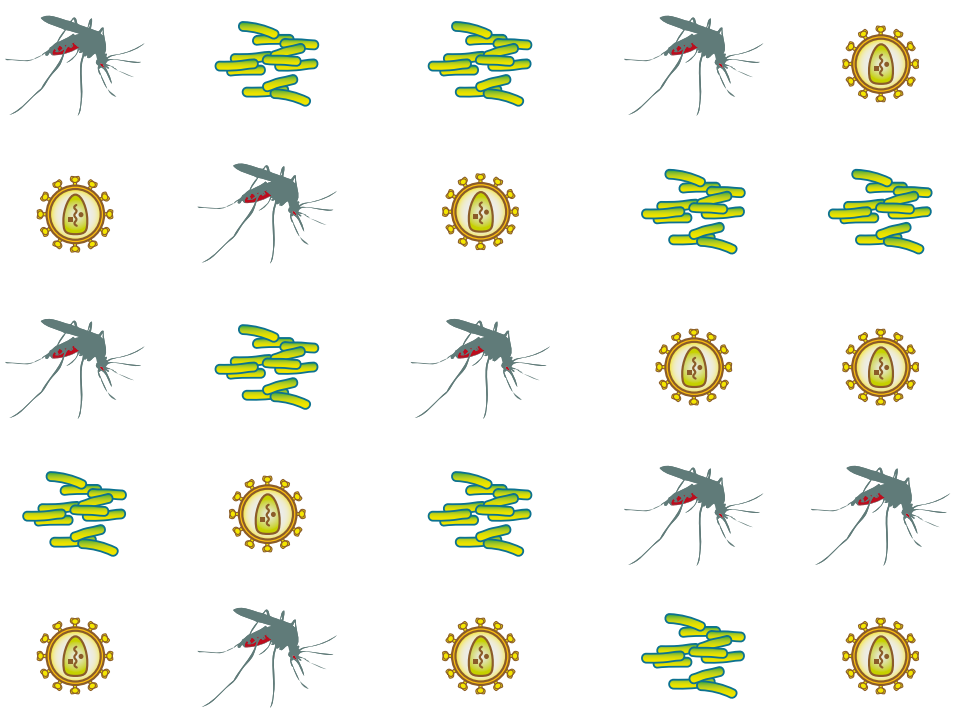
EDCTP

Sixth EDCTP Forum

9–12 October 2011 Addis Ababa, Ethiopia

PROCEEDINGS



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Acronyms and abbreviations

AAVP	African Aids Vaccine Partnership
ACT	Artemisinin combination therapy
Aeras	Product development partnership dedicated to the development of effective tuberculosis vaccine regimens
AMANET	African Malaria Network Trust
ANRS	French National Agency for Research on AIDS and Viral Hepatitis
ASLM	African Society for Laboratory Medicine
AAVP	African AIDS Vaccine Partnership
ANDI	African Network for Drugs and Diagnostics Innovation
APRIORI	African Poverty Related Infection Oriented Initiative
AU	African Union
ART	Antiretroviral therapy
ARVs	Anti-retroviral drugs
BCG	Bacillus Calmette-Guérin
CAPRISA	Centre for the AIDS Programme of Research, South Africa
CANTAM	Central African Network on TB, HIV/AIDS and Malaria
DNDi	Drugs for Neglected Diseases initiative
EACCR	East Africa Consortium for Clinical Research
EC	European Commission
EDCTP	European and Developing Countries Clinical Trials Partnership
EPI	Expanded Programme on Immunization
ELISA	Enzyme-linked immuno sorbent assay
ELISPOT	Enzyme-linked immunosorbent spot
ESSENCE	Enhancing Support for Strengthening the Effectiveness of National Capacity Efforts
EU	European Union
FP7	Seventh Framework Programme of the European Union for the funding of research and technological development
GCP	Good Clinical Practice
GCLP	Good Clinical Laboratory Practice
GLURP	Glutamate-rich protein
HAART	Highly-active antiretroviral therapy
HPV	Human papilloma virus
IAVI	International AIDS Vaccine Initiative
IPT	Intermittent preventive therapy
IPTp	Intermittent preventive therapy in pregnancy
IRIS	Immune reconstitution inflammatory syndrome
IRS	Indoor residual spraying
ISHReCA	Initiative to Strengthen Health Research Capacity in Africa
ITN	Insecticide-treated nets
MDP	Microbicides Development Programme
MDR-TB	Multiple-drug-resistant tuberculosis
MEMS	Medication Event Monitoring System
MMV	Medicines for Malaria Venture
Mtb	*Mycobacterium tuberculosis*
MVVC	Malaria Vectored Vaccine Consortium
NACCAP	Netherlands-African Partnership for Capacity Development and Clinical Interventions Against Poverty-related diseases
NoEs	EDCTP's Networks of Excellence
PACTR	Pan African Clinical Trials Registry
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
Pf	*Plasmodium falciparum*
PK	Pharmacokinetics
PMTCT	Prevention of mother-to-child transmission
PrEP	Pre-exposure prophylaxis
RCT	Randomized controlled trial
RTI	Reproductive tract infection
STI	Sexually transmitted disease
TDR	Transmitted drug resistance
TESA	Trials of Excellence for Southern Africa Network
TRREE	Training and Resources in Research Ethics Evaluation
UNITAID	An international facility for the purchase of drugs against HIV/AIDS, tuberculosis and malaria
WANETAM	West Africa Network of Excellence for TB, AIDS and Malaria
WHO	World Health Organisation
XDR-TB	Extremely drug-resistant tuberculosis

Contents

The Road from Rome to Addis

The journey that had started in Rome in 2004 to Addis Ababa in 2011 where we held the first and the sixth EDCTP forums respectively has been hard and long, but very gratifying. From those early days, EDCTP has been growing from strength to strength gaining in momentum from year to year. Whereas in the Rome forum there were less than 100 participants and no presentations, and at that time there were hardly any ongoing EDCTP funded projects, at the Sixth EDCTP Forum we had over 500 participants and 265 presentations of which 127 were oral and 138 posters. Furthermore, since Rome EDCTP has now funded nearly 200 projects including 56 clinical trials that are taking place in 29 sub-Saharan countries in partnership with the 16 participating European member states. These projects bring together researchers from 148 institutions from Africa and 42 from Europe many of whom participated at the forum in Addis Ababa signifying the importance of EDCTP and the EDCTP forums as important platforms for collaborative research and networking. As a matter of fact, EDCTP forums have now grown to be major conferences on poverty-related diseases in Africa. In Addis, researchers working on poverty-related diseases from EDCTP-funded and other programmes were joined by policy makers, international development partners, private sector and other stakeholders to share their research findings, exchange views, establish new or expand their respective networks and make recommendations to the programme.

It is very satisfying to note that over 60% of the presentations at the forum were from EDCTP-funded projects, underpinning the maturation of the programme. Moreover, the majority of the presenters were African scientists working in Africa comprising a good mix of senior researchers including project coordinators with young and upcoming scientists availing themselves of the opportunity to use the forum as a training and capacity development platform. This is all in keeping with the EDCTP philosophy of mutual partnership, capacity development, networking and fostering of sustainable programmes, very much in resonance with the forum theme of **Strengthening Research Partnership for Better Health and Sustainable Development.**

This short report, which summarises the proceedings of the forum, is meant to complement a scientific publication that will appear as forum proceedings in the *Journal of Tropical Medicine and International Health* later this year.

Charles S Mgone
Executive Director

Executive summary

Background and opening of the Forum

The theme of the Sixth European and Developing Countries Clinical Trials (EDCTP) Forum held 9–12 October 2011 in Addis Ababa, Ethiopia was **Strengthening Research Partnerships for Better Health and Sustainable Development.**

The event was attended by 535 participants from 32 African countries and 22 other nations worldwide. Speakers at the opening event agreed that EDCTP has achieved much in the last few years, notably the funding of 191 research projects and professional training of 158 African scientists. Whilst much had changed since the launch of the organisation in 2003, the strong commitment to improving health through partnership is still at the heart of EDCTP's activities, as is the belief that better health can help achieve sustainable development. Robert-Jan Smits, Director-General for Research & Innovation at the European Commission (EC) said what has been achieved provides a fine example of what can be done when there is a 'true and equal partnership between stakeholders'. His hope is that when the FP7 funding programme expires in 2013, its successor will provide support for EDCTP, allowing it to build on what has been achieved and also to expand its mandate.

Speakers agreed that innovation will play an important part both in tackling the burden of infectious diseases and in boosting the global economy. EDCTP Executive Director, Professor Charles Mgone said strengthening capacity and enabling environments was the 'soul' of EDCTP, and highlighted the important role played by the programme's four research Networks of Excellence (NoEs). Other speakers spoke of EDCTP's role in creating the next generation of leaders and champions for science in Africa.

Research presentations

Central to the structure of the Forum were three parallel sessions dealing, respectively, with HIV/AIDS, tuberculosis (TB) and malaria. For each disease there were keynote addresses summarising recent advances in research, plus over 30 presentations from EDCTP-funded researchers. These presentations had three overarching themes: Clinical research and achievements and findings in sub-Saharan Africa; Developing scientific research capacity in sub-Saharan Africa; and North-South and South-South partnerships for quality improvement research in sub-Saharan Africa.

The **HIV/AIDS** presentations dealt with a range of topics including: immunology and vaccine development; epidemiological studies at potential trial centres; preventing mother-to-child transmission; toxicity to antiretroviral medications; benefits of antiretroviral treatment for physical and mental health; concurrent infections with HIV (TB, bacterial vaginosis, syphilis, hepatitis B, human papilloma virus and methicillin-resistant *Staphylococcus aureus* (MRSA)); safety biomarkers, depression in people living with HIV, factors influencing disease progression, HIV subtype distribution, and good clinical practices in resource-limited countries.

Tuberculosis presentations also covered a variety of issues such as: the work of the Pan-African Consortium for Evaluation of Anti-tuberculosis Antibiotics Network (PanACEA), the pharmacokinetic (PK) variability of TB treatment drugs, progress in the multicentre RIFAQUIN trial, modifying drug dosage in HIV-infected patients receiving TB treatment. There were also several presentations on the diagnosis of TB, and on biomarker research. Further presentations dealt with *Mycobacterium africanum*, immune responses, vaccine research, spoligotyping to determine where infections take place, the genetic diversity of TB strains, nanomedicine to improve the efficacy of existing TB drugs, comparison of active and passive case finding, and working with communities in trial sites.

Several of the **malaria** presentations concerned the evaluation of antimalarial drug treatments, including an account of the WANECAM initiative to establish state-of-the art clinical trial sites in the West African sub-region; PK interactions of

HIV and malaria treatment were also studied. The burden of malaria on HIV-positive women and the use of intermittent preventive therapy in pregnancy was another area of research reported. Severe malaria in children was the subject of several presentations, as were vaccine studies including a viral-vectored vaccine and the GMZ2 vaccine. Other topics included: 'benchmarking' at trial sites, gametocyte infectivity, asymptomatic carriers (ACs), evaluating the impact of treating ACs on the number of symptomatic malaria episodes in the community, malarial intermittent prophylactic treatment and progression towards AIDS in HIV-infected patients, and quality management in clinical laboratories.

There were also ten presentations on **'issues cutting across the three disease areas'**, the first of which looked at trial registration. Six presentations then focused on research ethics, addressing both the functioning of ethics committees and teaching scientists themselves more about this increasingly important area. Other cross-cutting topics were clinical data management, and initiatives to help strengthen partnerships and build capacity.

Also, within the cross-cutting sessions the four NoEs were each described and comprehensive discussion took place concerning this core part of EDCTP's activities.

Partnerships

During the meeting twelve global health organisations that are EDCTP partners made presentations about their work and the areas where they collaborate or wish to collaborate with EDCTP. The activities of NACCAP (Netherlands-African partnership for capacity development and clinical interventions against poverty-related diseases), which is closely linked to EDCTP were also described. In addition there was a presentation on the ESSENCE project (Enhancing Support for Strengthening the Effectiveness of National Capacity Efforts).

Awards

The winner of EDCTP's Senior Scientist Award was Professor Salim Abdool Karim, Director of the Centre for the AIDS Programme of Research in South Africa (CAPRISA). He said in his acceptance speech that, in giving him the award, EDCTP was honouring not only him but also the entire team of some 380 people at CAPRISA.

EDCTP's Junior Scientist Award went to Hannock Tweya of the Lighthouse Trust, Malawi. The Trust is a centre of excellence currently providing care to over 22,000 people living with HIV.

Conclusions

The closing plenary session heard a summary of the conference proceedings, after which many comments were made from the floor. Professor Mgone discussed these and said that the remarks made would all be 'taken on board'. The final address to the meeting was from Dr Ruxandra Draghia-Akli, Director for Health Research, Directorate-General for Research & Innovation, European Commission, who called for the creation of 'an unbroken implementation chain, from discovery to better health'. She described EDCTP as a role model for partnering on global health challenges, which was breaking new ground in terms of collaboration, strategy, governance and implementation. But now the Partnership must move forward; she offered suggestions that would help in this process and in particular generate continued financial support.

1 Partnership and commitment

Opening addresses

The Sixth EDCTP Forum was formally opened on Sunday 9 October 2011. The Executive Director, Professor Charles Mgone gave a short history of the Partnership since its launch in 2003. He emphasised that, while there had been several changes during that time, a strong commitment to improving health through partnership was still at the heart of all EDCTP's activities. Also central to the Partnership's vision was the belief that better health could help achieve sustainable development. He thanked the sponsors of the organisation for their support, which had made possible the growth in EDCTP's activities.

Mr Robert-Jan Smits, Hon. Jean Ping, Prof. Charles Mgone, Dr Pascoal Mocumbi and Hon. Koen Vervaeake at the Sixth EDCTP Forum's official opening address, 9 October 2011

Some of EDCTP's success stories were highlighted by the organisation's High Representative, Dr Pascoal Mocumbi; he gave as an example the 174 EDCTP-funded projects and the training of 158 African scientists. He said that the Sixth Forum came at a time when EDCTP had reached a fruitful and crucial point in its development, hoping it would move on to its next phase. He described EDCTP as a 'true partnership' between Europe and Africa, noting the importance of African commitment and ownership in research and innovation. Important continuing activities for EDCTP include networking, seeking advice from other bodies, improving links with other institutions and developing synergies. EDCTP should build on experience and lessons learned so far. Participants at the conference should use it as an opportunity to share ideas and help develop the form that the programme's next phase would take.

The high regard in which EDCTP is now held was made clear in the address from Jean Ping, Chairperson of the African Union, who spoke of the Partnership's important contribution towards reducing the disproportionate burden of disease borne by Africa. Dr Ping officially declared the Sixth EDCTP Forum open.

The work of EDCTP was then enthusiastically endorsed by Robert-Jan Smits, Director-General of Research & Innovation, European Commission (EC). He described the organisation's results so far as 'impressive'. What had been achieved provided a 'brilliant example' of what can be done when there is a true and equal partnership between stakeholders. He spoke of his hopes for what might be achieved by EDCTP in the future; especially if there can be an enlargement of its mandate. Nevertheless, he stressed that there was much to be done and that input was needed from all stakeholders. In particular, this must include a high level of commitment from member states.

The first plenary session on Monday 10 October – the 'Forum prologue' – began with an address from EDCTP General Assembly Chairperson, Professor Hannah Akuffo. She said that following the launch of the Partnership in 2003 things had got off to a slow start, but all partnerships require trust and establishing trust can take some time. It was also a multi-actor programme using new instruments and that had presented many challenges. In the last few years, however, EDCTP has achieved a great deal. Internal and external evaluations of the programme have been favourable and have concluded that the Partnership should be continued and its mandate extended. EDCTP has applied to the EC for further funding. Professor Akuffo noted that, as results from EDCTP-funded research continue to come in, there will be an increasing need to conduct more Phase III clinical trials, and this of course is an expensive process. Robert-Jan Smits then addressed the Forum for a second time, stressing that the current global

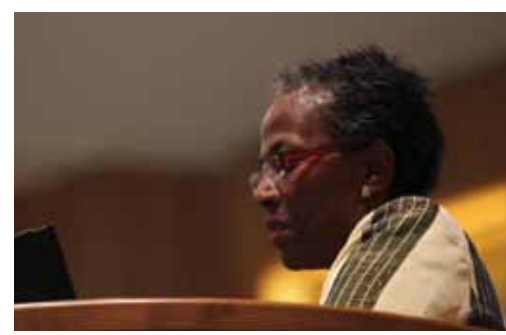
financial crisis was unprecedented and that it affected everyone. The way forward was to create conditions that would allow innovation to flourish, and the EC was firmly committed to doing this. To address the world's biggest health challenges, including poverty-related infections, the world's best scientists must be brought together, in which process the FP7 funding programme was playing a major role. EDCTP was a success story and it was Mr Smits hope that when FP7 expires in 2013, its successor will provide support for EDCTP and allow the programme to build on what has been achieved and also to expand its mandate. He called for greater dialogue between innovators and the users of products, speaking of the need for 'an unbroken chain' between the laboratory and the people who need the products. Innovation was not a one-way street; it should not been seen simply as a flow from Europe to Africa.

Professor Jean-Pierre Ezin, the African Union (AU) Commissioner of Human Resources, Science and Technology, spoke of the human and economic costs of malaria, TB and HIV/AIDS. The proportion of medical research funding devoted to the priority health concerns of developing countries was still too low. Nevertheless, matters have improved in recent years and many African governments are now devoting more resources to health. EDCTP was playing an important role and he congratulated the programme on its achievements.

Professor John Gyapong of the University of Ghana, who also represents African health ministers on the EDCTP General Assembly, then gave a stimulating and well received address. His focus was research as a tool for development. Scientists needed champions who could engage with policy makers and make the case that research should be high on the priority list. This required leaders. 'Where is the next generation of leaders in our region?' he asked. It was essential for today's leaders to consider who their successors will be, so that their institutions continue to prosper. 'We need partnerships to succeed and we need others who will succeed us'.

Professor Charles Mgone reminded the meeting of the objectives and mission of the Partnership. Funding clinical trials as core activity integrated with strengthening capacity and enabling environments were the 'heart and soul' of EDCTP. He highlighted the important role played by the programme's four research Networks of Excellence; there were now very few countries in Africa where EDCTP was not supporting research. South-South, North-South and North-North partnerships were all important in achieving the goals of better health and sustainable development. He wanted to see closer collaboration with industry and other partners.

There were some spirited contributions from the conference floor, with one delegate answering the question of where Africa's next generation of health leaders could be found, saying 'We are here!' When one delegate asked how many of the scientists funded by EDCTP to gain their PhDs were still actually working in Africa, Professor Mgone replied, 'Almost all'. A speaker from the floor who referred to the difficulties in making grant applications and the need for simplification of the process received warm applause.



