EDCTP

The power of sharing science

Annual Report 2021

Achieving excellence and equity in global health research

Supported by the European Union

About EDCTP

The European & Developing Countries Clinical Trials Partnership (EDCTP) is a public–public partnership between 14 European and 18 African countries, supported by the European Union.

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

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

The second EDCTP programme is implemented by the EDCTP Association supported under Horizon 2020, the European Union's Framework Programme for Research and Innovation. Cofunding from the following organisations is gratefully acknowledged: Agence nationale de recherche sur le sida et les hépatites virales (ANRS, France), Botnar Research Centre for Child Health (BRCCH, Switzerland), Bundesministerium für Bildung und Forschung (BMBF, Germany), Calouste Gulbenkian Foundation (Portugal), Coalition for Epidemic Preparedness Innovations (CEPI, Norway), Department of Health and Social Care (DHSC, United Kingdom), Fondation Botnar (Switzerland), Fonds National de la Recherche (FNR, Luxembourg), Foreign, Commonwealth & Development Office (FCDO, United Kingdom), Foundation for Science & Technology (FCT, Portugal), Fundación Mundo Sano (FMS, Argentina/Spain), GlaxoSmithKline (GSK, United Kingdom), Institut national de la santé et de la recherche médicale (Inserm, France), Instituto de Salud Carlos III (ISCIII, Spain), Joint Global Health Trials Scheme (JGHT, United Kingdom), Leprosy Research Initiative (LRI, Netherlands), Medical Research Council (MRC, United Kingdom), Ministère de l'Enseignement supérieur, de la Recherche et de l'Innovation (MESRI, France), Novartis International AG (Switzerland), NWO-WOTRO Science for Global Development (NWO-WOTRO, Netherlands), South Africa Department of Science and Innovation (DSI, South Africa), South African Medical Research Council (SAMRC, South Africa), Swedish International Development Cooperation Agency (Sida, Sweden), Swiss Agency for Development and Cooperation (SDC, Switzerland), Swiss National Science Foundation (SNSF, Switzerland) and The Special Programme for Research and Training in Tropical Diseases (TDR, Switzerland).

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Building on success

The third EDCTP programme – Global Health EDCTP3 – will build on and extend the successes of EDCTP2.

Among the many impacts of COVID-19 was the disruption of research activities, as multiple projects had to suspend recruitment or other activities. Last year saw many COVID-19-related barriers overcome, with project activities returning to near normal. As can be seen from the stories in this Annual Report, research collaborations have been highly active progressing projects, recruiting participants and publishing results.

EDCTP has now developed an extremely strong portfolio across its diseases of interest. The studies it is funding promise to make a significant contribution to the advancement of diagnostics, vaccines, drugs and other interventions for the most important infectious diseases affecting sub-Saharan Africa, benefiting its most vulnerable populations, including infants, children, adolescents and pregnant women.

At the same time, EDCTP has played an important role in the development of health research system capacities in sub-Saharan African. It is essential that these activities are developed in partnership with local agencies, and EDCTP has made great efforts in 2021 to strengthen its relationships with key regional partners.

For example, EDCTP has a long-standing partnership with the WHO Regional Office for Africa. In 2021, it also strengthened its ties with the African Union, signing a landmark memorandum of understanding that will see close collaboration on the key health issues facing the region, particularly in relation to infectious disease control and pandemic preparedness. A critical element of this partnership will be a close working relationship with the Africa Centres for Disease Control and Prevention (Africa CDC).

The most noteworthy aspect of this partnership in 2021 was the award of funding to ten consortia that will be running training programmes for 150 epidemiologists and biostatisticians. These programmes will train a new generation of experts who will make an important contribution to the monitoring and response to existing and new infectious disease threats across a wide swathe of countries in sub-Saharan Africa, including those with a high disease burden but currently underdeveloped health research systems.

As outlined elsewhere in this Annual Report, EDCTP is represented on multiple committees and advisory groups with an interest in health research in sub-Saharan Africa. This is vital to enable us to stay abreast of the key issues facing the region and to build the relationships needed to ensure coordinated and effective responses to them. EDCTP has made important contributions to the rapid response to the pandemic in the region, through specific project funding but also by helping to build research platforms and scientific expertise that could be harnessed to address pandemic challenges.

Following a COVID-19-related delay, the Tenth EDCTP Forum finally took place in 2021, providing opportunities for EDCTP grant holders to showcase their work and network with international colleagues. Hosted by Mozambique, the Forum was a hybrid event, with delegates attending in person or virtually. Although meeting others personally has advantages, the virtual element enabled many others to participate in a very exciting programme of scientific events.

The theme of the Forum, **equity in health research**, highlighted an important aspect of our work. While excellence must always be core to the research we fund, we also need to acknowledge that countries are not equally well placed to generate compelling research proposals. Indeed, some countries with the greatest disease burdens are those least able to do so. By linking researchers and research institutions in these countries to regional and global networks, we are helping to build the capacity of all countries to carry out research to better understand and address their health challenges.

Similarly, female scientists face multiple barriers as they seek to develop their research careers, particularly at senior levels. We are taking steps to understand and address these barriers, and to ensure that our own activities are not inadvertently discriminatory. The launch of a new UK-funded Participating States-Initiated Activity to support early-career female researchers, in association with EDCTP Regional Networks of Excellence, is an important indication of the importance we attach to this issue.

Finally, 2021 has been notable for the great progress made in the development of the successor to the EDCTP2 programme – Global Health EDCTP3. This exciting new Joint Undertaking will have a new legal basis, but will continue to have the same core mission as EDCTP2 and will carry forward the principles that have made EDCTP2 such a success.

However, not only will Global Health EDCTP3 be on a grander scale, with an anticipated budget potentially in excess of €1.6 billion, but it will also have an expanded scope, including activities related to the emergent threats of antimicrobial resistance and climate change. It will also provide additional flexibility, enabling innovative new partnerships to be developed with additional countries, global funders and the private sector.

EDCTP2 and Global Health EDCTP3 will continue to run side by side as the new programme launches and EDCTP2-funded projects carry on their planned activities. A seamless transition will ensure that the core EDCTP elements are carried through to the new programme – helping to drive forward health research for Africa, led by Africa, for the benefit of African people.

Professor Yazdan Yazdanpanah
Chair, EDCTP Association Board

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Excellence, equity and impact

Nine years since its launch, EDCTP2 is already achieving its objectives – successfully advancing the development of medical interventions and building sustainable clinical research capabilities in sub-Saharan Africa.

Launched in 2014, the second EDCTP programme (EDCTP2) has invested more than €800 million – from the centrally managed funds – in projects that have the ultimate goal of enhancing the health and wellbeing of people living in sub-Saharan Africa. The majority of this funding, €684.5 million, is supporting 140 international collaborative clinical research projects, including clinical trials of interventions targeting the region's most important infectious disease challenges – HIV/AIDS, TB, malaria, lower respiratory tract infections (LRTIs), diarrhoeal diseases and emerging infections, including Ebola and COVID-19. A further €85 million has been committed to projects building clinical research and creating an enabling environment for research, and €44.5 million is dedicated to fellowship programmes supporting the research leaders of today and of the future.

These activities have brought together researchers and research institutions from 29 European countries and 44 countries in sub-Saharan Africa. As well as African countries with a well-established clinical research infrastructure, projects have embraced nations with limited past experience of research but a high burden of disease. While research excellence has been a central principle of EDCTP2 activities, schemes have been organised to build the research capacity of countries with less experience of clinical research, for example through partnering with centres of excellence in Africa and Europe, so they are better able to compete for funding.

Achieving objectives

EDCTP2 funding and other activities have been shaped by a very clear set of objectives, with explicit numerical and qualitative targets. In most cases, EDCTP performance is far surpassing expectations.

Our first objective relates to the **advancement of medical interventions**. Our initial aim was to launch one phase III clinical trial a year. In reality, we have supported 39 phase III trials. Furthermore, while our ambition was to fund 150 clinical trials in total, our portfolio now extends to 332 clinical studies, including 213 clinical trials.

EDCTP2 also aimed to promote African scientific excellence and leadership of clinical studies. A third of the clinical projects have an African coordinator managing the grant, and all studies within host countries are led by African investigators. More than half of the value of grants awarded (55%) has been allocated to Africa and 62% of publications have a first or last author from an African institution.

The programme also had a goal to generate at least 1000 peer-reviewed papers. More than 500 have been published to date and, with many studies yet to finish, this target is also likely to be surpassed. Achievement of a further goal, to reduce the time to completion of trials, has been hampered by COVID-19, which disrupted many clinical trial activities.

Of critical importance, EDCTP-funded studies are beginning to generate essential evidence on the safety and efficacy of interventions. This Annual Report includes some key examples, including:

- The validation of a refined treatment for cryptococcal meningitis, a leading cause of death in people living with HIV, which has already led to a change in WHO recommendations.
- Confirmation of the safety and efficacy of a formulation of praziquantel suitable for young children, which will enable them to benefit from mass drug administration campaigns to control flatworm parasite infections.
- The phase II trial of a malaria vaccine that for the first time achieved the WHO's 75% efficacy target.

These and other projects are likely to have a major impact on the health of African populations, and particularly African children.

A second key EDCTP objective relates to **capacity building and collaboration**. As well as being an important element of clinical trial projects, capacity building is also supported through specific projects – 295 of which have been funded to date, well above the target of 74 capacity-building activities. A total of 44 African countries are partners in EDCTP2 projects, more than the 33 targeted. Ethics and regulatory capacity building projects have been funded in 37 sub-Saharan African countries and regulatory systems are being strengthened in 28 countries.

Human capacity building is a critical EDCTP focus. As well as 205 fellows, EDCTP is supporting more than 600 trainees (master's and PhD students), as well as 150 epidemiologists and biostatisticians through a partnership with the African Centres for Disease Control and Prevention (Africa CDC), and more than 36,000 individuals are benefiting from short-term training. Again, these numbers far exceed initial targets.

Coordination of European activities has been a further EDCTP objective. An additional €1.2 billion has been committed to EDCTP-aligned projects by EU member states through Participating States-Initiated Activities (PSIAs). A total of 19 European countries are partners in EDCTP projects, in comparison to 16 in EDCTP1.

The fourth EDCTP objective relates to **strengthening of external partnerships**. Committed contributions to EDCTP from African countries through the PSIA mechanism have increased to €67 million (target: €30 million), and two new sub-Saharan African countries – Côte d'Ivoire and Kenya – have joined the EDCTP Association.

In terms of third-party public or private funding, €26.9 million has been provided through joint and coordinated calls and €374.0 million through strategic calls. The target of €500 million is likely to be reached once other contributions to clinical studies and fellowship projects have been accounted for.

The final EDCTP objective relates to **EU cooperation and coordination with development assistance agencies**. Four calls have been launched with development cooperation partners and co-funding has been secured with a range of agencies, including USAID, Unitaid, Gavi, the Vaccine Alliance, and Médecins Sans Frontières (MSF). Multiple strategic partnerships have been established with development partners in Africa, including the African Union, with EDCTP recognised by the Advisory Group on Research and Innovation for Africa-Europe Cooperation as "the most cited joint programme strengthening health research and health systems in Africa and the flagship EU–Africa partnership in health R&D cooperation, with large successful long-lasting research networks".

The foundations of success

Underpinning this success has been the unique approach adopted by EDCTP. **Partnerships** lie at the heart of our activities. The overwhelming majority of our grants support goes to international collaborations, but on top of that EDCTP seeks to work with like-minded partners to ensure activities are aligned, duplication avoided, and activities build on and extend each other.

EDCTP has always been committed to **scientific excellence**. High-quality research is the most efficient way to generate the evidence needed to evaluate medical interventions and ensure that they are effective and safe. Poor quality science wastes valuable resources and risks exposing people to unsafe or ineffective interventions. However, EDCTP combines this principle with that of **equity**, recognising that some individuals, institutions and countries may have the potential to carry out high-quality

research but in practice lack the training, infrastructure and experience. Central to EDCTP's work has been expanding the number of people, institutions and countries able to carry out high quality clinical research in Africa, through networking and targeted capacity building.

On a global scale, our funds are limited, and we have sought to maximise our impact by establishing a clear **niche**. This includes a focus on wider capacity-building as well as individual clinical studies, on priority infectious diseases affecting sub-Saharan Africa, and on key populations, including infants and children, pregnant women, and people with co-infections and co-morbidities, who are often excluded from clinical trials.

A further important aspect of EDCTP's work is its particular interest in **late-stage (phase II and III) clinical studies and post-licensing implementation studies**, dovetailing with organisations that focus on earlier stages of intervention development. This focus also recognises the need for an 'end to end' perspective on product development, including the chaperoning of innovations through the entire development pathway, licensing and implementation within national health systems.

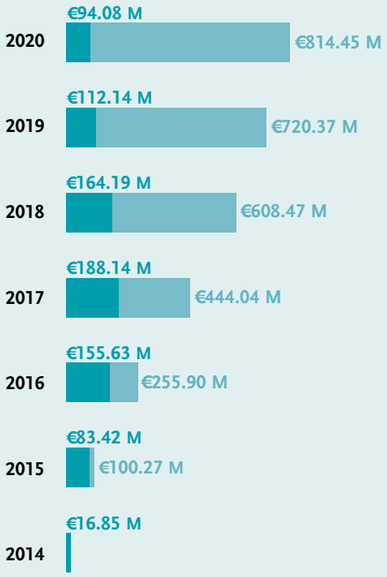
Last year saw an acceleration in EDCTP-funded activities as the disruption caused by the COVID-19 pandemic began to subside. The stories in this Annual Report highlight just a small selection of the progress being made across our areas of interest. The global response to the pandemic has illustrated the power of research and innovation to tackle public health issues. The challenge now is to build on this experience and momentum to accelerate efforts to control the other infectious disease threats facing sub-Saharan Africa.

Dr Michael Makanga
Executive Director


OLYMP
OLYMP

Investment to calls

(2014-2021)



- **Investment to call for proposals by year**
- **Cumulative investment to call for proposals by year**

Towards EDCTP's objectives

(2014-2021)

Medical interventions

New or improved medical interventions against poverty-related infectious diseases.

332
clinical studies supported by EDCTP2 since 2014. Of these, 64% (213) are interventional (clinical trials) and 36% (119) are non-interventional studies.

63% (91)
of clinical trials are phase II and III studies of drugs and vaccines which aim to deliver key evidence on safety and efficacy, as well as provide data to support product registration.

16% (23)
of the clinical trials involve post-licensing (phase IV) studies with a view to influencing health policies and practice and optimising the delivery of medical interventions for the wide range of sub-Saharan African health systems and diverse populations.

12% (37)
of all studies target pregnant women and their children. Other key populations are also involved in the studies, such as newborns and infants (77; 25%), children (103, 33%) and adolescents (102; 33%).

38
sub-Saharan African countries host recruitment sites of EDCTP-funded collaborative clinical studies.

Collaboration and capacity development

Increase cooperation with sub-Saharan Africa through capacity building for conducting clinical trials according to ethical principles and regulatory standards.

44
sub-Saharan African countries participate in EDCTP projects involving 310 African organisations. They receive 60% of the total EDCTP grant value.

37
sub-Saharan African countries have received EDCTP support for the establishment of functional regulatory systems and capacities for ethical review of clinical research.

205
fellowships have been awarded that focus on the career development of researchers from 24 sub-Saharan African countries.

580
trainees from 33 sub-Saharan African countries are supported through EDCTP projects. Trainees include 217 Master's (37%) and 227 PhD students (39%).

18
sub-Saharan African countries are members of the EDCTP Association. Cote d'Ivoire and Kenya have joined the EDCTP Association in 2021.

European coordination

Improve coordination, alignment and integration of European National Programmes.

14
European countries are members of the EDCTP Association.

€186.77 M
cash received from the European Participating States to the EDCTP programme.

€1.157 Bn
committed through 301 Participating States' Initiated Activities (PSIAs) submitted by the European Participating States by end of 2020.

External partnerships

Increase international cooperation with public and private partners.

71
countries participate in EDCTP-funded activities: 44 sub-Saharan African and 19 European countries as well as 8 others.

526
institutions are involved in EDCTP projects, including 310 sub-Saharan African institutions, 206 European institutions, and 10 institutions from other countries.

338
private sector entities are involved in EDCTP projects. By the end of 2021, these institutions have received €176.30 M of EDCTP grant value.

€26.84 M
has been leveraged from partners for the launch of joint or coordinated calls for proposals.

€373.95 M
has been leveraged (cash and in-kind) as co-funding to EDCTP projects through the EDCTP strategic calls for proposals.

EU cooperation

Increase interaction with other EU initiatives, including those linked to development assistance.

4
calls have been launched targeting development cooperation initiatives and involving 11 projects with development cooperation partners and co-funders.

€23.15 M
in co-funding has been secured through two dedicated calls requiring collaboration with development cooperation initiatives, with co-funding from Sida, USAID, Gavi, The Global Fund, UNITAID, AECID and Médecins Sans Frontières.

EDCTP in 2021

January

January

EDCTP and the Amsterdam Institute for Global Health and Development (AIGHD) publish a new **Global Roadmap for TB Vaccine R&D**, developed in partnership with WHO and after global stakeholder consultations.

February

February

The European Commission announces its proposal to set up 10 new European Partnerships – including **Global Health EDCTP3**, the successor to the EDCTP2 programme.

EDCTP and the Global Health Innovative Technology (GHIT) Fund announce a €7.8 million joint investment in the **ADOPT programme**, to lay the ground for introduction of a new formulation of praziquantel for pre-school-aged children.

EDCTP and the **Botnar Research Centre for Child Health** jointly support three consortia working on COVID-19 projects, uniting groups previously funded independently by the two organisations.

EDCTP and the Global Health Network organise a webinar on protocol development linked to the **EDCTP Knowledge Hub**.

March

March

EDCTP and Africa CDC launch a major joint regional initiative to train a new generation of **epidemiologists and biostatisticians** in Africa.

EDCTP organises a webinar to bring together researchers working on its **COVID-19-related projects**.

The Global Research Collaboration for Infectious Disease Preparedness (GloPID-R), the UK Collaborative on Development Research (UKCDR) and the COVID-19 Clinical Research Coalition organise a **virtual conference on COVID-19 research in low- and middle-income countries**.

April

April

A *Lancet* paper reports that the **R21/Matrix-M malaria vaccine** showed 77% efficacy in an EDCTP-funded phase IIb trial, becoming the first vaccine to meet the WHO goal of 75% efficacy.

EDCTP and AIGHD in collaboration with WHO launch the **Global Roadmap for TB Vaccine R&D** at the Virtual Global Forum on TB Vaccines.

May

May

New **support tools for TB vaccine R&D** developed by the Tuberculosis Vaccine Initiative with EDCTP funding are published, to support groups organising clinical trials and applying for regulatory approval.

EDCTP contributes to a **commentary in the *Lancet*** summarising discussions held at the March 2021 GloPID-R/UKCDR/COVID-19 Clinical Research Coalition conference.

June

June

An IAVI-led consortium receives €22.8 million funding from EDCTP and the Coalition for Epidemic Preparedness Innovations (CEPI) for a phase IIb clinical trial of a **novel vaccine for Lassa fever.**

EDCTP and the European Clinical Research Infrastructure Network (ECRIN-ERIC) organise a joint session at the Africa-Europe Science and Innovation Summit on capacity building and development of clinical research infrastructure in Africa.

EDCTP Executive Director Dr Michael Makanga speaks at the opening ceremony the Africa-Europe Science and Innovation Summit, highlighting EDCTP's role in supporting clinical research in sub-Saharan Africa.

July

July

Biofabri and IAVI announce a partnership to advance **MTBVAC**, a new TB vaccine being evaluated in two EDCTP-funded studies, into large-scale efficacy trials.

August

August

Recommendations from the EDCTP/ECRIN session held in June 2021 are integrated into the consultation of the **Advisory Group on Research and Innovation for Africa-Europe Cooperation**, which provides the European Commission with advice on boosting cooperation between the two continents through research and innovation.

September

September

The African Union and EDCTP sign a **memorandum of understanding** as the basis for cooperation in activities linked to their shared goals around health protection.

EDCTP organises a virtual meeting on global health research and cooperation at the Science Summit associated with the **76th United Nations General Assembly** (UNGA76).

October

October

The **Tenth EDCTP Forum** is hosted by Mozambique and features the theme of equity in research for health.

EDCTP Prizes for 2020 are awarded to individuals and research teams in recognition of scientific excellence and promotion of international networking.

Professor Aboulaye Djimdé (Mali) is appointed to the EDCTP Association Board and consequently the EDCTP Association Board now comprises three African and three European members.

WHO recommends widespread use of the **RTS,S/AS01 malaria vaccine**, the first to gain the WHO seal of approval; EDCTP has helped to advance development of RTS,S/AS01 and several EDCTP2-funded RTS,S/AS01 post-registration studies are ongoing.

The first epidemiologists and biostatisticians funded through the **EDCTP and Africa CDC joint initiative** start their master's training.

November

November

The legal basis for the **Global Health EDCTP3 Joint Undertaking** is adopted by the European Commission, signalling the start of the third EDCTP programme.

The Pediatric Praziquantel Consortium announces positive results from its **pivotal EDCTP-funded phase III trial of arpraziquantel**, a new medication to treat schistosomiasis in preschool-aged children.

December

December

EDCTP organises a special session at the **Seventh Annual Science Forum South Africa (SFSA21)**, focusing on advancing the African agenda for partnerships for global health sciences.

As a deliverable of the PAVIA grant, the **Eswatini national pharmacovigilance policy and implementation framework** was formally launched at an event attended by the Principal Secretary of the Ministry of Health and the Honourable Minister of Commerce of Eswatini.

EDCTP's funding of research and capacity development

(2014-2021)

Total funding

€814.45 M

for **435 projects** awarded to date.

Clinical studies

€684.50 M

to support **140 collaborative research projects** with large-scale clinical trials and other clinical research activities conducted by European-African consortia.

Clinical research capacity

€85.47 M

to support **90 grants** that strengthen the enabling environment for conducting clinical trials and clinical research.

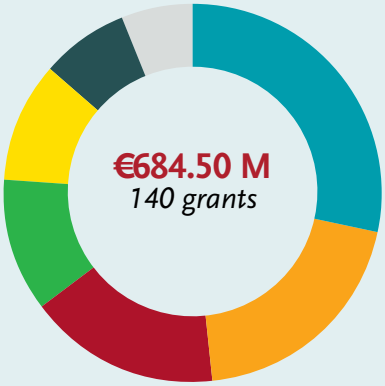
Fellowship programme

€44.48 M

to support **205 fellowships projects** that focus on the career development of African scientists.

Collaborative clinical trials and clinical studies

By disease



- Tuberculosis, *33 grants*
  €194.83 M (28%)
- Malaria, *17 grants*
  €136.47 M (20%)
- HIV & HIV-associated infections, *20 grants*
  €113.05 M (17%)
- Emerging diseases, *37 grants*
  €77.61 M (11%)
- Neglected infectious diseases, *19 grants*
  €70.60 M (10%)
- Diarrhoeal diseases, *6 grants*
  €51.19 M (8%)
- Lower respiratory tract infections, *8 grants*
  €40.75 M (6%)

By intervention

- Drugs, *51 grants*
  €282.01 M
- Vaccines, *26 grants*
  €243.05 M
- Diagnostics, *47 grants*
  €121.32 M
- Non-intervention-specific topics, *9 grants*
  €31.90 M
- Product-focused implementation research, *7 grants*
  €6.22 M

3.1

Tuberculosis

TB remains the bacterial pathogen responsible for the greatest burden of disease, causing well over a million deaths every year. Control of TB has been set back markedly by the COVID-19 pandemic, and drug resistance is a growing global challenge. Methods of timely diagnosis and shorter treatment regimens remain key goals for clinical TB research, alongside the development of vaccines to prevent TB infection and progression to active disease.

Tuberculosis in numbers

33 grants
€194.83 M

Drugs
10 grants
€66.76 M

Vaccines
19 grants
€76.88 M

Diagnostics
4 grants
€51.19 M

An alternative to BCG for newborns

Exciting progress is being made in the development of MTBVAC, a possible alternative to BCG vaccination to prevent TB.

Newborns are typically given BCG vaccine at birth to protect against TB – about 100 million infants are vaccinated with BCG each year. However, BCG provides variable degrees of protection, does not protect against all forms of TB and is less effective when given at older ages.

