together the Kenyan NRA (the Pharmacy and Poisons Board) and the University of Nairobi. Partners will jointly develop e-learning materials to enable academic staff to contribute to practical national pharmacovigilance activities.

Impact

The three projects will strengthen collaboration across multiple stakeholders in complementary fashion, enabling countries to better monitor the safety of newly introduced drugs and other interventions in all disease areas. The projects will also enhance the capacity of countries to assess clinical research proposals and oversee clinical trials in a sustainable fashion. Such activities are urgently needed as populations in Africa gain access to new medicines.



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a searchable
GIS-based map
displaying clinical
trial locations
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Mapping clinical trial activity across Africa

The Pan-African Clinical Trials Registry (PACTR), the only WHO-endorsed clinical trial database in Africa, is the premier source of information on African trials.

The challenge

Registration of clinical trials in online registries is now internationally recognised best practice. Public dissemination of clinical trial information through open registries ensures operational transparency, enables trials to be followed from initiation to completion, and provides a means to assess whether trials are conducted and their data analysed as originally specified. Open registries also provide patients with access to information about ongoing clinical trials.

The project

The Pan-African Clinical Trials Registry (PACTR) was established in 2006 as a repository tailored to the needs of researchers working on trials in Africa. Initially focused on HIV/AIDS, TB and malaria, it was expanded in 2008 to include clinical trials in all areas of medicine. In 2009, PACTR was officially recognised as a WHO primary registry, and is the only WHO-endorsed primary registry in Africa.

PACTR is based at the South African Medical Research Council in Cape Town and is operated by Cochrane South Africa. It is specifically tailored to the needs of African scientists, for example offering scope for registration by email, fax or paper mail for those with poor internet connections. It is open access and trials can be registered free of charge.

PACTR was also the first trial registry to introduce a searchable and interactive GIS-based map, providing a visual display of clinical trial locations across the continent. From eight registered trials in 2008, PACTR has grown rapidly – its 1500th trial was registered in 2018, which also saw the launch of its redeveloped website (<https://pactr.samrc.ac.za>).

Impact

PACTR has provided a convenient and high-quality trial registration system for researchers working in Africa, encouraging adherence to

Project at a glance

Project: Pan-African Clinical Trials Registry (PACTR)

Project lead: South African Cochrane Centre

Year funded: 2006

EDCTP funding: €0.3M

Total project funding: €0.3M

internationally recognised standards in clinical trial conduct. In addition, it provides a valuable tool for exploring the current status of research in Africa in different areas of medicine, on different infections, and in different countries. Thus, as well as aiding researchers, PACTR is also a critical tool for policymakers, funders and other stakeholders – including the public – seeking to understand clinical trial activity across Africa. PACTR also supports the work of regulatory agencies, ethics boards and systematic reviewers in Africa.

Strategic partnerships

International cooperation and coordination are vital for achieving our mission goals and are at the heart of the EDCTP approach. We expect the best results through alignment and coordination of national research programmes in partnership with the private sector and other stakeholders including international development partners. Capacity development in sub-Saharan Africa in the areas of clinical research, ethical review and regulatory functions remains an important element of this approach.





Photo:
Laboratory staff part of the DREAMM project (Malawi)

Portfolio of projects (2014-2018)