Prof. Hannah Akuffo, EDCTP General Assembly Chairperson, at the Forum prologue session on Monday 10 October

A welcome message, on behalf of Ethiopia's Minister of Health, Dr Tedros Adhanom, was delivered to the Forum by Dr Abraham Aseffa, Director of the Armauer Hansen Research Institute. Ethiopia was experiencing a period of transformation and growth. The issues addressed by EDCTP and the theme of the Forum itself were highly relevant to Ethiopia and other African nations. Collaboration, capacity building and the empowerment of African scientists would 'benefit all of us in this globalized world'.

Closing remarks

During the Forum's final plenary session on Wednesday, 10 October 2011, an overview of the conference proceedings so far was delivered by the Chief Rapporteur, Paul Chinnock. Following this, the session Co-chair, Professor Shabbar Jaffar, asked participants for their own conclusions on the meeting, and for recommendations concerning the EDCTP's future research strategy. Two topics featured most strongly in the comments that followed – the EDCTP's Networks of Excellence, and the functioning of ethics committees.

Dr Ruxandra Draghia-Akli, Director for Health Research, Directorate-General for Research & Innovation, European Commission

It was suggested that the four Networks of Excellence should network between each other to share experience and expertise. In particular, the eastern and southern networks (which are larger and more highly developed) should share expertise with the central and western networks. Multi-network strategies are needed.

Ethics committees should endeavour to work more efficiently. Ethics reviews of multi-centre trials could be conducted by ethics committees working collaboratively. This would save researchers much time and avoid their having to answer the same questions several times. Ethics committees could agree to each specialize on a particular aspect of ethics, and then share their expertise with each other.

A number of other suggestions were also made.
- Consider the needs of trial participants more closely
- Redouble efforts to obtain the extra funding needed for large trials
- Establish initiatives to address the quality of drug supply
- Improve data sharing within Africa; data management skills should be developed and shared
- Close the funding gap for the period between fellowship and senior fellowship
- Train new leaders in laboratory medicine
- Continue support for basic science
- National regulatory authorities are lagging behind and EDCTP should endeavour to assist in their development
- Find ways of measuring the beneficial impact of research on society, to justify the case for future funding.

Following this input from the conference floor, there was a response from Professor Mgone. He said many of the issues raised were already being addressed. Thus, it had always been intended that the four networks should share experience and expertise; there was no need to set up a 'network of networks'. The networks have grouped together institutions that have complementary strengths, and this would help address several of the concerns that had been raised. The fellow–senior fellow gap was also now receiving attention and EDCTP was already providing support to national regulatory authorities. Nevertheless, he was grateful for the comments and suggestions, which would all be taken on board. Professor Mgone also thanked all those who had made the Forum possible. It was intended that the Seventh Forum should take place in October 2013 but it was not yet possible to specify the venue, which might be either in Africa or in Europe. He hoped that the Seventh Forum would be the occasion for the official launch of 'EDCTP-II'.

Further concluding remarks were then made by Dr Ruxandra Draghia-Akli, Director for Health Research, Directorate-General for Research & Innovation, European Commission. She described EDCTP as a role model for partnering on global health challenges, which was breaking new ground in terms of collaboration, strategy, governance and implementation. She went on to ask, 'How can we move forward?' Her own suggestions included: the addition of more countries to the programme, integration of national activities and investments, increased investments from the private sector, expanded links with health providers and local manufacturers, expanded synergies, and more international activities.

Dr Draghia-Akli said she wished to see 'an unbroken implementation chain, from discovery to better health'. Such a chain would map activities, identify gaps, link partners, take ownership of innovations, and bring results to patients.

She looked forward to the Seventh Forum, which she hoped would be a bigger event at which the results of the 56 EDCTP-funded trials now under way would be presented. 'God and [EU] member states willing', more funding would be forthcoming. However, EDCTP should develop a strong business plan, choose one way of moving forward (rather than spreading activities too thinly), secure a high level of political and financial commitment from a critical mass of countries, and bring in funding from industry and other private partners that the EC would endeavour to match. It was important to increase the visibility of EDCTP and to communicate to politicians what research can deliver in terms of health and economic gains. All this would increase the likelihood of further funding.

Co-chair Dr Michael Makanga then thanked all Forum participants for their contribution to the meeting and its 'intense discussions and deliberations' which would play an important part in the future development of EDCTP.

Awards

The final plenary session also saw the presentation of the two EDCTP Awards to outstanding senior and junior African scientists working on HIV/AIDS, tuberculosis and malaria.

The winner of the Senior Scientist Award was Professor Salim Abdool Karim, Director of the Centre for the AIDS Programme of Research in South Africa (CAPRISA). He said in his acceptance speech that, in giving him the award, EDCTP was honouring not only him but also the entire team of some 380 people at CAPRISA.

'Work with people who value excellence' was Professor Karim's advice to younger scientists in his acceptance speech. He also urged them to 'Be persistent', using as an illustration his own research into microbicides, which initially produced some very disappointing trial results. It took seventeen years and eight trials before success was achieved. But the burden of HIV in young girls in southern Africa (many times higher than the burden amongst young males, and a driver of the epidemic) gave him and his colleagues sufficient motivation to continue their work, despite the setbacks.

Prof. Salim Abdool Karim

He thanked EDCTP, the CAPRISA team and his other colleagues, most notably his wife who has been a co-investigator with him in many of his studies. Finally to much applause, he thanked the patients who had participated in his trials.

EDCTP's Junior Scientist Award went to Hannock Tweya of the Lighthouse Trust, Malawi. The Trust is a centre of excellence currently providing care to over 22,000 people living with HIV. Mr Tweya has been involved in many aspects of the work of the Trust, including home-based care, ART provision and other services. He has published papers on topics including loss to follow-up and HIV in pregnancy.

Mr Hannock Tweya

Thanking EDCTP for the award, Mr Tweya said he would use the money to advance research that would improve people's lives. His strong belief is that research should be linked to practice. He was driven by his commitment to improve his country's health system. He thanked all those who had supported him so far and closed by saying that winning the award was 'just a beginning' in his research career.

2 Research reports: HIV/AIDS

KEYNOTE ADDRESS
RECENT ADVANCES IN HIV/AIDS RESEARCH

Professor Elly Katabira, Makerere University, Uganda

Professor Katabira began with a brief historical review of the pandemic and the response to it from the international community, including the launch of the Global Fund and the US President's Emergency Plan for AIDS Relief (PEPFAR). The number of patients receiving treatment continues to increase and research advances have brought us to the point where many patients can now be treated with 'one pill per day', instead of receiving a cocktail of drugs. However, while highly active antiretroviral therapy (HAART) suppresses infection, it does not eliminate the virus.

He went on to describe the study of 'The Berlin Patient' who was successfully given stem-cell therapy;[1] Even though there was only one patient, this study should be regarded as an important advance and it has already led to further research in this area.

By treating infected patients, we can reduce the risk of them transmitting the virus to others, hence the concept of 'Treatment as prevention', which has been supported by the findings of several studies. For example, it has been shown that if HAART is started at diagnosis it considerably reduces the rate of further transmission, compared with delayed HAART.[2]

Also of key importance is the CAPRISA 004 trial[3] which has provided proof of principle for the use of topical microbicide gels for pre-exposure prophylaxis (PrEP); some recent studies on gels have, however, produced disappointing results. The Partners PrEP and iPrEx studies have generated some evidence that oral pre-exposure prophylaxis can be effective.[4]

Many challenges remain. These include scaling up access to testing, and to treatment for patients and discordant partners. People *do* want to be tested but they are failed by inadequate infrastructure. Ensuring continued adherence to treatment is also a major issue.

Professor Katabira called for the development of a combination package for prevention and treatment. Elements would include male circumcision, condoms, counselling, oral/topical PreEP, HAART, and hopefully in time a vaccine.

1 Hütter G, Nowak D, Mossner M, Ganepola S, Müssig A et al. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. N Engl J Med 2009; 360(7):692-698.

2 Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC et al.; HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011; 365(6):493-505.

3 Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C et al.; CAPRISA 004 Trial Group. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science 2010; 329(5996):1168-1174.

4 Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY et al.; iPrEx Study Team. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med 2010; 363(27):2587-2599.

In the parallel sessions devoted to progress against HIV/AIDS, researchers reported on the results achieved in over 30 studies. These had elements of three overarching themes regarding sub-Saharan Africa.

- Clinical research, its achievements and findings
- Development of scientific research capacity
- North-South and South-South partnerships for quality improvement research

The four opening presentations concerned vaccines. In the first [HO 01], HIV inhibitory antibodies were elicited by a DNA-MVA vaccine trial in Tanzania. The inhibition activity was partially dependent on NK cells. During the discussion, there was interest in whether V1V2 antibodies were elicited, as these have recently been shown to correlate negatively with risk in the Thai RV144 trial. If funding is forthcoming this will be analysed in future studies. There are also plans to boost the vaccine with a gp140 protein.

A presentation on PedVACC [HO 02] described the work of this capacity building project in the conduct of two HIV vaccine clinical trials in Kenya and The Gambia. PedVACC's input includes infrastructure development, staff training and student enrolment. The vaccine platform tested was a recombinant MVA expressing HIV genes. It was shown to be safe in infants and to be marginally immunogenic, which it is hoped to improve by combining it with a boosting vaccine. The discussion focused around interactions of this candidate HIV vaccine with other Expanded Programme on Immunization (EPI) vaccines. The researchers are addressing this issue by looking at antibody responses to EPI vaccines. No impact on EPI vaccines was detected in the cohort in The Gambia; the analyses in Kenya are not yet complete. Many challenges must be addressed in this project, such as the large sample size needed to evaluate efficacy.

A study that created particular interest [HO 03] concerned the use of a therapeutic vaccine. The goal of a therapeutic HIV vaccine is to provide a cellular response to reduce viral set-point and thereby prolong the time to AIDS or the need for HAART, as well as limit secondary spread. Two successful HIV vaccine trials were performed in HIV-infected populations in Guinea Bissau and Denmark, with no serious adverse events. The vaccines were immunogenic in antiretroviral naïve HIV-infected populations, even in the presence of high viral loads. However, viral loads were not reduced compared with pre-vaccination. Forum participants considered this to be a promising approach, though the challenges of inducing effective immunity in the context of a damaged immune system are considerable. The researchers are now considering performing future studies in the presence of antiretroviral therapy to preserve or restore some immune function prior to vaccination. There are also ongoing studies to sequence the infecting virus, to see whether the epitopes the vaccine elicited were present in viruses in the trial participants.

So far, most HIV vaccine trials have not focused on men. However, a South Africa study [HO 04] has attempted to evaluate the feasibility of recruiting and retaining healthy men in a vaccine trial by using the hepatitis B vaccine as a surrogate; the vaccine was given either immediately or deferred. The researchers have concluded that enrolling high-risk men in future vaccine trials is feasible and acceptable; follow-up studies are continuing. Amongst the issues raised by the audience were that such studies can keep clinical trial sites going when no candidate HIV vaccine is yet available, and that they offer the opportunity to provide study participants with other vaccines that are not presently a part of EPI.

A small study in Tanzania [HO 05] measured adherence to ART and examined the feasibility and acceptability of the medication event monitoring system (MEMS), a medication bottle cap with a microprocessor that records the occurrence and time of each bottle opening. Qualitative interviews with participants showed that there were no barriers to MEMS use amongst patients, although patients were less likely to use MEMS when they travelled. When using MEMS, participants were more motivated to adhere to their medication. The MEMS data also showed that some clinicians were not prescribing sufficient medication to cover the interval between clinic visits. MEMS may be useful in helping to ensure treatment adherence but some concerns were raised in the discussion – would the intervention still be effective if taken to scale and might some patients open their bottles without necessarily taking their medication?

Data were then presented [HO 06] from the PROMISE-PEP trial in Burkina Faso, which is intended to compare regimens to reduce HIV transmission during breastfeeding. The presentation focussed on the PMTCT regimens (preventing mother-to-child transmission) received by women in the trial. Few transmission events were observed in this cohort. PMTCT is a rapidly changing field with guidelines updated regularly as new data become available. There is a move towards providing HAART during pregnancy to protect both mother and infant. This approach is thought to be less likely to lead to drug resistance than regimens that use monotherapy.

In a non-randomised trial [HO 07] involving 200 HIV-infected pregnant women in Tanzania, participants were allocated to receive single-dose nevirapine for PMTCT either alone or in combination with single-dose carbamazepine, in order to evaluate the potential benefit of the latter as an enzyme inducer for reducing the long half-life of nevirapine, which may predispose to the development of resistance. The data showed that, a week after administration, nevirapine concentrations were higher in those women who had been given carbamazepine. Resistance rates also appeared to be lower in this group. The study highlights the importance of innovation when dealing with the challenges of monotherapy in PMTCT. However, now that HAART is being recommended for all HIV-infected pregnant women, such interventions may no longer be required. In situations where monotherapy is used, the risk of resistance needs to be weighed against the risk of transmission events.

Four studies focused on toxic reactions to ART, two of them on hepatoxicity and two on immune reconstitution inflammatory syndrome (IRIS).

A secondary analysis [HO 08] of Kenyan data from the Kisumu Breastfeeding Study (KIBS) found that severe hepatotoxicity (3%) or rash (2%) were rare amongst 522 pregnant women who were receiving HAART; there did not appear to be an association between the development of hepatotoxicity or rash with CD4+ counts of over 250. The data were considered to be reassuring, regarding the use of nevirapine in women with higher CD4+ counts, particularly as guidelines are now recommending earlier initiation of HAART. Nevertheless, these findings need to be confirmed in other settings. An Ethiopian study [HO 10] [5] looked for predictors of ARV drug-induced liver injury (DILI) in TB-HIV co-infected patients; 30% of patients were observed to have DILI and 90% of events occurred within the first eight weeks of initiating therapy. 12% of patients died, and of those deaths 44% had DILI. High plasma efavirenz, slow NAT2 acetylators, and ABCB1 genotype were found to be associated with DILI. This was also observed to be higher in women, those with a low haemoglobin levels, lower albumin, and with an elevated AST/ALT ratio at start of therapy. The study also suggested that DILI is the result of a direct effect of EFZ, rather than its metabolites. This study highlighted the importance of more careful monitoring of TB/HIV patients on therapy, particularly those with obvious risks for DILI. The prospect of identifying genetic markers of risk is attractive, and would be important to consider given the recent calls by the NIH-funded H3 Africa project to do more genome-wide associated studies.

IRIS in HIV-schistosomiasis co-infected patients was the focus of a study conducted in Kenya [HO 11]. Of 126 fisherman or fish handlers undergoing HAART, 24% experienced schistosoma-associated IRIS within the first 3 months of therapy; low egg count and low CD4+ count were predictive for the development of IRIS. The release of eggs is an immune-facilitated function and the studies based on egg counts may have underestimated the prevalence of schistosomiasis in populations with high HIV prevalence. Improved diagnostics that do not rely on egg detection for diagnosis are needed to improve management of schistosomiasis in HIV positive populations. This important presentation highlighted the need for the recognition and management of co-infection with neglected tropical diseases such as schistosomiasis.

A descriptive study of 186 patients [HO 12] receiving HAART in Addis Ababa highlighted the importance of TB as the primary cause of IRIS in this population. IRIS events were recorded in 17% of cases, with 75% considered to be a result of unmasking disease. The majority of these events were TB-associated. As in other studies, IRIS was more common in those that started treatment at low CD4+ counts. The discussion highlighted the importance of excluding a diagnosis of TB at the

5 Presentation HO 09 did not take place.

time of HAART initiation, and the need for strict monitoring of patients initiating therapy at low CD4+ counts for evidence of IRIS.

Three presentations focussed on African fishing communities, who are often considered to be at high-risk for HIV infection; finding out more about such populations is necessary to determine whether they would be suitable for inclusion in efficacy trials of interventions to prevent or treat HIV. A study in Uganda [HO 13] sought information on prevalence and incidence rates and on behaviours predisposing to HIV acquisition. It was found that: incidence and prevalence were higher than the national average, populations were mobile but the community was fairly stable, education levels were low, and young people were most at risk. Factors associated with HIV infection included: mobility, alcohol, smoking, and number of sexual partners. (Data were not collected on the prevalence of male circumcision.) The community studied was concluded to be ideal for future trials, but HIV prevention measures on the ground were considered poor and should be improved. A related study [HO 14] additionally explored transmission dynamics and drug resistance patterns in the same cohort. Virus subtype D is still the most prevalent. Levels of transmitted drug resistance (TDR) are around 6%, which is lower than found previous surveys elsewhere in Uganda. Nevertheless, the level seems to be rising; it is highest in younger age groups. Five transmission clusters were identified, indicative of varying and in some instances complex sexual networks. All study participants were ART-naïve; in response to an audience question it was clarified that the study focus was TDR that can be passed on to naïves, as opposed to resistance acquired while on therapy. An audience suggestion was that further research should investigate whether the use of PMTCT in Uganda could be responsible for the rise of TDR. Concern was expressed that the reported retention rates in such a high-risk population would be too low for a trial.

A study on two Malawian fishing communities [HO 15] used prospective study design to estimate HIV prevalence and incidence rates, and levels of sexually transmitted infections and high-risk sexual behaviour. Preliminary data indicate that HIV prevalence rates are not significantly higher than the national average. High-risk behaviour was nevertheless noted at both sites. HSV-2, but not syphilis was associated with HIV prevalence. Other reported factors associated with HIV prevalence included prior HIV testing, low educational level and marital status. Cohort retention rates were generally low. Regarding prior testing being associated with HIV acquisition, it was pointed out that more women had prior HIV testing than men, making this a confounder in the analysis. Some of the discussion that followed focused on the question of whether the most mobile members of the community might be at highest risk of infection.

A study in Ghana [HO 16] examined the impact of ART on the physical and mental health of AIDS patients, their care givers and family. Neighbouring families were used as controls. Quality of life, in terms of physical and mental wellbeing was measured through questionnaires using wellbeing indices. ART improved both the physical and mental health of the patients, though it remained lower than that of immediate family members and neighbours. Factors associated with positive outcomes included counselling and time on ART. The study authors urged that ways be found to incorporate their findings on counselling into policy. Wellbeing could perhaps be further improved through patient associations and insurance schemes might be able to increase ART coverage. Audience comments included the need to tease out depression from other psychological disorders.

Using data from a trial of an antimicrobial gel (SAVVY) conducted in Ghana, a study [HO 17] found that 31% of the 788 women in this trial had bacterial vaginosis (BV). The aim was to seek for any association between BV and HIV acquisition, as has been found in other prospective studies. The findings are so far unclear but the study highlights the need for further research for interventions to prevent and control BV, a common, recurrent condition which may place women at increased risk for HIV and poor pregnancy outcomes.