MTBVAC[1] is a live attenuated form of *Mycobacterium tuberculosis* (Mtb), the cause of TB. Following successful phase I safety studies in Europe and South Africa, it is being evaluated in an EDCTP-funded phase II study in South Africa, focusing on HIV-negative newborns. The protective efficacy of three different MTBVAC vaccine dose levels is being compared with BCG. During 2021, the trial completed its enrolment of nearly 100 newborns.

Also in 2021, MTBVAC's developers, Biofabri, and IAVI announced plans to partner on the clinical evaluation of MTBVAC. IAVI will support the further development of MTBVAC and mobilisation of resources for phase III trials in adults and adolescents.

This work will complement a further commitment recently made by EDCTP, to support a phase III trial in newborns, through the **MTBVACN3** project. This trial, which is due to launch in 2022 and will ultimately recruit 7000 newborns in South Africa, Senegal and Madagascar, will be based on the optimal dose identified in the MTBVAC-newborns trial.

By ensuring that studies in babies take place at the same time as other trials in adults, MTBVACN3 will ensure that they would be among the first groups to benefit from the new vaccine if trials confirm its efficacy.

1 Martín C, Marinova D, Aguiló N, Gonzalo-Asensio J. MTBVAC, a live TB vaccine poised to initiate efficacy trials 100 years after BCG. Vaccine. 2021;39(50):7277-7285. doi: 10.1016/j.vaccine.2021.06.049.

An alternative to BCG for prevention of TB infection

The priMe phase III TB vaccine trial, which hopes to provide an alternative to BCG, hit its 50% recruitment target in 2021.

The only TB vaccine of proven efficacy, BCG, has been in use for 100 years. Although widely given to infants around the world, it has significant limitations. For example, it does little to control the spread of pulmonary TB and some vaccinated children still develop TB meningitis; it is also not suitable for infants with HIV infections.

The EDCTP-funded phase III **priMe** trial is evaluating a potential alternative to BCG. The VPM1002 TB vaccine is similar to BCG, also being based on a weakened form of *Mycobacterium bovis*, the bacterium that causes bovine TB. However, precise genetic changes have been introduced that cause it to stimulate more powerful immune responses than BCG (and also enable it to be used in people with HIV infections).

The priMe trial, taking place in Gabon, Kenya, South Africa, Tanzania and Uganda, is comparing VPM1002 and BCG head to head. It aims to recruit around 7000 infants, and in 2021 it began enrolling at all its trial sites and achieved its 50% recruitment milestone.

The trial will provide essential information on the use of VPM1002 in infants. As it is relatively easy to manufacture, it could help to overcome the supply issues associated with BCG, and provide an option for infants with HIV infection.

Preventing latent TB progression

The POR TB consortium has completed recruitment into its trial of a novel TB vaccine designed to prevent the development of active TB disease.

Mycobacterium tuberculosis (Mtb), the cause of TB, is the world's most common bacterial pathogen. However, not everyone who is infected with Mtb develops active TB disease. Thus, as well as prevention of infection, an alternative therapeutic strategy is to prevent disease development in those already infected – a critical goal as around 2 billion people are thought to be infected with Mtb globally.

The **POR TB** consortium is evaluating an adjuvanted vaccine candidate, **H56:IC31**, that has been specifically designed to target established Mtb infections and block disease progression. It comprises a fusion protein (H56) made up of Mtb antigens produced at different stages of its life cycle plus an immune-stimulating adjuvant (IC31).

The phase II POR TB trial, taking place in South Africa and Tanzania, is assessing the efficacy of H56:IC31 in an innovative 'prevention-of-recurrence' trial design. The vaccine is being given to patients who have completed a standard course of TB antibiotic treatment, to see if it can reduce the numbers of patients – typically around one in 10 – who relapse due to reinfection or reactivation of dormant bacteria that survived drug treatment. One critical advantage of this design is that it provides data on efficacy relatively quickly compared with conventional TB treatment trials.

During 2021, the POR TB consortium completed recruitment of 831 patients, who are being followed for two years to assess safety and prevention of recurrence. Successful results would also support further evaluation of H56:IC31 for prevention of recurrence of drug-resistant TB and prevention of Mtb infection.

Accelerating TB vaccine development

EDCTP has worked closely with WHO on a new roadmap for TB vaccine development, and supported a range of activities to enhance coordination across TB vaccine studies.

EDCTP is supporting multiple TB vaccine projects, including the **POR TB consortium**, **priMe** and **MTBVAC**. As candidate vaccines move towards large-scale trials, it is important that any potential obstacles to vaccine research and development (R&D), evaluation and implementation are identified and addressed.

In April 2021, EDCTP and the Amsterdam Institute for Global Health and Development (AIGHD) launched a Global Roadmap for research and development of TB vaccines. Developed through an iterative global consultative process and with close involvement of WHO, the Roadmap identifies the key barriers to TB vaccine R&D and implementation, and potential ways in which they might be overcome. It provides a shared set of priorities to guide the activities of all stakeholders with an interest in TB vaccine development and use.

The consultation led to the identification of three priority areas: (1) diversifying the pipeline; (2) accelerating clinical development; and (3) ensuring public health impact. Three cross-cutting enabling factors were also identified: funding, open science and stakeholder engagement. The roadmap is available via the EDCTP website[2] and a summary has been published in *Lancet Infectious Diseases*[3].

The Roadmap was launched at the **Virtual Global Forum on TB Vaccines in April 2021,** in partnership with AIGHD, during a special session attended by more than 250 participants, including researchers, developers, funders, regulators and other stakeholders.

In collaboration with the Tuberculosis Vaccine Initiative (TBVI), EDCTP has also been carrying out other activities to **support projects planning TB vaccine trials and regulatory submissions**. In 2021, a range of new tools were made available, including guidance on developing a plan for obtaining regulatory approval, guidance and a template to promote good data-management practices, and templates for developing clinical trial protocols related to the three priority needs identified by WHO (TB prevention in neonates/infants; prevention of active pulmonary disease in adults/adolescents; and use of a vaccine to treat TB in those already infected)[3].

In addition, a **registry** has been developed providing information on clinical trial sites with the capacity to carry out TB vaccine trials in sub-Saharan Africa[4]. The registry and guidance materials are all available on the EDCTP website[5].

Advancing TB drug development

The PanACEA Consortium is making excellent progress towards its goal of shorter and simpler treatments for TB.

TB treatment typically requires patients to take multiple medications for several months. This is a significant burden, and often leads to patients dropping out of treatment. Shorter and simpler treatment regimens are therefore a key priority in TB research.

The EDCTP-funded **PanACEA Consortium** brings together multiple institutions in Europe and sub-Saharan Africa, providing a platform for multicentre TB treatment studies and developing capacity in Africa for high-quality clinical trials.

In 2021, PanACEA published important findings on the **optimal dose of rifampicin**, a critical component of TB treatment. First used in the 1970s, the recommended dose of rifampicin

2 www.edctp.org/publication/global-roadmap-for-research-and-development-of-tuberculosis-vaccines/
3 Cobelens F, Suri RK, Helinski M et al. Accelerating research and development of new vaccines against tuberculosis: a global roadmap. Lancet Infect Dis. 2022 Apr;22(4):e108-e120. doi: 10.1016/S1473-3099(21)00810-0.
4 www.edctp.org/our-work/coordination-tb-vaccine-funded-research/guidance-and-templates/
5 www.edctp.org/our-work/coordination-tb-vaccine-funded-research/directory-tb-vaccine-clinical-trial-sites-sub-saharan-africa/

was set as 10 mg/kg, balancing cost, efficacy and concern about side effects. However, no formal studies were carried out to determine the maximum tolerated dose – the highest dose that could be safely given to patients. This is important, as there is growing evidence that higher doses of rifampicin would be more effective and potentially allow for shortened treatment.

To provide firm data, the PanACEA team evaluated different rifampicin regimens – 10, 20, 25, 30, 35, 40 and 50 mg/kg rifampicin daily over 2 weeks – supplemented with standard doses of isoniazid, pyrazinamide and ethambutol in the second week. Although the 50 mg/kg dose had the highest bactericidal activity on mycobacteria, it led to jaundice and had other side effects so was not well tolerated; 40 mg/kg was therefore proposed as the maximum tolerated dose[6]. PanACEA is now conducting a series of trials using high-dose rifampicin in combination with other TB drugs to develop an effective treatment-shortening regime. A phase II trial (STEP2C) is being planned to test the efficacy of the 40 mg/kg dose of rifampicin in a larger patient population.

The PanACEA team has also collated data on the impact of **different doses of pyrazinamide**, which boosts the impact of other TB drugs and could also help to reduce the duration of treatment. However, modelling of data from several trials suggests that increasing pyrazinamide dosing would only help to shorten treatment if rifampicin dosing was increased in parallel[7]. The planned STEP2C study will include a high-dose rifampicin (40 mg/kg) and high-dose pyrazinamide (20 mg/kg) arm.

During 2021, progress was also made in other studies in the PanACEA portfolio. In early 2022, recruitment was completed into the **SUDOCO** trial, being carried out at four clinical sites in South Africa and Tanzania. The SUDOCO trial is aiming to identify the optimal dose of **sutezolid**, a potential alternative to linezolid. The study will provide critical data to guide the choice of dose for definitive efficacy studies of sutezolid in combination with existing or new TB drugs.

Recruitment has also been completed in the **PHENORIF** study, which is assessing how high-dose rifampicin affects key metabolic processes when given in combination with other TB drugs. Planning is also underway on the **STEP2C** study, a phase II trial that will evaluate multiple regimens incorporating high-dose rifampicin, high-dose pyrazinamide and an optimised dose of sutezolid.

The value of the PanACEA Consortium's trial infrastructure has been illustrated by its involvement in the testing of **BTZ043**, first TB drug developed in Europe by academia and national research institutes without the involvement of a drug company or a large product development partnership. Through a Participating States Initiated Activity (PSIA) funded by Germany, PanACEA has contributed to the early development of BTZ043. Positive phase I results supported progression to an EDCTP-funded phase IIa early bactericidal efficacy and tolerability study, being carried out in South Africa, which will provide supportive data for planned advanced phase IIb/c and III studies with pharmaceutical industry partners.

The results generated by PanACEA projects provide critical background data for a large public–private initiative, UNITE4TB, supported by the Innovative Medicines Initiative (IMI). With €185 million IMI funding, multiple company and associated partners are working through UNITE4TB to advance treatment-shortening regimens to phase II trials.

6 Te Brake LHM, de Jager V, Narunsky K et al. Increased bactericidal activity but dose-limiting intolerability at 50 mg·kg^{-1} rifampicin. Eur Respir J. 2021;58(1):2000955. doi: 10.1183/13993003.00955-2020.

7 Zhang N, Savic RM, Boeree MJ et al. Optimising pyrazinamide for the treatment of tuberculosis. Eur Respir J. 2021;58(1):2002013. doi: 10.1183/13993003.02013-2020.

Statins for TB

Could statins offer a novel way to reduce lung damage caused by TB infections and slow the spread of disease?

Best known as treatments for cardiovascular disease, statins have a wide range of effects on human physiology, including anti-inflammatory activity. The **StatinTB** study is assessing whether this medicinal property of statins could be harnessed to benefit TB patients.

On infection with *Mycobacterium tuberculosis* (Mtb), the body launches a complex immune response that leads to the formation of granulomas – fibrous capsules containing a multitude of different immune cells. Long thought to be a way of isolating and controlling Mtb infections, granulomas are now considered to reflect subversion of host immune responses by Mtb in order to create a protective 'safe haven'. Indeed, granulomas may be positively harmful to the host, causing long-lasting damage to the lungs and facilitating the multiplication and spread of Mtb.

The perspective, reviewed by the StatinTB team in 2021[8], opens up the prospect of alternative approaches, targeting host immune responses alongside Mtb itself. Given their anti-inflammatory properties, widespread use and excellent safety record, statins are a good candidate for such 'host-directed therapies'.

To test this idea, the StatinTB team is carrying out a proof-of-principle trial of the use of statins, as a complement to antibiotic treatment. After their antibiotic treatment has been completed, patients with TB are being given a 12-week course of atorvastatin, a widely used statin. Lung scans will be used to assess the presence of active disease and extent of lung damage.

If this initial trial identifies a benefit associated with the use of statins, it would open the way to a larger trial to provide formal evidence of efficacy.

A new approach for treatment of TB-related meningitis

All four countries involved in the INTENSE-TBM project, which is investigating a new way to treat tuberculous meningitis, began recruiting patents in 2021.

Although predominantly a lung disease, TB can affect the brain, leading to a potentially fatal form of meningitis. The fatality rate for tuberculous meningitis (TBM) is around 30%, and higher still in patients with HIV infections or with drug-resistant TB. It particularly affects young children.

Treatment of TBM is complicated, as some TB drugs do not readily gain access to brain tissue, and there is much uncertainty about the best choice of treatment. The **INTENSE-TBM** project is carrying out a large clinical trial to evaluate an intensified treatment regimen, based initially on high-dose rifampicin (which does not easily enter the brain), linezolid (which shows good brain uptake), plus other TB drugs and steroids.

After a week, patients are being switched to a less intense oral regimen for up to seven months. Use of aspirin to reduce inflammation and lung damage is also being assessed.

In 2021, recruitment into the trial began in Côte d'Ivoire, Madagascar, South Africa and Uganda, and by the end of the year almost 100 patients had been enrolled. In total, 768 patients are due to be recruited across the four countries, including patients with and without HIV infections.

Although outcomes have remained poor, recommended treatments for TBM have not changed for many years. With new TB drugs unlikely to be applicable to TBM – their chemical structures mean they do not easily gain access to the brain and they are not suitable for high-dose use – making best use of existing treatments will be essential to reduce mortality and disability among survivors.

8 Guler R, Ozturk M, Sabeel S et al. Targeting Molecular Inflammatory Pathways in Granuloma as Host-Directed Therapies for Tuberculosis. Front Immunol. 2021;12:733853. doi: 10.3389/fimmu.2021.733853.

Optimising molecular testing for TB

In 2021, the TB CAPT project hit its 50% recruitment milestone for its study of TB drug susceptibility testing, and made preparations for two other studies that will answer key questions about new testing technologies for TB.

Molecular testing for TB offered the prospect of rapid detection of infection and timely initiation of treatment. However, its impact has not been as great as expected, highlighting the need to consider practical issues of how molecular testing fits into pathways of patient assessment and care in different settings.

The **TB CAPT** project is organising three clinical studies focused on optimising the use of different molecular testing tools in sub-Saharan African settings. Its **TB CAPT XDR** trial is examining use of the Xpert MTB/XDR test which, as well as reliably identifying TB infections, also assesses susceptibility to rifampicin, a commonly used TB drug, and provides results within hours rather than days or weeks. The project, which hit its 50% recruitment target in October 2021, is exploring the feasibility and impact of this tool when integrated within the existing TB diagnostic infrastructure in South Africa.

Planning also continued on two other clinical studies, due to begin recruiting in 2022. The **TB-CAPT CORE** trial will provide evidence on a new TB diagnostic and resistance-profiling test, Truenat, which was endorsed by WHO in 2020. As it is battery-powered and portable, Truenat technology has the key advantage that it can be used at peripheral primary health care facilities. The trial will compare use of Truenat and Xpert MTB/XDR approaches, recruiting more than 4000 patients at 28 primary health care facilities in Tanzania and Mozambique.

The third study, **TB-CAPT EXULTANT HIV**, is evaluating potential approaches for improving diagnosis of TB in people living with HIV admitted to hospital, who often have undiagnosed TB. As sputum is generally difficult to obtain from such patients, the study will investigate the use of alternative sample sources, such as urine or stool, and diagnostic technologies such as the highly sensitive Xpert Ultra assay and urine-based AlereLAM assay.

‘Universal’ screening for HIV and TB

The TREATS study has found that a community-based approach shown to improve detection of HIV and prevention of HIV infection does not deliver similar benefits for TB.

The ground-breaking PopART study set out to evaluate whether a ‘universal test-and-treat’ strategy for HIV and TB, whereby all members of a community are screened for disease and referred for treatment when appropriate, would cut the number of cases of infection. The PopART study was focused primarily on HIV and found that the universal test-and-treat strategy reduced the incidence of HIV by 20%.

The EDCTP-funded TREATS study built on this foundation, aiming to determine whether the universal test-and-treat strategy had a similar impact on TB. Population screening should, in theory, improve detection of TB infections and timely start of treatment, thereby reducing the risk of transmission, and also reduce TB by preventing HIV infections, as people with HIV are at increased risk of TB.

The study’s fieldwork was completed in June 2021 and initial findings were communicated at conferences (including the EDCTP Forum) in October 2021[9, 10]. Contrary to expectation, the PopART intervention was found to have had no impact on either the prevalence or

9 Klinkenberg E. Impact of population level screening for tuberculosis, combined with universal testing and treatment (UTT) for HIV on TB prevalence. 52nd Union World Conference on Lung Health. 2021. Symposium abstracts p. S33. Available at https://theunion.org/sites/default/files/2021-10/UNION2021_Abstracts_High.pdf

10 Telisinghe L. Did HpTN 071 (popART) reduce notified TB disease incidence? 52nd Union World Conference on Lung Health. 2021. Symposium abstracts p. S33. Available at https://theunion.org/sites/default/files/2021-10/UNION2021_Abstracts_High.pdf

incidence of TB[11]. Possible explanations include the challenges associated with active TB case finding in communities, unexpected complexity in the impact of antiretroviral therapy on TB infection and disease, and the extended period between the completion of the PopART trial and the TREATS follow-up.

Nevertheless, the study was able to gather important information on sociocultural attitudes to TB and stigma in South Africa and Zambia. It also provided a platform for testing of novel TB diagnostics[12]. In addition, the results have raised questions that will stimulate further research into the interactions between antiretroviral therapy in TB. The TREATS team also carried out a systematic review in 2021, compiling the evidence on whether TB screening improves individual outcomes, which highlighted the lack of high-quality data relating to patient outcomes[13].

From a policy perspective, the results do not undermine the value of universal test-and-treat as an HIV prevention strategy but do emphasise that additional efforts will still be required to tackle the TB pandemic.

Seeking out TB cases

The CUT-TB study, which began recruiting participants in December 2021, is assessing whether testing of all household contacts of patients with TB improves TB case detection.

A major challenge in TB control is the identification of cases. Worldwide, only around two-thirds of new cases are currently identified each year. Those who are missed do not receive appropriate treatment and can contribute to the spread of infection.

As a result, there is a drive to identify these missed infections, for example through 'active' case finding – searching for cases rather than waiting for people to access health services. Active case finding typically targets high-risk groups, including household contacts of newly diagnosed patients. Although recommended by WHO, household contact tracing has not been widely adopted because it is thought to identify relatively few new cases.

However, new approaches are being developed that enhance the public health benefits of household contact tracing. A major drawback of traditional methods is that they rely on symptom screening, which is a highly inefficient way of detecting TB disease and does not identify cases of latent TB, which can activate and become harmful to health.

The **CUT-TB** team is carrying out a trial assessing an approach known as **universal household contact tracing**, in which all household and community contacts are screened and TB preventive therapy initiated among contacts when appropriate. The CUT-TB project, being carried out in three countries with high TB burdens Lesotho, South Africa and Tanzania, will determine whether this 'test-and-treat' approach increases the number of cases identified compared with the traditional approach of symptom screening. Recruitment into the trial was launched in 2021, with around 400 people due to be recruited into the study in each of the three countries.

Sub-studies will examine the practicalities of testing childhood contacts, how stigma affects case finding and take up of treatment, and the economics of universal contact tracing compared with other screening approaches. The project will therefore generate evidence of direct relevance to policymakers considering different approaches to active case finding.

11 TREATS. Understanding the impact of universal test-and-treat programme (TREATS project final report). 2021. Available at https://treatsproject.org/latest-news

12 Kaaba C, Ruperez M, Kosloff B et al. Assessing usability of QIAreach QuantiFERON-TB platform in a high tuberculosis prevalence, low-resource setting. ERJ Open Res. 2021;7(4):00511-2021. doi: 10.1183/23120541.00511-2021.

13 Telisinghe L, Ruperez M, Amofa-Sekyi M et al. Does tuberculosis screening improve individual outcomes? A systematic review. EClinicalMedicine. 2021;40:101127. doi: 10.1016/j.eclinm.2021.101127.

More efficient detection of TB

Multiple studies evaluating different strategies to better detect TB infections have been launched.

TB is difficult to diagnose on the basis of clinical symptoms, culture methods take weeks to deliver results, and molecular diagnostics are expensive and often require special facilities. As a result, there is an urgent need for novel tools and testing practices to efficiently and more rapidly detect TB cases so that treatment can be started promptly – benefiting patients and reducing the risk of further disease transmission.

One potential approach is to use simple point-of-care tests to triage potential cases, identifying those most likely to have TB infection for confirmatory testing. The **TB TRIAGE+** project, for example, is assessing two possible tools as a step between symptom screening and use of molecular testing. These are a novel digital chest X-ray analysis tool (CAD4TB) and a point-of-care test for a protein in blood associated with active infection (POC-CRP). The first patients were enrolled in the TB TRIAGE + ACCURACY TRIAL in Lesotho and South Africa in February and April 2021, respectively.

As well as assessing the accuracy of the two tools, the TB TRIAGE+ project is also undertaking a large community-based study, involving 20,000 participants, to evaluate the use of the two tools in combination to identify cases in the community.

A second collaboration with similar aims, the **TriageTB** consortium, began recruiting its first participants in The Gambia, South Africa and Uganda in September 2021. The TriageTB is evaluating use of a simple point-of-care fingerprick test to detect active TB infections[14]. Previous EDCTP-funded projects have identified markers in blood that can act as a distinctive signature of TB infection. The TriageTB project has used samples from sites around the world to refine the test so it could be used globally. Use of the test is now being evaluated in the three African countries, with 900 patients in total due to be recruited.

Ultimately, the test could have most value as a 'rule out' test, with a negative test suggesting a TB infection is highly unlikely, so just those testing positive undergo molecular testing. Initial results suggest that this could avoid up to 75% of expensive negative molecular tests.

Recruitment also began in 2021 to the **SeroSelectTB** study, which is evaluating the SeroSelectTB diagnostic tool, a rapid antibody-based lateral flow test for TB. Again, the purpose of the tool is to rapidly identify potential patients at the health facility level for further assessment. The study, being carried out in Ethiopia, South Africa and Tanzania, will determine what impact SeroSelectTB could have on the timeliness of treatment initiation and reductions in transmission, as well as the cost implications of its introduction.

Ultimately, these tools could improve the efficiency of testing and make it easier to detect the 'missing' TB cases – globally, only two-thirds of new cases are detected each year using current methods.

14 Sutherland JS, van der Spuy G, Gindeh A et al. Diagnostic accuracy of the Cepheid 3-gene host response fingerstick blood test in a prospective, multi-site study: interim results. Clin Infect Dis. 2021: ciab839. doi: 10.1093/cid/ciab839.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3.2

Malaria

After a prolonged period of falling case numbers, malaria control has stalled in recent years. However, exciting progress in vaccine development may help to re-energise the push towards malaria elimination and eradication.

Malaria in numbers

17 grants
€136.47 M

Drugs
12 grants
€85.35 M

Vaccines
4 grants
€48.12 M

Diagnostics
1 grant
€3 M

Advancing implementation and development of malaria vaccines

EDCTP has been supporting the post-registration evaluation studies of the first malaria vaccine of proven efficacy, and funded a phase IIb trial of the first vaccine to achieve the WHO's efficacy target of 75%.

With malaria control currently stalled and resistance to key antimalarial drugs recently detected in Africa, there is an urgent need for an effective malaria vaccine.

In October 2021, WHO recommended widespread use of the most advanced malaria vaccine, RTS,S/AS01, following decades of development and evaluation, including three pilot programmes in Ghana, Kenya and Malawi that reached more than 800,000 children. Through its funding for capacity-building, EDCTP has made an important contribution to ensuring that sub-Saharan African countries were able to carry out high-quality clinical studies on RTS,S/AS01.

EDCTP is also supporting the **MVPE-CC** study which aims to provide additional safety and effectiveness data on the RTS,S/AS01 malaria vaccine through a series of case-control studies embedded in the pilot implementation programmes. These studies will provide important data on the added value of the fourth dose of the RTS,S/AS01 course, which is programmatically challenging to administer and could be making little additional contribution to protection, and on safety signals detected in phase III studies.