Career development of researchers						Ethics capacity and regulatory framework
Clinical R&D Fellowships	Career Development Fellowships			Senior Fellowships		
Dr Isidore Traore Burkina Faso	Dr Ilse Marion Sumari-de Boer Tanzania	Dr Misaki Wayengera Uganda	Dr Marisa Kloppe South Africa	Dr Roma Chilengi Zambia	Dr Selidji Todagbe Agnandji Gabon	CREDU Uganda
Dr Solomon Mequanente Abay Ethiopia	Dr Obinna Ekwunife Nigeria	Dr Humphrey Kariuki Njaanake Kenya	Dr Charles Drago Kato Uganda	Dr Immaculate Nankya Uganda	Dr Catherine Riou South Africa	Lib-Regul-Trials Liberia
Dr Stephen Ian Walimbwa Uganda	Dr Jane Frances Namukasa Wanyama Uganda	Dr Michael Frimpong Ghana	Assistant Professor Laurent Dembele Mali	Professor Collen Masimirembwa Zimbabwe	Dr George Kyei Ghana	C2C-TEP The Gambia
Dr Suzanne Staples South Africa	Dr Tchounga Boris Kevin Cote d'Ivoire	Dr Dziedzom de Souza Ghana	Dr Clifford George Banda Malawi	Dr Peter Olupot-Olupot Uganda	Associate Professor Maia Lesosky South Africa	Enhancing Ethics in Sudan Sudan
Dr Armel Martin Zemsi Kala Cameroon	Dr Joseph Fokam Cameroon	Dr Justin Komguel Nono Cameroon	Dr Symon Kariuki Kenya	Professor Faith Osier Kenya	Dr Derseree Archary South Africa	REECAO Mali
Dr Mwaka Kakolwa Tanzania	Dr Mercy Karoney Kenya	Dr Alexander Kwarteng Ghana	Dr Virginie Rozot South Africa	Prof Dr John Lusingu Tanzania	Assit Professor Jonathan Peter South Africa	BERC-Luso Portugal
Asst. Prof. Ahmed Zeynudin Kasim Ethiopia	Dr Agnes Kiragga Uganda	Dr Ali Esmail South Africa	Dr Gbolahan Ajibola Botswana	Dr Francis Ndungu Kenya		DREIN Nigeria
Dr Alphonse Liyoyo Tanzania	Dr Admire Chikandiwa South Africa	Dr Stephanus Malherbe South Africa	Dr Charissa Naidoo South Africa	Dr Dawit Wolday Ethiopia		SteRN Ethiopia
Dr Workineh Shibeshi Alemayehu Ethiopia	Dr Aida Sivo South Africa	Dr Sean Wasserman South Africa	Dr Grace McHugh Zimbabwe	Dr Richard Phillips Ghana		HATUA – KENYA Kenya
Dr Ezenwa James Onyemata Nigeria	Dr Tecla Temu Kenya	Dr Christine Sekaggya-Wiltshire Uganda	Dr Tacilta Nhampossa Mozambique	Professor Grant Theron South Africa		IGORCADIA Spain
Dr Isaque Bartolomeu Silva Guinea-Bissau	Dr Deogratius Ssemwanga Uganda	Dr Nelita du Plessis South Africa	Dr Mosepele Mosepele France	Professor Keertan Dheda South Africa		AFREENET France
Dr Nneka Onyejebu Nigeria	Asst. Professor Yaya Kassogue Mali	Dr Sylvie Kwedi Cameroon		Dr Stellah George Mpagama Tanzania		LusoAfro-BioEthics Mozambique
Dr Micah Ongeri Kenya	Dr Yunia Mayanja Uganda	Dr Evaezi Okpokoro Nigeria		Professor Wendy Burgers South Africa		SMERT Tanzania
	Dr Kingsley Badu Ghana	Dr Michael Owusu Ghana		Dr Barbara Castelnuovo Uganda		STReK Kenya
	Dr Atinuke Olaleye Nigeria	Dr Marieke van der Zalm South Africa		Prof. Dr Andre Pascal Kengne South Africa		BUCARERZ Zambia
	Dr Richard Mwaiswelo Tanzania	Dr Maina Edward Kenya		Dr George PrayGod Tanzania		Reg. Science-Fellows Zimbabwe
	Dr Jean-Bertin Bukasa Kabuya Zambia	Dr Babatunde Adeagbo Nigeria		Professor Dorothy Yeboah-Manu Ghana		BREEDSAFCA Cameroon
	Dr Dan Kajungu Uganda	Dr Moses Masika Kenya		Professor Marielle Bouyou-Akotet Gabon		ERUDIT Togo
	Dr Moustapha Mbow Senegal	Dr Hadija Hamisi Semvua Tanzania		Assit Professor Pauline Byakika-Kibwika Uganda		S-ROC/Gabon Gabon
	Dr Caroline Cleopatra Chisenga Zambia	Dr Dominic Mosha Tanzania				SEN-ETHICS Senegal

Health system preparedness for outbreak response	Networks of Excellence	Clinical studies			Pharmacovigilance	Evidence-informed policy
SELeCT Spain	CANTAM2 venture Congo	DREAMM United Kingdom	IMPROVE United Kingdom	PREGART Ethiopia	EAPI Kenya	WISH United Kingdom
ENDORSE Italy	WANETAM II Senegal	LIFE Study Mozambique	IMPROVE-2* United Kingdom	Neo bnAb Germany	PAVIA Netherlands	IMPP-ACT United Kingdom
Capa-CT Uganda	TESA II Mozambique	CAPRISA 018 South Africa	MAMAH Spain	ASAAP Ghana	PROFORMA Sweden	TRIP Tanzania
RECAP-SL Sierra Leone	EACCR II Uganda	CHAPAS 4 Zimbabwe	MMVC United Kingdom	PediCAP Italy		IMPACT United Kingdom
CLINICAL CAPACITY Sierra Leone		AMBITION-cm United Kingdom	DiTECT-HAT France	PYRAPREG Mali		TWENDE United Kingdom
SECC Gabon		CHAPS United Kingdom	SOLID Belgium	EMPIRICAL Spain		EXIT-TB Tanzania
PANDORA-ID-NET Congo		PROMISE-EPI France	FREEBILY Netherlands	BabyGel United Kingdom		
ALERRT United Kingdom		GREAT United Kingdom	Afri-KA-DIA Switzerland	CAP-TB Switzerland		
		PrEPVacc United Kingdom	PZQ4PSAC Netherlands	CAPo12 SAMBA Trial South Africa		
		StopTB/HIV at one United Kingdom	PREV_PKDL Germany	Simplici-TB United Kingdom		
		Screen TB South Africa	NIFTY United Kingdom	ETEC Vaccine Efficacy Sweden		
		DIAMA Benin	COAST-Nutrition United Kingdom	PREVAC-UP France		
		Predict TB South Africa	TREATS United Kingdom	THECA United Kingdom		
		RaPaed TB Germany	MoxiMultiDoseMod United Kingdom	SINDOFO Germany		
		PanACEA Netherlands	STOP Spain	WANECAM - II Mali		
		VirTUAL United Kingdom	HAT-R-ACC Switzerland	CLICK-TB Spain		
		POR TB consortium Denmark	PEP4LEP Netherlands	PravaTB South Africa		
		MTBVAC - Newborns Spain	FibroScHot United Kingdom	INTENSE-TBM France		
		priMe Germany	PEOPLE Belgium			
			BREATHER Plus Uganda			

Intervention

Drugs

Diagnostics

Vaccines

Other

Product-focused implementation research

Behavioral and social sciences

Capacity building/training

Disease

HIV and HIV-associated infections

Tuberculosis

Malaria

Neglected infectious diseases

Emerging diseases

Lower respiratory tract infections

Diarrhoeal diseases

* Project funded through the UK Joint Global Health Trials scheme.

Note: This overview includes both signed and approved grants. Countries listed refer to country of Project Coordinator.

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European & Developing Countries Clinical Trials Partnership

The Hague, The Netherlands, September 2018

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The power of sharing science