Analysis of data from the records of 9504 HIV-infected Nigerians [HO 18] found a high prevalence (30%) of clinician-diagnosed anogenital warts (AGW). In 851 patients with STIs, more than half had low CD4+ counts. AGW were 3.2 times more common in patients not yet on ART, compared with ART-experienced patients; this

supports recommendations for earlier initiation of HAART. The study highlights the relationship between immunosuppression and AGW and the need for routine screening for genital warts. The authors also called for HPV vaccination for all HIV-infected patients aged 9-26 years. (WHO already recommends vaccination programmes for girls aged 9-14 years, prior to age of sexual debut)

The prevalence of HPV infection was measured [HO 19] in 250 pregnant Kenyan women from Mombasa who participated in the Kesho Bora trial. Women in this study were not yet eligible for HAART. 78.5% of the women were infected with multiple HPV types (mean = 2.5 types). The clinical significance of the finding is not as yet clear.

A Nigerian survey [HO 21][6] found that, after counselling, most HIV-positive women would be willing to pay for cervical cancer screening. The survey was conducted in a rural area (HIV prevalence 6.5%). Only 17% of the women knew about cervical cancer screening with pap smear, and only one woman had ever had a smear. Only 20% knew that HIV was associated with an increased risk for the development of cervical cancer. 95% reported being willing to pay for a pap smear, irrespective of cost. In those not willing to pay, cost was a main impediment to screening. The study demonstrates the importance of promoting knowledge and awareness of cervical cancer generally, but also more specifically to women at higher risk who are participating in HIV treatment programmes. The authors noted that knowledge and awareness was not sufficient to drive coverage, and that the provider-initiated cervical cancer screening had recently been introduced in the area of the study. Screening should ideally be targeted at older women, in whom persistent infection with HIV may lead to high-grade precancerous lesions. The presentation highlighted the debate around approaches to cervical cancer screening in low-resource settings. More research is needed to identify the optimal approach.

Prevalence and risk factors for depression amongst patients attending HIV clinics in Uganda were the subject of the presentation which followed [HO 22]. Using standardized tools based on DSM-IV criteria, the study showed that 8.1% of patients had a diagnosis of major depressive disorder (MDD), and 64% had significant neurocognitive disorder. The prevalence of other psychiatric diagnoses was much lower. In multivariate models, negative life events, psychosocial impairment, post-traumatic stress disorder, suicidal tendencies and generalized anxiety disorder were independently associated with MDD, suggesting that the main risks for MDD in this population are psychological and social rather than neurotoxic. The authors, therefore, recommend that current treatment approaches used in non-HIV infected populations are also appropriate in settings where HIV is highly prevalent. While no data on the effect of MDD on adherence to anti-retroviral therapy were presented, other studies have shown that MDD is associated with poor adherence. Effective screening tools that can be implemented in primary health care settings are needed to assist clinicians to identify those most at risk for MDD and to refer for treatment and support, to reduce the potential risk of poor adherence to therapy.

The feasibility of enrolling female hotel and bar workers in future HIV prevention and intervention trials was investigated in a study from Tanzania [HO 23]. The women targeted were workers in bars, hotels etc; they were followed for 12 months. Retention rate was good overall (77–84%). HIV prevalence was high (21% overall). Incidence was also high and associated with occupation, marital status, and level of education. Pregnancy rate was high (mostly among the married women) and associated with age, previous pregnancies, and lack of contraceptive use. The authors concluded that the women in these settings are suitable for future trials but other interventions are also needed. Audience members commented that the incidence rates seemed high; they may have been over-estimated by doing HIV tests during screening instead of at enrolment but would in any case be higher in this high-risk group than in the general population.

Preliminary findings from an ongoing baseline microbicide safety marker study [HO 24] were reported from centres in Rwanda, South Africa, and, Kenya. Sub-populations of varied HIV and risk-behaviour status have been enrolled to ensure inclusion of groups suitable for various phases of trials. Screens for various safety biomarkers were have been conducted over nine study visits, establishing that reproductive

6 Presentation HO 20 did not take place.

tract infections (RTIs) are common in these populations; overall rates were highest in South Africa. Other sexually transmitted infections, such as syphilis, were also detected and found to be higher amongst HIV-positive women. The authors argue that it is essential that the effects of RTIs on microbicide safety and efficacy should be evaluated. In their view syndromic treatment of STIs is failing in South Africa (though this was disputed by some audience members) and a system of confirmed laboratory treatment should be instituted.

A Nigerian study [HO26][7] set out to determine the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) and the rate of its nasal carriage, among 187 HIV-infected patients. MRSA nasal colonization is known to increase the risk of acquiring several other infections. Patients with nasal carriage (35%) were classified into non-carriers (48%), intermittent carriers (27%) and persistent carriers (25%) depending on growth in the sample collections. Persistent carriers have a high bacterial load and might be a good target for intervention, as their treatment might prove difficult. The rate of multi-drug resistance rate was high (15%). Resistance to cotrimoxazole was reported. The authors recommend that continuous surveillance and sensitivity testing should be instituted before the wide use of prophylactic antibiotics in African countries. New guidelines should be developed with modified regimens depending on resistance levels in the target population. The study was well received, with the session chair describing it as a wake-up call and an instance of how a locally conducted study could be used to influence clinical practice.

Monitoring HIV subtype distribution in epidemics where multiple HIV clades circulate is important, since recombination poses a challenge for the design of HIV vaccines. This was the focus of a Ugandan study [HO 27] amongst female sex workers (HIV prevalence 37%). The study also sought to understand sexual networks by strain typing. Subtype distribution results in Pol and Gp41 showed that subtype A accounted for 54 %, and subtype D 24%; subtype C, which is highly prevalent in southern Africa, only accounted for 3%. There was a 9% prevalence of multiple infections; four women had dual infection and one a triple infection. This rate was lower than in other studies of high-risk cohorts. Six pairs of women had similar viruses from Pol sequencing, possibly indicating that the source of infection was from the same individual. One network with three women was described using Env sequencing; these women were working in the same localities. The findings demonstrate the importance of surveillance in high-risk groups, which is where new subtypes and emerging circulating recombinant forms (CRFs) may first appear, and the need to combine basic and social sciences to understand the HIV epidemic. CRFs may only be characterized with full-length genome sequencing.

A study conducted in The Gambia and Guinea Bissau [HO 28] focused on HIV-2 and sought to determine the influence of HLA class I and HLA-KIR compound genotypes on infection and disease progression. (Determining the correlates of protection to HIV-2 may inform vaccine design against HIV-1.) HLA and KIR genotyping was performed in large cohorts of HIV-2 infected and uninfected people. Results indicate that HLA-B*0801 was associated with HIV-2 susceptibility. KIR2DL2/S2 in combination with C1 was found to be associated with HIV-2 infection, although these are in strong linkage disequilibrium. HLA-B*1503 was negatively implicated in HIV-2 disease progression. There appeared to be a unique immunogenetic profile in the Caio population of Guinea-Bissau. An important recommendation coming out of the discussion was that establishing a database of genetic profiles of different Africa populations may provide an extremely useful tool for researchers.

Major challenges exist in developing an HIV vaccine that can elicit neutralizing antibodies; rare broadly neutralizing antibodies have been identified that target particular regions of the HIV envelope. A study in Botswana [HO 29] has sought to characterize neutralizing antibodies in early HIV infection and their influence on disease progression. Viral clones were generated at baseline, and it is planned to test at serial time points. Neutralization in autologous plasma will also be tested. Preliminary results were reported of pseudovirus infectivity testing in nine individuals. The development of neutralizing antibodies was tracked in five individuals and was found to occur at 5–8 months post-infection; no correlation was found between viral set point and early appearance of neutralizing antibodies in

7 HO 25 was not presented.

this small cohort. This is in agreement with other studies which show that these antibodies do not influence disease outcome in the context of natural infection. A discussion point was the TZM-bl neutralization assay used, and how results might differ using a different neutralization assay, such as the PBMC assay.

The objective of a South African study [HO 30] was to compare the response to TB treatment in 21 patients co-infected with TB and HIV who were receiving TB treatment only with the response in 41 others receiving both TB treatment and antivirals. Interferon gamma release assays (IGRAs) developed for the diagnosis of TB were used in the analysis. There was a general decline in quantification results from six months onwards, consistent with smear and culture results. It was commented that there is now a large body of data showing that IGRAs are less reliable in the diagnosis of TB in the presence of HIV co-infection.

Co-infections with syphilis and hepatitis B contribute to significant morbidity in HIV-infected patients and the next presentation described a study [HO 31] that aimed to describe the prevalence of these two co-infections in HIV-infected patients beginning HAART in Cameroon. The mean CD4 count was low (155 cells/µl) and around 60% of patients were in WHO stages III and IV. Hepatitis B surface Ag prevalence was 12.6% and there was an overall prevalence of 11.3% for syphilis antibodies. For both infections, the prevalence was higher in males than females. The presenter recommended that hepatitis B and syphilis testing should be included before initiating antiretroviral therapy. One audience question concerned how the prevalence of hepatitis B in these patients compared with that in the HIV-uninfected population but no information was available on this point.

The final HIV/AIDS presentation [HO 32] was a description of an initiative on good clinical practice (GCP) in resource-limited countries, supported by the French Agency for Research on AIDS and Viral Hepatitis (ANRS). The programme aims to establish, by consensus, a range of indicators to assess capacity to implement GCLP and ethical principles in clinical trials. So far, it was stated, ethics and GCP principles have been more about rules than real indicators of implementation. ANRS runs a large number of clinical trials in a range of developing countries. A working group was established to identify typical clinical trial processes, discuss setting-specific difficulties and propose adapted quality indicators. Data were then collected at nine clinical trial sites. All steps of the clinical trial process were covered, from protocol writing to reports and close-out, in an attempt to identify difficulties at each stage of a clinical trial. A total of 58 quality indicators were developed for different processes within the clinical trials. Data collection is ongoing and the implementation assessment tool currently under development will be applied to ANRS-supported clinical trials. The presentation was regarded as particularly important, since setting up in-house but peer-reviewed trial monitoring processes is an excellent approach to reduce the large costs usually required for external monitors. The audience considered that this approach should be encouraged among the clinical trial networks in EDCTP.

A period of general discussion took placed at the end of the HIV/AIDS presentations but this did not lead to a specific list of recommendations for future research priorities.

3 Research reports: Tuberculosis

KEYNOTE ADDRESS
RECENT ADVANCES IN TUBERCULOSIS RESEARCH

Dr Abraham Aseffa, Armauer Hansen Research Institute, Ethiopia

Dr Aseffa began by emphasising the scale of the global TB burden and the disappointing level of progress. There were 9.4 million incident cases and 1.68 million deaths in 2009 – the highest figures ever recorded. The declines seen in prevalence and mortality rates in some developing countries have been very small. Interestingly, in Europe much larger declines were achieved before the era of TB drugs began. In Africa, he said, TB is out of control; it is driven by HIV. We seem to be a very long way off meeting elimination targets.

Multi-drug-resistant (MDR) TB now adds to the level of concern. There were an estimated 440,000 cases of MDR-TB in 2008 – 3.6% of all new cases. But probably only a small minority of cases (about 7%) are actually diagnosed. Many African countries have not yet begun to report MDR-TB. Few centres are equipped to conduct costly drug sensitivity tests.

Humanity has a long and complex relationship with *Mycobacterium tuberculosis* (*Mtb*) dating back perhaps 30 million years; it walked with mankind out of Africa and spread round the world. Dr Aseffa outlined recent research on the genetics of *Mtb* and our new understanding of the lineages of this organism, seven of which have now been identified. This knowledge is important, as the lineages vary with regard to immune response and progression to disease. Modern lineages seem to be more likely than ancient lineages to progress to disease. Response to drugs and possibly to vaccines may also vary between lineages.

Having given an overview of the immune response in TB and the pathogenesis of disease, Dr Aseffa then took his audience through the current state of research in several areas. Biomarkers of resistance, latency, protection are currently attracting attention as the markers currently used have limitations, but a greater understanding of TB immunology will be needed before much progress is made. Although the launch of the Xpert diagnostic test is a major advance, there is still much to be learned about its use in practice and it is not suitable for quantitative diagnosis. Further diagnostic research will therefore be crucial. Serological tests have disappointed so far but work continues.

Vaccines are of course a key area for research. BCG is still the only TB vaccine in use and its limitations are well known. Two or three new vaccines are needed, according to Dr Aseffa. Twelve candidates are currently being studied, of which two are at the Phase III trial stage. He cautioned that vaccine efficacy studies are costly and slow. There are also new drugs in the pipeline, two are at Phase III stage; the long duration of current treatment and the spread of drug resistance make this a crucial area of research.

In his conclusions, he said that while research efforts continue it was important to 'make the best of what we already have' and he cautioned that, even when efficacious new tools become available, they will only prove effective if adequate health systems are in place.

In common with the other disease-specific sessions, the presentations on TB were grouped around the three overarching themes with respect to sub-Saharan Africa.

- Clinical research and achievements and findings
- Development of scientific research capacity
- North-South and South-South partnerships for quality improvement research

Developing the TB research agenda through 'brokering' was the subject of the first presentation [TO 01] about the work of the Pan-African Consortium for Evaluation of Anti-tuberculosis Antibiotics (PanACEA) Network. Funding for trials is limited and there is, in particular, an urgent need to conduct more trials to develop shorter TB treatment regimens. An EDCTP expert meeting in 2007 concluded that a brokered call would offer new ways forward and this led to the launch of PanACEA. This capacity-building network encompasses 11 African institutions in six countries, currently with varying levels of capacity, and three European institutions. Activities now under way include the Phase III REMOX randomized clinical trial, the HIGHRIF dose-escalation study, and a Phase II trial involving SQ109. PhD and MSc projects and epidemiological studies are also ongoing. Audience questions followed concerning the nature and duration of drug treatments in the trials, PanACEA's relationship with the Global Alliance, and plans to include new drugs in PanACEA trials.

TB cure rates vary considerably and it is possible that pharmacokinetic (PK) variability may be one of the factors responsible. A Tanzanian study [TO 03], supported by PanACEA, therefore followed the plasma levels of four treatment drugs in 20 patients. Measurements were taken 1, 2, 3, 4, 6, 8, 10 and 24 hours after observed drug intake. Half of the patients had isoniazid peak levels below reference levels. In one third of patients the same was true for rifampicin levels. The researchers' view is that individual variability, spaced food and drug intake and compound stability could all be possible culprits and should be explored in further research. Responding to questions the presenter said that no association with HIV infection had been found. There are no plans at present to conduct research in which either CD4 levels or genetic factors are examined.

Progress in the multicentre RIFAQUIN (moxifloxacin and rifapentine) trial for the treatment of pulmonary TB was then described [TO 02]. The study, which began in 2008, is investigating the role of rifapentine and moxifloxacin in shortening treatment duration; 829 patients have been enrolled. Participating countries are Botswana, South Africa, Zambia and Zimbabwe. In total the researchers have had to deal with 18 different regulatory bodies. Other challenges have included the pausing of the study in Zimbabwe by regulatory authorities, few patients have been recruited in the rural Zambian site, and it has been necessary to add a new site in Botswana. The cost of replacing study drugs, and the number of screening failures have also been problematic. Drug distribution issues have varied between countries. A PK sub-study within RIFAQUIN is sponsored by the Wellcome Trust. Audience questions addressed issues including the primary endpoint (which is based on culture of *Mtb*), the background to the regulatory delays, cases where there were serious adverse effects (these were not associated with rifapentine), and the inclusion of HIV-infected patients.

Should the dose of efavirenz (EFV) given to HIV-infected patients be modified in those individuals who are also receiving rifampicin-based TB treatment? A study [TO 04] in over 800 Ethiopian and Tanzanian patients investigated the pharmacogenetic and PK interactions between the two drugs. Over a period of one year, treatment-naïve HIV patients without TB were compared with TB-HIV co-infected patients. The researchers found there was an effect of rifampicin on EFZ kinetics in early therapy but this had no significant effect in the long term. It was also noted that the effect of rifampicin was CYP2BH6 genotype dependent. CYP2B6 and CD4 response was found to differ between Ethiopians and Tanzanians. The study was considered important because the findings suggest that current guidelines should be changed as there is no need for EFV dosage adjustment during concomitant rifampicin-based TB treatment.

Several of the subsequent presentations concerned the diagnosis of TB. Early diagnosis of pulmonary TB is vital so that treatment may be started and the risk of further transmission reduced, but cases are often missed. Improving the diagnostic yield from sputum samples is

important. A Ghanaian microscopy study [TO 05], involving 257 patients with smear-positive TB, compared sputum samples taken at midnight, early morning or on a 'spot' basis. 10% of spot samples were not productive of sputum, compared with 0% for early morning and 0.5% for midnight samples. The yield from midnight sample was higher than that from early morning samples and much higher than for spot samples. The researchers therefore believe that night samples should be used in operational situations. Points raised in discussion included the need to counsel patients on the need for midnight samples; out-patients can bring samples with them to clinic. There is, however, a need for standardization in the timing of sputum collection.

WHO has recommended that, when HIV-infected people are suspected as having TB but test as smear negative, sputum culture diagnosis should then be conducted. However, the number of samples to be examined has not as yet been specified. A Ugandan study [TO 06] therefore set out to determine how many sputum samples are required for the most 'efficient' diagnosis of TB by culture in smear-negative HIV-infected patients. Analysis of data from the 203 patients in the study led to the conclusion that two is the optimum number of samples. Audience suggestions for further research included the measurement of CD4 levels. The need to lower the contamination rate, which the researchers are already attempting through increasing sodium hydroxide concentration, was also discussed.

There has been much excitement internationally over the development of the Xpert MTB/RIF diagnostic test – an automated polymerase chain reaction (PCR)-based assay. A Kenyan study [TO 07] compared its performance, in the detection of *Mtb* in the sputum of HIV-infected patients, with that achieved by Ziehl-Neelsen microscopy, a technique first developed in the 1880s. The researchers found that the Xpert test more than quadrupled the diagnostic yield. As a result, the new test has the potential to save many lives. Audience questions focused on the risk of *Mtb* contamination (which is low because a closed system is used), whether there were samples that were Xpert-negative but ZN-positive (there were not) and what was regarded as the gold standard diagnostic test (culture).

Good results with Xpert were also reported from South Africa [TO 08], where researchers' concern was the need to minimize TB transmission risks. They used the new test with suspected TB cases that had not undergone a smear microscopy test. The preliminary finding was that Xpert cycle threshold (CT) values correlated (inversely) very well with bacterial load. The results gave 'moderately high' values for smear positivity. There were several questions and comments from the floor. The role of chest X-ray was raised but there are logistical constraints; it is less available than Xpert. Information on specificity and sensitivity was requested; specificity is low but those incorrectly identified as negative by smear were most infectious. The cost of Xpert ($18 per cartridge) was also of concern; the test's cost-effectiveness is currently being analysed. The number of samples that may be tested is limited by module design; some devices have many modules. It is premature to label Xpert as the best measure of bacterial load as it also detects dead bacilli, so the test may be additional to culture, rather than replacing it.