EDCTP fellow **Dr Francis Ndungu** has followed up children who took part in an earlier phase II trial of RTS,S/AS01 in Kenya, looking at how vaccine-induced antibody levels varied up to 7 years after vaccination[15]. His findings suggest that the kinetics of different antibody classes differ markedly, with IgG levels declining rapidly at first and then more slowly, but with IgM levels showing much greater persistence. The findings are reassuring with regard to continuing protection against disease following

15 Mugo RM, Mwai K, Mwacharo J et al. Seven-year kinetics of RTS, S/AS01-induced anti-CSP antibodies in young Kenyan children. Malar J. 2021;20(1):452. doi: 10.1186/s12936-021-03961-2.

RTS,S/AS01 vaccination, particularly as no booster dose was used in the phase II trial.

In addition, the **SAVING** study is aiming to build capacity for implementation research in Ghana, to facilitate expanded access to RTS,S/AS01 as it is introduced into seven additional regions following the pilot programme in three regions. More generally, the project will build the capacity of key bodies in Ghana to introduce new vaccines efficiently. Finally, the **Mal-Brain** study is comparing neurobehavioural impairments and school attendance in children receiving RTS,S/AS01, insecticide-treated bed nets or placebo. The study should determine whether malaria prevention translates into benefits for children's intellectual and emotional development.

R21/Matrix-M

RTS,S/AS01 may soon be complemented by a second vaccine, following the publication of highly promising efficacy data from an EDCTP-funded phase IIb trial on the R21/Matrix-M vaccine, being developed by the **Multi-Stage Malaria Vaccine Consortium (MMVC)**.

The trial, in Burkina Faso, identified a vaccine efficacy of 77% in children aged 5–17 months over a year with a higher-dose of Matrix-M adjuvant, with no significant safety issues[16]. A phase III trial, supported by the Serum Institute of India, will provide definitive data on the efficacy of R21/Matrix-M.

As well as the impressive efficacy of R21/Matrix-M, the first vaccine to achieve the WHO's target of 75% efficacy, and markedly higher than that of RTS,S/AS01, R21/Matrix-M may have a further important advantage. Although based on the same antigen as RTS,S/AS01, R21/Matrix-M can be used at significantly lower doses, which should boost vaccine supply.

Over the longer term, malaria control would benefit from vaccines that not only protect those infected but also block transmission, by targeting the stage of the malaria parasite life

16 Datoo MS et al. Efficacy of a low-dose candidate malaria vaccine, R21 in adjuvant Matrix-M, with seasonal administration to children in Burkina Faso: a randomised controlled trial. Lancet. 2021;397(10287):1809–1818.

cycle taken up my mosquitoes (gametocytes). The **PfTBV** consortium is evaluating a portfolio of early-stage candidate transmission-blocking vaccines in order to identify those most suitable for large-scale evaluation. In 2021, it published important work on the production of one promising candidate, known as R0.6C, in sufficient quantities and quality for clinical studies[17, 18].

Triple therapy for malaria

Following completion of its pilot study in 2021, the ASAAP team has launched its main trial of triple artemisinin combination therapy for malaria.

Although artemisinin combination therapies (ACTs), the mainstay of antimalarial treatments, remain effective in Africa, the rise of antimalarial drug resistance in South-East Asia has highlighted the need to make preparations should drug resistance also become established in sub-Saharan Africa. Recent detection of drug-resistance genes in African parasites has provided an additional spur to such activities.

One possible countermeasure is the use of 'triple ACT' strategies – addition of a third drug to protect currently used ACTs. The **ASAAP** consortium, for example, is evaluating the joint use of artemether–lumefantrine (AL), a widely used ACT, with atovaquone–proguanil (AP), another antimalarial that is known to be effective. In addition, AP acts on multiple stages of the parasite life cycle, so could also reduce parasite transmission.

In 2021, the ASAAP project completed its pilot phase II trial of triple therapy in adults and adolescents. With no problems identified during the pilot, it was able to proceed with its main phase III trial involving its key target group, children aged 6–59 months. More than 1500 patients are due to be enrolled in Benin, Gabon, Ghana and Mali.

The project team has also summarised the challenges facing the development of triple therapies for malaria[19]. Ultimately, the findings of the main trial will identify whether AL–AP triple therapy would be suitable for young children in Africa, potentially increasing the range of treatment options available for this key group.

Malaria prevention in women living with HIV

The MAMAH project has completed recruitment into its trial of a new approach to prevent malaria infections in pregnant women living with HIV.

Malaria infections are harmful to both mothers and their unborn offspring. The impact of malaria is made much worse by the simultaneous presence of HIV infections. Around a million pregnancies every year are affected by both malaria and HIV infections.

To protect pregnant women, WHO recommends that they are treated pre-emptively with an antimalarial drug, sulfadoxine-pyrimethamine (SP), at key stages of pregnancy, so-called intermittent preventive treatment in pregnancy (IPTp). However, SP cannot be given to pregnant women living with HIV who are being given cotrimoxazole to prevent opportunistic infections.

17 Singh SK, Plieskatt J, Chourasia BK et al. Preclinical development of a Pfs230-Pfs48/45 chimeric malaria transmission-blocking vaccine. NPJ Vaccines. 2021;6(1):120. doi: 10.1038/s41541-021-00383-8.

18 Singh SK, Plieskatt J, Chourasia BK et al. A Reproducible and Scalable Process for Manufacturing a Pfs48/45 Based Plasmodium falciparum Transmission-Blocking Vaccine. Front Immunol. 2021;11:606266. doi: 10.3389/fimmu.2020.606266.

19 Bassat Q, Maïga-Ascofaré O, May J et al. Challenges in the clinical development pathway for triple and multiple drug combinations in the treatment of uncomplicated falciparum malaria. Malar J. 2022;21(1):61. doi: 10.1186/s12936-022-04079-9.

A previous trial found that an alternative to SP, mefloquine, reduced the risk of malaria but was not well tolerated by pregnant women and was associated with an increased risk of mother-to-child transmission of HIV. The MAMAH team is therefore evaluating an alternative approach based on dihydroartemisinin–piperaquine (DP) rather than SP[20].

In 2021, the study completed recruitment of 667 pregnant women with HIV in Gabon and Mozambique. It is assessing the protective effect of intermittent preventive treatment with DP on the risk of malaria during pregnancy, tolerability of DP, and impacts on mother-to-child transmission of HIV.

The MAMAH trial has also provided the basis for a project funded through the EDCTP's emergency COVID-19 funding call. Through the **MA-CoV** study, the trial platform is being used to recruit a cohort of 1000 pregnant women in order to characterise the COVID-19 disease burden and the nature of disease in malaria-endemic areas with a high prevalence of HIV infections. The study is also exploring the nature of clinical impacts on pregnant women, risk factors associated with poor outcomes, and the potential for mother-to-child transmission of SARS-CoV-2. The first woman was enrolled in this cohort in 2021.

20 González R, Nhampossa T, Mombo-Ngoma G et al. Evaluation of the safety and efficacy of dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria in HIV-infected pregnant women: protocol of a multicentre, two-arm, randomised, placebo-controlled, superiority clinical trial (MAMAH project). BMJ Open. 2021;11(11):e053197. doi: 10.1136/bmjopen-2021-053197.

Implementing integrated community case management for malaria

A Participating States-Initiated Activity (PSIA) funded by Uganda has identified some of the key factors associated with the effective implementation of community-based approaches to malaria treatment.

Integrated community case management (ICCM) is a strategy promoting care of common childhood illness within communities, to increase the availability of life-saving treatments and reduce reliance on health facilities. ICCM is typically implemented by village health teams, composed of five village health workers selected by the community. Inclusion of malaria in the package of care services is extending the range of common diseases that such teams can manage.

The PSIA project undertook an assessment of implementation activities co-funded by the Global Fund, to provide evidence to support wider use of ICCM in additional districts, with Ugandan Government support.

It found that 95% of villages in the 15 study districts had village health teams and almost all had been trained in ICCM during the previous two quarters. However, many teams lacked the commodities (including medications) needed to treat malaria, pneumonia or diarrhoea. The project also identified a range of barriers affecting how well the new approach was being integrated into existing logistics management and health information systems.

The study results found that the incidence of fever, cough/pneumonia and diarrhoea in areas where ICCM was being implemented was lower than seen in previous population surveys, suggesting a positive impact on disease control. Access to health services was increased and use of health facilities decreased, and village health teams were found also to be promoting preventive measures contributing to a decline in disease in children under-five.

Overall caretakers' satisfaction with village health team services was high (81% positive). Supply chain reliability received the lowest favourability ratings, and a range of shortcomings in the supply chain system were identified.

Despite these challenges, village health teams were highly motivated, particularly because of the trust invested in them by the community. Being a member of a village health team was also seen to confer respect and higher social status. Provision of bicycles and branded T-shirts were also found to be highly motivating, and several other practical factors supporting their work were identified.

The project team suggest a number of changes that could enhance the activities of village health teams, including stronger supervision, support with transport and provision of mobile phones. Continuing involvement of communities in selection of village health team members was felt to be essential. The potential extension of the approach to other age groups was highlighted, as well as its possible adoption by other government programmes outside health. The study's findings have been communicated to the Ugandan Ministry of Health to inform its decision-making.

Assessing antimalarial efficacy in Uganda

A Participating States-Initiated Activity (PSIA) funded by Uganda has confirmed that standard antimalarial therapies remain effective, despite fears about the spread of drug resistance, and has pointed to some possible adaptations to current treatment strategies.

In Uganda, artemether–lumefantrine (AL) is the standard first-line artemisinin combination therapy (ACT) for uncomplicated malaria, with dihydroartemisinin–piperaquine (DP) the recommended second-line treatment in case of treatment failure. With increasing evidence of resistance to ACTs in sub-Saharan Africa, an important priority is to determine whether current treatment regimens remain effective.

The PSIA project enrolled nearly 600 Ugandan children aged 6 months to 10 years with uncomplicated malaria at study sites in three different districts. The children were randomly assigned to treatment with either AL or DP.

No early treatment failures were identified. For cases with confirmed malaria infection, the efficacy of AL at 28 days ranged between 87% and 94% at different sites, and that of DP varied between 92% and 98%[21]. No resistance-associated mutations were found in sequenced samples.

The findings confirm the extremely high efficacy of DP. Although the results for AL are also positive, the efficacy in Busia district (87%) suggests that further monitoring of efficacy may be advisable, alongside pharmacokinetic studies.

Although the study provides reassurance that artemisinin resistance is not yet a problem in Uganda, the findings suggest that DP could be considered as a potential first-line treatment in Uganda. It has other advantages over AL, including once-daily dosing scheme and longer persistence, leading to a lower risk of recurrent malaria after the end of treatment.

21 Ebong C, Sserwanga A, Namuganga JF et al. Efficacy and safety of artemether-lumefantrine and dihydroartemisinin-piperaquine for the treatment of uncomplicated Plasmodium falciparum malaria and prevalence of molecular markers associated with artemisinin and partner drug resistance in Uganda. Malar J. 2021;20(1):484. doi: 10.1186/s12936-021-04021-5.

Enhancing seasonal malaria control programmes

The OPT-SMC project has been organising a wide range of implementation research activities to enhance the effectiveness of seasonal malaria chemoprevention across 13 sub-Saharan African countries.

Seasonal malaria chemoprevention (SMC), where all children are given antimalarial drugs at times of the year when malaria transmission is most intense, is known to be an effective strategy for reducing the burden of malaria. It has been adopted by multiple countries in sub-Saharan Africa, but coverage is suboptimal – only around half of eligible children actually receive SMC.

Implementation research can be used to identify and overcome the barriers that affect successful implementation of disease control interventions. The **OPT-SMC** project is working with national malaria control programmes in the 13 countries that have introduced SMC, as well as international and national partner organisations, on a range of implementation and operational research activities to improve the efficiency and coverage of national SMC programmes.

Activities have included community consultations in two districts of Guinea, which found that some people in mining areas were suspicious that a free treatment was being given to healthy children, and were concerned about drugs being provided by people from outside their community. These factors were used to inform local SMC activities in 2021.

Also in 2021, work continued on a case control study in northern Benin. By comparing the treatment history of cases and controls, the research team will be able to assess the effectiveness of SMC in the region.

In Ghana, an analysis of data collected in 2020 showed that 88% of children eligible for four treatments actually received the full course. Coverage was very low among older children (1%) and a range of supply- and demand-side barriers to SMC uptake were identified. Again, these are being used to inform the design of local SMC activities.

A further eight countries (Burkina Faso, Cameroon, Chad, Mali, Niger, Nigeria, The Gambia and Senegal) developed protocols for implementation research activities in 2021. OPT-SMC is also working with the WHO Global Malaria Programme on the development of an SMC module within the health information system that all countries use for malaria surveillance. This will enable countries to better track and analyse their SMC activities.

The OPT-SMC project also provided a platform for two COVID-19-related projects, funded by the Wellcome Trust and the WHO Special Programme for Research and Training in Tropical Diseases (TDR). These included a study revealing remarkable success in maintaining SMC in 2020, with more than 30 million children reached. In addition, video training tools were developed in French, English, Portuguese and Hausa, illustrating key steps that distributors should follow when administering SMC during the pandemic.

3.3

HIV & HIV-associated infections

Despite much progress in improving access to antiretroviral therapy and prevention of mother-to-child transmission, HIV/AIDS remains one of sub-Saharan Africa's greatest health challenges, but new approaches to disease prevention are on the horizon.

HIV and HIV-associated infections in numbers

20 grants
€113.05 M

Drugs
12 grants
€64.10 M

Vaccines
4 grants
€35.58 M

Diagnostics
4 grants
€13.36 M

Simpler and safer treatment of cryptococcal meningitis

The AMBITION-cm study has shown that a simplified treatment for cryptococcal meningitis – one of the most important causes of death in people living with HIV – is as good as the currently recommended treatment and safer to patients.

Infection of the brain by *Cryptococcus*, a fungal pathogen, can lead to a potentially fatal meningitis. Globally, cryptococcal meningitis is the second most common HIV-related cause of death, and most deaths occur in sub-Saharan Africa.

Current treatment is based on a one-week course of two drugs, amphotericin B deoxycholate and flucytosine. However, use of amphotericin B deoxycholate is associated with blood, kidney and other abnormalities, requiring careful patient monitoring, which may not be feasible in many resource-poor settings where the burden of disease is highest.

A possible alternative to week-long treatment with amphotericin B deoxycholate is a single dose of a liposomal formulation of amphotericin B. As well as simplifying treatment, it is less toxic and so can be given at higher doses, has a long half-life, and readily enters the brain.

The phase III AMBITION-cm trial, in five African countries, compared use of single-dose liposomal amphotericin B and flucytosine with the current recommended treatment, recruiting 844 patients with confirmed cryptococcal meningitis. Survival was not markedly different in the two arms (24.8% mortality in the liposomal amphotericin B group versus 28.7% in the control group) and fewer serious side effects were seen with liposomal amphotericin B[22].

The results argue in favour of use of liposomal amphotericin B, which would be easier to deliver in resource-poor settings, have fewer treatment complications and could potentially reduce the duration of hospital stays for some patients. Furthermore, with the study conducted across five countries in southern and eastern Africa, the results should be generalisable across the region. In April 2022, the WHO issued a rapid advice[23] to update guidance on treatment of cryptococcal meningitis based on the findings of the AMBITION-cm study.

22 Jarvis JN, Lawrence DS, Meya DB et al. Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis. N Engl J Med. 2022;386(12):1109–1120. doi: 10.1056/NEJMoa2111904.
23 https://www.who.int/news/item/20-04-2022-rapid-advice-new-guidelines-for-simpler-safer-treatment-for-cryptococcal-disease-in-plhiv

Backup options for children with HIV

The CHAPAS 4 study, which completed recruitment in 2021, aims to identify a suitable antiretroviral regimen for children in whom first-line treatment has failed.

WHO recommends that all children with HIV infections should receive antiretroviral drugs. Effective drug regimens suitable for children have been developed, but not all children respond to recommended drug combinations. In addition, as the number of children being treated increases, the number affected by drug-resistant infections is also rising.

These trends highlight the need for back-up or second-line treatments. However, some second-line treatments do not come in child-friendly formulations and limited data are available on the most effective regimens for children.

The CHAPAS Consortium has organised a series of highly influential clinical trials that have helped to shape international policy and practice on antiretroviral use in children. The CHAPAS 4 study, which completed its recruitment of 919 children with HIV in South Africa, Uganda, Zambia and Zimbabwe in 2021, has the specific aim of identifying a suitable second-line treatment for children. Because of excellent retention (only 0.5% of children lost to follow), the team has been able to slightly reduce the trial sample size.

The treatments being evaluated include formulations incorporating dolutegravir, a relatively new drug with significant advantages over existing treatments; atazanavir/ritonavir (ATV/r), which is now available in a single pill suitable for children; and tenofovir–alafenamide (TAF), a tenofovir pro-drug that may be particularly suitable for use in children, co-formulated with emtricitabine. These agents are being tested in different combination regimens against the current standard of care for children.

Participants will be followed until early 2023. Analysis of the CHAPAS 4 results should reveal which treatments are most appropriate for second-line treatment of children, helping to ensure that this vulnerable group benefits from the latest advances in antiretroviral drug development.

Identifying 'missing' children with HIV

The B-GAP study, a UK-funded Participating States-Initiated Activity (PSIA), has demonstrated the feasibility of community-based approaches to identify HIV infections in children and adolescents.

Great progress has been made in the implementation of programmes to prevent mother-to-child transmission of HIV. However, some infections do still occur during or after pregnancy. Ideally, these cases are identified early so that antiretroviral therapy can be started before the virus has a significant impact on health. Unfortunately, early infant diagnosis is suboptimal in many settings. Globally, only around half of children under 15 years of age with HIV infections are receiving antiretroviral therapy, mostly because of late diagnosis.

Because the numbers of children with HIV infection are relatively low, targeted strategies are generally adopted to identify 'missing' cases. These include 'index-linked testing', whereby children of adults diagnosed with HIV (index cases) are also tested for HIV infection. However, this approach relies on uptake of services by parents and carers. As the need to travel to health facilities could be a barrier to uptake, WHO recommends the use of lay community health workers for HIV testing, to reduce costs and increase uptake.

The **B-GAP** study sought to compare three different approaches to index-linked testing – one facility-based and two community-based; the latter involved either testing carried out by trained lay workers or self-testing, using recently developed home-testing kits. The study was carried out at a mix of urban and rural sites in Zimbabwe.

The index population of 2870 adults was linked to 6062 eligible children. Testing was accepted for 88% of children and test results were obtained for 60% in total. A total of 39 children tested positive for HIV, giving an HIV prevalence of 1.1% among those tested and an HIV yield of 0.6% among the total population of 6062 children[24].

Although more adults opted for facility-based testing, children were more likely to be tested when community-based testing was selected. Uptake was positively associated with female sex of the adult index case and negatively associated with age of child and costs of travel to clinics.

The yield was relatively low, possibly because Zimbabwe has a relatively effective programme for prevention of mother-to-child transmission. Even so, significant numbers of undiagnosed cases were identified. In addition, the study has shown that community-based approaches are feasible and are more likely to lead to testing of children.

An associated economic analysis has provided an indication of the costs associated with different testing strategies[25]. Both cost and uptake vary by setting, with uptake a key driver of cost per test. Strategies such as ensuring high acceptability of testing strategy and potentially broadening the scope of testing, for example to include all household members, could reduce the costs of new cases detected.

The findings provide support for community-based approaches to HIV testing, which identified as many missed cases as facility-based testing, even though more patients opted for the latter. Self-testing is not yet common in Zimbabwe so could become a more popular option as awareness grows. Importantly, as efforts intensify to identify missed cases, it is important that care-givers have a range of options available to them to ensure high uptake of HIV testing.

24 Dziva Chikwari C, Simms V, Kranzer K et al. Comparison of index-linked HIV testing for children and adolescents in health facility and community settings in Zimbabwe: findings from the interventional B-GAP study. Lancet HIV. 2021 Mar;8(3):e138-e148. doi: 10.1016/S2352-3018(20)30267-8.

25 Vasantharoopan A, Maheswaran H, Simms V et al. A costing analysis of B-GAP: index-linked HIV testing for children and adolescents in Zimbabwe. BMC Health Serv Res. 2021 Oct 12;21(1):1082. doi: 10.1186/s12913-021-07070-3.

Retention in care

A Participating States-Initiated Activity (PSIA) funded by Italy is shedding light on the retention of HIV-positive mothers and their children in care, and on the transfer of maternal antibodies to offspring.

Programmes for prevention of mother-to-child transmission of HIV are helping to minimise the numbers of infants living with HIV. However, both mothers and children remain vulnerable groups and it is important that they are retained in care. In addition, there may still be health risks for infants that are exposed to HIV, even if they are not actually infected.

This Italian PSIA, carried out in Malawi, enrolled two cohorts – a group of HIV-positive mothers and their children and a control group of HIV-negative mothers and their children – and followed them for 12 months after delivery. At 12 months, 85% of HIV-positive mothers enrolled were still enrolled in the programme (and 40% of those lost had transferred to another health facility), indicating good adherence.

In terms of impacts on offspring, no differences in growth were seen in the two groups of infants. However, infants exposed to HIV had higher rates of health issues of any type and experienced more lower respiratory tract infections, suggesting that, even when mothers are receiving antiretroviral therapy, infants of HIV-positive mothers remain a particularly vulnerable group.

To explore reasons for this vulnerability, the study examined transfer of antibodies across the placenta, an important mechanism by which infants are protected against infection early in life. HIV-exposed infants showed abnormalities in IgG class antibodies, particularly low levels of IgG2 antibodies[26]. In particular, they showed reduced levels of antibodies against a pneumococcal antigen, suggesting vulnerability to *Streptococcus pneumoniae* infections at an age when protection is largely mediated by maternal antibodies.

The findings suggest that, despite antiretroviral therapy, transplacental transfer of antibodies is impaired in women living with HIV. The immune system of infants seems not to be affected, as responses to common vaccines were similar in both groups.

The study's findings provide insights into the particular vulnerabilities of HIV-exposed infants. In addition, an analysis of factors affecting retention in care will help to refine the design of care programmes for HIV-positive mothers and their children.

26 Baroncelli S, Galluzzo CM, Orlando S et al. Immunoglobulin G passive transfer from mothers to infants: total IgG, IgG subclasses and specific antipneumococcal IgG in 6-week Malawian infants exposed or unexposed to HIV. BMC Infect Dis. 2022;22(1):342. doi: 10.1186/s12879-022-07335-0.

Monoclonal antibodies for HIV prevention

The CAPRISA 012 study has identified monoclonal antibodies with the best potential to provide long-lasting protection against HIV infection.

Despite some progress, 1.5 million new HIV infections occur each year. In southern Africa, women are at particular risk of infection. In the absence of an effective vaccine, there is hope that **broadly neutralising antibodies** – rare antibodies that neutralise a wide range of HIV types – could offer an alternative approach to prevent infection. The goal would be to manufacture large quantities of these antibodies, which could be injected and provide protection for several months.

This approach would enable women to be in control of protection against infection. Although this is already possible through the pre-emptive use of antiretroviral drugs, this is associated with significant adherence challenges linked to stigma and the need to take tablets regularly.

The CAPRISA 012 study is evaluating the safety and persistence of several broadly neutralising antibodies. In work published in 2021[27], it found that two such antibodies, known as VRC07-523LS and PGT121, were safe and well-tolerated, when given individually or in combination. Both retained virus-neutralising ability after injection and showed good persistence over time, particularly VRC07-523LS.

The results suggest that VRC07-523LS would be the best candidate to take forward into larger-scale efficacy studies. The CAPRISA 012 team is also evaluating VRC07-523LS in further studies alongside another broadly neutralising antibody, CAP256V2LS.

27 Mahomed S, Garrett N, Capparelli EV et al. Safety and pharmacokinetics of monoclonal antibodies VRC07-523LS and PGT121 administered subcutaneously for HIV prevention. J Infect Dis. 2022:jiac041. doi: 10.1093/infdis/jiac041.

A phase II study of CAP256V2LS and VRC07-523LS has also been initiated, with the first participants recruited in South Africa in November 2021. Recruitment in Zambia is due to start in 2022. As well as additional data on safety and antibody levels, this study will provide initial indications of the potential of the antibody combination to prevent HIV infection in young women.

The programme of work is also a notable example of therapeutic development driven from within sub-Saharan Africa. The broadly neutralising antibodies under investigation were isolated from people in the region, and their potential therapeutic application has been spearheaded by academic institutions in sub-Saharan Africa.