From Guinea-Bissau, the meeting heard a study [TO 09] that found a biomarker (soluble urokinase plasminogen activator receptor (suPAR)) to be a predictor of mortality risk in individuals presumed to be pulmonary TB-negative. Little is known about post-consultation mortality rate in patients who present with TB symptoms but with smear-negative test results. The study found that, amongst 1682 such individuals, mortality rate was three times that of the general population. Values for soluble urokinase plasminogen activator (suPAR) showed a linear relationship with mortality with each 1 mg/ml increase associated with a 27% rise in mortality rate. Measuring suPAR, which is already known to be associated with higher mortality in HIV-infected patients, could therefore be useful in post-discharge monitoring. The study did not measure other potential indicators or record such details as whether patients had diabetes.

The Gambia-based researchers [TO 10] have added to our knowledge of *Mycobacterium africanum*. This organism, which is responsible for a third of The Gambia's TB cases, induces an attenuated host immune response, compared to *Mtb*. The researchers tested the hypothesis that *M. africanum* lineages are deficient in ESAT6 secretion. They

found that *M. africanum* cases are less likely to be ELISPOT positive. Audience members asked whether there were plans to sequence the whole RD1 region (this has in fact been done; the gene affected is outside RD1) and whether there are antigens other than ESAT6 for which secretion is deficient (this is not yet known). The clinical relevance of the finding is unclear (*M. africanum* may or may not be less contagious) but there could be an evolutionary advantage resulting from the organism's longer incubation periods.

Serological tests for TB have so far proved disappointing but a prototype test worthy of further investigation was reported from Norway [TO 11]. The aim of the project is to develop a simple rapid TB screening. The prototype ELISA test involves a combination of five antigens. The antigens were identified as suitable from blood and saliva samples collected in four African and two Asian countries. Used with 2,500 well-defined samples in Ethiopia the serological test was found to have 70% sensitivity and 95% specificity. There are plans to improve sensitivity and to include additional antigens, but even with 70% sensitivity the test may have the capacity to help reduce transmission in the community. The research could also lead to the development of a test that can be used with saliva samples. There were no questions following the presentation owing to time constraints.

From the UK, work was reported aimed at developing a test to measure TB drug efficacy [TO 12]. Such a test would prove valuable in clinical trials of new drugs, and in monitoring rates of cure, failure and relapse in TB treatment. The basis of the test is the detection of early changes in host gene expression that reflect the killing of mycobacteria. The researchers have used a cohort of 300 new TB patients of whom 5% suffered relapse. A predictive accuracy of over 90% was achieved. The biggest changes detected by the test were after only one week of treatment. Different genes are expressed later in treatment during resolution/sterilization phase. Again there were no questions.

In South Africa a study [TO 13] of the close contacts of TB index cases has helped improve our understanding of innate immunity in the lung. Alveolar lavage cells and peripheral blood mononuclear cells (PBMCs) were obtained from 11 close contacts of TB index cases. Five latently infected and four non-infected individuals were used in the analysis and several differences were found between the two groups in terms of cellular pattern, recognition receptor and innate immune signatures. The presentation was well received by the audience and two important points were raised in discussion. Firstly, whether patients involved were healthcare workers; given their continuous exposure to *Mtb*, they are more likely to be 'non-converters'. (There were no health workers amongst the participants.) It was also suggested that vitamin D be investigated, given its known impact of boosting immunity.

The immune response to different *Mtb* strains was studied in Madagascar [TO 14]. Variation was found in IFN-γ responses to different infecting strains, both in acid-fast bacillus smear-positive index cases and their household contacts. 'Modern' *Mtb* strains (such as the Beijing and Central Asian strains) were found to induce weaker immune responses than 'ancient' strains (e.g. East African Indian). This finding may have both therapeutic and diagnostic implications, and could prove to be important in vaccine development. One audience suggestion was that, since the study was conducted in HIV-negative people, it should be repeated in a sample of HIV-infected individuals, given the high prevalence of TB-HIV co-infection in sub-Saharan Africa.

South African research [TO 15] compared the immune responses of 15 patients with extremely-drug-resistant TB (XDR-TB) with those of 15 with drug-sensitive TB and 7 with latent infection. Decreased IFN-γ and increased Cd4+Cd25+Foxp3+regulatory T-cells were found in those with XDR-TB. The findings could be relevant in TB vaccine design, drug development or future diagnostic approaches in the management of XDR-TB. The audience was shaken by the presenter's statistics on XDR-TB levels in South Africa (1,500 cases per year), the cost of treating drug-resistant cases (equivalent to 50% of the annual TB programme budget), and the poor outcomes obtained.

Pleural effusions resulting from TB are common in many countries but pleural TB is difficult to diagnose. In The Gambia [TO 16], biomarkers have been identified that could make possible a highly accurate diagnosis of the condition. Cellular and

soluble components were analyzed from the pleural fluid of 41 patients with pleural effusion, 30 of whom were later found to have TB and 11 not. Biomarkers, absent from the peripheral blood, were identified that were found to be accurate (95% sensitivity and 100% specificity) in diagnosing pleural TB. The findings also suggest that diagnostic tests for TB that rely on the peripheral blood are likely to be inaccurate at this acute stage of the disease. In discussion it was noted that the number of patients was small and the findings would need to be validated in larger studies.

The development of vaccines was the topic of the next few presentations. An overview [TO 17] was given of progress with trials of MVA85A, the most clinically advanced TB candidate vaccine. MVA85A is an attenuated poxvirus that cannot replicate in humans. It has proved to be safe and immunogenic in 15 Phase I and IIa trials held in the Gambia, South Africa, Senegal and UK. These trials have included infants, children, adolescents, adults, latently-infected adults and HIV-infected adults. Two efficacy trials are now under way and more are planned. Trial participants will include infants and HIV-infected adults.

A Phase I trial of the MVA85A vaccine in Senegal was also reported [TO 18]. The safety and immunogenicity of the vaccine was evaluated in 24 HIV-infected volunteers who were in good health, ART-naïve, and had low CD4 levels (>350) and relatively low viral load (<100,000 copies). Despite a few minor local reactions, the vaccine was proved to be safe. A significant immune response was noted seven days after administration. This had declined by day28 but a second dose) of MVA85A was found to enhance the magnitude and durability of the immune response.

The VPM1002 candidate TB vaccine is also undergoing trials. A presentation [TO 19] described this vaccine which is based on the Bacille Calmette-Guérin (BCG) vaccine, the immunogenicity of which has been raised through two modifications. VPM1002 induces multifunctional T-cell subsets thought to play a critical role in protection against tuberculosis. Phase I trials involving 104 healthy participants, stratified for history of BCG vaccination, in Germany and South Africa have shown it to be immunogenic and safe. A Phase II clinical trial involving vaccination of neonates has now been initiated. One key issue debated during questions was the expected cost of VPM1002, should it be proved to be effective; the speaker assured the audience that it would be as cheap as the current BCG.

The AERAS 402 candidate vaccine is intended to boost BCG. A presentation [TO 20] described a Phase IIb double-blind, placebo-controlled trial of this vaccine, in which 96 HIV-negative infants were randomized to receive either two doses of the vaccine or a placebo. There were several instances of adverse events in the infants who received the vaccine but these were attributed to malaria and pneumonia, which are common in the area of the study. The drop-out rate was low and the vaccine proved to be highly acceptable.

The hypothesis that BCG would be more effective if given at six weeks, instead of soon after birth as recommended, was investigated in a Ugandan study [TO 21]. Researchers compared blood samples taken from 44 nine-month-old infants who had received BCG at birth with samples from 40 others of that age who had received the vaccine when they were six weeks old. They found a robust immune response in all the infants. However, birth-vaccinated infants showed a higher frequency of CD4 and CD8 T-cells producing IFN-γ than those who were vaccinated at six weeks. The birth-vaccinated infants also had a higher frequency of BCG-specific CD8 T-cells producing TNF-α. The evidence does not therefore support the researchers' hypothesis. They argue that further research is needed before the hypothesis can be rejected but, without evidence to the contrary, BCG should continue to be given at birth.

Mtb has not been well explored for immune epitopes. *In silico* mapping techniques were used in Botswana [TO 22] to identify proteins with high epitope densities. The researchers also showed that different HLA-DR alleles have different binding affinities for peptides from these proteins. Their findings could help in determining universal epitopes to be used for vaccine design, immunodiagnostics and monitoring.

To make progress in the battle against both TB and HIV, it is essential to improve understanding of the immune interactions of these two diseases. A study in South Africa [TO 23] carried out a detailed functional assessment of the immune response to *Mtb* in HIV-TB co-infected

individuals. These individuals were in the early stages of HIV infection and had CD4 counts of over 500 cells/µl; this criterion was set to avoid confounding with depletion due to immunodeficiency associated with late stages of the disease. The researchers found that HIV infection caused a quantitative defect (*not* qualitative as expected), as measured by cytokines and cytokines mediators. One audience comment was that the CD4 count of the HIV-positive patients was lower than in HIV-uninfected patients and this might have affected the result. The presenter accepted this but stated that the research team had tried to use participants with as high CD4 counts as possible. It was also suggested from the audience that the researchers should consider stratifying or adjusting their findings by level of viral load, to see whether the results differed. This is and other investigations and validations are already planned.

Where do the majority of infections with TB occur – in the household or elsewhere? A presentation [TO 24] described a study in which, by genotyping isolates from patients and their diseased household contacts, the proportion of secondary cases that were acquired in the household could be calculated. The research was conducted within the Tuberculosis Case Contact Study, based at the Medical Research Council in The Gambia, which enrols smear-positive (index) cases and their immediate contacts. From 130 index cases, 41 individual secondary cases were identified amongst their household contacts; of the 41 pairs (index plus secondary) 34 pairs were found to have the same genotype, as established by spoligotyping. 20 of these pairs had similar spoligotyped patterns and mycobacterial interspersed repetitive-unit-variable number tandem-repeat (MIRU-VNTR) typing was conducted with them; nine pairs had the same allele number (suggesting household transmission) but 11 were different. The researchers argue from their findings that the majority of TB transmission occurs outside the household. Such information could help inform policy makers as to whether to isolate index TB cases. However, selected members of the audience raised concerns about the validity of such a conclusion, because of the limited sample size, the limitations of spoligotyping and the fact that some concordant patterns on spoligotyping may have had acquired TB outside of the household (mixed infections). Questions were also asked about the stability of the index and secondary cases, which the researchers agreed was a limitation of the study.

Genotyping techniques were also used in a study from Cameroon [TO 25], which sought to investigate genetic diversity and the drug resistance that is spreading in *Mtb* isolates in this country. Molecular typing and DNA sequencing were both performed on 120 isolates (including both drug-resistant and drug-susceptible strains) obtained from consecutive smear-positive TB patients in a major referral hospital. Analysis of the data suggested that transmission and emergence of drug resistance during treatment might occur simultaneously in Cameroon, emphasizing the importance of early diagnosis and adequate treatment. The study also confirmed the dominance of the 'Cameroon family', which accounted for 65% of the strains identified in the study. This was attributed by the presenter to Cameroon's well functioning national TB control programme. Another group of Cameroonian researchers also set out to increase the amount of epidemiological and molecular data available on TB in this part of Africa [TO 27]. They used isolates from 69 sputum-culture-positive symptomatic TB patients in Cameroon's coastal region and made use of MIRU-VNTR typing and spoligotyping. The former technique was found to have greater resolving power. Analysis showed that 'Ghanaian strains' of *Mtb* were the most common amongst the isolates studied. These strains have become more common perhaps because of migration; previously *M. africanum* was the dominant cause of TB in this area but only one case of this infection was identified in this study.

South African researchers have been investigating whether the techniques of nanomedicine can be used to improve the efficacy of existing TB drugs [TO 26]. The aim is to improve the bioavailability of the drugs, increase their half-life, and reduce toxicity. With improved efficacy, lower dose rates could also be used without reducing efficacy, which might improve patient compliance levels. Two drugs (isoniazid and rifampicin) were nano-encapsulated and then administered to TB-infected mice once per week for four weeks. Bacterial burdens in the spleen and lung were measured and lung pathology performed. The treatment was as effective as daily administration of the drugs in conventional form. Human trials

will it is hoped take place, once analysis of safety/toxicity data from the mice research is complete. The technique could potentially also be applied to drugs for other conditions, including malaria and HIV/AIDS. The presentation met with a very positive response from the audience. Questions were asked as to whether nano-encapsulated medicines were likely to be expensive and inaccessible to the poor. The response was that the research is mainly funded by the South African government which it is hoped would make further investments to ensure that the drugs could be provided free to all who need them, as is the case with current TB treatment in South Africa.

The incidence and clinical significance of non-tuberculous mycobacteria (NTM) has seldom been studied in Africa but was the subject of research reported from Uganda [TO 28]. This large study involved two cohorts 2,500 infants and 5,000 adolescents under active TB surveillance for 12–18 months. Samples from the study participants were investigated; the frequency and characteristics of children with NTM were reviewed. NTM were isolated from 1% of infants (70% of whom were symptomatic) and 5% of adolescents. None of those with NTM were HIV-positive or receiving treatment for TB. No clear clinical significance of NTM emerged from the study but NTM infection may complicate the diagnosis of pulmonary TB. Audience questions included whether treatment was given to NTM-positive participants (it was not) and whether there were any instances of mixed growth (no).

Another Ugandan study [TO 29] sought to increase what is known about the prevalence of TB infection and disease amongst adolescents. As part of the Ugandan TB vaccine trial site preparation project, 5,000 adolescents were given a tuberculosis skin test (TST); 16% of the tests were positive. Positive results were more common amongst: males (1.5 times more likely than in females), those with a BCG scar (1.3 times more likely than other participants), and those with a history of contact with diagnosed TB cases (2.5 times more likely). Rates were highest amongst those who had never been to school. The findings may help inform TB control programmes and contact tracing. Questions focused on the TST threshold chosen (10mm), the lack of an explanation for the higher rate in boys, and whether overcrowding has been investigated as a factor (it had not).

Also as part of the Ugandan TB vaccine trial site preparation project, a sensitization exercise was conducted [TO 30] to provide the study population with background information on the studies, and to respond to concerns identified in an earlier community study. The aim was to increase the level of community acceptance of the research. 180 villages, 138 schools, 14 health facilities and community leaders were targeted within the study area (population 110,000). A number of challenges were encountered, including misconceptions that had arisen and the difficulties in delivering messages close enough to the community. However, the exercise was considered a success: the misconceptions were addressed, there was good community acceptance, and trial staff became familiar with community. Points arising from questions were that each community group was met separately, female community members attended talks but decisions are still made by males in this area, information was provided regarding BCG vaccination.

Jean Paul Assam Assam, Parallel Session Tuberculosis, Wednesday 12 October 2011

Adolescents were the focus of a Kenyan study [TO 31]. This age group is a prime target for new TB vaccines as, at this age, the risk for infected individuals of developing TB disease is known to increase. It is essential therefore that any vaccine trial should have the ability to track and retain an adolescent cohort. The study enrolled 5,004 male and female adolescents, who were followed up every four months for up to two years. The overall retention rate was 79%, other participants being considered lost to follow-up if they did not complete the minimum follow-up time of 12 months. The retention rate declined with age, being highest in 12–14 year-olds (85%) and lowest

in 18 year-olds (60%). Lower rates of retention were found amongst females and those who were not attending school (60%); trials would need to develop retention strategies for these important groups. Audience members expressed surprise that 6% of the participants were not attending school; it was pointed out that enrolment was not school-based and that one consequence was that it was hard to reach those in boarding schools.

Active case finding for TB requires time and resources. Is it sufficient to rely on passive case finding? This question was addressed in a Ugandan study [TO 32] where the two approaches were compared, again focusing on adolescents. For active case finding, the researchers screened 5,000 adolescents on the basis of TB signs and symptoms, with suspected cases then tested by smear and culture. The passive approach involved reviewing nearly 57,000 adolescent patient records from all health units in the study area during the same time period. Eleven TB cases (rate: 220/100,000 population) were detected with the active approach compared with 32 (56/100,000) through passive case finding. Active case finding therefore has the potential to achieve early identification of TB cases that otherwise might have been missed. (It was also noted that the active approach could distinguish between prevalent and incident cases, which was not possible with passive case finding.) This has important implications for trials as well as for TB control programmes. Questions included whether the two groups were comparable (yes, as diagnosis by culture was used in both instances) and whether the health service data were considered reliable (yes).


Sixth EDCTP Forum

4 Research reports: Malaria

KEYNOTE ADDRESS

RECENT ADVANCES IN MALARIA RESEARCH

Professor Robert Sauerwein, St Radboud University Medical Centre, Netherlands

Professor Sauerwein told the audience that the malaria toolbox is much larger now, which should help achieve the target set in Millennium Development Goal MDG6 to halt and reverse the incidence of malaria and other infectious diseases. Major progress has already been made, with nine African countries (and 29 others elsewhere) reporting over 50% falls in case numbers and deaths. The improved accessibility of artemisinin combination therapy (ACT), which was used to treat an estimated 71% of cases in 2010, has played a key role but other malaria tools are also of importance: insecticide treated nets (ITNs) and long-lasting insecticide-treated bednets (LLNs); indoor residual spraying (IRS); intermittent preventive therapy (IPT); rapid diagnostic tests (RDTs); and improved microscopy services.

The eradication of malaria is now on the agenda, although this remains controversial; eradication may be feasible in some locations whereas elimination is the more realistic target for others. Nevertheless, the disease burden is still too high and we know that control gains can be very fragile.

Transmission is the driving force in malaria but it has often been ignored in research. We need, for example, to understand more about the carriers of gametocytes and whether people with low carriage rates are able to transmit malaria.

Professor Sauerwein gave a brief history of artemisinin research from the 1970s to the present, including encouraging findings of its use in injectable form for the treatment of severe cases. However, the appearance of resistance to the drug in Thailand-Cambodia is now of much concern; it is to be hoped that this will be held in check by the Global Plan for Containment and expanded action against counterfeit and falsified drugs, but the development of new treatments is crucial. Most of the new drugs in the global pipeline are artemisinin preparations but there are also some non-ACTs. He described the encouraging results that had been achieved with IPT, including its use in pregnancy (IPTp). The reversal of chloroquine resistance when used in combination with azithromycin remains poorly understood.

Research on the diagnosis of malaria must continue; diagnosis needs to be more defined and brought closer to the care setting. Professor Sauerwein listed the criteria for an optimal diagnostic tool. Loop-mediated isothermal DNA amplification (LAMP) is an important technology that will play a role in diagnostics in elimination programmes. He spoke of the work of the Foundation for Innovative New Diagnostics (FIND), which is focussing on three diagnostic fields: case management, elimination settings and the detection of non-malarial febrile infections.

Summarising the latest position on vaccine research, he said that while the RTS,S vaccine is an important advance, it is only expected to provide around 50% protection; the goal should be over 90% protection, lasting at least two years. Other vaccines are now at trial stage. The use of combined chloroquine prophylaxis and vaccination is also under investigation and results are encouraging. The injection of live sporozoites is another approach receiving attention. Blocking parasite development in the mosquito is also of interest.

An area of great concern (and a threat of which many are unaware) is the spread of resistance to pyrethroid insecticides, used in the treatment of bednets. Mosquito biting behaviour may also now be changing, bringing a risk of transmission at times of the day when nets are not in use. Other approaches to mosquito control are therefore important priorities for research; these include IRS, larviciding and entomopathogenic fungi.

Professor Sauerwein described some of the exciting research taking placed in his own laboratory, before concluding that to maintain and build on what has been achieved in malaria control a high level of funding will have to be continued for a long period.

The presentations on malaria were again grouped around the three themes, in regards to sub-Saharan Africa.

- Clinical research and achievements and findings
- Developing scientific research capacity
- North-South and South-South partnerships for quality improvement research

The first few presentations concerned the evaluation of antimalarial drug treatments. Most notably, three ACTs were compared head-to-head in a large randomized controlled trial (RCT) in 12 sites in 7 countries [MO 01]. Studies such as this one are needed to establish how alternative treatments compare, for example with regard to recurrent infections, in different regions. Over 4,000 children, aged 6–59 months, were randomized for treatment with either amodiaquine-artesunate (ASAQ), dihydroartemisinin-piperaquine (DHAPQ), artemether-lumefantrine (AL) or chlorproguanil-dapsone plus artesunate (CD+A). However, the CD+A arm was abandoned for safety reasons, on the advice of the manufacturers. The children were actively followed up till day 28, at which PCR-adjusted efficacy was calculated and three pair-wise comparisons were made between the treatments. The children were also followed up passively for the next six months, with treatment efficacy assessed at day 63. Overall, all three treatments showed excellent PCR-adjusted efficacy at day 28 (>95%). PCR-unadjusted figures, however, showed that DHAPQ was most efficacious followed by ASAQ and then AL. Day 63 results were similar to those at day 28. The risk of re-infection was significantly lower for DHAPQ, followed by ASAQ and then AL. The researchers concluded that DHAPQ should be deployed on a large scale and that ASAQ was suitable for use in eastern and southern Africa. One issue emerging was that as the malaria burden has reduced in some areas, more time has been required to enrol the specified number of participants. The discussion that followed focused on policy implications regarding which ACT to adopt as first-line treatment. (This will depend on local malaria endemicity.) The three ACTs had very similar efficacy but with a difference in the post-treatment prophylactic effect. In areas with high malaria transmission and high risk of re-infection, DHAPQ and ASAQ would be better that AL, due to the superior post-treatment prophylactic effect.

The experiences of the West African Network for Clinical Studies of Antimalarial Drugs (WANECAM) were then described [MO 02]. WANECAM was established with the participation of four West African countries (Burkina Faso, The Gambia, Guinea and Mali) and four from Europe (France, Germany, Sweden, UK). The objective is to establish state-of-the art clinical trial sites in the West African sub-region; laboratories, researchers, and well-characterized populations are all required to make possible quality clinical trials (Phase I to IV). The programme is also intended to act as a model of what can be achieved in low-resource settings. Achievements so far include a baseline epidemiological study and major steps towards the launch of longitudinal trials in the context of repetitive drug treatments. Highlights of the discussion that followed included the challenges posed by poor infrastructure, leading for example to cold chain problems. Political instability was also a concern in some countries. Difficulties in transferring funds had caused delays. However, with hard work from the dedicated team good progress was being made. (EDCTP's Executive Director highlighted the fact that the presenter of this session was a former EDCTP senior fellow who is now a principal investigator, and that this project displayed commendable capacity development for malaria clinical trials in Africa.)

Anti-retroviral drugs (ARVs) for HIV/AIDS may inhibit or induce liver enzymes that metabolize ACTs; this could lead either to reduced levels of ACTs or to an increased level of ACT toxicity. A number of studies have therefore focused on the treatment of malaria in HIV-infected patients. Co-administration of ACTs and ARVs was the subject of a pharmacokinetic (PK) and safety study in Malawi [MO 03]. In an open-label trial half the adult doses of AL, AS-AQ or DHA-PPQ were administered to otherwise healthy HIV-infected individuals receiving ARVs containing nevirapine (NVP), efavirenz (EFZ) or protease inhibitors (PIs) – six patients in each ARV category. 18 HIV-infected patients not receiving ARVs were used as controls. Participants were followed up for 28 days with blood samples taken at predefined intervals for PK assays. Analysis of the results is now taking place. The discussion involved issues on safety and quality control mechanisms. The presenter stressed that there was no evidence of toxicity. Regarding quality control mechanisms, the trial site had quality assurance systems that

included double checks on drug administration, data and laboratory procedures.

Data were also presented from a cross-over study in Uganda on the PK interactions of efavirenz (EFV) and AL [MO 04]. A marked reduction was found in AL plasma concentrations when co-administered with EFV, which could predispose to antimalarial treatment failure, with risks for resistance. It was recommended that dosage modification of AL should be considered when the two are used together. Further analysis of data from this study is still under way. Additional research is also needed to generate data on the clinical relevance of the interaction between these drugs. The discussion highlighted the absence of enhanced toxicity during ACT-ARV co-administration and the need for additional studies to explore genetic/allelic predisposition of cytochrome P450 (CYP) interactions and the synergistic or antagonistic effects of concomitant therapy.

The setting up of a Phase IV trial of the use of artesunate-mefloquine (ASMQ) for children was then described [MO 05]. This new treatment has been developed by the Fixed-Dose, Artesunate-Based Combination Therapies (FACT) consortium, led by the Drugs for Neglected Diseases initiative (DNDi). The trial involves Burkina Faso, Kenya and Tanzania with input from agencies in France, Luxembourg and Switzerland. The aim is to enrol 940 children who will be followed up for 63 days. ASMQ will be compared with AL. Enrolment began in December 2010. No safety issues have yet been encountered. The discussion mainly involved options for rescue treatment after failed initial ACT. Patients with treatment failure can be switched from one ACT to the other; patients who fail on ASAQ will receive AL and vice versa. However, in Burkina Faso the second-line treatment is quinine. It was noted that there are currently no data and no guidelines on the choice of a second ACT after an initial ACT regimen has failed. Also discussed were the delays in getting ethical approval for multi-centre trials and whether EDCTP should take a more active role in addressing this problem.

A study in Zambia [MO 06] compared two malaria treatments – AL (currently first-line treatment in Zambia) and dihydroartemisinin-piperaquine (DHAPQ). 304 children (6–59 months old) were enrolled and randomized to receive either AL or DHA/PQP. They were followed up for 42 days. No early treatment failure was found in either group. Higher PCR-uncorrected adequate clinical and parasitological response (ACPR) was found in the DHA/PQP group at days 28 and 42, but PCR-corrected figures were similar for both treatments. New infections detected during the follow-up period were more common in the AL group. Except for cough (more common with DHA/PQP) there were no differences between the two groups in the occurrence of adverse events. An audience member inquired why AL was given as crushed tablets when a dispersible formulation for children has been launched; this, however, was not available when the study was conducted in 2005–2006.

A Nigerian study [MO 07] found that malaria imposes a significant burden on HIV-positive women, indicating that malaria control measures are vital in this situation. Malaria parasitaemia was found in 56% of 408 HIV-positive pregnant women booking into clinics at a tertiary hospital, compared with only 5.9% amongst 406 who were HIV-negative. Other findings included lower haematocrit in the HIV-infected women (whether they were parasitaemic or malaria-parasite free), and that the prevalence of parasitaemia amongst HIV-positive women receiving ARV treatment was similar to that in those who were untreated. The researchers urge that HIV-infected pregnant women should be targeted for malaria preventive measures (IPTp, ITNs and IRS). Audience contributions included surprise at this association between malaria and HIV in pregnant women, as data from Malawi have not shown such an association in children. It was also noted with great concern that the researchers had found increased use of artesunate monotherapy amongst women in their study. (Such therapy is strongly discouraged because it is likely to increase the likelihood of the development of artemisinin resistance.) It was also interesting that cotrimoxazole prophylaxis was not associated with malaria protection in pregnant mothers, but this could be a result of the small sample size.

A Burkina Faso study [MO 08] concluded that both health-facility and community approaches might be needed to maximize the impact of intermittent preventive therapy for pregnant women (IPTp). At present, in many African coun-

tries, ITPp is only delivered to women attending antenatal clinics (ANCs), which may not bring this important intervention to all of those who need it. In an open randomized, controlled trial, using sulfadoxone-pyrimethamine (IPTp-SP), the researchers investigated three delivery modes: passive health centre services (control), extended delivery outreach services, and community-based distribution. Clinical and biological data were collected at the start and end of the trial. IPTp delivery by community health workers led to better coverage (33%) than health centre based delivery (24%) but the rates are in both cases disappointing. Compliance was found to be higher in the control group. Parasitaemia and the prevalence of anaemia were also lower in this group. Audience members noted that many pregnant women do not attend ANCs and those who do often fail to comply with drugs prescribed there; perhaps better health education would improve this situation. Concerns were also expressed as to the sustainability of community-based IPTp delivery.

Children treated for severe malaria anaemia are known to be at high risk of morbidity and mortality following their discharge from hospital. In an RCT in Malawi [MO 09], 1402 children (age 4–59 months) were randomized to receive either a single dose of AL at discharge (control group) or one dose at discharge followed by doses one and two months later (IPTd group). The children were followed up for six months and the incidence recorded of death, severe anaemia and severe malaria. Amongst those children who were HIV-negative and under three years of age, death, severe anaemia and severe malaria were 32% lower in the IPTd group. Uncomplicated malaria was 25% lower. These reductions are evidence in favour of implementing IPTd as part of malaria control activities. The discussion that followed the presentation dealt with several issues: the need for more data on the impact of the intervention on haemoglobin recovery, the sustainability of AL use as prophylaxis especially in centres with inadequate drugs, concerns of the risk of resistance when AL is used for prophylaxis, and the need to also protect children with interventions other than drugs.

It is currently recommended that, when artesunate is used to treat severe malaria in children, five doses should be given intravenously. However, there is a need to develop a simplified regimen. A collaborative study involving the Severe Malaria in African Children (SMAC) network reported a Phase II trial [MO 10] that compared the conventional approach with a three-dose regimen. Patients were aged 6–72 months and were hospitalized with *P. falciparum* (*Pf*). All received the same total dose of artesunate (12 mg/kg). The proportion who cleared at least 99% of their parasitaemia was the primary endpoint; other efficacy, safety and PK endpoints were also included. The primary endpoint was achieved by 85% of children on the conventional therapy and 78% in the three-dose group. Further research is planned that will consider dose optimization and also the use of the intramuscular route for artesunate administration. Some audience members wondered whether the cost of the study was justified by the aim of reducing therapy by just two doses, but the research will also yield important data on the PK and pharmacodynamics of artesunate. Other studies addressing the issue have used mortality as the primary endpoint but that requires much larger numbers of participants.

Children with life-threatening infections, including malaria, often go into shock and it is common to give such children fluid resuscitation. The effectiveness of this had not been established but has now been investigated [MO 11] in the Fluid Expansion as Supportive Therapy (FEAST) trial which took place in Kenya, Tanzania and Uganda. 3,141 children aged over 60 days with severe febrile illness and impaired perfusion were randomized to receive albumin or saline boluses or no boluses (control). 48-hour mortality in the three groups was, respectively, 10.6%, 10.5% and 7.3%. Mortality patterns were consistent across centres and subgroups: malaria, coma, sepsis, acidosis, severe anaemia and shock severity. The 3.3% increase in absolute risk resulting from albumin or saline bolus administration means that this procedure cannot be recommended in non-hypotensive children in resource-limited settings. The study also raises wider concerns about fluid administration in children elsewhere.

Blackwater fever is considered a rare complication of malaria but this serious condition has been seen in many children in Uganda's Mbale subregion. A presentation [MO 12] outlined a descriptive pilot study involving five children presenting with the condition. Their clinical features were outlined. All had a positive blood smear for

malaria parasites; there was no known toxic effect due to drugs. They were treated with quinine and their vital and clinical signs gradually stabilized leading to a good outcome. A larger study is now under way. An audience question was whether any association had been found with G6PD deficiency, but this had not been tested for in the pilot study.

The studies next presented [MO 13 and MO 14] are part of the Malaria Vectored Vaccine Consortium (MVVC): 'Integrating capacity building and networking in the design and conduct of Phase I and II clinical trials of viral-vectored candidate malaria vaccines in East and West African children and infants'. This project arose from an EDCTP call made in 2008. EDCTP funding of € 6,500,000, member state cofunding and third-party contributions provided a total budget of approximately € 9.5M. The project commenced officially in December 2009. The two main objectives of MVVC are: (i) to demonstrate the safety and immunogenicity of an adenoviral vector and modified vaccinia Ankara virus (MVA) prime-boost regime encoding malaria antigens, in adults and young children in sub-Saharan Africa; and (ii) to assess the efficacy, safety, and immunogenicity of this new prime-boost regimen in protection against clinical malaria in 5–17 month-old children. Secondary objectives include: the development of clinical trial capabilities, infrastructure and human resources that would ensure the sustainability of the clinical trial sites after the end of the project; the development of partners in the consortium into a well established network for further research; and the establishment of relationships with existing like-minded networks.

The Kenyan study [MO 13] involved 30 adult male participants, who received either a single low or single high dose of ChAd63 ME-TRAP vaccine intramuscularly (IM) as a prime and a single MVA ME-TRAP boost, administered either IM or intradermally (ID). There were three main objectives: to assess safety and reactogenicity of the vaccine regimen, to evaluate its immunogenicity, and to compare the reactogenicity and immunogenicity of intra-muscular and intra-dermal MVA ME-TRAP. The regimen was found to be safe and highly immunogenic for induction of IFN-γ T-cell responses in adult Kenyan men using either ID or IM MVA administration, but due to increased reactogenicity with the ID route the IM route will be used for future trials. There was a question on T-cells responses at the beginning of the trial; these were very low. Another query concerned the pre-existing level of adenovirus antibodies level at the in the community; a high level of antibodies can damage a potential vaccine and there has been research elsewhere on this point with further studies planned. There was also a discussion as to whether it would become possible for HIV and malaria vaccines to be combined.

The Gambian viral vector study [MO 14] also used ADCh63 ME-TRAP prime and MVA ME-TRAP boost. 16 consenting healthy adults were allocated into high or low-dose groups. In addition 36 children aged 2–6 years were randomized into vaccine and control groups. Safety was determined by comparing adverse events, reactogenicity, biochemical and haematological data in high and low-dose groups in the adult study, and between vaccine and control arms in the paediatric study. Immunogenicity was measured by IFN-γ ELISpot and flow cytometry. The objectives were to assess safety and immunogenicity and to compare the immunogenicity of low and high doses in children. The mean haemoglobin, white blood cell count, alanine transaminase and creatinine (at pre- and post-vaccination visits) were within acceptable ranges in both adults and children. Adverse events included pain, swelling and itching at injection site, headache, malaise, nausea and arthralgia. In the paediatric study, low-grade fever, reduced oral intake and reduced activities were reported. In the adult study, the vaccines were safe and immunogenic at high doses. It was concluded that the vaccine regimens were safe and immunogenic in semi-immune Gambian adults and children. Issues arising during the discussion included the following: the T-cell responses were against ME-TRAP (probably against all six epitopes); the study was not powered for efficacy (an efficacy study will follow later; a Phase IIb study is planned but the protocol has not yet been developed).

Researchers working in Ghana and Burkina Faso have identified two antigens as potential candidate vaccines in a multisite Phase II study [MO 15] that is part of the Afro-Immuno Assay

(AIA) project.[8] Standardized ELISA and statistical methods were used to assess isotypes and IgG subclass levels against GLURP R2, MSP1-block and 2 hybrid and AS202, in relation to protection from clinical malaria. Data from Burkina Faso supported the vaccine potential of MSP1-block 2 hybrid but data from Ghana did not. Both studies failed to support the potential of AS202.11 in reducing incidence of clinical malaria, but both confirmed the potential of cytophilic subclass (IgG3) against GLURP-R2. Antibody levels to the malaria peptide AS202.11 were not associated with the risk of malaria in the study sites. Amongst the differences between the two studies was the finding that IgM levels to MSP1-block 2 hybrid were associated with reduced risk to malaria in Burkinabe but not Ghanaian children. There was however evidence of GLURP R2 and MSP1-block2 antigens as potential malaria vaccine candidates. Discordant results may be due to differences in malaria transmission and genetic background of the population studied. The analyses presented did not include old antigens tested in previous studies. In answer to a question, the presenter said there was as yet no explanation for the poor results obtained with AS202; it had not been possible to assess IgG sub-classes as the responses were generally low, so total IgG responses only were used.

The GMZ2 malaria candidate vaccine (a fusion protein of *Pf* GLURP-R0 and the c-terminal part of *Pf* MSP3 expressed in the Lactococcus system) was the subject of several presentations. It is the second most advanced vaccine against malaria. A novel formulation has been established by Danish researchers [MO 16]. They tested sera from three European and African Phase I clinical trials on GMZ2 in Al(OH)3, using xMAP technology in adults and children from Gabon. New adjuvant formulations were also screened in mice.

Comparative analysis of the serum samples found that immunizations elicited anti-GMZ2 IgG antibody levels in malaria-exposed children comparable to those elicited in non-exposed and exposed adults. Thus, a pre-existing IgG response against GLURP and MSP3 does not prevent or reduce the vaccine response. Epitope mapping studies demonstrated that peptides containing the P3 epitope were strongly recognized by all groups. The current adjuvant formulation cannot elicit IgG responses that exceed those found in exposed individuals, hence the screening of the new formulations in mice. An oil-in-water formulation supplemented with the toll receptor agonist GLA (MPL analogue) was found to elicit a strong antibody response predominantly consisting of cytophilic IgG2a and IgG2b mouse antibodies. This formulation also induced strong B-cell memory. The main conclusion was that the novel formulation of GMZ2 is superior to the previous formulation with Al(OH)3. In discussion it was noted that these are recent results and time is needed to evaluate the data more closely; for example the response of IgG subclasses requires detailed study.

Experience of use of the vaccine in a multi-centre trial by the GMZ2 Consortium was then shared with the meeting [MO 17]. Funded by EDCTP, the consortium was set up, with six African and two European partners, to foster capacity in African sites through the conduct of GMZ2 malaria vaccine trials and networking. The consortium has four clinical trial sites, which vary in their level of experience and capacity. As implementing trials is the best way to acquire experience, a strategy was agreed upon whereby experienced sites mentor upcoming sites. Joint review of trial applications is the current trend for multicentre trials in Africa; it is efficient and allows for further development of African regulatory authorities. However, joint review was not possible in this project and this led to delays. Expenditure on capital equipment took place early in the project. In one of the sites the trial could not be initiated due to a decline in malaria. Other challenges included, financial management, communication and reporting issues, delay in regulatory approval and harmonization of data. To ensure successful clinical trials in a consortium, issues such as planning for trial approval, timely expenditure and mentorship for younger sites need to be addressed. The audience then participated in a discussion of the progress, challenges and lessons learned.