A novel approach to HIV vaccine design

The GREAT partnership has completed recruitment into a phase I trial of a novel HIV vaccine designed to stimulate T-cell responses to fend off HIV infection.

It has proven extremely difficult to develop effective HIV vaccines, with results from most clinical trials proving disappointing. HIV vaccines have typically been designed to stimulate production of antibodies to neutralise the virus and prevent infection of cells. The Globally Relevant AIDS Vaccine Europe–Africa Trials (GREAT) partnership is taking a different approach, aiming to stimulate T-cell immunity to counter virus replication.

The team has used information on HIV genome sequences to identify its most conserved genomic features across different strains. These have been stitched together into a 'mosaic' vaccine, known as HIVconsvX, that covers the six most conserved and functionally relevant sequences. Targeting these structures will ensure that the vaccine provides protection against the widest possible range of virus types.

The phase I HIV-CORE 006 trial is assessing the safety and tolerability of HIVconsvX, as well as its ability to stimulate potentially protective immune responses. Recruitment of 88 participants at sites in Kenya, Uganda and Zambia was completed on World AIDS Day in December 2021.

The results of the study could help the research team to optimise the design of the vaccine. They will also inform decisions on whether to run larger trials to assess the vaccine's efficacy at preventing infection, either alone or in combination with an antibody-generating vaccine.

3.4

Neglected infectious diseases

Neglected infectious diseases include some of the world's most common and debilitating conditions. Flatworm and other parasite infections affect millions, typically the poorest populations, and disrupt the growth and development of countless children in sub-Saharan Africa. For many, new treatments are becoming available, but a key challenge is getting them to populations in need.

Neglected infectious diseases in numbers

19 grants
€70.60 M

Drugs
13 grants
€47.50 M

Vaccines
1 grant
€8 M

Diagnostics
5 grants
€15.10 M

Bringing schistosomiasis flatworm treatment to under-fives

With the successful completion of the PZQ4PSAC phase III trial, children under five years of age should soon be benefiting from an effective drug for schistosomiasis infections.

Schistosomes are responsible for a huge global burden of disease, with 230 million people affected. A safe and effective treatment, praziquantel, is available and widely used in drug control programmes. However, it is not available in a formulation suitable for young children, 50 million of whom remain infected and at risk of a range of health and development issues.

The public–private Pediatric Praziquantel Consortium has been developing a potential new pediatric treatment, known as arpraziquantel, that is suitable for children under five years of age. The new tablet is smaller, dissolves in the mouth, can be taken with or without water, has an improved taste, and is stable under hot and humid conditions.

Through the **PZQ4PSAC** project, EDCTP and the Japan-based Global Health Innovative Technology (GHIT) fund partnered to support a phase III trial of arpraziquantel in Kenya and Côte d'Ivoire. The Pediatric Praziquantel Consortium announced the results of the trial in November 2021, confirming that arpraziquantel showed excellent efficacy, achieving cure rates of 90% or above, and was safe and well-tolerated by young children.

Based on these findings, the trial sponsor, Merck, is applying for a scientific opinion from the European Medicines Agency (EMA). A positive scientific opinion from the EMA would facilitate the inclusion of arpraziquantel on the WHO list of prequalified medical products and accelerate regulatory approvals in affected countries.

To ensure smooth introduction of arpraziquantel, EDCTP and GHIT have also partnered on an implementation research project, **ADOPT**, being carried out in Côte d'Ivoire, Kenya and Uganda. The five-year €7.8 million project (including an EDCTP contribution of €5.7 million) will explore a range of issues, including technology transfer and local manufacturing capacity, distribution mechanisms, and community sensitisation and demand generation.

Improving treatment of acute sleeping sickness

The HAT-r-ACC project has completed recruitment into its study of fexinidazole as a potential treatment for an acute sleeping sickness.

Great progress has been made in control of sleeping sickness (human African trypanosomiasis, HAT), particularly the most common form, caused by infection with the *Trypanosoma brucei gambiense* parasite. Of particular value has been the highly effective and easy to administer drug fexinidazole, the development of which has been led by the Drugs for Neglected Diseases *initiative* (DND*i*).

However, a second, 'acute' form of sleeping sickness, caused by *T. brucei rhodesiense*, is also a significant public health problem in parts of eastern and southern Africa. This form of the disease, known as rHAT, progresses more rapidly and can lead to death within weeks or months if untreated.

Fexinidazole is not yet licensed for use against rHAT, although there is good evidence that it should be effective, so toxic and less effective existing treatments are still being used. The **HAT-r-ACC** consortium is carrying out a clinical trial to assess the efficacy of fexinidazole against rHAT and its safety in rHAT patients, focusing on Uganda and Malawi, which account for more than 90% of current cases of rHAT. Recruitment was successfully completed in 2021 and patients will be followed up during 2022.

In addition, the project is also working with communities and national disease control programmes to raise awareness of rHAT, explore community attitudes, and to prepare the ground for the introduction of a new treatment. In 2021, the project published a report on community and healthcare worker perceptions of sleeping sickness and its treatment in an area of Malawi[28]. These activities will inform the design of plans for efficient implementation of fexinidazole for rHAT should the main trial confirm its efficacy.

28 Munthali AC. An anthropological study on local community and peripheral health centre staff perceptions and practices regarding sleeping sickness in Vwaza Marsh Wildlife Reserve in Malawi. 2021. Drugs for Neglected Diseases *Initiative*. Available at: https://dndi.org/wp-content/uploads/2021/06/DNDi-Malawi-rHAT-Ethnographic-Study-Report-2021.pdf

Extending river blindness treatment to under-fives

The MoxiMultiDoseMod study has started recruitment into trials designed to enable young children to benefit from moxidectin, a highly effective new treatment for river blindness.

The parasitic worm *Onchocerca volvulus* generates millions of tiny larvae, microfilariae, that can find their way into the eye, potentially leading to loss of sight ('river blindness'). Around 200 million people are at risk of infection, most of them in sub-Saharan Africa.

Ivermectin is widely used in mass drug administration campaigns but other treatments would be required to achieve disease elimination. In 2018, the US Food and Drug Administration approved use of moxidectin, the first new treatment for river blindness in 20 years, which is more effective at clearing microfilariae and persists in the body for longer than ivermectin, so holds promise as an alternative therapeutic for use in mass drug administration.

However, moxidectin was approved only for single use in people aged 12 years and older. Before it can be introduced into mass drug administration campaigns, its safety and efficacy need to be confirmed in younger children and when given repeatedly. To generate this evidence, the **MoxiMultiDoseMod** study is carrying out studies to compare the safety and efficacy of moxidectin and ivermectin given annually or every six months over three years. It is also conducting detailed studies to monitor the safety and metabolism of moxidectin in children aged 4–11 years old.

Recruitment into all these studies began in May 2021 in the Democratic Republic of the Congo and Ghana. Recruitment into the initial young-children study has been completed, and analysis of these data will be used to determine a suitable dose of moxidectin for use in children aged less than 12 years of age.

Ultimately, the project will generate key evidence to enable policymakers to consider use of moxidectin in mass drug administration campaigns, as part of concerted disease elimination efforts.

Also in 2021, the related **MiniMox** project held its kick-off meeting. It aims to develop a formulation of moxidectin suitable for young children, who may struggle to swallow the existing 2 mg pill.

Eliminating sleeping sickness in Côte d'Ivoire

The DiTECT-HAT project has made key contributions to the WHO-certified elimination of human African trypanosomiasis (HAT) in Côte d'Ivoire.

Enormous progress has been made in the control of human African trypanosomiasis (HAT), also known as sleeping sickness, with the disease earmarked for elimination as a public health threat. In 2021, WHO verified elimination in Côte d'Ivoire, an achievement that drew heavily on the work of the EDCTP-funded **DiTECT-HAT** project.

The DiTECT-HAT project has been evaluating three different testing strategies for HAT, each of which would have a distinct role to play in achieving and sustaining elimination. **Achieving elimination** will depend on the use of routine testing for HAT in healthcare facilities[29]. The project has been evaluating three point-of-care rapid diagnostic tests and comparing results with laboratory-based methods, at sites in the Democratic Republic of the Congo, Côte d'Ivoire and Guinea. The Côte d'Ivoire studies identified tests suitable for use in the country, as well as symptoms associated with positive test results, which could act as a trigger for testing for HAT.

29 Koné M, Kaba D, Kaboré J et al. Passive surveillance of human African trypanosomiasis in Côte d'Ivoire: Understanding prevalence, clinical symptoms and signs, and diagnostic test characteristics. PLoS Negl Trop Dis. 2021;15(8):e0009656. doi: 10.1371/journal.pntd.0009656.

The project has also been assessing a potential approach for **post-elimination monitoring**, which will require testing on a population scale. Health workers have been carrying out house-to-house visits to collect blood on filter paper, which is then sent to a central laboratory for large-scale analysis[30]. More than 13,000 people have been tested in Cote d'Ivoire, Burkina Faso, and in the Democratic Republic of the Congo and analysis of samples is ongoing. The results will be used to identify the optimal approach to population-based post-elimination monitoring.

A further strand of the project is evaluating highly sensitive tests, including detection of parasite RNA[31], which could be used to **track response to treatment** in research studies and will be important in the development of new therapeutics.

Côte d'Ivoire's submission to WHO included DiTECT-HAT's passive case-detection activities. In addition, the country has expressed interest in the project's post-elimination monitoring work, which could form part of its elimination validation/verification process up to 2030.

The use of rapid diagnostic tests could also lead to a significant change in case management in primary care, with treatment initiated without the need for parasitological analysis to confirm infection.

As well its contribution to Côte d'Ivoire's success in 2021, the DiTECT-HAT project's work will also be highly relevant to other countries targeting HAT elimination.

30 Alfred Compaoré CF, Ilboudo H, Kaboré J et al. Analytical sensitivity of loopamp and quantitative real-time PCR on dried blood spots and their potential role in monitoring human African trypanosomiasis elimination. Exp Parasitol. 2020 Dec;219:108014. doi: 10.1016/j.exppara.2020.108014.

31 Ngay Lukusa I, Van Reet N, Mumba Ngoyi D et al. Trypanosome SL-RNA detection in blood and cerebrospinal fluid to demonstrate active gambiense human African trypanosomiasis infection. PLoS Negl Trop Dis. 2021;15(9):e0009739. doi: 10.1371/journal.pntd.0009739.

Detecting schistosomiasis infections in pregnant women and infants

The freeBILy study has recruited more than 5000 pregnant women in Madagascar, as part of its evaluation of a 'test-and-treat' strategy for parasitic schistosomiasis infections.

More than 230 million people worldwide are infected with schistosomes (parasitic flatworms), making schistosomiasis the neglected tropical disease with the highest global disease burden. Chronic infections can cause a range of problems, including serious liver disease and urogenital complications that can affect women's health, pregnancy outcomes and infant development.

Control of schistosomiasis is primarily based on mass drug administration campaigns using praziquantel, mostly targeting school-age children. However, this typically excludes groups such as pregnant women and children under five years of age.

To avoid unnecessary exposure to praziquantel, its use could be extended just to those pregnant women or young children with confirmed infections. The **freeBILy** study is evaluating whether a commercially available point-of-care test of schistosome infection, detecting a parasite protein known as circulating cathodic antigen (CCA), could be used at scale in primary healthcare centres to detect infection in pregnant women and children under the age of 2, so they can be given praziquantel[32].

The study is being carried out in Madagascar, which is particularly badly affected by schistosomiasis. In February 2021, the project completed its recruitment, with 5203 pregnant women enrolled in its study. The cluster randomised trial will compare the effectiveness of the test-and-treat strategy with usual practice, and assess the cost-effectiveness of the new approach.

A complementary diagnostics-based study is being carried out in Gabon[33]. It is assessing an alternative, highly accurate test for schistosome infection, based on detection of a second parasite protein, circulating anodal antigen (CAA), which is not yet available as a point-of-care test. This study is evaluating the accuracy of the CAA test, monitoring CAA levels in pregnant women who test positive and are treated with praziquantel, and following up treated women and their offspring to gather more information on schistosome infection over the ensuing two years.

The Gabon study will provide valuable data on the usefulness of the CAA test for detecting infection and for monitoring response to treatment (as well as information on the safety of praziquantel in pregnant women). This will determine whether it is suitable for use in treatment trials and disease control and elimination campaigns, which will require highly accurate tests.

32 Fusco D, Rakotozandrindrainy R, Rakotoarivelo RA et al. A cluster randomized controlled trial for assessing POC-CCA test based praziquantel treatment for schistosomiasis control in pregnant women and their young children: study protocol of the freeBILy clinical trial in Madagascar. Trials. 2021;22(1):822. doi: 10.1186/s13063-021-05769-6.

33 Honkpehedji YJ, Adegnika AA, Dejon-Agobe JC et al. Prospective, observational study to assess the performance of CAA measurement as a diagnostic tool for the detection of Schistosoma haematobium infections in pregnant women and their child in Lambarene, Gabon: study protocol of the freeBILy clinical trial in Gabon. BMC Infect Dis. 2020;20(1):718. doi: 10.1186/s12879-020-05445-1.


Dr. Ouma Lilian

3.5

Emerging and re-emerging diseases

Recent decades have seen the emergence of alarming new threats to health, including Ebola and, most recently, COVID-19. At the same time, re-emerging infections such as yellow fever provide an ever-present threat of outbreaks. Wherever animals and humans live in close association, the risk that pathogens jump species barriers will persist. As well as new vaccines and treatments, these threats to health require a strong focus on surveillance and preparedness, so new threats can be detected and responses launched as rapidly as possible.

Emerging and re-emerging diseases in numbers

37 grants
€77.61 M

Drugs
1 grant
€0.2 M

Vaccines
6 grants
€43.51 M

Diagnostics
17 grants
€8.42 M

Non-intervention - specific topics,
13 grants
€25.38 M

Combating COVID-19

Through its Emergency Funding Mechanism, EDCTP has been supporting multiple projects answering key questions about COVID-19 in Africa, while other EDCTP-funded consortia have also pivoted to work on the pandemic.

At the start of the COVID-19 pandemic, EDCTP moved swiftly to enact its Emergency Funding Mechanism. Funding was awarded to 27 international consortia working in 26 African countries (an additional COVID-19-related project was funded through the Participating States-Initiated Activities (PSIAs) mechanism). Several of these projects draw upon existing EDCTP project researchers, infrastructure and study populations. These projects have been delivering results shedding important light on the pandemic in Africa and how it can best be controlled.

Six-month EDCTP funding for the **ANTICOV project**, coordinated by the Drugs for Neglected Disease *Initiative* (DND*i*), was pivotal in enabling it to put in place mechanisms for the rapid launch of international multicentre trials of COVID-19 therapeutics in sub-Saharan Africa. With EDCTP funding, the project was able to complete the study protocol, secure rapid reviews by regulatory and ethics authorities, and begin preparing trial sites. The ANTICOV Consortium went on to secure major international funding, undertaking the largest clinical trial in Africa of treatments for mild to moderate COVID-19, spanning 13 countries.

The **Profile-Cov** project has been tracking the dynamics of immune responses to SARS-CoV-2 in an African population, generating evidence to inform vaccine development and use. Notably, it found an association between co-infection with parasites and protection against progression to severe COVID-19[34]. Unravelling the mechanisms underlying this protection could suggest new ways to protect against severe disease. In addition, the findings suggest that parasite infections might have implications for the efficacy of COVID-19 vaccines in Africa.

34 Wolday D, Gebrecherkos T, Arefaine ZG et al. Effect of co-infection with intestinal parasites on COVID-19 severity: A prospective observational cohort study. EClinicalMedicine. 2021;39:101054. doi: 10.1016/j.eclinm.2021.101054.

The **ITAIL-COVID-19** also focused on immune responses to SARS-CoV-2. It screened for SARS-CoV-2 antibodies in a sample population in the Republic of Congo during the early months of the pandemic, to provide insights into the spread of infection and to inform epidemic management in the country. The study found that a high proportion of those screened, nearly 20%, had antibodies to SARS-CoV-2, suggesting that many infections were not being detected or were asymptomatic[35].

Building on the work of the **PREPARE** study (see page 54), the **periCOVID-Africa** project has been collecting data on COVID-19 infections in pregnant women and their children in Uganda, Kenya, Malawi, The Gambia and Mozambique. The project has also found that lockdown measures were associated with an increase in pregnancy complications and adverse foetal and infant outcomes, probably because fewer women had access to healthcare services[36]. The findings emphasise the need for pandemic responses to consider potential impacts on existing services.

The **Covid-19 HCW** project, which monitored a cohort of healthcare workers exposed to COVID-19 patients at an academic hospital in South Africa, found that more than 40% of healthcare workers had evidence of SARS-CoV-2 infection during the first six months of the pandemic[37]. This is a higher rate than seen in Europe and North America, and probably reflects poor ventilation and crowded wards. Rates elsewhere on the continent are likely to be higher than in South Africa, a relatively well-resourced African country. The study team's later work found that past infection and vaccination provided limited protection against infection with the omicron SARS-CoV-2 variant[38].

In March 2021, EDCTP organised a webinar enabling its COVID-19 grant holders to share information and their experiences.

35 Batchi-Bouyou AL, Lobaloba Ingoba L, Ndounga M et al. High SARS-CoV-2 IgG/IGM seroprevalence in asymptomatic Congolese in Brazzaville, the Republic of Congo. Int J Infect Dis. 2021;106:3-7. doi: 10.1016/j.ijid.2020.12.065.

36 Burt JF, Ouma J, Lubyayi L et al. Indirect effects of COVID-19 on maternal, neonatal, child, sexual and reproductive health services in Kampala, Uganda. BMJ Glob Health. 2021;6(8):e006102. doi: 10.1136/bmjgh-2021-006102.

37 Nunes MC, Baillie VL, Kwatra G et al. Severe Acute Respiratory Syndrome Coronavirus 2 Infection Among Healthcare Workers in South Africa: A Longitudinal Cohort Study. Clin Infect Dis. 2021;73(10):1896-1900. doi: 10.1093/cid/ciab398.

38 Nunes MC, Mbotwe-Sibanda S, Baillie VL et al. SARS-CoV-2 Omicron Symptomatic Infections in Previously Infected or Vaccinated South African Healthcare Workers. Vaccines (Basel). 2022;10(3):459. doi: 10.3390/vaccines10030459.

Presentations and videos of the webinar are available on the EDCTP website[39]. In 2021, EDCTP also collaborated on a new funding initiative with the **Botnar Research Centre for Child Health (BRCCH)**, which had independently funded COVID-19-related projects. Through this partnership, three further projects, based on collaborations across BRCCH- and EDCTP-funded projects, received further financial support (see page 83).

Pivoting to COVID-19

Important contributions to the COVID-19 response have also been made by the EDCTP's pandemic preparedness networks (**PANDORA-ID-NET** and **ALERRT**; see page 49) and its Regional Networks of Excellence (see page 62). The networks have facilitated the rapid collection of standardised data on SARS-CoV-2 infections and organised multiple activities to share knowledge and build capacity to respond to the pandemic.

Similarly, several EDCTP fellows have been an important source of expertise in sub-Saharan Africa. For example, Senior Fellow **Roma Chilengi**, was appointed Special Advisor for COVID-19 to President Hakainde Hichilema of Zambia (see page 69). In addition, Dr **Misaki Wayengera** is Chair of the Ugandan Ministry of Health and the national task force's scientific advisory committee on COVID-19 (see page 66). Fellows have also led important studies of COVID-19. For example, the unit led by EDCTP fellow **Dr Catherine Orrell** in Cape Town, South Africa, took on responsibility for two network studies funded by the US National Institutes of Health (NIH), to generate data on immune responses during COVID-19 infection and recovery, and is contributing to a study exploring the impact of MMR vaccination on COVID-19 prevention (see page 68).

These examples illustrate the benefit of research capacity building, which has provided a foundation on which to build a diverse portfolio of studies to answer important questions about COVID-19 in an African context, as well as the expertise to guide national responses to the pandemic.

39 http://www.edctp.org/event/webinar-edctp-covid-19-emergency-funding-mechanism-2/

Networks unite against COVID-19

EDCTP's pandemic preparedness consortia, PANDORA-ID-NET and ALERRT, have been making important contributions to the fight against COVID-19 in Africa.

The EDCTP-funded epidemic preparedness networks, **ALERRT** and **PANDORA-ID-NET**, were established to develop capacity for research studies during infectious disease outbreaks, and also to provide an infrastructure to support effective responses during outbreaks. As the COVID-19 pandemic struck, they rapidly pivoted to support regional COVID-19 response efforts, while also raising awareness of the impact of the pandemic on other infectious diseases.

To inform the policy response to COVID-19, members of the **PANDORA-ID-NET** consortium have published more than 120 articles on COVID-19[40]. These have examined multiple aspects of the detection, prevention, treatment and surveillance of COVID-19, as well as other key issues such as the impact of lockdown measures on women and children's health[41] and implications for other diseases of poverty, such as TB, HIV/AIDS and malaria[42].

PANDORA-ID-NET has also organised a range of **online workshops** focusing on laboratory quality control, as well as infection prevention and control and research ethics during epidemics. In partnership with The Global Health Network (TGHN), the consortium developed a PANDORA hub on the TGHN website, making available training materials and other resources[43].

In terms of practical activities, in partnership with two states in Nigeria, as well as the Nigeria Center for Disease Control (NCDC) and the Federal Ministry of Health of Germany, PANDORA-ID-NET deployed a mobile laboratory in Nigeria for identification of SARS-CoV-2 infections. In addition, PANDORA-ID-NET researchers received funding from the British Society for Microbial Chemistry to undertake a project on the impact of COVID-19 infection prevention and control measures on transmission of hospital-acquired infections and antimicrobial resistance in Africa.

At the same time, PANDORA-ID-NET continued its studies on other diseases, including a project in Uganda on surveillance of Crimean Congo haemorrhagic fever and studies on Lassa fever in Sierra Leone. The consortium also completed studies in Tanzania to determine the seroprevalence of chikungunya, dengue and Zika virus infections in diverse ecological zones.

Staying ALERRT

The ALERRT consortium is carrying out a major study, **FISSA** (Febrile Illness in Sub-Saharan Africa), to better understand the causes, treatment and outcomes of fever in children and adults in widely spread sites across sub-Saharan Africa. In response to the pandemic, ALERRT revised the protocol of the FISSA study to include a research response component in the event of a declaration of a Public Health Emergency. In December 2021, ALERRT stopped recruitment into the FISSA study after enrolment of 8867 participants. The FISSA sample size is the largest of any fever study to date. Analysis is ongoing, and results are expected in the second quarter of 2022.

With funding from the Wellcome Trust and the UK Government, and working closely with the WHO Regional Office for Africa, Africa CDC and other networks across Africa, ALERRT set up the COVID-19 clinical characterisation protocol (CCP), which enables data and biological samples to be collected in a globally harmonised manner[44]. The CCP study aims to understand the pathogen characteristics associated with virulence, the replication dynamics and in-host evolution of the pathogen, the dynamics of the host response, the pharmacology of antimicrobial or host-directed therapies, the transmission dynamics, and factors underlying individual susceptibility.

40 https://www.pandora-id.net/publications
41 Russo G, Jesus TS, Deane K et al. Epidemics, Lockdown Measures and Vulnerable Populations: A Mixed-Methods Systematic Review of the Evidence of Impacts on Mother and Child Health in Low-and Lower-Middle-Income Countries. Int J Health Policy Manag. 2021. doi: 10.34172/ijhpm.2021.155.
42 Velavan TP, Meyer CG, Esen M et al. COVID-19 and syndemic challenges in 'Battling the Big Three': HIV, TB and malaria. Int J Infect Dis. 2021;106:29-32. doi: 10.1016/j.ijid.2021.03.071.
43 https://pandora.tghn.org/training/
44 https://alerrt.tghn.org/alerrt-ccp/

As of December 2021, the consortium had retrospectively and prospectively recorded data from 10,225 patients in Cameroon, Democratic Republic of the Congo, Ghana, Guinea, Senegal and Uganda.

The next step will be a laboratory testing of samples collected across these countries. This will feed into a study, nested within FISSA, that is investigating risk factors and outcomes for COVID-19, with a particular focus on co-morbidities common in Africa, such as anaemia, helminth infections, malaria, HIV, TB and hepatitis.

ALERRT has also conducted a review of community engagement in sub-Saharan Africa during epidemics[45]. Much of the evidence to date derives from the 2014–16 West African Ebola epidemic, and there is a need to extend the evidence base.

Part of ALERRT's work has been carried out in collaboration with EDCTP Regional Networks of Excellence. ALERRT has a close relationship with the Eastern Africa Consortium for Clinical Research (EACCR). For example, the Uganda Virus Research Institute, part of EACCR, is participating in both the FISSA study and in the COVID-19 CCP. ALERRT has also collaborated with EACCR on several workshops and, with the Central African Network on Tuberculosis, HIV/AIDS and Malaria (CANTAM3) and PANDORA-ID-NET, jointly organised several workshops on laboratory technologies in 2021.

The ALERRT consortium has secured more than €10 million in additional funding, enabling more institutions across Africa to become involved in its activities. One particularly significant project, **LASCOPE**, funded by Wellcome and others, is systematically collecting data in Nigeria on key aspects of Lassa fever, such as clinical course, biological characteristics, case management and outcomes[46]. This will help to identify factors associated with severe disease and shed important light on disease mechanisms, to inform the development of much-needed new therapeutics.

Preventing Lassa fever

EDCTP partnered with the Coalition for Epidemic Preparedness Innovations (CEPI) in order to progress a promising Lassa fever vaccine developed by the International AIDS Vaccine Initiative (IAVI).

Lassa fever, an acute viral disease mainly affecting West Africa, causes at least 5000 deaths every year and presents a constant risk of deadly outbreaks. Current treatment is of limited efficacy and no vaccine of proven efficacy is yet available.

In 2021, EDCTP announced €22.8 million funding for a new international collaboration, **LEAP4WA**, to advance development of a highly promising new vaccine against Lassa fever, rVSVΔG-LASV-GPC. The vaccine is based on the viral vector 'backbone' of the highly effective ERVEBO Ebola vaccine, now registered for use in eight African countries. The LEAP4WA consortium, which is coordinated by IAVI and also funded by the CEPI, spans institutions in Africa, Europe and North America.

A key LEAP4WA activity will be a phase II trial of rVSVΔG-LASV-GPC, the overall development of which is being supported by IAVI and CEPI. The trial is due to recruit adults and children in Liberia, Nigeria and Sierra Leone, starting with 375 participants to assess safety across the full age range and to determine a suitable dose for an efficacy study. Ultimately, it will provide crucial efficacy data to inform decision-making on a definitive phase III evaluation.

In addition, the project will help to strengthen the capacity of participating centres to undertake clinical studies on Lassa fever and other viral infections with epidemic potential.

45 Vanderslott S, Van Ryneveld M, Marchant M et al. How can community engagement in health research be strengthened for infectious disease outbreaks in Sub-Saharan Africa? A scoping review of the literature. BMC Public Health. 2021;21(1):633. doi: 10.1186/s12889-021-10348-0.

46 Duvignaud A, Jaspard M, Etafo IC et al. Lassa fever outcomes and prognostic factors in Nigeria (LASCOPE): a prospective cohort study. Lancet Glob Health. 2021;9(4):e469-e478. doi: 10.1016/S2214-109X(20)30518-0.


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• Sore throat
• Shortness of breath.
You can prevent getting infected by:
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• Avoiding contact with anyone with a cold or flu-like symptoms
• Covering the nose and mouth when sneezing and coughing with tissue or flexed elbow
• Thoroughly cooking meat and eggs
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3.6

Diarrhoeal diseases

Diarrhoeal disease remains one of the most important causes of ill-health in low-resource settings. Caused by multiple viral, bacterial and parasitic pathogens, diarrhoeal diseases are potentially fatal but can also have long-term consequences for children's growth and development. Alongside improvements in water, sanitation and hygiene, advances in vaccine development are beginning to provide additional tools for disease control.

Diarrhoeal diseases in numbers

5 grants

€51.19 M

Vaccines
4 grants
€45.21 M

Product-focused implementation research
1 grant
€5.98 M

Advancing a key *E. coli* vaccine

Two projects focused on prevention of harmful E. coli infections in children made excellent progress in 2021.

Enterotoxigenic *E. coli* (ETEC) infections cause a severe and life-threatening diarrhoea responsible for at least 50,000 deaths a year, mainly of young children. Death rates are highest in sub-Saharan Africa.

ETVAX® is the most advanced oral vaccine against ETEC. It contains a combination of engineered strains of *E. coli* that produce high levels of four proteins known to stimulate powerful immune responses, as well as a hybrid protein that combines *E. coli* and cholera toxins.

In 2021, the **ETEC Vaccine Efficacy** study completed a phase I safety study in Zambia on progressively younger age groups (6–23 months). With no safety issues identified, a phase IIb study has begun in The Gambia, which will assess the ability of ETVAX® to prevent ETEC-associated diarrhoea in infants aged 6–18 months.

The related **ETEC ETVAX** project is developing a new formulation of ETVAX® that will be better suited to young children, as well as a convenient device for administering the vaccine. This new all-in-one formulation will be evaluated in an EDCTP-funded phase III trial in Zambia, involving infants 6–18 months of age. Ultimately, the project aims to recruit 7500 infants, and the results will pave the way to an application for WHO prequalification of ETVAX®, facilitating its introduction into countries in sub-Saharan Africa.

Together, the projects will advance development of a vaccine projected to protect against 80–85% of the ETEC strains that affect young children in Africa.

Accelerating typhoid vaccine introduction

The THECA study has begun recruitment into a major trial of the Typbar-TCV typhoid conjugate vaccine.

More than 20 million cases of typhoid fever, caused by infections with *Salmonella* Typhi, occur each year, with sub-Saharan Africa particularly badly hit.

Given the scale of the typhoid fever disease burden, a typhoid conjugate vaccine, Typbar-TCV, has been licensed based on immunogenicity and safety studies, in advance of further data collection on its effectiveness, especially in Africa. Globally, major clinical studies are being organised to close this gap in knowledge, including two in Ghana and the Democratic Republic of the Congo (DRC) funded by EDCTP through the **THECA** project.

In Ghana, a large-scale cluster randomised trial is being organised, which will provide further data on vaccine efficacy and population-level protection[47]. The Ghana trial began to recruit participants in August 2021, and has a target for recruitment of 26,000 children.

The DRC study is a mass vaccination campaign, which will provide data on vaccine effectiveness in a programmatic setting as well as insight into factors such as the feasibility, safety and cost-effectiveness of mass vaccination campaigns. Preparations for the launch of the DRC study continued during 2021, ahead of a scheduled launch in February 2022.

The THECA project is also working with potential 'early adopter' countries, Burkina Faso, DRC, Ghana and Madagascar, to facilitate rapid regulatory assessment and approval of Typbar-TCV.

The work in Africa will fill important gaps in knowledge related to vaccine performance and also provide data to inform decision-making on its introduction. Collectively, these activities will help to accelerate the introduction of Typbar-TCV in typhoid-endemic countries in sub-Saharan Africa.

47 Haselbeck AH, Tadesse BT, Park J et al. Evaluation of Typhoid Conjugate Vaccine Effectiveness in Ghana (TyVEGHA) Using a Cluster-Randomized Controlled Phase IV Trial: Trial Design and Population Baseline Characteristics. Vaccines (Basel). 2021;9(3):281. doi: 10.3390/vaccines9030281.

Vaccinating mothers to protect newborns

The PREPARE project is collecting data on the prevalence of group B streptococcus, a leading neonatal infection in sub-Saharan Africa, and is evaluating vaccines to protect newborns against infection.

Group B streptococci (GBS) are widely distributed bacteria that generally cause no ill-effects. However, during childbirth, there is a risk that they may be transmitted to newborn babies, potentially leading to severe pneumonia, sepsis or meningitis. Globally, more than 300,000 cases occur each year, leading to 57,000 stillbirths and 90,000 infant deaths.

Control of GBS is likely to depend on safe and effective vaccines, administered to pregnant women. The **PREPARE** consortium is carrying out clinical trials of two promising candidate vaccines – **GBS6**, to be evaluated in Uganda, and **GBS-NN/NN2**, being tested in South Africa. The latter trial is recruiting pregnant women (with and without HIV infections) to assess safety and immunological responses in this key group. During 2021, recruitment into the **GBS-NN/NN2** trial was completed.

GBS disease is relatively rare, making clinical trials to assess efficacy difficult to carry out. The PREPARE consortium therefore aims to collect data on immune responses in vaccine recipients from sub-Saharan Africa and Europe, in order to identify 'correlates of protection' – elements of the immune response that are associated with protection against GBS infection. Such correlates of protection could be used to assess the likely efficacy of vaccines more easily, accelerating their clinical development.

The PREPARE team is also conducting studies to provide more information on the GBS disease burden, so the impact of vaccination can be better assessed. The team has also been carrying out research into perceptions of maternal vaccination against GBS among pregnant women, influential community representatives and healthcare workers in Uganda, to identify any potential barriers to the implementation of GBS vaccination in these key groups[48].

The PREPARE study also provided a platform for research into the impact of COVID-19 on pregnancy, immune responses in mothers and babies, and work with communities on infection control and prevention in pregnant women. The **periCOVID Africa** study, funded through EDCTP's emergency COVID-19 call, is being carried out in The Gambia, Kenya, Malawi, Mozambique and Uganda and aims to collect data on 70,000 pregnancies.

48 Nalubega P, Karafillakis E, Atuhaire L et al. Maternal Vaccination in Uganda: Exploring Pregnant Women, Community Leaders and Healthcare Workers' Perceptions. Vaccines (Basel). 2021;9(6):552. doi: 10.3390/vaccines9060552.


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3.7

Lower respiratory tract infections

Pneumonia is the world's biggest killer of young children, accounting for one in five deaths of children aged 1 to 5 years. Caused by a wide variety of viral, bacterial and fungal pathogens, new treatments and vaccines are urgently needed, particularly given the growing challenge of antimicrobial resistance.

Lower respiratory tract infections in numbers

8 grants
€40.75 M

Drugs
3 grant
€18.10 M

Vaccines
2 grants
€11.44 M

Diagnostics
1 grant
€4.56 M

Product-focused implementation research
2 grants
€6.65 M

Optimising antibiotic treatments for young children

The PediCAP trial, which hit its 25% recruitment milestone in 2021, is aiming to identify optimal treatments for young children hospitalised with pneumonia.

Pneumonia is the biggest global killer of children under five years of age, with at least half a million deaths estimated to occur in sub-Saharan Africa every year. For severe or very severe pneumonia, WHO recommends that children should be given injectable antibiotics for at least five days. However, this leads to long hospital stays, is costly, and increases the risk of hospital-acquired infections. Shorter and simpler treatments, particularly based on oral antibiotics, could therefore be beneficial to both patients and health systems.

The **PediCAP** trial is assessing the potential of less intensive treatments, including the switch from injected to oral antibiotics, either amoxicillin or co-amoxiclav (a combination of amoxicillin with clavulanic acid).

The PediCAP team is using an innovative trial design to maximise the amount of useful evidence generated by the study. It is assessing different durations of treatment following the switch from injected antibiotics to amoxicillin or co-amoxiclav, and is monitoring side effects and the development of antibiotic resistance. It will also analyse whether the optimal type and duration of treatment depends on factors such as age or severity of pneumonia, which could enable treatment strategies to be further refined.

More than 1000 babies and young children aged from 3 months to 6 years are being recruited. During 2021, the project achieved its 25% recruitment milestone. Among other activities, it also carried out a project examining the global scale of amoxicillin or co-amoxiclav use and associated costs, which revealed that co-amoxiclav accounts for a major proportion of total treatment costs in comparison to the scale of its use[49]. This suggests that restricting co-amoxiclav use to severe cases could generate significant efficiency gains.

49 Levine GA et al. Global estimates of the relative pediatric consumption and cost of oral amoxicillin and amoxicillin plus clavulanic acid. Presented at 31st European Congress of Clinical Microbiology and Infectious Diseases (ECCMID). Available at: https://projectpedicap.org/wp-content/uploads/2021/07/PediCAP_ECCMID-2021_FINAL.pdf

The project has also developed tools enabling the creation of more realistic 'virtual populations' of children for modelling studies of drug metabolism. Although WHO and others have generated standard growth charts for children, these may not be suitable for some populations, such as those who are malnourished, have HIV infection, or are affected by severe disease.

Applied to WHO standards, the adjustments showed a better correlation with the data obtained from 1200 African children living with HIV[50]. The methods will allow other groups to adjust existing standards to generate simulations that better represent actual populations being studied.

Protecting infants with HIV infections

The EMPIRICAL project, which is assessing whether treatment against TB or a common virus improves the survival of HIV-infected infants with severe pneumonia, celebrated the recruitment of its 100th participant in 2021.

Despite much progress in prevention of mother-to-child transmission of HIV, more than 2 million children are living with HIV, most of them in sub-Saharan Africa. Young children are particularly vulnerable to the effects of HIV infection – death rates are highest in children aged less than 4 years of age, with pneumonia the main cause of death.

Opportunistic infections are a major cause of death of children living with HIV. Recent studies have suggested that two infections – TB and cytomegalovirus, a common virus that rarely causes disease – may have a larger than suspected impact on such children, each potentially accounting for one in five deaths.

Because simple and accurate diagnostic tests suitable for children are not yet available for either of these infections, the **EMPIRICAL** project is examining whether empirical treatment of the two infections – based on clinical signs rather than diagnostic evidence – improves survival of infants with severe pneumonia.

HIV-infected infants aged between one month and 12 months are receiving the usual pneumonia treatment of antibiotics plus cotrimoxazole and prednisolone. Those thought to have a TB infection receive anti-TB treatment, and half are also being given an antiviral, valganciclovir. Those not thought to have TB randomly receive either valganciclovir or anti-TB treatment, on top of the usual pneumonia treatment.

The study is recruiting infants with pneumonia in six sub-Saharan African countries, Côte d'Ivoire, Malawi, Mozambique, Uganda, Zambia and Zimbabwe. During 2021, it hit the important recruitment milestone of 100 patients. Ultimately, the study plans to recruit more than 600 infants.

50 Wasmann RE, Svensson EM, Walker AS et al. Constructing a representative in-silico population for pediatric simulations: Application to HIV-positive African children. Br J Clin Pharmacol. 2021;87(7):2847-2854. doi: 10.1111/bcp.14694.

3.8

Building research capacity

As well as supporting clinical research, EDCTP also funds projects that strengthen the capacity of countries, research institutions and individual researchers in sub-Saharan Africa to carry out high-quality clinical studies. The scope of this support is broad, including projects designed to strengthen ethics review mechanisms, regulatory systems, and drug safety monitoring, to protect research participants and maintain public confidence. Other important objectives are to build research capacity in countries that do not have a long tradition in clinical research, for example by linking of sites through Regional Networks of Excellence, and to lower the barriers to participation of female scientists in research.

Building ethics review and regulatory capacity

EDCTP-funded projects organised multiple events and training activities in 2021 to build capacity in ethics review and clinical research oversight.

As well as having scientific capacity for clinical research, it is also critical that countries in sub-Saharan Africa are able to ensure effective governance of all stages of clinical research studies. This includes ethics review of research proposals, through institutional and national research ethics committees, and monitoring of clinical studies in progress. These activities are important for protecting the interests, health and wellbeing of study participants, and to maintain public trust in research.

EDCTP funds multiple South–South and South–North consortia aiming to build capacity in ethics review and other key oversight activities, providing opportunities to share experience and encouraging mutual learning. Although the COVID-19 pandemic meant that many planned activities took place online rather than in person in 2021, projects were still able to advance their capacity-building agendas, and organise activities of direct relevance to the pandemic.

Building on the success of the BCA-WA-ETHICS project, its follow-up – **BCA-WA-ETHICS II** – was launched in 2021. The project, spanning institutions in Benin, Mali, Senegal and Spain, has had a strong emphasis on gender issues and mainstreaming a gender perspective into all aspects of ethics review. In 2021, it published the French version of its publication 'The ethicist's practical guide to the evaluation of preclinical research from a sex and gender perspective'[51]. It also organised a virtual conference, 'Lumière Du Sud: Établir des alliances pour l'Agenda 2030 avec les femmes scientifiques africaines' (Light from the South: Establishing alliances for the 2030 Agenda with African women scientists), to promote the contributions of African women scientists.

In November 2021, BCA-WA-ETHICS II launched its webinar series 'Biostatistics for ethicists', which aims to strengthen the capacities of ethicists and research evaluators in biostatistics and research methodology. The webinar attracted 32 participants from six sub-Saharan African countries. Further webinars are being held in 2022, and are available to view on the project's website[52]. At the end of 2021, the project also opened registration for the first virtual training programme in its e-learning work package, 'Training on research ethics, gender mainstreaming, NREC governance, and audit preparedness'. The course took place over seven days in January 2022.

In 2021, the BCA-WA-ETHICS II project also launched its **virtual research ethics secretariat**. This is a virtual helpdesk available to all West African national research ethics committees (NRECs) free of charge. The aim of the

51 Nabil AMF. The Ethicist's Practical Guide to the Evaluation of Preclinical Research from a Sex and Gender Perspective. University of Zaragoza, Spain. 2021. doi:10.13140/RG.2.2.12655.97443. Available at https://www.researchgate.net/publication/349462836

52 https://www.bcawaethicsii.com/dissemination

secretariat is to strengthen the process of ethical research review in West Africa and to harmonise protocol-evaluation tools. The secretariat works directly with members of NRECs, assesses their needs, and provides technical support to improve their capacities in governance, research ethics, gender mainstreaming and systematic evaluation of research protocols.

The year also saw the launch of the latest edition of the **Procedural Manual of the National Health Research Ethics Committee of Senegal.** This gender-sensitive manual, developed in collaboration with the BCA-WA-ETHICS project, aims to improve the quality of health research conducted in Senegal, taking into account the needs and experiences of different population groups. The manual will be shared, to inspire other national ethics committees to integrate sex and gender considerations into their procedures.

The **BERC-Luso** project, which is building ethics review and clinical research oversight capacity in five Portuguese-speaking countries (Angola, Cape Verde, Guinea Bissau, Mozambique and Sao Tomé and Príncipe), organised more than 30 webinars and meetings with partner institutions in 2021. Topics discussed included informed consent in pandemic times, clinical research and procedures during pandemics, and innovation and clinical research.

The project also organised intensive training sessions on biomedical research and clinical trials, which were attended by five trainees from each of the five countries participating in the project. It also offered a six-day practical internship opportunity in Lisbon, Portugal.

The **Reg. Science-Fellows** project is developing a cohort of people in southern Africa with practical experience of regulatory assessment. It is organising a fellowship scheme jointly managed by the Medicines Control Authority of Zimbabwe and the University of Zimbabwe. Its aim is to develop a cohort of medicines reviewers and regulatory science professionals with particular expertise in key areas of product assessment. During 2021, it continued to organise short courses for regulators and regulatory affairs professionals in southern Africa.

Among other events, the **SEN-ETHICS** project, which is enabling Senegal to strengthen and harmonise its regulatory processes for clinical research, hosted a webinar on 'Ethical Issues on the response against the COVID-19 pandemic: Experts' viewpoint' in 2021. In addition, the **AFREENET** project, which concluded in February 2021, held a training session dedicated to the questions that arise during outbreaks, bringing together 40 participants from ethics committees in Guinea, Côte d'Ivoire and Benin.

Building capacity for drug safety monitoring

EDCTP projects have been promoting cross-sectoral and international collaborations to build national pharmacovigilance capacity in multiple sub-Saharan African countries.

As new interventions are introduced across sub-Saharan Africa, it is important that they are monitored to identify and respond to any potential safety issues and to ensure public confidence in drug safety. EDCTP capacity building funding has included several collaborative projects focused on building national pharmacovigilance capabilities.

The **PAVIA** project, for example, is developing a model for strengthening of pharmacovigilance systems through enhanced cross-sectoral collaboration, focusing on four countries – Eswatini, Ethiopia, Nigeria and Tanzania. The project has carried out landscape analyses of pharmacovigilance systems in each country and developed country-specific roadmaps for development of national pharmacovigilance capacity. In September 2021, the consortium published a guidance document, 'Effective Implementation of a Pharmacovigilance Policy in Resource Limited Settings'[53] and is finalising a complementary guide to funding and financial models for sustainability of pharmacovigilance programmes.

In December 2021, the **Eswatini** national pharmacovigilance policy and implementation framework was formally launched at an event attended by key officials from the ministry of health, other government departments, and a range of national and regional stakeholders. The Principal Secretary of the Ministry of Health for Eswatini and the Honourable Minister of Commerce both acknowledged the support of the PAVIA team and other international stakeholders in the development of the policy.

In **Tanzania**, the PAVIA team has been supporting the development of an electronic reporting tool (**aDSM**) for reporting of adverse reactions associated with the use of TB medicines, work led by the Tanzania Medicines and Medical Devices Authority (TMDA). A multi-stakeholder meeting was held in July 2021 to finalise the tool, which is available on the TMDA website and as an Android app.

In parallel with the introduction of new TB drugs and treatment regimens for multidrug-resistant TB, **Ethiopia** has introduced a new aDSM system. Led by the Ethiopian Food and Drug Administration (EFDA), PAVIA supported the introduction of this new system at a range of training events in 2021. In addition, in June 2021 PAVIA contributed to a two-day inaugural meeting of a Causality Assessment Committee, which will investigate adverse drug reactions received via aDSM.

PAVIA also organised a range of other training events during the year, including introductory pharmacovigilance workshops for 140 health care workers in Tanzania, with a particular focus on TB treatments and use of electronic tools for reporting of adverse drug reactions. In addition, the third PAVIA session was held in June 2021, focusing on developing the capacity of national medicines regulatory authorities, with input from PAVIA project partners, the European Medicines Agency (EMA) and the Ghana Food and Drugs Authority (FDA).

Together with the EDCTP-funded **PROFORMA** project (see below), PAVIA is exploring the possibility of extending its remit to COVID-19 vaccination. In April 2021, the project organised a webinar on COVID-19 vaccine safety surveillance, involving project and regional partners including the WHO Regional Office for Africa, the African Vaccine Regulatory Forum (AVAREF) and the African Union Development Agency/New Partnership for Africa's Development (AUDA-NEPAD).

PROFORMA and PAVIA also jointly sponsored a symposium, 'Equity in safety: improving pharmacovigilance of drugs and vaccines in Africa', at the Tenth EDCTP Forum in October 2021. The symposium provided an opportunity to share the lessons learned from the two projects, and how they can be applied to COVID-19 vaccine safety surveillance.

The goal of the **PROFORMA** project is to improve pharmacovigilance infrastructure, post-marketing surveillance systems and clinical trial regulatory capacity in Ethiopia, Kenya, Rwanda and Tanzania. The project conducted a baseline assessment of the pharmacovigilance systems

53 https://static1.squarespace.com/static/61c1d6045fb033710879e4f1/t/61d58effacebe13a2b1250de/1641385730865/PAVIA-Guide-for-Effective-Implementation-of-a-Pharmacovigilance-Policy-in-Resource-Limited-Settings-2021.pdf

and infrastructure in each country to identify capacity-building priorities[54, 55] and developed associated national roadmaps. Based on these findings, medicines regulatory authorities in each country have developed and begun to implement national pharmacovigilance plans.

Activities in 2021 focused on the strengthening of pharmacovigilance programmes, based on the national roadmaps. In addition, in each of the four countries, academic, national medicine regulatory authorities and public health programmes conducted joint active cohort surveillance studies of mass drug administration and vaccination campaigns[56].

In terms of training, 12 individuals are working towards postgraduate qualifications under the PROFORMA umbrella (seven PhDs and five Master's students). In addition, an undergraduate pharmacovigilance curriculum (short course), a postgraduate pharmacoepidemiology and pharmacovigilance curriculum (Master's programme), and pharmacovigilance E-learning module for healthcare professionals have been developed and launched.

The third PROFORMA five-day pharmacovigilance training course on 'Signal Detection and Management' was held online in January–February 2021. A total of 48 individuals working at national medicine regulatory authorities, universities, neglected tropical diseases programmes and immunisation programmes, healthcare professionals and pharmacists from Ethiopia, Kenya, Rwanda and Tanzania participated in training.

A third project, **SPaRCS**, aims to strengthen pharmacovigilance systems and the clinical trials oversight capacity of national regulatory authorities in Eswatini, Namibia, South Africa and Zimbabwe. Having mapped the pharmacovigilance systems in the four countries and identified areas of strength, gaps and opportunities for learning, the project team developed a programme of activities to share expertise and build capacity. This included a webinar on pharmacovigilance and clinical trials oversight in sub-Saharan Africa in the era of COVID-19, held in May 2021.