The development of sites for GMZ2 vaccine testing in Uganda was also described [MO 18]. Investigators conducted capacity building activities

8 AIA includes African institutions and Northern partners and was initiated to standardize immunological assays in order to: validate promising malaria vaccine candidate antigens in immuno-epidemiological studies, assess immunogenicity in clinical trials and provide essential baseline data to allow comparisons between trials, and enhance quality assured laboratory capacity and capability.

including a baseline study designed to characterize one site, to enhance community awareness about malaria and assess the incidence of malaria in local children. A team of young professionals has also been established and trained. The site underwent several site assessment and audit visits. Investigators undertook training in standard operating procedures for clinical, community, data management and laboratory procedures. Some staff travelled abroad to attend workshops or gain hands-on skills and several staff members registered for long-term training. There is now a strong team consisting of senior scientists, a senior paediatrician, an internist, several other physicians, pharmacists, nurses, well trained laboratory and data personnel, and more than 20 trained field workers. Malaria patterns at baseline have been assessed and malaria risk factors determined. Other work has included genotyping of the *P. falciparum* chloroquine resistance transporter (*Pf* CRT), parasite density determination, blood chemistry and haematology etc. Questions included how many people had double mutations (10), and what strategies were in place to retain MSc and PhD trainees; all have positions at local universities and the project is seeking funding to support them.

From a proposed GMZ2 trial site Burkina Faso, preliminary results were reported from a prospective study [MO 19] of the incidence of clinical malaria in children aged 6–60 months. One aim was to pilot the surveillance system to be used in the trial of the malaria vaccine candidate. Two cohorts of children were followed up during the high malaria transmission season. In an active detection cohort (ADC), field workers visited 513 children twice a week to document occurrence of malaria episodes. In the passive detection cohort (PDC), the caregivers of 597 children were encouraged to attend the nearest health facility, should the child feel sick. In both cohorts, a malaria smear was obtained when there was fever. Using the most stringent case definition for a malaria episode, 122 episodes were recorded in the PC and 147 in the ADC. The cumulative incidence of episodes was 24.7 in the PDC vs 26.5 in the ADC. The researchers concluded that either method (active or passive) could be used with confidence to capture the maximum data required for efficacy analysis. Questions focused on details within the study protocol and it was asked why malaria rates were so high in Burkina Faso when there has been a decrease in West Africa as a whole; the lack of national programmes for ITN distribution and RDT implementation could be a factor. It was also recommended that the researchers should consider doing time-interval analysis.

A baseline epidemiological study [MO 20] was also conducted in preparation for a GMZ2 trial in The Gambia, where malaria incidence is known to have fallen in recent years. PDC and ADC cohorts of children aged 3–84 months were followed throughout the malaria season. The mothers/guardians of the 1328 children in the PDC cohort were encouraged to take their child to the health centre closest to their home at any time after enrolment if the child became unwell. The 353 children in the ADC cohort were visited by trained field workers twice a week. In both cohorts, a malaria smear was obtained whenever fever or history of recent fever was present. 18 first or only clinical episodes of malaria were recorded in the PDC cohort (incidence 0.1 per 1,000 child days at risk) and 10 in the ADC cohort (incidence 0.3 per 1,000 child days at risk). The reduction in the incidence of malaria in The Gambia has been dramatic and a vaccine trial in the study area would require large sample sizes. In the discussion it was noted how important such information is; changes have had to be made to plans for trials elsewhere because of the decline in case numbers. One approach might be to include older children in trials; in The Gambia, malaria incidence is now higher in 6–10 year-olds than in their in younger siblings. So far, the fall in malaria cases has not led to any cuts in research funding.

A Phase Ib trial of GMZ2 in 1–5 year old Gabonese children was reported [MO 21], again in a target population for future vaccine efficacy trials. The primary objective was to assess safety, tolerability and reactogenicity of the candidate vaccine; the secondary objective was to evaluate the humoral immune response. 30 children were randomized to receive 3 doses of either 30µg, 100µg of GMZ2, or rabies vaccine. All participants were followed up for one year. Both vaccine doses were well tolerated and induced antibodies and memory B cells against GMZ2 as well as its antigenic constituents MSP3 and GLURP. After three doses of vaccine, the geometric mean concentration of antibodies to GMZ2 was 19-fold higher in the 30µg GMZ2 group than in the rabies vaccine

controls. Both doses of intramuscular GMZ2 were therefore concluded to be immunogenic, and were well tolerated. This confirms previous findings in naïve and malaria-exposed adults and supports further clinical development of GMZ2. Points emerging during the discussion were that immunogenicity at one year was observed to be low, and that future studies will a 100µg dose because of the better MSP3 response. Only total IgG levels were assessed and no functional analyses have been done so far.

A study [MO 22] from Portugal investigated the potential of new diagnostic tests based on detection of haemozoin. Flow cytometery was used to measure haemozoin from *P. falciparum* cultures and from rodents infected with *P. berghei*. Using rodent blood only 65% of GFP-positive parasites showed the presence of haemozoin, while in non-synchronized *P. falciparum* cultures only 16%-23.5% were positive by depolarization. In a synchronized *P. falciparum* culture (1.5% parasitaemia, ringworms) only 2% of all parasites showed depolarization. The results were considered to have confirmed that this new approach to diagnosis has some potential. However, at best, 60–70% of parasites could be detected. Insufficient amounts of haemozoin may lead to false negatives and 98% of a population of immature parasites were not detected. Questions focused on what uses such a test might have after further development, for example whether it might be useful as quantitative test or in differentiating *P. falciparum* from other species.

A Nigerian [MO 23] study combined clinical studies with essential molecular parasitology, epidemiology and genomics analysis of fresh *P. falciparum* samples. Novel biomarkers were identified (single nucleotide polymorphisms and copy number variation of genes) that could potentially be used in monitoring reduces susceptibility/resistance to artemisinin derivatives or partner drugs. The investigators suggest that their findings introduce the possibility of developing high-throughput chips that can be used to diagnose drug resistant malaria in the field. Their study has in addition established an assay to detect malaria parasites from saliva samples, providing a reliable non-invasive alternative method of parasite detection. It was also noted that a novel *Pf* CRT haplotype is emerging in Nigeria, which may be associated with amodiaquine resistance.

A Kenya–UK study [MO 24] based on a meta-analysis of data from an online database (the Malaria in Pregnancy Library) concluded that pregnant mothers in low-transmission settings are more likely to present with malaria symptoms than those from medium and high-transmission settings. The study highlighted that passive case detection detects between 20–40% of cases and suggested that alternative approaches may be needed to optimize detection of all cases. In the discussion, the justification for the arbitrary cut off points applied when defining low, medium and high transmission settings was questioned. The presenter clarified that the cut-offs were applied to allow comparison between these and other published studies, and that the definition of high, medium and low transmission was based on Malaria Atlas project (MAP) models of prevalence data in children. Again, the justification of using prevalence data in children to estimate prevalence in pregnant women was questioned. The author clarified that further analysis could be explored.

Sulfadoxine-pyrimethamine (SP) is recommended for use in IPTp. However, based on evidence of an increasing prevalence of dhfr gene triple mutations, a Nigerian study [MO 25] concluded that SP may be losing its efficacy. The researchers used thick and thin blood films confirmed by PCR for malaria parasite detection in samples from 200 women, and a questionnaire was used to collect data on their use of antimalarials. The study also found that the women commonly used non-recommended drugs (e.g. chloroquine, dihydroartemisinin, pyrimethamine), and very few used bednets. In the discussion, it was advised that caution should be applied when interpreting the findings because dhfr gene mutation alone (which is a marker of the pyrimethamine component) is not enough to predict SP failure, and dhps gene mutations (which are linked with the sulfadoxine component) should also be considered. Further it was recommended that a better approach to determine the usefulness of SP for IPTp would be to assess the correlation between SP mutations and pregnancy outcomes such as low birth weight, anaemia in pregnancy and other pregnancy related morbidities. Clinical trials to address this question were recommended.

The need for benchmarking during clinical trial implementation was highlighted in the next presentation [MO 26]. Benchmarking can identify

implementation differences between sites, export best practices from sites that are performing better, and optimize study design and methodologies in future studies. Two multisite IPTp clinical trials are currently under way in five sub-Saharan countries and, with a view to benchmarking, an on-site evaluation is currently being carried out by the trial management team, firstly to identify best practices for implementation across all sites and secondly to assess the impact of the trials on health service delivery training, community involvement and on infrastructure upgrades. In the discussion, it was highlighted that benchmarking is different from standardization of study procedures, and is a necessary ingredient to support the smooth integration of clinical trials with routine health services at trial sites. In further discussion it was stated that implementation of IPTp should be re-evaluated; it was initially recommended for areas with stable transmission but many endemic sites are now witnessing an epidemiological transition, we need to evaluate at what point we should shift from IPTp to screening and treating.

The impact of ACTs on gametocyte infectivity is unclear. A randomized trial [MO 27] in Mali therefore evaluated the impact of three ACTs (ASAQ, AL, AS-SP)) on gametocyte infectivity to mosquitoes. Gametocytes carriage was assessed by microscopy after treatment and whenever gametocytes were found, starved mosquitoes were direct fed and the presence of oocysts subsequently determined eight days post-feeding. The findings demonstrated that AL and ASAQ significantly increased gametocyte infectivity to mosquitoes while AS-SP did not. The study concluded that the impact of ACT on gametocyte infectivity (and thus transmission of malaria) may vary from one ACT to another, and highlighted that these findings could have important implications for the wide deployment of ACTs in Africa. In the discussion session, the blinding of microscopists involved in the detection of oocysts was questioned; the presenter clarified that there was no proper blinding measures embedded in the study protocol, but he was confident that laboratory personnel detecting oocysts were not aware of treatment allocation. It was also highlighted that data on the proportion of gametocyte positive patients in each arm would be important to consider when interpreting the findings. The authors said data on proportion of gametocyte positives were available elsewhere although not presented here.

Asymptomatic carriers (ACs) are the reservoir of infection in malaria; modelling studies show that treatment of ACs could reduce transmission. A proof of concept study [MO 28] in Burkina Faso is evaluating the impact of treating ACs on the number of symptomatic malaria episodes in the community. In this 18-cluster RCT, all age groups in the intervention arm are screened with rapid diagnostic tests for the presence of malaria parasites during the dry season; those found positive are treated with AL. The number of symptomatic malaria episodes is then assessed in the wet season. Follow-up is over a 12-month period. In the discussion, the issue of adherence to AL in asymptomatic carriers was raised. As RDTs do not detect gametocytes it was not clear how the impact of the intervention on malaria transmission would be assessed; the presenter clarified that blood slides were also collected and PCR samples would be collected later for PCR estimation of gametocyte prevalence. It was also argued that, while mass screening and treatment could work if the timing is right, it could result in the development of resistance to artemisinin derivatives. The presenter argued that, if the concept can be shown to work, the fear of drug resistance might be unwarranted as we could eliminate the parasite before resistance emerges.

Presentation at Parallel Session Malaria on Wednesday 12 October 2011

Malaria infection is known to cause a transient increase in HIV viral load and to decrease CD4 count; it may therefore accelerate HIV disease progression. A Zambian trial [MO 29] sought to

determine whether mefloquine (MQ) prophylaxis had an impact on progression towards AIDS in HIV-infected patients. Only patients still immune competent, semi-immune for malaria and with high CD4 count were eligible for inclusion in the study. 149 MQ-treated and 149 controls were followed up (mean duration 16 months) and their CD4 counts and haemoglobin measured. It was concluded that MQ prophylaxis had no impact on progression towards AIDS. It was noted that the study might be considered underpowered; malaria transmission decreased during the period of the study. A question was raised in discussion regarding adherence to mefloquine in the study subjects considering its well known side effects; the presenter said no significant safety issues arose during the study.

Clinical laboratories in Africa face many challenges and this often adversely impacts on the quality of their services. Quality is important if the laboratories are to support clinical trials. Researchers in Kenya [MO 30] have developed an 80-question survey form and established a web-based system for the assessment of African laboratories. All 40 of the laboratories targeted so far are 'model' clinical laboratories that have previously been involved in clinical trials; 37 responses have been received. From their study of these responses the researchers concluded that there is a positive trend in quality levels in African laboratories. The application of quality indicators is feasible and should be developed further. Model practices should be cascaded to other laboratories. During the discussion, the study methodology was questioned; self-reporting is likely to be associated with high positive response rates. The cadre of personnel (laboratory managers or quality managers) who responded could also have skewed the reports.

Another study [MO 31], this time from Nigeria, also focused on quality management in clinical laboratories. The aim was to highlight the strengths and the gaps existing in the country's laboratories. A random selection was made of laboratories across Nigeria and a questionnaire was administered to 106 of the 111 that agreed to take part (69% public, 31% private). Overall, good results were reported from a good-practice checklist. 35% of staff were qualified medical laboratory scientists. Only a minority of laboratories had preventive maintenance agreements or internet access. Most laboratories were not registered for proficiency testing in the diagnosis of HIV (67%), TB (79%) or malaria (82%). The lack of external quality assurance, attributed largely to its high cost, was also a concern; laboratories unregistered for quality assurance expressed an interest in enrolling in an appropriate scheme. During the discussion, collaboration with the newly formed African Society for Laboratory Medicine (ASLM) was suggested. The presenter informed the audience some funding had been secured and an initiative to train laboratories about quality management systems was now underway, but sustainability was an issue; it was hoped that EDCTP would in future consider supporting such activities. 23 laboratories were already being prepared for WHO accreditation in consultation with ASLM.

The final presentation [MO 32] was a description of an initiative, Global Health Trials that seeks to use digital technology to support and enhance clinical trials in resource-limited settings. It is described as, 'a free open-access platform where anyone working on trials not only can access guidance, tools and resources but also share their knowledge, views and experiences'. Launched in 2010, the initiative attracted over 1,000 members from 56 developing countries within its first year. In the discussion, concerns were raised about the security of the website; the presenter said that they had used the best security technology and did not consider themselves as target as data on the site are not sensitive. The issue of sustainability was also raised; the presenter clarified that they were confident that they would be able to sustain the initiative on donor funding at least for the next five years. Beyond this, there were possible options to make the initiative self-funding (e.g. by introducing subscription fees for users in developed countries or commercial advertising).

Participants in the malaria sessions considered them to be highly interactive with good questions and comments from the floor.

5 Capacity development, networking and other cross-cutting issues

This chapter summarizes the presentations made at the Forum by EDCTP partner organisations. It also deals with presentations and discussions in the cross-cutting, i.e. the not disease specific sessions.

The Netherlands-African partnership for capacity development and clinical interventions against poverty-related diseases (NACCAP)

Tuesday morning's parallel session on cross-cutting topics began with a summary of the aims and activities of NACCAP, presented by Dr Eva Rijkers. NACCAP, funded by the Dutch government, is an EDCTP member state programme with a close connection to EDCTP. It was launched in 2003 with the following goals: contributing to the development of clinical interventions, strengthening research capacity through existing African–European research partnerships, and creating African owned research institutes. It is a demand-driven programme that addresses African priorities. It is envisaged that, when the NACCAP programme concludes, its activities will be integrated into EDCTP's Networks of Excellence (NoEs).

Brief presentations were then made describing four NACCAP-funded research programmes. The College of Medicine, Malawi-Amsterdam-Liverpool (CoMAL) partnership for research capacity development helps train Malawians in basic research. The intake cohort has increased from 15 to 90 per year. One major success is the funding of four PhD students, who have all returned to Malawi after gaining their qualifications. CoMAL also manages four EDCTP-funded projects as spin off activities.

The Infectious diseases Network for Treatment and Research in Africa (INTERACT) is a partnership involving Rwanda and Uganda. It aims to build sustainable, multi-disciplinary capacity to perform trials and public health interventions. Many courses and workshops are run. Improving patient care is a priority. Trials address issues such as ARV treatment for adults and children, HIV drug resistance, and malaria in pregnancy. The Affordable Resistance Test for Africa (ART-A) project is a public-private partnership that aims to address the present lack of tests for monitoring HIV viral load and drug resistance that are suitable for use in resource-limited settings. New tests are needed that are affordable and can be used where laboratory facilities and the cold chain are poor. Activities conducted so far include training, capacity building and writing a book about intellectual property in Africa.

The African Poverty-Related Infection Oriented Initiative (APRIORI) is supporting a number of initiatives in Tanzania. Through this grant, the Kilimanjaro Clinical Research Institute was created. Research includes the Phase I and Phase II testing of malaria vaccines and of drug regimens to shorten TB treatment. Capacity building and the establishment of a trial centre are also supported.

The presentations were followed by a panel discussion and question-and-answer period. The issues raised ranged, from how to gain access to the training courses described, to questions exploring the types of partnerships established in the development of the training centres and programmes.

ESSENCE

The cross-cutting parallel session then heard a presentation from Professor Hannah Akuffo on the ESSENCE project (Enhancing Support for Strengthening the Effectiveness of National Capacity Efforts). ESSENCE aims to harmonize efforts amongst funders, to encourage them to work together in planning, monitoring and evaluating the framework for research capacity strengthening.

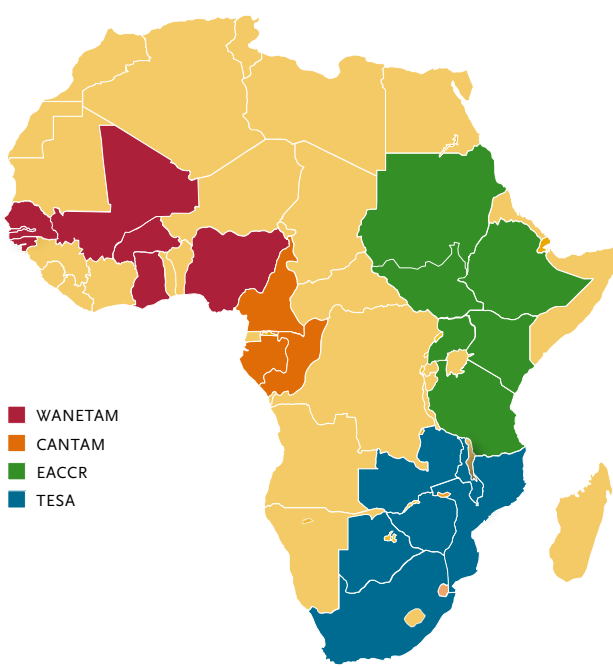
ESSENCE is not a funding agency but a platform that provides an evaluation framework for clinical research that brings together research funders, scientists, philanthropists and others. Different projects often have similar objectives but outcomes are measured and reported differently, hence the need for harmonization.

Harmonization is also required in such research management areas as costing and monitoring and evaluation. ESSENCE will assist institutions to evaluate their capacity building efforts. It seeks to avoid situations where funders tell institutions what to do.