During 2021, these activities focused primarily on pharmacovigilance, with clinical trials oversight a priority for 2022. The team has developed a training presentation on adverse drug reaction reporting, targeted at community health workers. This has been piloted in South Africa and will be adapted for use in the other countries.

54 Barry A, Olsson S, Minzi O *et al*. Comparative Assessment of the National Pharmacovigilance Systems in East Africa: Ethiopia, Kenya, Rwanda and Tanzania. *Drug Saf* 2020, 43, 339–350. https://doi.org/10.1007/s40264-019-00898-z

55 Barry A, Olsson S, Khaemba C et al. Comparative Assessment of the Pharmacovigilance Systems within the Neglected Tropical Diseases Programs in East Africa—Ethiopia, Kenya, Rwanda, and Tanzania. *Int. J. Environ. Res. Public Health* 2021, *18*, 1941. https://doi.org/10.3390/ijerph18041941

56 Khaemba C, Barry A, Omondi WP et al. Safety and Tolerability of Mass Diethylcarbamazine and Albendazole Administration for the Elimination of Lymphatic Filariasis in Kenya: An Active Surveillance Study. Pharmaceuticals 2021, 14, 264. https://doi.org/10.3390/ph14030264

Spreading good practice

EDCTP Regional Networks of Excellence have been building their capacity for high-quality clinical research, and also supporting the sub-Saharan African response to the COVID-19 pandemic.

The four EDCTP Regional Networks of Excellence provide an infrastructure for coordinated development of health research capacity and platforms for multicentre trials. They have a particular focus on building capacity in countries with less well-developed health research infrastructures.

The networks have provided an opportunity for infrastructural upgrades to meet international standards. To date, seven laboratories in the networks have achieved and/or maintained **ISO accreditation** which demonstrates the high quality and reliability of their medical laboratories' services. These accredited laboratories, in Senegal, The Gambia, Kenya, Mozambique, Uganda, Tanzania and Nigeria, are now able to compete globally for high-quality research projects adhering to the highest international standards, and are helping to raise quality standards at other upcoming laboratories in the networks.

A priority for the **Central African Network on TB, HIV and Malaria (CANTAM)** has been to address the gender gap in clinical research capacity, and it has developed a strategy to involve more women in medical research. It has begun a project, 'Women and Science', targeted at local schools and has launched a career development fellowship scheme for postdoctoral female researchers to mitigate the marginalisation of female scientists in Central Africa. This strategy is a core element of the new PhD training programme for female PhD candidates launched in 2021, supported by a Participating States-Initiated Activity (PSIA) funded by the UK (see page 64).

The network also contributed to studies demonstrating that the pyronaridine–artesunate antimalarial combination had good tolerability and effectiveness in a representative African population under conditions similar to everyday clinical practice[57]. The results confirm its potential as a treatment for acute uncomplicated malaria in the region.

Other CANTAM activities in 2021 included a sub-regional training workshop on laboratory accreditation, held in October 2021, and capacity building support for national regulatory authorities and ethics committees. The latter included a two-day webinar in September 2021, 'Analysis of national COVID-19 vaccination strategies by the ethics committees and national regulatory authorities of Central Africa', organised with the Ministry of Health and Population of the Republic of Congo and including representatives from multiple Central African countries.

The **East African Consortium for Clinical Research (EACCR)** helps to prepare resource-limited clinical research sites for clinical trials on locally important infectious diseases. EACCR has developed an e-learning centre that hosts peer-reviewed short courses required for high-quality clinical studies. In addition, through its reciprocal monitoring scheme, the network has established a regional pool of trained clinical trial monitors, who have overseen multiple clinical research studies across Africa.

The network is also working with the ALERRT and PANDORA-ID-NET pandemic preparedness networks to build capacity in research during epidemics. Two EACCR2 member institutions – the Uganda Virus Research Institute (UVRI) and the Centre for Global Health Research of the Kenya Medical Research Institute (KEMRI) – are the East African sites collaborating in the ALERRT study on clinical characterisation of COVID-19 in Africa (see page 49).

In addition, the EDCTP-funded **EAPOC-VL** project was launched at the lead EACCR site, UVRI, in April 2021. The EAPOC-VL project is examining the feasibility, acceptability and effectiveness of using point-of-care viral load (PoC VL) monitoring to improve suppression of HIV replication in children and adolescents living with HIV in Kenya, Rwanda, Tanzania and Uganda.

57 Tona Lutete G, Mombo-Ngoma G, Assi SB et al. Pyronaridine-artesunate real-world safety, tolerability, and effectiveness in malaria patients in 5 African countries: A single-arm, open-label, cohort event monitoring study. PLoS Med. 2021;18(6):e1003669. doi: 10.1371/journal.pmed.1003669.

The **Trials of Excellence in Southern Africa (TESA)** network has established specific reference laboratories on HIV (Botswana–Harvard AIDS Institute Partnership), TB (Stellenbosch University, South Africa) and malaria (Manhiça Health Research Centre, Mozambique). The laboratories serve as a training platform to optimise the use of resources across member institutions. Building on the capacity developed through TESA, its site in Zambia is leading a national study characterising COVID-19 patients. The sub-investigators who received Good Clinical Practice (GCP)/Good Clinical Laboratory Practice (GCLP) and data-management training under TESA are now actively involved in clinical research. For example, Dr Mwansa Ketty Lubeya has developed a protocol on COVID-19 in pregnancy and served as member of the editorial committee for the Clinical Guidance for Management of Patients with COVID-19 developed by the Zambian Ministry of Health.

Through a PSIA funded by Portugal, TESA is also implementing a **data centre certification project** at the Manhiça Health Research Centre in Mozambique. This TESA reference data centre will be the first in Africa to be accredited by the European Clinical Research Infrastructure Network (ECRIN).

The **West African Network for Tuberculosis, AIDS and Malaria (WANETAM)** has been collaborating with Africa Centres for Disease Control and Prevention (Africa CDC) and the West Africa Health Organization (WAHO). WAHO and WANETAM have established a framework to support laboratories in the region aiming to achieve accreditation.

During the COVID-19 pandemic, WANETAM laboratories played a leading role in providing diagnostics services in Burkina Faso, The Gambia, Ghana, Guinea Bissau, Guinea Conakry, Côte d'Ivoire, Mali, Nigeria and Senegal, and the network has contributed to a cross-sectional survey on the impact of COVID19 on tuberculosis services[58].

58 Nkereuwem O, Nkereuwem E, Fiogbe A et al. Exploring the perspectives of members of international tuberculosis control and research networks on the impact of COVID-19 on tuberculosis services: a cross sectional survey. BMC Health Serv Res. 2021;21(1):798. doi: 10.1186/s12913-021-06852-z.

Advancing women in health research in Africa

A new Participating States-Initiated Activity (PSIA), funded by the UK, is enabling EDCTP Regional Networks of Excellence to recruit female PhD candidates.

EDCTP has made a major contribution to scientific capacity building in sub-Saharan Africa, in terms of both physical research infrastructure and human resources for health research. However, significant disparities exist across the region, with countries with less well-developed health research systems less able to compete for funding. In addition, there is a significant gender imbalance, with women less likely to apply for and receive fellowship funding or to coordinate research consortia.

In 2019, EDCTP and the Africa Centres for Disease Control and Prevention (Africa CDC) jointly organised a workshop to discuss inequities in research. Key obstacles to more equitable funding and potential ways to overcome them were summarised in a report from the meeting[59].

Building on this experience, EDCTP and the UK collaborated on a PSIA that leveraged the established research platforms of EDCTP Regional Networks of Excellence as a training base for early-career female researchers.

Each network was invited to bid for up to €500,000 to support research training for five female PhD candidates. The networks had to demonstrate how they would ensure adequate supervision and mentorship opportunities for PhD students, support their career progression, and ensure the participation of under-represented countries within each region. They were also expected to develop or refine a network policy on gender equality, diversity and inclusion to be implemented at each institution in the network.

All four networks were successful in their bid. For this initiative, the **East African Consortium for Clinical Research (EACCR)** programme, led from Uganda, has implementing parters from Kenya, Rwanda and Tanzania; the **Trials of Excellence in Southern Africa (TESA)** programme, led from Mozambique, includes partners from Angola, Botswana, Eswatini, France, Malawi, Namibia, The Netherlands, South Africa, Spain, Zambia and Zimbabwe; the **West African Network for Tuberculosis, AIDS and Malaria (WANETAM)** programme, led from Senegal, also includes Ghana and the UK; and the **Central African Network on TB, HIV and Malaria (CANTAM)** programme, led from the Republic of Congo, has partners from Cameroon, Gabon, Germany and The Netherlands.

Galvanised with additional resources, over four years, the programmes will support the PhD training and wider development of female researchers, helping to address health research workforce inequities at an early career stage and further strengthening health research capacity in sub-Saharan Africa.

59 EDCTP. Collaborating to improve gender-related and regional disparities in research funding: EDCTP-Africa CDC Workshop, 19–20 November 2019, Africa Union Headquarters, Addis Ababa, Ethiopia. Available at: https://edctpprint.maglr.com/edctp-africa-cdc-networking-workshop/cover1

Sharing knowledge in global health research

The EDCTP Knowledge Hub has established itself as a key resource for those working in global health research.

Developed by EDCTP and The Global Health Network (TGHN), the EDCTP Knowledge Hub provides an integrated set of resources and associated activities to support and guide those planning and carrying out clinical research studies. Comprising a Protocol Development Toolkit, Data Management Portal and Data Sharing Toolkit, the Knowledge Hub takes a researcher through the steps from framing a research question through the appropriate conduct of clinical studies and sharing of data.

A second introductory webinar on tools and guidance for protocol development was organised by EDCTP and TGHN in 2021, and was attended live by more than 350 participants from around the globe. The initiative was warmly welcomed, with the protocol development toolkit highlighted as an excellent resource bringing practical guidance and templates together in one place.

An evaluation of the Knowledge Hub in September 2021 found that it had attracted more than 40,000 page views. More than 53 requests for accounts had been received for the SEPTRE (SPIRIT Electronic Protocol Tool and Resource), 60% of them from low- and middle-income countries. As most users were from anglophone countries, parts of the site have been translated into Spanish, French and Portuguese with the aim to offer a translation of all pages to enable researchers from across the world to benefit from the resources.

The Knowledge Hub was promoted at several scientific meetings in 2021 (including the 12th European Congress on Tropical Medicine and International Health (ECTMIH 2021) and the American Society of Tropical Medicine and Hygiene (ASTMH) 2021 Annual Meeting). In addition, EDCTP and TGHN held a well-attended virtual interactive workshop at the Tenth EDCTP Forum in Mozambique. A paper summarising the resource has been published as an open access commentary[60].

Notably, in 2021 the EDCTP Knowledge Hub was referenced in a draft WHO policy and guidance document on facilitating greater sharing of health-related research datasets generated by WHO-funded or -sponsored research projects. This highlights the recognition by external global stakeholders of the potential for the EDCTP Knowledge Hub to have global impact.

60 Driver, S., Gray, S., Sikhondze, W. et al. The European & Developing Countries Clinical Trials Partnership (EDCTP) Knowledge Hub: developing an open platform for facilitating high-quality clinical research. Trials 23, 374 (2022). https://doi.org/10.1186/s13063-022-06311-y

3.9

Building human capacity – EDCTP Fellows

As part of long-term sustainable development, research on Africa's health challenges needs to be led by Africans, plugged into global knowledge networks. To build the expertise, experience and exposure of African scientists to global science, EDCTP runs a range of career schemes, from Preparatory Fellowships for those embarking on a career in research, through Career Development Fellowships for those showing early promise, and Senior Fellowships for the most outstanding research leaders. Through the Senior Fellowship Plus scheme, Senior Fellows also mentor an up-and-coming researcher from a country with a less well-established research base.

Fellowship programme

EDCTP-AREF Preparatory Fellowships

Objective: to enhance the competitiveness of up-and- coming post-doctoral sub-Saharan African scientists and clinicians aspiring to receive international/ regional/ national fellowships or grant support.

Clinical Research and Development Fellowships

Objective: to offer researchers and key members of clinical research teams the opportunity to acquire technical and project skills in clinical R&D through placement in pharmaceutical companies, PDPs and CROs.

Career Development Fellowships

Objective: to support early and mid-career scientists to develop their individual clinical research skills, providing an opportunity for talented scientists to establish themselves as independent researchers and team leaders.

Senior Fellowships

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

Senior Fellowships Plus

Objective: to support capacity development of potential African research leaders and to mentor junior researchers with emphasis on hands-on research training linked to clinical trial activities conducted in sub-Saharan Africa.

A Senior Fellowship Plus grant provides for two fellowships: a Senior Fellowship paired with a Career Development Fellowship.

From Ebola to COVID-19

Former EDCTP fellow Dr Misaki Wayengera has been applying lessons learned from Ebola outbreaks to the control of the COVID-19 pandemic in Uganda.

Dr Misaki Wayengera, an EDCTP Career Development Fellow between 2018 and 2020, has developed an impressive range of skills in medicine, research and innovation. Having trained in medicine, he has developed research interests in the molecular genetics of infectious diseases, including emerging infections such as Ebola – work that underpins the development of diagnostics, therapeutics and vaccines.

Dr Wayengera's EDCTP-funded fellowship research focused on the characterisation of viral epitopes from Ebola virus isolates from

the 2014–2016 Ebola outbreak in Sierra Leone. He has also led the development of a rapid diagnostic test that detects Ebola and related viruses (a pan-filovirus rapid diagnostic test, Pan-filo-V RDT), research that was supported in part through EDCTP emergency funding associated with the Ebola outbreak. The RDT validation is undergoing partially supported by the EDCTP Ebola Emergency Grant.

This breadth and depth of experience made Dr Wayengera ideally placed to contribute to Uganda's response to COVID-19, another emerging viral threat. Since early 2020, Dr Wayengera has chaired the Uganda Ministry of Health and the national task force's scientific advisory committee on COVID-19.

In addition, Dr Wayengera has applied his expertise in rapid diagnostics to further the development of low-cost and easy-to-use testing platforms for COVID-19, including simple lateral flow tests suitable for use in remote settings. He has also advocated for the development and use of novel small-molecule inhibitors of SARS-CoV-2, to prevent the progression of COVID-19 to severe disease.

At the same time, Dr Wayengera has continued to contribute to a wide range of scientific studies, including evaluation of hydroxychloroquine as a then potential treatment for COVID-19[61], application of whole genome sequencing for SARS-CoV-2 genomic surveillance in Africa[62], and genetic factors affecting HIV progression[63, 64].

61 Byakika-Kibwika P, Sekaggya-Wiltshire C, Semakula JR et al. Safety and efficacy of hydroxychloroquine for treatment of non-severe COVID-19 among adults in Uganda: a randomized open label phase II clinical trial. BMC Infect Dis. 2021;21(1):1218. doi: 10.1186/s12879-021-06897-9.

62 Mboowa G, Mwesigwa S, Kateete D et al. Whole-genome sequencing of SARS-CoV-2 in Uganda: implementation of the low-cost ARTIC protocol in resource-limited settings. F1000Res. 2021;10:598. doi: 10.12688/f1000research.53567.1.

63 Kyobe S, Mwesigwa S, Kisitu GP et al. Exome Sequencing Reveals a Putative Role for HLA-C*03:02 in Control of HIV-1 in African Pediatric Populations. Front Genet. 2021;12:720213. doi: 10.3389/fgene.2021.720213.

64 Mwesigwa S, Williams L, Retshabile G et al. Unmapped exome reads implicate a role for Anelloviridae in childhood HIV-1 long-term non-progression. NPJ Genom Med. 2021;6(1):24. doi: 10.1038/s41525-021-00185-w.

Applying clinical trials knowledge to COVID-19

Dr Catherine Orrell, an EDCTP Career Development Fellow in the first EDCTP Programme, has developed extensive skills in the design and conduct of clinical trials – expertise she has now applied in the testing of COVID-19 vaccines and therapeutics.

A clinical pharmacologist and HIV clinician, **Dr Catherine Orrell** has accumulated extensive experience in clinical trial management, leading 15 clinical trials and contributing as an investigator to more than 30 others. One area of particular interest has been retention in clinical trials and improving adherence to treatment, particularly antiretrovirals. In her EDCTP Career Development Fellow, she led a randomised controlled trial of real-time electronic adherence monitoring with text message reminders in people starting first-line antiretroviral therapy.During the COVID-19 pandemic, the unit Dr Orrell leads became heavily involved in the research response to COVID-19. This has included taking on responsibility for two projects supported by the US National Institutes of Health (NIH) – the CoVPN 5001 study, which is exploring immune responses early in SARS-CoV-2 infection, and HVTN 405, which focuses on immune responses during recovery. The unit is also contributing to the CROWN Coronation study, which is assessing whether mumps, measles and rubella (MMR) vaccination provides protection against COVID-19.

In addition, she has contributed to the Sisonke study[65], which administered 20,000 vaccine doses to South African healthcare workers.

Dr Orrell is also principal investigator for the AGILE-consortium in South Africa[66]. This international consortium is focusing on the evaluation of promising drugs for COVID-19, including those in early phase development.

The first study is exploring the use of nitazoxanide, an existing drug used to treat parasite and virus infections.

At the same time, Dr Orrell has been contributing to multiple other trials, including assessments of broadly neutralizing antibodies for prevention of HIV infection[67], clinical pharmacological studies of new antiretrovirals and neonatal exposures[68], new treatment regimens for novel antiretrovirals[69], and use of electronic dose monitoring to explore risk of treatment dropout[70].

In 2021, Dr Orrell was also awarded an **EDCTP Senior Fellowship Plus**. This will support further research into retention, extending an NIH-funded study exploring methods to more rapidly identify patients showing signs of lack of adherence to antiretroviral therapy in resource-poor communities in South Africa. The EDCTP-funded study will add an intensive therapeutic monitoring component to those identified as at risk of drop out. The studies will examine impacts on adherence and longer-term viral suppression.

The fellowship will also enable Dr Orrell to mentor and facilitate the research of an upcoming researcher, **Dr Olaposi Olatoregun**, who is conducting a pilot study to explore whether a medication adherence app can improve adherence and retention in antiretroviral treatment programmes in newly diagnosed adolescents living with HIV in Benue state, Nigeria. She will also oversee a master's and PhD student, further helping to build research capacity.

65 https://clinicaltrials.gov/ct2/show/NCT04838795

66 Griffiths GO, FitzGerald R, Jaki T et al. AGILE: a seamless phase I/IIa platform for the rapid evaluation of candidates for COVID-19 treatment: an update to the structured summary of a study protocol for a randomised platform trial letter. Trials. 2021;22(1):487. doi: 10.1186/s13063-021-05458-4.

67 Corey L, Gilbert PB, Juraska M et al. Two Randomized Trials of Neutralizing Antibodies to Prevent HIV-1 Acquisition. N Engl J Med. 2021;384(11):1003-1014. doi: 10.1056/NEJMoa2031738.

68 Overton ET, Richmond G, Rizzardini G et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. Lancet. 2021;396(10267):1994-2005. doi: 10.1016/S0140-6736(20)32666-0.

69 Dickinson L, Walimbwa S, Singh Y et al. Infant Exposure to Dolutegravir Through Placental and Breast Milk Transfer: A Population Pharmacokinetic Analysis of DolPHIN-1. Clin Infect Dis. 2021;73(5):e1200-e1207. doi: 10.1093/cid/ciaa1861.

70 Zelnick JR, Daftary A, Hwang C et al. Electronic Dose Monitoring Identifies a High-Risk Subpopulation in the Treatment of Drug-resistant Tuberculosis and Human Immunodeficiency Virus. Clin Infect Dis. 2021;73(7):e1901-e1910. doi: 10.1093/cid/ciaa1557.

Presidential advisor

EDCTP Senior Fellow Professor Roma Chilengi has been appointed as Special Advisor for COVID-19 to President Hakainde Hichilema of Zambia.

Professor Roma Chilengi is a clinical trials specialist with extensive experience of trials of vaccines and other interventions, as well as a growing interest in controlled human infection studies. His past work with the Ministry of Health in Zambia and local NGOs, including rollout of rotavirus vaccination, has had a significant impact on child mortality locally.

In his EDCTP Senior Fellowship, Professor Chilengi is assessing whether adding a third dose of rotavirus vaccine at nine months boosts rotavirus-specific immune responses at 1 year, providing longer-lasting protection. The study will monitor safety, analyse infants' immune responses, and assess the impact of diarrhoeal disease on growth rates.

Alongside this work, Professor Chilengi has also been involved in studies confirming the immunogenicity and safety of two new rotavirus vaccine products in Zambian children[71], exploring *Shigella* antibodies in the first year of life, to guide timing of vaccination[72], and contributing to a trial examining the impact of delayed administration of a second dose of oral cholera vaccine, which may be warranted in emergency contexts[73]. He has also been involved in studies exploring attitudes to participating in human challenge studies in Zambia[74].

In addition, Professor Chilengi is a member of the Steering Committee for an EDCTP-funded project evaluating a new *Shigella* vaccine. He is also a member of the *Lancet* Commission on Water, Sanitation and Hygiene, and Health[75].

In September 2021, Professor Chilengi was appointed as Special Advisor for COVID-19 to President Hakainde Hichilema of Zambia. In this role, he has had a high public profile within Zambia, appearing on television, radio and the press to promote vaccination and other ways to control COVID-19.

71 Chilengi R, Mwila-Kazimbaya K, Chirwa M et al. Immunogenicity and safety of two monovalent rotavirus vaccines, ROTAVAC® and ROTAVAC 5D® in Zambian infants. Vaccine. 2021;39(27):3633-3640. doi: 10.1016/j.vaccine.2021.04.060.

72 Chisenga CC, Bosomprah S, Simuyandi M et al. Shigella-specific antibodies in the first year of life among Zambian infants: A longitudinal cohort study. PLoS One. 2021;16(5):e0252222. doi: 10.1371/journal.pone.0252222.

73 Mwaba J, Chisenga CC, Xiao S et al. Serum vibriocidal responses when second doses of oral cholera vaccine are delayed 6 months in Zambia. Vaccine. 2021;39(32):4516-4523. doi: 10.1016/j.vaccine.2021.06.034.

74 Kunda-Ngándu EM, Chirwa-Chobe M, Mwamba C et al. Exploring willingness to participate in future Human Infection Studies in Lusaka, Zambia: A nested qualitative exploratory study. PLoS One. 2021;16(7):e0254278. doi: 10.1371/journal.pone.0254278.

75 Commissioners of the Lancet Commission on Water, Sanitation and Hygiene, and Health. The Lancet Commission on water, sanitation and hygiene, and health. Lancet. 2021;398(10310):1469-1470. doi: 10.1016/S0140-6736(21)02005-5.

A globally rising star

EDCTP Senior Fellow Dr Mareli Claassens has been appointed a member of the Global Young Academy, and in 2021 took up a LEAD fellowship at the Harvard Global Health Institute.

Born in Namibia, Dr Mareli Claassens spent the early part of her research career in South Africa before returning to her home country, where she is currently an Associate Research Professor at the University of Namibia.

In 2021, Dr Claassens was appointed a member of the Global Young Academy, a body that aims to give a voice to the rising stars of scientific research. Its 200 members have shown great promise at the early stages of their research career and a commitment to engaging with wider society. Through the Academy, members get involved in a range of working groups, strategic projects and collaborations with international partner organisations.

Also in 2021, Dr Claassens was awarded a Harvard LEAD Fellowship for Promoting Women in Global Health, an initiative run by the Harvard Global Health Institute and the Global Health and Population Department within the Harvard TH Chan School of Public Health.

The year-long programme is designed to build the leadership skills of talented global health leaders from low- and middle-income countries who are committed to the mentorship of future women leaders in medicine and public health. Fellows spend their time at Harvard engaging in tailored leadership training, mentoring and networking opportunities, including independent work supported by Harvard-based mentors.

Dr Claassens' research focuses primarily on the epidemiology, treatment and control of *Mycobacterium tuberculosis*, the cause of TB. She has been involved in projects examining TB mortality rates in South Africa[76] and in South African children and adolescents[77], as well as follow up of TB testing[78]. In her EDCTP fellowship project, she is carrying out a detailed investigation of drug-resistant TB in hotspots of this deadly pathogen in Namibia, including among disadvantaged ethnic minority populations. She is synthesising multiple sources of data, including whole genome sequence data, to provide a clearer picture of patterns of transmission and to identify potential strategies for active case finding.

Tackling malaria and malnutrition

EDCTP Career Development Fellow Dr Paul Sondo has begun studies to determine whether addressing malnutrition will improve the effectiveness of seasonal malaria chemoprevention.

Every year, more than 1000 children die from malaria in Burkina Faso. One approach used to minimise such deaths is seasonal malaria chemoprevention (SMC), administration of antimalarial drugs to healthy children at times of year when malaria transmission is highest. However, the impact of SMC has not been as high as hoped.

Malaria prevention has been a specific interest of **Dr Paul Sondo**, a molecular parasitologist based at the Clinical Research Unit of Nanoro in Burkina Faso. Dr Sondo was awarded a Clinical Research and Development Fellowship, through a scheme jointly run by EDCTP and the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), which allowed him to spend time at the Worldwide Antimalarial Resistance Network (WWARN), enabling him to develop his technical skills, research planning expertise, and international networks.

76 Burger R, Caldwell J, Claassens M et al. Who is more likely to return for TB test results? A survey at three high-burden primary healthcare facilities in Cape Town, South Africa. Int J Infect Dis. 2021;113:259-267. doi: 10.1016/j.ijid.2021.10.015.

77 Osman M, van Schalkwyk C, Naidoo P et al. Mortality during tuberculosis treatment in South Africa using an 8-year analysis of the national tuberculosis treatment register. Sci Rep. 2021;11(1):15894. doi: 10.1038/s41598-021-95331-w.

78 Osman M, du Preez K, Seddon JA et al. Mortality in South African Children and Adolescents Routinely Treated for Tuberculosis. Pediatrics. 2021;147(4):e2020032490. doi: 10.1542/peds.2020-032490.

After successful reintegration back in Burkina Faso, he has become more competitive and won an EDCTP Career Development Fellowship, which is supporting a trial of nutritional supplementation as a strategy for improving the effectiveness of SMC. His hypothesis is that malnutrition, common in children in Burkina Faso, is increasing susceptibility to malaria. He is therefore carrying out a randomised trial that will assess the impact of supplementation with combinations of vitamin A, zinc and Plumpy'Doz (a fortified peanut butter-like paste) on antimalarial immune responses as well as growth[79].

Alongside this EDCTP-funded project, he is also leading work on other strategies to enhance the impact SMC, for example by screening and treating household members for malaria during SMC[80]. He will also be continuing studies on the genetic diversity of malaria parasites[81] and its impact on malaria infections and transmission[82].

79 Sondo P, Tahita MC, Rouamba T et al. Assessment of a combined strategy of seasonal malaria chemoprevention and supplementation with vitamin A, zinc and Plumpy'Doz™ to prevent malaria and malnutrition in children under 5 years old in Burkina Faso: a randomized open-label trial (SMC-NUT). Trials. 2021;22(1):360. doi: 10.1186/s13063-021-05320-7.

80 Sondo P, Tahita MC, Ilboudo H et al. Boosting the impact of seasonal malaria chemoprevention (SMC) through simultaneous screening and treatment of household members of children receiving SMC in Burkina Faso: a protocol for a randomized open label trial. Arch Public Health. 2022;80(1):41. doi: 10.1186/s13690-022-00800-x.

81 Sondo P, Bihoun B, Tahita MC et al. Plasmodium falciparum gametocyte carriage in symptomatic patients shows significant association with genetically diverse infections, anaemia, and asexual stage density. Malar J. 2021;20(1):31. doi: 10.1186/s12936-020-03559-0.

82 Sondo P, Bihoun B, Kabore B et al. Polymorphisms in Plasmodium falciparum parasites and mutations in the resistance genes Pfcrt and Pfmdr1 in Nanoro area, Burkina Faso. Pan Afr Med J. 2021;39:118. doi: 10.11604/pamj.2021.39.118.26959.

Boosting epidemiology capacity in Africa

EDCTP Senior Fellow Dr Peter Olupot-Olupot has led a successful bid for an EDCTP/Africa CDC Epidemiologists and Biostatisticians training programme grant.

In 2021, EDCTP and the Africa Centre for Disease Control and Prevention (Africa CDC) announced the ten consortia that had been successful in their bids to host a training programme for epidemiologists and biostatisticians, part of a joint initiative to build capacity in these crucial fields for infectious disease control and pandemic preparedness (see page 81).

One of the ten successful bids, the **IDEA Fellowship** programme, is being led by Senior Fellow **Dr Peter Olupot-Olupot**. The IDEA consortium, led from Busitema University in Uganda, spans the Uganda Ministry of Health and other institutions in Uganda, as well as the Open University in the UK. Ultimately, the EDCTP/Africa CDC programme will support the training of 150 epidemiologists and biostatisticians in sub-Saharan Africa over a period of three years, boosting the capacity of countries to carry out public health research and to plan for and respond to infectious disease outbreaks.

Although based in Uganda, Dr Olupot-Olupot also holds a position at the KEMRI/Wellcome Research Programme in Kenya, contributing to a wide range of pediatric studies. While his principal interest is in malaria, he has also been involved in studies of transfusions for children with severe anaemia[83], clinical diagnosis of sickle cell anaemia[84], rehydration of children with severe acute malnutrition[85] and refeeding strategies for children with severe acute malnutrition[86].

He is also participating in the EDCTP-funded **COAST-Nutrition** study, which is examining whether additional nutritional support improves outcomes in children recovering from pneumonia[87].

Dr Olupot-Olupot is using his EDCTP fellowship to develop his own research and leadership skills and also to enhance the research capacity of the Mbale Clinical Research Unit in Uganda. During the COVID-19 pandemic, he was also able to set up a COVID-19 testing laboratory in Mbale to assist the Ugandan Government response to COVID-19.

African research leadership funding

Several researchers funded through the Research Leaders scheme, a Participating States-Initiated Activity (PSIA) funded by the UK, have gone on to secure EDCTP Senior Fellowships.

The UK Medical Research Council (MRC) and the Foreign and Commonwealth Development Office (FCDO, previously the Department for International Development, DFID) launched the African Research Leaders scheme to strengthen research leadership across sub-Sahara Africa. The scheme provided support for up to five years for exceptionally talented 'rising star' researchers, enabling them to lead high-quality research programmes related to local health challenges.

83 George EC, Uyoga S, M'baya B et al. Whole blood versus red cell concentrates for children with severe anaemia: a secondary analysis of the Transfusion and Treatment of African Children (TRACT) trial. Lancet Glob Health. 2022;10(3):e360-e368. doi: 10.1016/S2214-109X(21)00565-9.

84 Olupot-Olupot P, Connon R, Kiguli S et al. A predictive algorithm for identifying children with sickle cell anemia among children admitted to hospital with severe anemia in Africa. Am J Hematol. 2022;97(5):527-536. doi: 10.1002/ajh.26492.

85 Olupot-Olupot P, Aloroker F, Mpoya A et al. Gastroenteritis Rehydration Of children with Severe Acute Malnutrition (GASTROSAM): A Phase II Randomised Controlled trial: Trial Protocol. Wellcome Open Res. 2021;6:160. doi: 10.12688/wellcomeopenres.16885.1.

86 Calder N, Walsh K, Olupot-Olupot P et al. Modifying gut integrity and microbiome in children with severe acute malnutrition using legume-based feeds (MIMBLE): A pilot trial. Cell Rep Med. 2021;2(5):100280. doi: 10.1016/j.xcrm.2021.100280.

87 Kiguli S, Olopot-Olupot P, Alaroker F et al. Children's Oxygen Administration Strategies And Nutrition Trial (COAST-Nutrition): a protocol for a phase II randomised controlled trial. Wellcome Open Res. 2021;6:221. doi: 10.12688/wellcomeopenres.17123.2.

The scheme was open to researchers based in sub-Sahara African countries or looking to return and establish a research programme. The principal investigators had to demonstrate a supportive local environment for their research programme and have strong linkage to a UK partner.

Several of those who successfully applied to the African Research Leaders scheme also received fellowship support from the EDCTP.

These include:

- **Professor Richard Phillips** (Ghana) received funding to investigate Buruli ulcer, a bacterial skin infection common in West Africa, focusing on disease mechanisms and responses to antibiotic therapy. This research enabled him to develop a successful application for an EDCTP Senior Fellowship.
- **Professor Faith Osier** (Kenya) was supported to undertake studies on the mechanisms of protective immunity to malaria, to inform vaccine design. She also went on to secure an EDCTP Senior Fellowship, and was recently included in a list of the 100 most influential women in Africa.
- **Professor Eugene Kinyanda** (Uganda) received funding for studies of the mental health of HIV-infected children and adolescents in Kampala. This followed the highly promising work he carried out during his EDCTP1 fellowship.

These examples illustrate how complementary fellowship funding from EDCTP and European funders can advance the careers of Africa scientific leaders at key stages of a research career.

Advancing scientific careers in Africa

Several EDCTP-funded Career Development Fellows made excellent progress during 2021, contributing new data on antimalarial use in pregnant women living with HIV, cardiovascular disease in adolescents living with HIV, and use of primaquine to reduce malaria transmission.

EDCTP Career Development Fellowships play a key role in enabling rising stars of health research in sub-Saharan Africa to establish independent research skills, enhance their research expertise and make international connections through networking. These researchers have the potential to be the scientific leaders of the future in Africa.

Dr Clifford Banda completed his Career Development Fellowship in 2021 and was successful in his application for a three-year Wellcome–NIHR International Training Fellowship. He was also appointed therapeutics lead at the Kamazu University of Health Sciences in Malawi and the Malawi/Wellcome Trust Clinical Research Programme.

A specialist clinical pharmacologist, Dr Banda has a particular interest in dose optimisation and safety, particularly for drugs given to special populations, such as pregnant women, young children and people with co-morbidities. In 2021, he completed studies showing that dihydroartemisinin/piperaquine, a potential drug for malaria prevention during pregnancy, is probably safe to use in pregnant women living with HIV receiving dolutegravir-based antiretroviral therapy, as it leads to only a modest increase in circulating levels of dolutegravir[88].

Dr Edith Majonga completed an EDCTP Preparatory Fellowship in 2021 and began a Career Development Fellowship. She has a particular interest in cardiovascular disease in adolescents who acquired HIV as infants, and in her new fellowship is examining whether delayed start of antiretroviral therapy is associated with an increased risk of cardiovascular disease. In her previous work associated with the BREATHE trial, Dr Majonga has found that, although azithromycin reduced the risk of acute respiratory attacks in children and adolescents with HIV-associated chronic lung disease, it had no impact on right heart function, which is commonly also impaired in such patients[89].

In his Career Development Fellowship, **Dr Dominic Mosha** is evaluating the safety of primaquine given alongside artemisinin-based combination therapy (ACT) for malaria. Although WHO recommends use of primaquine to block transmission in areas approaching disease elimination and to address ACT resistance, it is little used in Africa because of concerns about its safety, particularly in people with a deficiency in a key metabolic enzyme (G6PD).

In his fellowship, Dr Mosha has carried out research into the perceptions and performance of a new primaquine roll out pharmacovigilance tool, known as PROMPT. Responses to single-dose primaquine were positive among patients and healthcare providers and PROMPT was seen to be useful and reliable by the latter[90]. Dr Mosha has also contributed to a systematic review confirming the transmission-blocking efficacy of primaquine and its greater impact when used in conjunction with ACTs[91].

88 Banda CG, Nkosi D, Allen E et al. Effect of dihydroartemisinin/piperaquine for malaria intermittent preventive treatment on dolutegravir exposure in pregnant women living with HIV. J Antimicrob Chemother. 2022:dkac081. doi: 10.1093/jac/dkac081.

89 Majonga ED, Mapurisa GN, Rehman AM et al. The effect of azithromycin for management of HIV-associated chronic lung disease on right heart function: Results from the BREATHE trial. Int J Cardiol Heart Vasc. 2021;37:100920. doi: 10.1016/j.ijcha.2021.100920.

90 Mosha D, Kakolwa MA, Mahende MK et al. Safety monitoring experience of single-low dose primaquine co-administered with artemether-lumefantrine among providers and patients in routine healthcare practice: a qualitative study in Eastern Tanzania. Malar J. 2021;20(1):392. doi: 10.1186/s12936-021-03921-w.

91 Stepniewska K, Humphreys GS, Gonçalves BP et al. Efficacy of Single-Dose Primaquine With Artemisinin Combination Therapy on Plasmodium falciparum Gametocytes and Transmission: An Individual Patient Meta-Analysis. J Infect Dis. 2022;225(7):1215-1226. doi: 10.1093/infdis/jiaa498.

Improving survival of adolescents living with HIV

EDCTP Career Development Fellow Dr Joseph Fokam has generated important data on the evolution of HIV infections and emergence of drug resistance in adolescents living with HIV.

As more children infected with HIV during infancy gain access to antiretroviral drugs, greater numbers are surviving to adolescence. At this stage, they transition from pediatric to adult treatment regimens. However, while HIV/AIDS death rates are generally declining, they are continuing to rise in adolescents living with HIV, potentially because of factors such as reduced adherence to antiretroviral treatment regimens and the emergence of drug resistance. Understanding the evolution of HIV infection and best management of the transition to adult treatment is therefore an urgent priority.

For his EDCTP Career Development Fellowship project, **Dr Joseph Fokam** recruited cohorts of adolescents living with HIV from urban and rural areas of Cameroon. Participants were followed for a year to track viral load and CD4+ T cell numbers, with genotyping of HIV isolates from individuals showing signs of treatment failure.

Analyses of these data have revealed worryingly high levels of HIV drug resistance, exceeding 90% in both settings[92]. High viral loads, indicative of failure to control HIV replication, were seen in more than a third of adolescents in the urban setting and more than half of those at rural sites. Poor adherence was seen in about a third of participants.

In addition, adolescents failing treatment were found to be harbouring high levels of hidden or 'archived' drug-resistance genes[93], suggesting that additional tools might need to be used to profile HIV infections and provide early warning of emerging drug resistance and impending treatment failure.

Other analyses have shown that a switch to second-line treatment in children is delayed on average by nearly a year[94]. Switching is driven almost entirely in response to virological failure (high viral load), emphasising the importance of monitoring of viral load in this group.

In other studies, Dr Fokam has helped to develop and validate an in-house genotyping tool for the HIV integrase gene[95]. Variants of this gene are associated with reduced efficacy of a relatively new HIV drug, dolutegravir. The genotyping tool could therefore be used to monitor integrase-resistance mutations and inform decision-making on a transition to regimens including dolutegravir. A cross-sectional study of integrase drug-resistance mutations found relatively low levels in Cameroon, arguing that dolutegravir-based regimens should be effective[96].

In addition, Dr Fokam carried out a systematic review of HIV-1 Gag gene mutations in different viral subtypes and the clinical implications of resistance to ritonavir-boosted protease inhibitors (PI/r)97. Findings will provide insights into the likely role of Gag gene mutations in PI/r treatment failure and suggest whether Gag genotyping is warranted.

92 Fokam J, Takou D, Njume D et al. Alarming rates of virological failure and HIV-1 drug resistance amongst adolescents living with perinatal HIV in both urban and rural settings: evidence from the EDCTP READY-study in Cameroon. HIV Med. 2021;22(7):567-580. doi: 10.1111/hiv.13095.

93 Fokam J, Mpouel Bala ML, Santoro MM et al. Archiving of mutations in HIV-1 cellular reservoirs among vertically infected adolescents is contingent with clinical stages and plasma viral load: Evidence from the EDCTP-READY study. HIV Med. 2021 Dec 23. doi: 10.1111/hiv.13220. Online ahead of print.

94 Njom-Nlend AE, Efouba N, Brunelle Sandie A, Fokam J. Determinants of switch to paediatric second-line antiretroviral therapy after first-line failure in Cameroon. Trop Med Int Health. 2021;26(8):927-935. doi: 10.1111/tmi.13595.

95 Fokam J, Ngoufack Jagni Semengue E, Armenia D et al. High performance of integrase genotyping on diverse HIV-1 clades circulating in Cameroon: toward a successful transition to dolutegravir-based regimens in low and middle-income countries. Diagn Microbiol Infect Dis. 2022;102(2):115574. doi: 10.1016/j.diagmicrobio.2021.115574.

96 Semengue ENJ, Armenia D, Inzaule S et al. Baseline integrase drug resistance mutations and conserved regions across HIV-1 clades in Cameroon: implications for transition to dolutegravir in resource-limited settings. J Antimicrob Chemother. 2021;76(5):1277-1285. doi: 10.1093/jac/dkab004.

97 Nka AD, Teto G, Santoro MM et al. HIV-1 Gag gene mutations, treatment response and drug resistance to protease inhibitors: A systematic review and meta-analysis protocol. PLoS One. 2021;16(7):e0253587. doi: 10.1371/journal.pone.0253587.

3.10

EDCTP Forum – bigger and better than ever

The Tenth EDCTP Forum, held in 2021 rather than 2020 because of the COVID-19 pandemic, took place in Maputo, Mozambique, as well as virtually, attracting more than 2000 online registrants.

The EDCTP Forum is held every two years, alternating between Africa and Europe. It provides an opportunity for researchers to share their findings, network and forge new relationships, and for representatives from a diversity of groups with an interest in global health – development agencies, ministries of health, funders, public and private research and development partners, regional bodies, civil society and other – to meet and discuss progress, challenges and opportunities.

Because of the continuing COVID-19 pandemic, the 2021 Forum (held on 17–21 October 2021) was a hybrid event, hosted by the National Institute of Health (INS) Mozambique and the Manhiça Health Research Centre (CISM). Around 50 delegates attended the event in Maputo, Mozambique, and 2252 delegates from 75 countries registered for online attendance.

The Forum was opened by the President of Mozambique, His Excellency **Mr Filipe Jacinto Nyusi**, and featured a presentation by Mozambique's Minister of Health, Hon. Dr Armindo Tiago. Forum participants were welcomed by Dr Leonardo Simão, Chair of the Local Organising Committee and EDCTP High Representative for Africa. Welcome addresses were also delivered by European Commissioners **Mariya Gabriel** (Innovation, Research, Culture, Education and Youth) and **Jutta Urpilainen** (International Partnerships), and by WHO's Chief Scientist, **Dr Soumya Swaminathan**.

The Forum also provided a further opportunity to celebrate health research in Mozambique as CISM marked its 25th anniversary in 2021. A special session was organised before the main opening of the Forum, with multiple presenters from Africa and Europe highlighting the key role the Institute has played in strengthening the science base in Mozambique, regionally and more generally in Portuguese-speaking African countries.

Discussions also highlighted the critical contributions made by **Dr Pascoal Mocumbi**, former Health Minister and Prime Minister of Mozambique, who was appointed EDCTP's High Representative for Africa in 2003. Dr Mocumbi played a key role in the development of EDCTP and in the building of strong relationships with African governments. Dr Mocumbi's name is commemorated in the EDCTP's foremost Prize, the **Dr Pascoal Mocumbi Prize,** which recognises outstanding achievements in health research and capacity development in Africa with significant impact on the wellbeing of African populations.

From left to right: Prof. Yazdan Yazdanpanah, Dr Armindo Tiago, H.E. Filipe Jacinto Nyusi and Dr Leonardo Simão.

H.E. Filipe Jacinto Nyusi, President of Mozambique.

Ms Albertina Palalane, Prof. Moses Bockarie and Dr Leonardo Simão at the Forum's welcome session.

Equity in research and health

The theme of the 2021 Forum was **equity in research for health**. Consistent with this ideal, almost half the presenters (44%) were female and more than half the keynote addresses were delivered by researchers from Africa. The Forum included a special debate on equity in innovation, partnerships and research, moderated by **Professor Catherine Hankins**, Chair of the Forum Programme Committee, as well as a session on equity in research participation, chaired by **Dr Richard Horton**, editor of *The Lancet*.

Among the highlights of a comprehensive and diverse set of scientific symposia was a special session on **malaria vaccines**, co-hosted by EDCTP and WHO. This included an update on the first WHO-recommended malaria vaccine, RTS,S/AS01, as well as a presentation on the EDCTP-funded trial of the R21/Matrix-M malaria vaccine, which has generated exciting phase II data (see page 26).

A recurring theme throughout the Forum was the impact of COVID-19 in sub-Saharan Africa. In a keynote address, **Dr John Nkengasong**, Director of the Africa Centres for Disease Control and Prevention (Africa CDC), summarised the current situation in Africa, while multiple presentations on SARS-CoV-2/COVID-19 were included in sessions devoted to emerging infections and across several other Forum symposia.

To promote virtual networking, **meet-the-expert sessions** provided an opportunity for delegates to interact with senior researchers, ask them questions and exchange ideas. **Networking groups** were active every day, enabling Forum delegates to connect with colleagues from around the globe. Scholarships, in the form of data bundles, were awarded to the highest scoring abstract presenters to facilitate their participation.

The Forum featured multiple sessions sponsored by **partner organisations**, including Merck, the Medicines for Malaria Venture, the European Global Health Research Institutes Network, the Drugs for Neglected Diseases *Initiative* and the Deutsche Stiftung Weltbevölkerung (German Foundation for World Population).

In the final plenary session, **Ms Andrea Spelberg** from the German Federal Ministry of Education and Research (BMBF) identified EDCTP as a blueprint for international cooperation in global health. Given the success of the 2021 conference, the next Forum – to be held in Europe in 2023 – will also be a hybrid event, ensuring wider participation from those who would find it difficult to attend in person.

A report on the 2021 Forum is available on the EDCTP website (https://publications.edctp.org/emagazine-november-2021/forum-overview).

Recognising excellence in research and collaboration

EDCTP Prizes for 2020, presented at the EDCTP Forum in 2021, honoured the work of teams and individuals who have significantly advanced health research in Africa and collaboration between Europe and Africa.

Every two years, EDCTP awards a number of prizes that recognise outstanding individuals and research teams from Africa and Europe who have made significant achievements in their research field. The prizes are awarded at EDCTP's biennial Forum. After postponement of the 2020 Forum, the prizes for that year were awarded at the Tenth EDCTP Forum in October 2021. The prize winners are:

Dr Pascoal Mocumbi Prize winner: Professor Sir Alimuddin Zumla, UK
Born in Zambia, Professor Sir Alimuddin (Ali) Zumla is Professor of Infectious Diseases and International Health at University College London, UK, and a globally renowned researcher specialising in respiratory diseases, particularly TB and more recently COVID-19, and other diseases of poverty. He is a highly influential author and has worked tirelessly to strengthen collaborations between the UK, Europe and Africa, to focus world attention on diseases of poverty, and to enhance science-based health policymaking.

Outstanding Female Scientist Prize winner: Professor Margaret Gyapong, Ghana
Professor Gyapong is Director of the Institute for Health Research and Coordinator of the Centre for Health Policy and Implementation Research (CHPIR) at the University of Health and Allied Sciences, Ghana. With a background in social research, she has particular interests in socio-cultural aspects of tropical diseases, particularly neglected tropical diseases, implementation research, health systems, and maternal and child health. Under her leadership, CHPIR was designated a WHO/TDR Satellite Training Centre for Implementation Research in 2018. Among many international advisory roles, Professor Gyapong is a member of the Sight Savers Board of Trustees, the Swiss Tropical and Public Health External Review Board, and the WHO Scientific and Technical Advisory Group on Neglected Tropical Diseases.

Scientific Leadership Prize winner: Professor Graeme Meintjes, South Africa
Professor Meintjes, Deputy Head of the Department of Medicine at the University of Cape Town, South Africa, has been recognised for his outstanding track record of research on the diagnosis, prevention and treatment of conditions affecting patients with advanced HIV disease in Africa, particularly HIV-associated TB, HIV-associated cryptococcal meningitis, immune reconstitution inflammatory syndrome (IRIS), the complications of antiretroviral therapy and drug-resistant TB. His EDCTP-funded projects have included landmark studies on the use of prednisone to treat and prevent TB-IRIS.

Outstanding Research Team Prize winner: African-European Tuberculosis Consortium (AE-TBC)
AE-TBC is an international collaboration, encompassing seven African and five European institutions, which focuses on the development of innovative TB diagnostics based on host biomarkers. Founded in 2010 under the AE-TBC project, the consortium is continuing its work through the EDCTP-funded ScreenTB and TriageTB projects.

More information about EDCTP Prizes:
www.edctp.org/prizes/

3.11

Partnerships for progress

EDCTP is committed to working with a wide range of partners that share the goal of enhancing the health of people in sub-Saharan Africa through research. Globally, EDCTP has established close working relationships with international funding organisations, multilateral bodies such as WHO, and the private sector, to align and coordinate activities and to organise joint funding schemes. Regionally, it has developed partnerships with key organisations within Africa, including the WHO Regional Office for Africa, the African Union, the African Union Development Agency/New Partnership for Development (AUDA/NEPAD) and the Africa Centres for Disease Control and Prevention (Africa CDC).