The EDCTP Networks of Excellence

In the afternoon, the cross-cutting session moved on to consider EDCTP's Networks of Excellence (NoEs). There are four NoEs:

- The East Africa Consortium for Clinical Research (EACCR) strengthens clinical trial sites in Eastern Africa
- The West Africa Network of Excellence for TB, AIDS and Malaria (WANETAM) builds capacity to prepare West African sites for clinical trials on HIV, TB and malaria
- The Central African Network on TB, HIV/AIDS and Malaria (CANTAM) joins institutions involved in clinical trials in central Africa, the continent's least developed sub-region in this regard
- The Trials of Excellence for Southern Africa (TESA) Network focuses on the Southern African region. It started in November 2009.



EDCTP Networks of Excellence

The achievements of the NoEs so far, and the challenges that lie ahead, were described to the meeting in brief presentations from each of the Networks. EACCR is large, with 34 institutions in Africa and six in Northern countries. Operations began in May 2009. Training has been a focus; EACCR has supported 21 MSc students and four EDCTP fellowships. It brings together institutions with clinical trial centres and 'weak institutions', to share knowledge and experience. 'Sister institutions' that have previously not conducted trials have also been given training.

WANETAM is smaller with 14 institutions in seven countries, none of them as yet in the North. Operations began in July 2009. Disease-specific and cross-cutting training has been undertaken, with topics including ethics, data management and analysis, good clinical and laboratory practices. Laboratory infrastructure is being upgraded throughout the network. A web-based platform has been established.

CANTAM began its activities in December 2008. There are seven institutions in three countries. Activities planned include establishment of a training platform, upgrading infrastructure, strengthening local collaborations and raising local funds. Five publications have been produced. The intention is to collaborate closely with national programmes and policy makers for sustainability purposes.

TESA has ten partner sites in seven countries. The decision was taken to adopt a pragmatic strategy, with each site defining its needs in terms of capacity development. The focus has been on short courses (good practices, ethics, data analysis, and disease specific topics) and 492 people have been trained so far. Long-term fellowships to support MA and PhD students are being developed. The acquisition of IT and laboratory equipment has been supported, as these are often not funded by standard research grants.

As well as the differences in size, the networks vary in their aims and mode of operation. They have encountered different problems, for example problems due to language differences vary between the regions. The presenters all stressed their network's concerns as to how sustainability might best be achieved.

The NoEs session involved considerable discussion with input from a response panel and the audience. A great many comments were made. These included:

- It is challenging to progress well in both the two realms (research and training/career development)
- It is vital to monitor successes and progress in capacity building and learn lessons
- The need for sustainability must never be forgotten
- Future activities should map capacities to maximize sharing between networks
- The ownership of data is an important issue and requires careful thought
- We need to look differently at how support is accepted and shaped.

Questions were then asked on a several issues: how to evaluate networks, how to maintain the networks beyond the grant period, and the value of networking. Nevertheless, despite the concerns expressed, it was universally agreed that the NoEs are a worthwhile and important part of EDCTP's strategy; they deserve further development.

Conclusions on the NACCAP and NoE sessions

Dr Andrew Kitua, as one of the day's co-chairs, gave a summary of the sessions so far, incorporating his own reflections and those of other participants.

- There had been rich discussions. There are major similarities between the activities of NACCAP and EDCTP. Both organisations aim to build capacity, whether it is individual, institutional, national or regional
- Career-path building within institutions and environments is crucial. The challenge of managing time between research and clinical work has been noted and we must consider how to streamline activities to ensure that there is interplay between these two realms
- Partnerships take time. Engagement does not just happen; it depends on transparency, discussions and dialogue between partners. Partners should know each other's needs and expectations, and what each brings to the table. Creating chemistry in partnerships is a challenge and takes time to build
- Sustainability is perhaps the greatest challenge – what happens after 2012? Fortunately, most of the NACCAP and EDCTP centres have shown that they are able to bring in other funding. To ensure that we are able to continue moving forward, efforts to gather further support must continue
- It is good to see that what have been called the 'less endowed partners' are making progress. They can become equal partners, with the opportunity to share both their burden and the fruits of their labour.

Partner presentations

On Wednesday morning, the third plenary session heard short presentations on the work of the following 12 global health organisations that are partners of EDCTP.

- International AIDS Vaccine Initiative (IAVI): Jean-Louis Excler described the activities of the collaborative network in Africa. One of its links with EDCTP is through the support it is providing for the Uganda Virus Research Institute (UVRI)'s new study of fishing communities in Uganda and Malawi
- UNITAID: Ambachew Yohannes gave an account of the innovative ways in which UNITAID raises funding for health and the support it provides to many organizations, including EDCTP
- The Bill & Melinda Gates Foundation: Siobhan Malone focused on the Foundation's approach to strengthening research partnerships. The foundation funds 15 product development partnerships (PDPs) that specialize in different diseases and modalities. It too emphasizes the necessity to build and strengthen partnerships to achieve better health
- ESSENCE: Garry Aslanyan of WHO spoke on this initiative (already described above) focusing on how ESSENCE seeks to avoid fragmentation of efforts. EDCTP is one of its 14 current members

- Medicines for Malaria Venture: Stephan Duparc spoke on the theme of partnering to develop the next generation of medicines to combat malaria. Past and current collaborations with EDCTP include two studies in which four ACTs are compared. A number of other possible collaborations are also now under discussion
- Aeras: Vicky Cárdenas outlined how EDCTP and Aeras are working together to support TB vaccine clinical trials. The two organizations share many common objectives and several collaborations are under way. The focus in many cases is on capacity building, either at clinic site level (currently in five countries) or nationally. Aeras and EDCTP have in addition collaborated with local research institutions in training, cohort studies, and developing quality management and data management infrastructure. EDCTP also supports Aeras in TB vaccine trials (MVA85A, AERAS 402/Crucell Ad35 and Hybrid-I+IC31)
- African Society for Laboratory Medicine (ASLM): Giorgio Roscigno spoke of this new society which seeks to advance the laboratory profession and to create networks in Africa
- African AIDS Vaccine Partnership (AAVP): Chidi Nwneka's theme was building partnerships for the common good. Established funding organizations, including EDCTP, will administer AAVP's R&D grants. Dr Nwneka said AAVP would be able to add value to EDCTP's work in a number of areas
- Global Health Trials: Trudie Lang described this recently launched online project which seeks to support clinical research through sharing practice, methods and knowledge (also described in presentation MO32). EDCTP is one of the organizations with which the new initiative is now working
- Microbicides Development Programme (MDP). Sheena McCormack outlined the development and future plans of this initiative, which is well networked with EDCTP's own activities. EDCTP is providing support for the MDP302 study, which involves administration of tenofovir vaginal gel
- African Network for Drugs and Diagnostics Innovation (ANDI): This African initiative to promote the discovery, development and delivery of affordable new drugs and diagnostic tests was the subject of a presentation by Alexander Ochem. EDCTP is a strategic partner for ANDI. The two organizations seek to work together in moving candidate drugs or vaccines into clinical development, and to collaborate in taking products into manufacture and access. EDCTP is also involved in ANDI's Scientific and Technical Advisory Committee.

A planned presentation concerning the research capacity building initiatives of the Wellcome Trust was unavoidably cancelled. The Trust is a key EDCTP partner.

Trial registration

The work of another EDCTP-funded project the Pan African Clinical Trials Registry (PACTR) was described within a cross-cutting parallel session [CO 01] on Wednesday morning. The audience was reminded of the benefits of trial registration and why this registry is needed, despite the existence of others such as clinicaltrials.gov. Registration reduces publication bias, fulfils ethical obligations, ensures transparency and promotes data sharing. As a regional registry, PACTR encourages awareness and local ownership. It also provides networking and training. It was also worth noting that clinicaltrials.gov does not support use of its information where there is limited internet access

The PACTR initiative is progressing, with 122 applications received so far, 67 of which have been registered – most of these trials are on HIV, TB and malaria. Many links have been established, including with national regulators. Sustainability and securing continuing funding are ongoing challenges.

Ethical issues

Also on Wednesday morning, a cross-cutting session [CO 02] heard that Africa's scientists need to be able to meet the emerging ethical challenges in research; stem cell research and the development and release of genetically modified mosquitoes are examples of situations where ethical dilemmas will emerge. The African Malaria Network Trust (AMANET) has attempted to address the issues through a health ethics course. It is developing real-life African ethics case studies as a teaching tool. Issues covered include: the

role of researchers in sharing, ownership and storage of samples and data; intellectual property; patents; publications and the re-package of research findings for targeted stakeholders; and the responsibilities of scientists after a trial has been completed. Much of the discussion following this presentation focused on capacity within Africa to deal with ethical issues emerging from the use of new technologies.

A three-year project to map all ethics review committees (ERCs) in Africa is under way [CO 03]. Mapping African Research Ethics Review and Medicines Regulatory Capacity (MARC) is a three-year project aimed at creating Wiki-type, cloud-based African maps. The project is a collaborative initiative between the Council on Health Research for Development (COHRED) in Geneva, Switzerland and the University of KwaZulu Natal in South Africa. The tiered information collection system has four levels of data collection: general information on each ERC and its scope, capacity for review, supplementary information and social networking. The benefits are: increased visibility, positive competitive pressures, availability of a free platform for institutions or countries without ERCs, and instant access to information and resources. To date, 125 ERCs have been mapped in over 25 African countries. Questions focused on the details of MARC's procedures, including the validation of information added to the website.

The presentation that followed [CO 04] concerned an online project based in Cameroon, known as Training and Resources in Research Ethics Evaluation (TRREE), which is available in four languages. Following its launch in 2009, priority training needs were identified through a survey of ERCs. Tailored training materials were then developed to meet these needs. TRREE now has 1869 subscriptions from 103 countries globally; 44% of its 1761 certified participants are African. Future plans include extending training to low-coverage regions and inviting countries to participate in the development of national training modules. It is planned to hold a global forum for ethics committees in Tunisia in 2012. Questions mainly dealt with the support that TRREE might be able to supply to specific countries.

Obtaining informed consent from study participants is one of the most important ethical concerns. Researchers working in Zambia [CO 05] sought to gain an understanding of participants' consent in an entero-toxigenic vaccines trial that had been proceeding for nine years. Their aim was to address the social relations associated with research – issues of information, understanding and trust. Using purposeful sampling and a gender-balanced approach, the researchers conducted participant observations, in-depth interviews, and focus group discussions. Qualitative methods of data analysis were then applied. The main conclusions were that interactions are more important than the information provided; and that trial participants in Africa raise ethical issues that, rather than being based on specifically African values, are the same as are found in trials conducted amongst poor, vulnerable and disadvantaged groups elsewhere. Motivations (most notably the expectation of access to free health care) emerged as being more important than understanding. Points raised in discussion included that: analysis of participants' understanding should not focus entirely on the application of ethical principles and rules; genuine understanding is dependent on literacy levels; understanding is not just an assimilation of information; and there is a need for exploring other models to describe the social and ethical content of the informed consent process.

The training of the lay members of ERCs was the focus of the next presentation [CO 06]. The role of lay persons should be geared towards addressing community needs and values in research during the review process. The training needs of 20 lay members in Nigeria were assessed and three sets of training modules were then offered: how to review, how to monitor research, and how to assess the community engagement process. Various methods of training were used, including role play. The impact of the training was assessed, tests being administered pre-training, and six and twelve months post-training. It was concluded that there had been significant knowledge and skills retention, and that this had impacted favourably on ERC functioning. The researchers noted that it was difficult initially to get lay persons to understand the science, but training increased their awareness of participants' rights and gave them the capacity to raise such issues in the review process. It was recommended that lay members should undertake such courses one per year.

Concerns have often been raised that the slow working of ERCs leads to unacceptable delays in commencing important research activities. A Zimbabwean project [CO 07] is seeking to improve the efficiency of ethics review through decentralization. There are presently multiple levels of review in Zimbabwe: institutional, national, medicines control, and registration with the research council for foreign nationals. The Medical Research Council of Zimbabwe (MRCZ) has about 10 recognized ethics review bodies. The many challenges and frustrations resulting from this system were described in the presentation: the delays cause the country to lose credibility; researchers may be tempted to flout regulations; coordination of reviews is difficult; the quality of review is poor; and there is potential for conflict of interests. In a centralized system, central bodies would train the ethics review boards and then accredit them, but then these boards would conduct the reviews. It is hoped to establish a process to achieve decentralization over the next two to three years. There will be three phases: survey to understand capacity, provide training and accreditation, and then launch of the decentralized system.

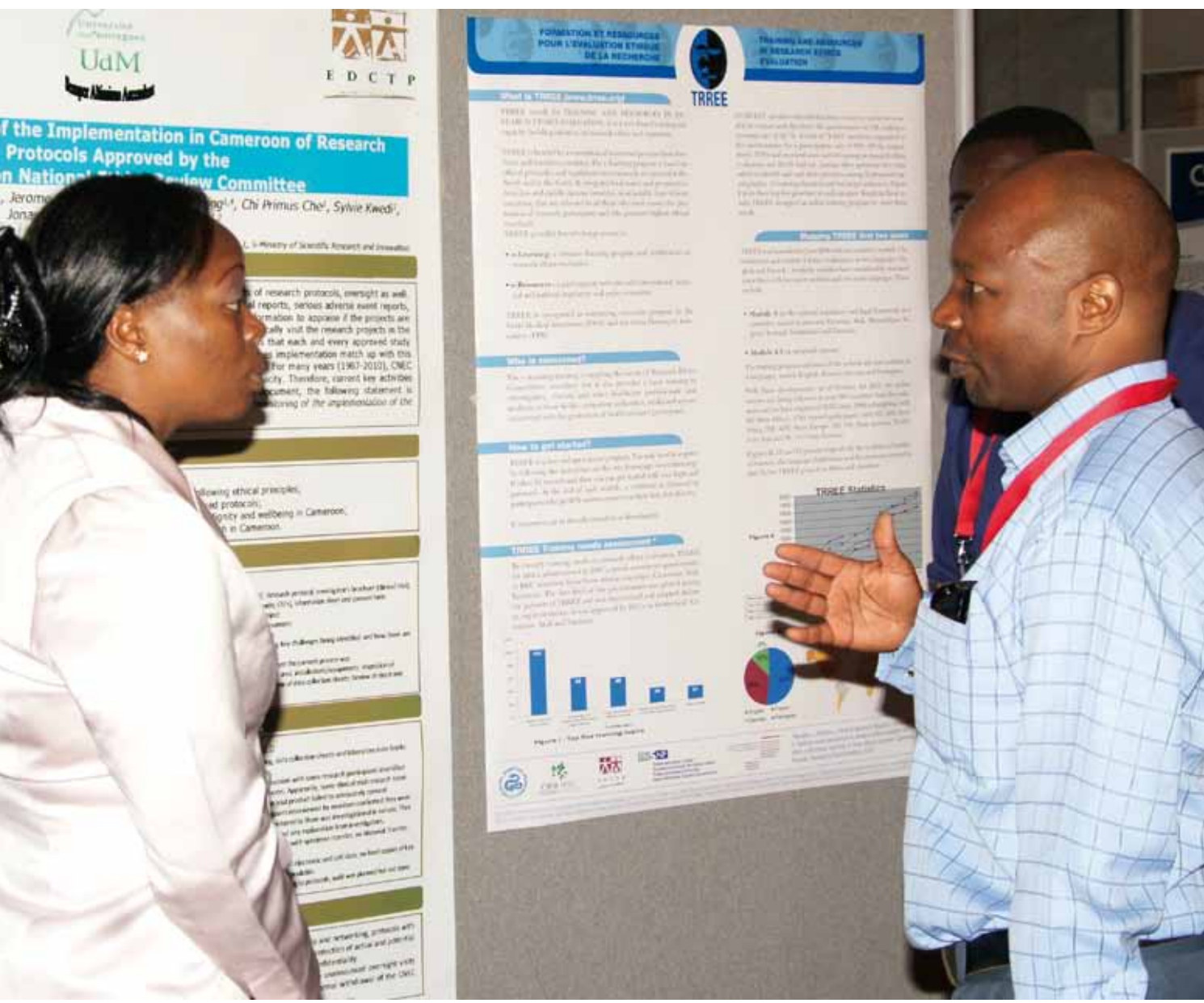
Other cross-cutting presentations

A high proportion of research in Africa is now conducted through international partnerships but how can these be sustained and be made more effective? A series of consultations has been conducted in order to develop the Partnership Assessment Tool (PAT), which is intended to make it easier to assess the performance of partnerships [CO 08]. The consultations were carried out by the Canadian Coalition for Global Health Research (CCGHR) and partners in Africa, Asia and Latin America; the African consultation took place in Ethiopia, involving eight African countries and Canada. Key elements of the consultation included the use of small working groups, case studies, and the sharing of information and success stories. Discussion within the consultation centred on capacity development, relationships within partnerships, and African networks. PAT will evaluate partnerships with regard to: inception, implementation, dissemination and 'good endings – new beginnings'. The tool will be disseminated to Northern institutions with a focus on donors and development organisations, in the hope that they will adopt it when entering into future global health partnerships. PAT is available at www.ccghr.ca. Questions asked mainly centred on which issues had been included as components of PAT.

The next presentation [CO 09] dealt with the important issue of clinical data management (CDM). There are currently many challenges in this area; because budgets are limited, CDM teams in the academic sector are generally small but they are nevertheless expected to comply with the same regulatory standards as the private sector and to keep pace with the rapid new developments taking place both in medical research and IT. The presentation was based on discussions at a meeting of Northern and Southern clinical data managers, held in Antwerp, Belgium in December 2010, at which experiences were shared with a particular focus on lessons learned from some EDCTP trials. The steps involved in CDM from implementation, conduct and after the study all received attention. Commonly encountered problems included: late involvement of CDM staff, workload underestimation, inadequate budgetary provision for some activities, failure to allow for poor internet connectivity, and difficulties in obtaining suitable open source software. Recommendations made in the light of these discussions included: adequate investment should be made to achieve quality on CDM, common operating procedures and document templates should be made available, data managers need more training (e.g. on the software that is being used in the commercial sectors), data managers should be involved early in the trial planning process, and a North–South collaborative platform should be establish to promote good CDM practices. Further suggestions were made during the audience discussion.

The final cross-cutting presentation [CO 10] was an account of the activities of the Initiative to Strengthen Health Research Capacity in Africa (ISHReCA). The three aims of this Africa-led initiative which began in 2007 are: to serve as a forum for African health researchers to discuss capacity building needs and approaches; to provide information on capacity building to African health researchers; and to establish an African health researchers' database. ISHReCA now has a membership of 1800 African heath researchers in 43 countries. There is a Secretariat based in Cameroon, and members can interact

through an e-forum. The presentation focused on consolidating gains and setting new directions for longer term-impact and sustainability in capacity building. The particular problems experienced in Central Africa were noted; no supportive policy mechanisms exist to support research in this sub-region. After an account of the work ISHReCA has so far done, and of the barriers which must be overcome before the expectations of African scientists can be met, a number of recommendations were put forward: information gathering is often subjective and must now be improved; different approaches are needed for different sub-regions; individual researchers need to do more to enhance the pace of research capacity building, and through ISHReCA they can provide more feedback; and ISHReCA must find new ways to track and consolidate gains. Matters arising in the discussion that followed included the issue of inequality in partnerships, the situation in Southern Africa, and how to become a member of ISHReCA. (Anyone in the research community is welcome to be a member free of charge and can then choose their desired level of involvement.)