EDCTP membership expands

Côte d'Ivoire and Kenya have recently been welcomed into the EDCTP family and the EDCTP Association Board has been enlarged.

EDCTP operates formally through the **EDCTP Association**, a partnership between countries in Europe and sub-Saharan Africa. In 2021, two additional countries joined the EDCTP Association –Côte d'Ivoire and Kenya[98] – bringing the total number of representatives from sub-Saharan Africa to 18. In addition, Angola continues to be an Aspirant Member of the EDCTP Association.

Research institutions in both Côte d'Ivoire and Kenya have already been making significant scientific contributions to EDCTP-funded consortia. The new affiliation of both countries with EDCTP will further strengthen EDCTP's position in sub-Saharan Africa and ensure strong participation of additional anglophone and francophone countries in its activities.

A key governance structure of the EDCTP Association is the **Board**, which is entrusted with the management of the Association, supervises the Secretariat on behalf of the EDCTP General Assembly, and is responsible for ensuring that the Association's resources are properly and efficiently managed.

In 2021, **Professor Abdoulaye Djimdé** from Mali was appointed as the sixth member of the EDCTP Association Board. With this appointment, the Board has now a balanced geographical representation, with 3 European Board members and 3 African Board members. Professor Djimdé is Chief of the Molecular Epidemiology and Drug Resistance Unit at the University of Bamako Malaria Research and Training Centre, Mali, and has led multiple projects exploring malaria treatments, including the EDCTP-funded WANECAM Consortium. Professor Djimdé brings a wealth of experience on laboratory science, clinical research and capacity building in West Africa and sub-Saharan Africa more generally.

Partnering with the African Union

EDCTP has been strengthening its links with the African Union and the Africa Centres for Disease Control and Prevention, including a major scheme to build epidemiology and biostatistics capacity in Africa to support pandemic preparedness and response.

In 2021, EDCTP signed a landmark memorandum of understanding with the African Union, to underpin collaborative efforts to address infectious disease with epidemic potential. This agreement will see the African Union – through the African Centres for Disease

98 Kenya has been admitted as an EDCTP Association Member but is still finalising the formal documentation.

Control and Prevention (Africa CDC) – and EDCTP cooperating on joint activities in key areas such as emerging and re-emerging infectious diseases, epidemic intelligence, and capacity building for preparedness and outbreak response.

The memorandum of understanding will build on existing fruitful collaborations between EDCTP and Africa CDC. In 2021, successful applications to the **joint EDCTP/ Africa CDC capacity development scheme for disease outbreak and epidemic response** were announced. The aim of this partnership is to establish an African cohort of epidemiologists and biostatisticians, as part of Africa CDC's framework for public health workforce development, with ten grants supporting institutions in sub-Saharan Africa and Europe that provide master's degree training in epidemiology and biostatistics.

In October 2021, the first eight 'Epi-Biostat Fellows' enrolled in their master's training at the London School of Hygiene and Tropical Medicine in the UK. Ultimately, the programme will boost the capacity of national public health institutes, ministries of health and other institutions in Africa to conduct public health research and respond to disease emergencies.

EDCTP continued to be represented on the Steering Committee of the **Africa CDC Consortium for COVID-19 Vaccine Clinical Trials (CONCVACT)**, set up to accelerate progress on COVID-19 vaccine trials in Africa. The initiative aims to provide support for and promote collaboration between vaccine developers and clinical trial sites on the African continent. There is significant overlap between EDCTP clinical trial sites and sites being considered by CONVACT.

EDCTP also continued to be represented in Africa CDC's **Africa Task Force for Novel Coronavirus (AFCOR)**, which was established to oversee preparedness and response to the COVID-19 pandemic and has been preparing various guidelines for African countries. Outputs in 2021 included a policy paper on Research and Development Priorities for COVID-19 in Africa and the Adapted Africa Joint Continental Strategy for COVID-19 Pandemic, which focused on prevention, monitoring and treatment of COVID-19.

Since June 2021, EDCTP has been a member of the Africa CDC **Scientific Advisory Group of Experts (SAGE)**, and has been contributing to policy statements and press releases as well as participating in an organising group for a COVID-19 conference. EDCTP was also a member of the organising committee for the **First International Conference on Public Health in Africa (CPHIA 2021)**, organised by Africa CDC and the African Union on 14–16 December 2021.

The strengthening of cooperation between EDCTP and Africa CDC was emphasised by the Director of Africa CDC, **Dr John Nkengasong**, during his presentation at the European Commission's Global Health Conference on 25 March 2021 on strengthening the EU contribution to global health.

AUDA-NEPAD

EDCTP has also had a long-standing relationship with the **African Union Development Agency – New Partnership for Africa's Development (AUDA-NEPAD)**. During 2021, EDCTP continued to participate as a member of the AUDA-NEPAD African Medicines Regulatory Harmonisation Partnership Platform (AMRH-PP) and the African Vaccine Regulatory Forum (AVAREF) platform, and provides technical guidance to the six AMRH Technical Committees.

At the EDCTP Scientific Advisory Committee (SAC) in May 2021, the AUDA-NEPAD Head of Health, **Margareth Ndomondo-Sigonda**, acknowledged the value of EDCTP support for the strengthening of ethics and regulatory bodies in 27 African countries, and its contribution to the creation of AVAREF. She was also invited to speak at two further events organised by EDCTP in 2021, including the EDCTP Science Summit session held in association with the United National General Assembly in September 2021 (UNGA76) and the EDCTP session at the Science Forum South Africa 2021 in December 2021.

In June 2021, EDCTP's High Representative for Africa, **Dr Leonardo Simão**, attended a high-level meeting to discuss a continental vision and strategy for the African Medicine Agency (AMA). The Executive Director of the European Medicines Agency (EMA), **Emer Cooke**, identified AVAREF as a model platform for collaboration between the AMA and the EMA. AUDA-NEPAD has organised a stakeholders meeting on the operationalisation of AMA that will take place in the first quarter of 2022. EDCTP looks forward to renewing its agreement with AUDA-NEPAD in 2022.

Strengthening Africa–Europe ties

EDCTP has been contributing to European and global initiatives to strengthen health research capacity and improve health outcomes in sub-Saharan Africa.

In September 2021, EDCTP organised a meeting at the Science Summit associated with the **76th United Nations General Assembly (UNGA76)**. This session aimed to stimulate discussion on product scale-up, implementation and access in sub-Saharan Africa and globally, in order to achieve the health-related targets of the Sustainable Development Goals.

The session was chaired by **Dr Leonardo Simão**, EDCTP's High Representative for Africa, and featured contributions from representatives from the European Commission, WHO, US National Institutes of Health, national and philanthropic funding agencies, industry and researchers from institutions in Africa and Europe.

The session also provided an opportunity to discuss the recommendations on clinical trial infrastructure and capacity building in Africa that were developed at a session co-organised by EDCTP and the **European Clinical Infrastructure Networks** (ECRIN) at the Africa–Europe Science and Innovation Summit in June 2021. The recommendations have been integrated into the consultation of the European Commission's **Advisory Group on Research and Innovation for Africa–Europe Cooperation**, which is providing the Commission with advice on how best to boost cooperation between the two continents through research and innovation. The Advisory Group held virtual consultation workshops late in 2021 where it presented its own recommendations for public scrutiny. EDCTP was specifically recognised as a success story.

EDCTP has also been engaging in discussions with the **European Centre for Disease Prevention and Control** (ECDC) in support of a new EU-funded ECDC and Africa CDC partnership initiative launched in December 2020, which aims to strengthen the capacity of Africa CDC to prepare for and respond to public health threats in Africa. A meeting between EDCTP, ECDC, Africa CDC and the EC's Directorate-General for International Partnerships (INTPA) took place in February 2021, to exchange information and explore how each organisation could support each other.

The initiative will facilitate harmonised surveillance and disease intelligence and support the implementation of Africa CDC's public health workforce strategy. EDCTP is specifically mentioned in the project proposal as a stakeholder and will continue to engage with ECDC on potential future collaboration in the project's activities, including through the EDCTP Regional Networks of Excellence, its epidemic preparedness consortia (PANDORA-ID-NET and ALERRT) and other projects.

Partnerships with funders

EDCTP has continued to seek opportunities to collaborate with other partners on joint funding schemes or specific programmes of work, including landmark projects on COVID-19 and parasitic flatworm treatment for children.

EDCTP enters into a range of funding partnerships, including joint and coordinated calls in areas of common interest. Joint fellowship calls, for example, have been organised with Novartis, GlaxoSmithKline (GSK), Fondation Botnar, TDR, the Special Programme for Research and Training in Tropical Diseases, and the Africa Research Excellence Fund (AREF).

Another example of a joint initiative announced in February 2021 is the new partnership between EDCTP and the **Botnar Research Centre for Child Health (BRCCH)**. Initial discussions held in 2020 led to a joint BRCCH–EDCTP Collaboration Initiative to support further work on three EDCTP-funded COVID-19-related projects (TREATS-COVID, Suitcaselab project and COVAB).

Both BRCCH and EDCTP had launched emergency COVID-19 calls in 2020. Recognising the potential for collaboration, the two organisations invited proposals from applicants keen to develop collaborative projects spanning consortia supported in the first round of funding. The partnership involves around €880,000 funding over two years.

Extending the EDCTP-funded TREATS-COVID study and BRCCH-funded MistraL project, one project is investigating the effects of community-led interventions, rapid point-of-care diagnostics and swab self-collection in mitigating the COVID-19 epidemic in Lesotho and Zambia. The TREATS-COVID study generated important data on SARS-CoV-2 seroprevalence in Zambia and risk factors for COVID-19 infection to inform public health responses[99].

A second new project is developing a rapid lateral flow diagnostic assay and a portable PCR device operated in a mobile suitcase for use in low-resource settings. This project is building on the EDCTP-funded Suitcaselab project, which developed a highly sensitive and specific field-deployable COVID-19 detection system, with comparable accuracy to gold-standard PCR testing[100], in collaboration with the BRCCH grantee for a rapid diagnostic test project and for the BRCCH peakPCR project The third project, extending the EDCTP-funded COVAB project and the BRCCH-funded B-Cell Immunity project, is exploring B-cell responses in people with natural infections, with and without HV infections, and after vaccination.

EDCTP also develops strategic partnerships with like-minded organisations around individual projects or consortia, with partners contributing co-funding or supporting complementary activities. Co-funding to the tune of €384 million has been leveraged through this mechanism, including €374 million from third parties (private and public bodies that are not members of the EDCTP Association).

A good example of this type of cofinancing is the long-term partnership between the **Global Health Innovative Technology (GHIT) Fund** and EDCTP, which is supporting the Pediatric Praziquantel Consortium for the development of a new pediatric medication, arpraziquantel, to treat schistosomiasis in preschool-aged children (see page 40). A phase III trial has been successfully completed through this funding partnership and, with the announcement in February 2021 of their further joint funding of the **ADOPT** programme, EDCTP and GHIT are already co-investing in research to prepare the ground for large-scale access and delivery of arpraziquantel in Côte d'Ivoire, Kenya and Uganda.

99 Shanaube K et al. SARS-CoV-2 seroprevalence and associated risk factors in peri-urban Zambia: a population-based study. Int J Infect Dis. 2022:S1201-9712(22)00158-8.

100 El Wahed AA et al. Suitcase lab for rapid detection of SARS-CoV-2 based on recombinase polymerase amplification assay. Anal Chem. 2021;93(4):2627–2634.

Working with other funders to mutual advantage

EDCTP has been working with a wide range of funders to align activities and promote coordination of efforts towards common goals.

In 2021, EDCTP continued to participate as a member-observer of the **Global Research Collaboration for Infectious Disease Preparedness (GloPID-R)**, which brings together research funding organisations with an interest in new or re-emerging infectious diseases with epidemic and pandemic potential.

GloPID-R and the UK Collaborative on Development Research (UKCDR) have developed a platform, the COVID CIRCLE, to encourage the exchange of information and coordination of research activities related to COVID-19. As well as GloPID-R's working group on research in low- and middle-income countries (LMICs), EDCTP is also represented on its COVID CIRCLE working group, the COVID CIRCLE steering committee and the GloPID-R Clinical Trials Networks and Funders Working Group.

Key events with EDCTP involvement in 2021 included a virtual meeting in March 2021 on COVID-19 research priorities in LMICs, co-organised by GloPID-R, UKCDR and the COVID-19 Clinical Research Coalition, which brought together research funders and researchers working in LMICs. An article was subsequently published in *The Lancet* outlining what is needed for a more effective and global research response to the pandemic[101].

In addition, a virtual event in November 2021, co-hosted by UKCDR and GloPID-R, was used to launch a **report on the lessons learned from research funding during the COVID-19 pandemic**[102]. The report highlighted key lessons and future guidance for research funders to address the challenges of funding and conducting research in the context of an epidemic or pandemic, particularly in LMICs. EDCTP's 2020 Emergency Funding Mechanism was one of the case studies highlighted, and EDCTP was commended for the rapid initiation of research in sub-Saharan Africa through this scheme.

To promote alignment and coordination, EDCTP contributes to multiple funders' forums and working groups, including the following:

- Since 2020, EDCTP has been represented in the **Equitable Partnerships Task Force** convened by UKCDR, which aims to support work to improve funder practices on equitable partnerships. In early 2021, UKCDR and ESSENCE on Health Research joined forces to develop guidance and case studies on barriers and enablers of equitable partnerships, as well as recommendations on good funder practice. In September 2021, EDCTP was invited to develop a case study on its epidemic preparedness networks (ALERRT and PANDORA-ID-NET). At the Tenth EDCTP Forum in October 2021, UKCDR and ESSENCE organised a workshop on equitable research partnerships, discussions at which will inform the final guidance document to be published in 2022.

- In 2021, EDCTP continued to participate as an institutional member of the **COVID-19 Clinical Research Coalition**, hosted by the Drugs for Neglected Diseases *initiative* (DND*i*), which aims to promote multi-centre trials of COVID-19 interventions in resource-limited settings. This has included representation on a Data Management working group.

- EDCTP continues to participate as an observer in the **Clinical Research Initiative for Global Health (CRIGH)**, a consortium of research institutions, funding organisations and research consortia. CRIGH aims to optimise clinical research programmes in participating countries, develop global standards on clinical research, promote the take-up of innovative methodology and technologies, and encourage international cooperation to respond to global health challenges. EDCTP hosted and participated in CRIGH's Fourth General Assembly, which took place in October 2021 in conjunction with the Tenth EDCTP Forum.

101 GloPID-R, UKCDR, and COVID-19 Clinical Research Coalition Cross-Working Group on COVID-19. Research in LMICs. Priorities for COVID-19 research response and preparedness in low-resource settings. Lancet. 2021;397(10288):1866–1868.

102 GloPID-R, UKCDR. Funding and undertaking research during the first year of the COVID-19 pandemic: COVID CIRCLE lessons for funders. 2021. Available at: https://www.glopid-r.org/wp-content/uploads/2021/11/funding-and-undertaking-research-during-the-first-year-of-the-covid-19-pandemic-covid-circle-lessons-for-funders.pdf

- EDCTP continued to actively participate in the **Product Development Partnerships (PDPs) Funders Group (PFG)** in 2021. This included attendance at the donor roundtables organised by the Medicines for Malaria Venture (MMV), DND*i* and the International AIDS Vaccine Initiative (IAVI), as well as a second strategic discussion between the PFG and PDP Chief Executive Officers to discuss opportunities for PDPs to collaborate more, particularly to implement access strategies.

- EDCTP continued to be an active member of the **ESSENCE on Health Research** platform in 2021, attending the annual members meeting in April 2021 as well as Steering Committee meetings throughout the year. This initiative provides a platform enabling funders to identify synergies and increase the value of their investments in health research. During 2021, EDCTP contributed to the ESSENCE Working Group on Review of Investments, which is developing a coordination mechanism for reviewing investments in clinical research capacity building in response to the World Bank and Coalition for Epidemic Preparedness Innovations (CEPI) report 'Money and Microbes: Strengthening Research Capacity to Prevent Epidemics'. EDCTP also contributed to a good practice document for funders on the best ways to invest in implementation science[103] as well as the UKCDR–ESSENCE Equitable Partnership Project discussed above. An ESSENCE members virtual mini-meeting was organised on the margins of the Tenth EDCTP Forum.

103 Cardoso-Weinberg A et al. Funders' Perspectives on Supporting Implementation Research in Low- and Middle-Income Countries. Glob Health Sci Pract. 2022. https://doi.org/10.9745/GHSP-D-21-00497

3.12

Global Health EDCTP3 – a new beginning

The legal foundation of the third EDCTP programme – Global Health EDCTP3 – was agreed in 2021, paving the way for its public launch in 2022.

In November 2021, the European Commission adopted a Council Regulation establishing the Joint Undertakings under Horizon Europe, the European Union's key funding programme for research and innovation. This regulation provides the legal basis for the third EDCTP programme, **Global Health EDCTP3** (as well as eight other Joint Undertakings in other areas of science and technology).

The adoption marked the official launch of the Global Health EDCTP3 programme. Formally, it represents a partnership between the European Union (represented by the European Commission) and the EDCTP Association, the membership of which comprises multiple European and African countries.

The Global Health EDCTP3 Joint Undertaking will be led by a Governing Board, in which the European Commission and EDCTP Association will have equal votes. The implementation of the Joint Undertaking will be undertaken by a programme office being established in Brussels, under the leadership of an Executive Director. The Joint Undertaking will be advised by a Scientific Committee and a Stakeholders Group.

The Global Health EDCTP3 programme budget will include up to €800 million from the EU, conditional on contributions of at least €439 million from the EDCTP Association and €400 million from contributing partners, such as philanthropic organisations and industry.

With the launch of the new programme, no new funding calls will be launched by EDCTP2 but existing grants will continue to be managed through the EDCTP2 programme until their completion.

New calls for proposals will be launched by the Global Health EDCTP3 Joint Undertaking in 2022. These will draw upon a **Strategic Research and Innovation Agenda**, which outlines the new programme's priority areas and general funding principles.

Conceptually, the EDCTP3 programme aims for continuity with past EDCTP programmes, for example by maintaining its focus on poverty-related diseases affecting sub-Saharan Africa, advancing medical interventions through high-quality clinical research carried out by international consortia, and capacity building for clinical research in sub-Saharan Africa. However, as well as increased funding compared to EDCTP2, the scope of the EDCTP3 programme has been widened to include antimicrobial resistance and the impact of the climate crisis on infectious disease.

A **work programme for 2022** has been developed for the EDCTP3 programme. Calls for proposals in 2022 will focus on promoting implementation of research results into policy and practice, implementing adaptive platform trials, and genomic epidemiology for surveillance and control of poverty-related and emerging/re-emerging infections in sub-Saharan Africa (in partnership with the Bill & Melinda Gates Foundation). Capacity strengthening calls will focus on creating a sustainable clinical trial network for infectious diseases in sub-Saharan Africa and strengthening regulatory capacity for supporting conduct of clinical trials.

For more information, please visit the Global Health EDCTP3 website: https://ec.europa.eu/info/research-and-innovation/research-area/health-research-and-innovation/edctp_en.

EDCTP Governance

The EDCTP programme is governed by the General Assembly of the EDCTP Association, the legal structure for the implementation of the second EDCTP programme (2014-2024). The Board of the EDCTP Association is entrusted by the General Assembly with the management of the Association and the oversight of the Secretariat. The Scientific Advisory Committee is the principal advisory body to EDCTP. The programme is implemented by the Secretariat.

For more information on the EDCTP governance, please consult the EDCTP website: www.edctp.org.

Mandated representative entity

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National Institute of Public Health

Austria
Medical University of Vienna

Burkina Faso
Centre National de Recherche et de Formation sur le Paludisme

Cameroon
Ministry of Public Health

Congo
University Marien Ngouabi

Côte d'Ivoire
Ministry of Higher Education and Scientific Research

Denmark
Statens Serum Institute

Ethiopia
Armauer Hansen Research Institute

Finland
Academy of Finland

France
Aviesan, Institut thématique multi-organismes

Gabon
Centre de Recherches Médicales de Lambaréné

The Gambia
Ministry of Health and Social Welfare

Germany
Bundesministerium für Bildung und Forschung

Ghana
Ghana Health Service

Ireland
Irish Health Service Executive

Italy
Istituto Superiore di Sanità

Kenya
TBD

Luxembourg
Fonds National de la Recherche

Mali
University of Science, Techniques and Technology of Bamako

Mozambique
Ministry of Health

Netherlands
NWO-WOTRO Science for Global Development

Niger
Ministry of Public Health

Nigeria
Federal Ministry of Health

Norway
Research Council of Norway

Portugal
Foundation for Science and Technology

Senegal
University Cheikh Anta Diop

South Africa
Department of Science and Technology

Spain
Instituto de Salud Carlos III

Sweden
Swedish International Development Cooperation Agency

Switzerland (Aspirant member)
Swiss Tropical and Public Health Institute

Tanzania
Tanzania Commission for Science and Technology

Uganda
Uganda National Health Research Organisation

United Kingdom
Medical Research Council

Zambia
Ministry of Health

Summary financial statements 2021

Statement of profit or loss and other comprehensive income

for the year ended 31 December 2021. Expressed in thousands ('000) of euro.

	EC 2021	Donor 2021	Total 2021	Total 2020
Calls (Grants)				
Contributions	119,017	24,857	143,874	144,895
Grant expenditure	(119,017)	(24,857)	(143,874)	(144,895)
Results for the year	-	-	-	-
Others				
Contributions	5,433	718	6,151	6,581
Other expenditure	(5,433)	(718)	(6,151)	(6,581)
Results for the year	-	-	-	-
Total results for the year	-	-	-	-

The EDCTP Association has no other comprehensive income.

All income and expenditure relate to continuing activities.

For the full statements and accompanying notes, please visit www.edctp.org.

Statement of financial position

as at 31 December 2021 (after appropriation of result). Expressed in thousands ('000) of euro.

	31 December 2021	31 December 2020
Non-current assets		
Right-of-use assets	1,618	1,590
Debtors and other receivables	155,375	154,844
Total non-current assets	**156,993**	**156,434**
Current assets		
Debtors and other receivables	98,137	74,769
Cash and cash equivalents	44,781	79,884
Total current assets	**142,918**	**154,653**
Total assets	**299,911**	**311,087**
Non-current liabilities		
Grants and other payables	167,922	174,858
Deferred income EC	-	-
Deferred income Donor	-	-
Lease liabilities	1,423	1,395
Total non-current liabilities	**169,345**	**176,253**
Current liabilities		
Grants and other payables	125,356	128,006
Deferred income EC	-	-
Deferred income Donor	5,015	6,633
Lease liabilities	195	195
Total current liabilities	**130,566**	**134,834**
Total liabilities	**299,911**	**311,087**

The financial statements were approved by the Executive Director on behalf of the Board:

Dr Michael Makanga
Dated: 23 May 2022

Statement of changes in EC and donor's equity

Expressed in thousands ('000) of euro

	Reserve: EC	Reserve: Donor	Total
Balance as at 31 December 2020	**-**	**-**	**-**
Total comprehensive income for the year	-	-	-
Balance as at 31 December 2021	**-**	**-**	**-**

EDCTP has no unrestricted reserves.

Statement of cash flows

for the year ended 31 December 2021. Expressed in thousands ('000) of euro.

	2021	2020
Cash flows from operating activities		
Result for the year	-	-
Adjustment for:		
Depreciation charge for right-of-use assets	167	167
Lease interest	48	53
Reversal of depreciation and lease interest	(20)	(25)
(Increase) decrease in debtors and other receivables	(143)	149
Increase (decrease) in grants and other payables	(9,586)	19,177
Increase (decrease) in deferred income	(25,205)	(53,656)
Net cash flows from operating activities	(34,739)	(34,135)
Cash flows from investing activities		
Interest received/(paid)	(169)	(179)
Payment of lease liabilities	(195)	(195)
Net cash flows from investing activities	(364)	(374)
Net increase (decrease) in cash and cash equivalents	**(35,103)**	**(34,509)**
Cash and cash equivalents at 1 January	79,884	114,393
Exchange rate effects		
Cash and cash equivalents at 31 December 2021	**44,781**	**79,884**

Acknowledging our funders

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Colophon

European & Developing Countries Clinical Trials Partnership

The Hague, the Netherlands, July 2022

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The power of sharing science