Appendix 1: Forum programme

Sunday 9 October 2011	Monday 10 October 2011
	08:00–09:00 **Registration** [LOBBY]
	09:00–10:30 **Plenary session I** Forum prologue [CONFERENCE ROOM 1]
	10:30–11:00 Coffee / Tea break
	11:00–12:00 **Parallel sessions** Clinical research achievements and findings in sub-Saharan Africa HIV/AIDS [CONFERENCE ROOM 1] Tuberculosis [CONFERENCE ROOM 3] Malaria [CONFERENCE ROOM 5]
	12:00–13:00 **Poster presentations / Marketplace** [EXHIBITION AREA]
15:00–17:00 **Registration** [LOBBY]	12:30–14:00 **Satellite meeting** Medicines for Malaria Venture meeting on drug access [DELEGATES LOUNGE]
	13:00–14:00 Lunch
14:00–16:00 **Satellite meeting** Professional recognition, career development and training for clinical trial investigators and staff [CONFERENCE ROOM 3]	14:00–16:10 **Parallel session** Clinical research achievements and findings in sub-Saharan Africa (cont.) HIV/AIDS [CONFERENCE ROOM 1] Tuberculosis [CONFERENCE ROOM 3] Malaria [CONFERENCE ROOM 5]
	16:10–16:40 Coffee / Tea break
17:00–18:20 **Official opening addresses** [CONFERENCE ROOM 1]	16:15–17:30 **Satellite meeting** The Seventh EU Research Programme (FP7) – Supporting international health and bio-medical research cooperation [CONFERENCE ROOM 3] 16:40–17:40 **Poster presentations / Marketplace** [EXHIBITION AREA]
18:20–20:30 Welcome reception [BANQUET ROOM]	19:00–20:30 Conference dinner

Tuesday 11 October 2011	Wednesday 12 October 2011
08:00–09:00 **Special sessions** Grant writing for scientists [CONFERENCE ROOM 3] Scientific publication writing for scientists [CONFERENCE ROOM 5]	08:00–09:00 **Special sessions** Grant writing for scientists [CONFERENCE ROOM 3] Scientific publication writing for scientists [CONFERENCE ROOM 5]
09:00–10:30 **Plenary session II** Recent advances in HIV/AIDS, tuberculosis and malaria [CONFERENCE ROOM 1]	08:00–10:30 **Plenary session III** Presentations from EDCTP partners [CONFERENCE ROOM 1]
10:30–11:00 Coffee / Tea break	10:30–11:00 Coffee / Tea break
11:00–12:00 **Parallel sessions** Developing scientific research capacity in sub-Saharan Africa HIV/AIDS [CONFERENCE ROOM 1] Tuberculosis [CONFERENCE ROOM 3] Malaria [CONFERENCE ROOM 5] 11:00–13:00 Cross-cutting: EDCTP-NACCAP [CONFERENCE ROOM 6]	11:00–12:00 **Parallel sessions** North-South and South-South partnerships for quality improvement research in sub-Saharan Africa HIV/AIDS [CONFERENCE ROOM 1] Tuberculosis [CONFERENCE ROOM 3] Malaria [CONFERENCE ROOM 5] Cross-cutting [CONFERENCE ROOM 6]
12:00–13:00 **Poster presentations / Marketplace** [EXHIBITION AREA]	12:00–13:00 **Poster presentations / Marketplace** [EXHIBITION AREA]
12:30–14:00 **Satellite meeting** Clinical trials in practice: how to achieve the best protection of the study subjects? [DELEGATES LOUNGE]	
13:00–14:00 Lunch	13:00–14:00 Lunch
14:00–16:10 **Parallel sessions** Developing scientific research capacity in sub-Saharan Africa (cont.) HIV/AIDS [CONFERENCE ROOM 1] Tuberculosis [CONFERENCE ROOM 3] Malaria [CONFERENCE ROOM 5] Cross-cutting: EDCTP-NACCAP [CONFERENCE ROOM 6]	14:00–15:30 **Parallel sessions** North-South and South-South partnerships for quality improvement research in sub-Saharan Africa (cont.) HIV/AIDS [CONFERENCE ROOM 1] Tuberculosis [CONFERENCE ROOM 3] Malaria [CONFERENCE ROOM 5] Cross-cutting [CONFERENCE ROOM 6]
16:10–16:40 Coffee / Tea break	15:30–16:00 Coffee / Tea break
16:40–17:40 **Poster presentations / Marketplace** [exhibition area]	16:00–17.20 **Plenary session IV** Recommendations, award giving ceremony and closing remarks [CONFERENCE ROOM 1]

Appendix 2: Forum presentations

HIV/AIDS

HO 01 **Agricola Joachim:** HIV inhibitory antibodies elicited by heterogeneous HIV-DNA prime boosted with HIV-MVA vaccine in healthy Tanzanian volunteers

HO 02 **Thomas Hanke:** PedVacc001 and 002: Building foundations for infant HIV-1 vaccine trials against breast milk transmission of HIV-1

HO 03 **Anders Fomsgaard:** Therapeutic HIV-1 vaccination of untreated healthy HIV-1+ individuals in Republic Guinea Bissau using HLA-supertype CTL epitope peptides in new CAF01 adjuvant: a phase 1 study

HO 04 **Sinead Delany-Moretlwe:** AfrEVacc 001: feasibility and acceptability of an HIV vaccine trial among men in Johannesburg, South Africa – results from screening

HO 05 **Ramsey A Lyimo:** Measuring adherence to antiretroviral therapy in northern Tanzania: feasibility and acceptability of the medication event monitoring system

HO 06 **Wendyam Marie Christelle Nadembega:** Evaluation on HIV-1 viral load among mothers under PTMCT program with lymphocytes T CD4 count above 350cells/µl

HO 07 **Eva Muro:** Intrapartum single-dose carbamazepine shortens nevirapine elimination half-life and may reduce resistance after a single dose of nevirapine for perinatal HIV prevention

HO 08 **Frank Angira:** Nevirapine-associated hepatotoxicity and rash among HIV-infected pregnant women in Kenya

HO 09 **Wondwossen Amogne Degu:** Efficacy as well as safety of immediate versus deferred initiation of HAART in TB/HIV co-infected patients with CD4 counts less than 200 cells/mm3

HO 10 **Getnet Yimer:** High plasma efavirenz, slow NAT2 acetylators and ABCB1 genotype are associated with anti tubercular and efavirenz based ARV drugs induced liver injury in TB-HIV patients

HO 11 **Pauline Mwinzi:** Case definition for immune reconstitution inflammatory syndrome (IRIS) in HIV-schistosomiasis co-infected patients undergoing HAART

HO 12 **Kahsay Huruy Ghezehegn:** Immune reconstitution inflammatory syndrome among HIV/AIDS patients during highly active antiretroviral therapy in Addis Ababa, Ethiopia

HO 13 **Gershim Asiki:** Behavioural determinants for HIV incident infections in a fishing population being prepared for future HIV prevention research

HO 14 **Jamirah Nazziwa:** Transmission clusters and evidence of HIV-1 transmitted drug resistance among recently infected ART-naive individuals from Ugandan fishing communities of Lake Victoria.

HO 15 **Victor Mwapasa:** Is the fishing community a hotbed for HIV and STI transmission? Evidence from Mangochi, Malawi

HO 16 **Sybill Sory:** An assessment of the quality of life of HIV/AIDS patients and their families during the scaling-up of the delivery of anti retroviral treatment in Ghana

HO 17 **Innocent Afeke:** Bacterial vaginosis as a risk factor for acquiring sexually transmitted diseases

HO 18 **Samuel Adetona Fayemiwo:** Prevalence of anogenital human papilloma virus among Plwha in Ibadan, Nigeria.

HO 19 **Kishor Mandaliya:** Prevalence of human papilloma virus infection in HIV infected women during the third trimester of pregnancy.

HO 20 **Omondi Ochieng:** Mothers' and their adolescent daughters' attitudes and intentions relating to the adoption of human papiloma virus vaccination in Akinyele local area, Rachuonyo

HO 21 **Cyril Dim:** Cervical cancer screening among HIV-positive women in Enugu, Nigeria: an assessment of current use, and willingness to pay in the absence of donor support

HO 22 **Eugene Kinyanda:** Prevalence and risk factors of major depressive disorder in HIV/AIDS as seen in semi-urban Entebbe district, Uganda

HO 23 **Joseph Elieza Chilongani:** A prospective cohort study among female bar and hotel workers in northwestern Tanzania in preparation for future phase III microbicides and other HIV preventive clinical trials.

HO 24 **Mary Mwaura:** Prevalence reproductive tract infections (RTI) in women targeted for microbicide trials: the microbicide safety biomarkers study in Kenya, Rwanda, and South Africa

HO 25 **Stephen B. Kennedy:** Community trial to prevent HIV/STDs among rural youths in post-conflict Liberia

HO 26 **Adesola Olalekan:** Methicillin Resistant *Staphylococcus aureus* nasal carriage in HIV-infected patients in Lagos, Nigeria

HO 27 **Deogratius Ssemwanga:** HIV-1 subtype distribution, multiple infections, sexual networks and partnership histories in female sex workers in Kampala, Uganda

HO 28 **Louis Marie Yindom:** Influence of HLA class I and HLA-KIR compound genotypes on HIV-2 infection and markers of disease progression in a community in West Africa

HO 29 **Keabetswe Bedi:** Evolution of neutralizing antibodies against HIV-1C molecular envelope clones from acute heterosexually acquired infections in Botswana

HO 30 **Thuli Muthiyane:** Assessment of TB-HIV treatment responses in co-infected patients receiving combined treatment

HO 31 **Elias Onyoh:** High prevalence of hepatitis B and syphilis co-infection among newly diagnosed HIV patients in the northwest region of Cameroon

HO 32 **Mina Hanna:** French agency of research on AIDS and viral hepatitis (ANRS) initiative on clinical trials good clinical practices in resource-limited countries: development of quality indicators

Tuberculosis

TO 01 **Martin Boeree:** PanACEA: using brokering to develop a research agenda
TO 02 **Amina Jindani:** An international multicentre controlled clinical trial to evaluate high dose rifapentine and a quinolone in the treatment of pulmonary tuberculosis (Rifaquin)
TO 03 **Charles Mtabho:** Plasma levels of tuberculosis drugs in tuberculosis patients in northern Tanzania
TO 04 **Eleni Aklillu:** Optimization of tuberculosis and HIV co-treatment: pharmacokinetic and pharmacogenetic aspects of interaction between rifampicin and efavirenz
TO 05 **Samuel Kudzawu:** Comparison of yield in sputum smear microscopy from specimens collected at different times in the diagnosis of pulmonary tuberculosis.
TO 06 **Willy Ssengooba:** Optimal number of samples required to diagnose tuberculosis by sputum culture among HIV infected smear negative suspects in Kampala, Uganda
TO 07 **Albert Okumu:** Comparison of performance between Ziehl Neelsen (ZN) microscopy and the Xpert MTB/RIF assay in detection of *Mycobacterium tuberculosis (Mtb) in sputum at KEMRI/CDC TB Laboratory*
TO 08 **Grant Theron:** Cycle-threshold values of an automated TB-specific PCR platform (Xpert MTB/RIF) as a predictor of smears status and grade
TO 09 **Paulo Rabna:** High mortality risk among individuals assumed to be TB-negative can be predicted using a simple test
TO 10 **Florian Gehre:** Population structure of *Mycobacterium africanum* and differences in ESAT-6 immunogenicity between different lineages
TO 11 **Carol Holm-Hansen:** Development of a rapid serological screening test for TB
TO 12 **Hazel Dockrell:** Distinct phases of changes in host gene expression reflect successful tuberculosis drug treatment
TO 13 **Keertan Dheda:** *M. tuberculosis*-specific lung innate immunity in close contacts of TB index cases
TO 14 **Niaina Rakotosamimanana:** Variation in gamma interferon responses to different infecting strains of *Mycobacterium tuberculosis* in acid-fast bacillus smear-positive patients and household contacts
TO 15 **Keertan Dheda:** Decreased interferon gamma and increased Cd4+Cd25+Foxp3+ regulatory T-cells in patients with extensively drug resistant tuberculosis
TO 16 **Jayne Sutherland:** Cellular and soluble biomarkers in the pleural fluid, absent from the peripheral blood, accurately diagnose pleural TB in A TB-endemic setting
TO 17 **Martin Ota:** Clinical Trials With MVA85A, a candidate TB vaccine
TO 18 **Allé Baba Dieng:** A phase I study evaluating the safety & immunogenicity of a new TB vaccine, MVA85A, in healthy volunteers who are infected with HIV in Senegal
TO 19 **Leander Grode:** VPM1002 in a Phase II clinical trial: All steps to neonate immunization
TO 20 **Grace Kiringa Kaguthi:** Updates from a randomised, double blind placebo controlled phase IIb tuberculosis vaccine trial in HIV negative infants in western Kenya to determine safety and efficacy
TO 21 **Fredrick Lutwama:** Reduced frequency of specific IFN-gamma producing T cells in Ugandan infants when Bacillus Calmette-Guerin vaccination is delayed from birth to 6 weeks of age
TO 22 **Simani Gaseitsiwe:** *In silico* mapping of *Mycobacterium tuberculosis* proteins for CD4+ T-Cell epitope
TO 23 **Wendy Burgers:** Detailed functional assessment of the immune response to *Mycobacterium tuberculosis* in HIV-TB co-infected individuals
TO 24 **Tutty Isatou Faal:** *Mycobacterium tuberculosis* complex within the tuberculosis case contact study in MRC Unit The Gambia
TO 25 **Larissa Kamgue Sidze:** Estimates of genetic variability of *Mycobacterium tuberculosis* complex and its association with drug resistance in Cameroon
TO 26 **Rose Hayeshi:** Nanomedicine for improved efficacy of tuberculosis drugs
TO 27 **Jean Marie Assam Assam:** Predominance of the Ghanaian strain of *Mycobacterium tuberculosis* in the coastal region of Cameroon
TO 28 **Anne Wajja:** Non tuberculous Mycobacteria among children with suspected TB in a rural setting in Uganda
TO 29 **Ronald Mutunzi:** Risk factors for tuberculosis infection among adolescents in rural Uganda
TO 30 **Elizabeth Nangobi Mwanja:** Community sensitization in preparation for enrolment of infants and adolescents into a study to assess TB incidence
TO 31 **Patience Oduor:** Retention patterns of an adolescent cohort in western Kenya in preparation for future TB vaccine trials
TO 32 **Amos Ndaabe:** Comparison between active and passive case finding of tuberculosis among adolescents in eastern Uganda

Malaria

MO 01 **Umberto D'Alessandro:** A head-to-head comparison of four artemisinin-based combinations for treating uncomplicated malaria in African children: A randomized trial
MO 02 **Abdoulaye Djimde:** Clinical research capacity development: the experience of the West African network for clinical studies of antimalarial drugs (WANECAM)
MO 03 **Victor Mwapasa:** Co-administration of artemisinin-based combination therapies (ACTs) and antiretroviral (ARV) drugs: Any evidence of adverse events or poor ACT pharmacokinetic profile?
MO 04 **Pauline Byakika-Kibwika:** Efavirenz significantly affects pharmacokinetic exposure of artemether-lumefantrine in HIV-infected Ugandan adults

MO 05 **Nathalie Strub-Wourgaft:** Assessment of the fixed-dose combination of artesunate mefloquine (ASMQ) as an alternative antimalarial treatment for children in Africa
MO 06 **Michael Nambozi:** Safety and efficacy of dihydroartemisinin-piperaquine versus artemether-lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria in Zambian children
MO 07 **Catherine Falade:** Burden of malaria in HIV-positive pregnant women in Ibadan, south-west Nigeria
MO 08 **Alphonse Ouedraogo:** Different approaches for delivery of intermittent preventive treatment with sulfadoxine-pyrimethamine (IPTp/SP) to pregnant women in Burkina Faso
MO 09 **Kamija Phiri:** Intermittent preventive therapy post-discharge (IPTpd); an innovative approach in the prevention of rebound severe malaria anaemia and mortality in young children
MO 10 **Peter Kremsner:** A simplified artesunate regimen for severe malaria in children
MO 11 **Peter Olupot-Olupot:** FEAST trial: mortality after fluid bolus in African children with impaired perfusion
MO 12 **Judith Atiang:** Rare clinical features of severe malaria in children in Eastern Uganda
MO 13 **Caroline Ogwang:** Safety and immunogenicity of prime-boost immunization of Kenyan adults with candidate malaria vaccines based on a chimpanzee adenovirus and modified vaccinia ankara
MO 14 **Muhammed Afolabi:** Safety and immunogenicity of heterologous prime-boost vaccine strategy with AdCh63 ME-TRAP and MVA.ME-TRAP in healthy adults and children in the Gambia
MO 15 **Daniel Dodoo:** Antibody levels to MSP1-block 2 hybrid, GLURP R2 and AS202.11 and the risk of malaria in under five year old children of Burkina Faso and Ghana: an Afro-immuno assay project.
MO 16 **Michael Theisen:** Studies of new adjuvants and formulations of GMZ2 with the aim to enhance immunogenicity
MO 17 **Dawit Ejigu:** Challenges in carrying out multicentre clinical trials in a consortium; the GMZ2 experience
MO 18 **Fred Kironde:** Successful experiences in setting up a new site for phase II malaria vaccine testing – Uganda
MO 19 **Tiga David Kangoye:** Prospective study of the incidence of clinical malaria in the malaria vaccine candidate GMZ2 future trial site
MO 20 **Kalifa Bojang:** Baseline epidemiological study in preparation for a phase IIb efficacy trial of GMZ2 candidate malaria vaccine
MO 21 **Larissa Aurore Bouyoukou Hounkpatin:** A randomized controlled phase Ib trial of the malaria vaccine candidate GMZ2 in African children
MO 22 **Thomas Hänscheid:** Novel methods to diagnose malaria by detecting hemozoin in intra-erythrocytic parasites -possible limitations
MO 23 **Happi Christian:** Validation of new biomarkers for monitoring *Plasmodium falciparum* reduced susceptibility/tolerance or resistance to artemisinin derivatives and partner drugs in Nigeria.
MO 24 **Anna Maria van Eijk:** Documented fever and malaria in pregnancy in Africa
MO 25 **Daniel Olusola Ojurongbe:** High prevalence of *Plasmodium falciparum* DHFR mutations correlates with sulfadoxine-pyrimethamine usage among pregnant women in Nigeria.
MO 26 **Golbahar Pahlavan:** Benchmarking two multi-site intermittent preventive treatment of malaria in pregnancy (IPTp) clinical trials in 5 sub-Saharan countries
MO 27 **Bakery Fofana:** Impact of artemisinin-based combination therapy on malaria transmission in Mali
MO 28 **Ogutu Bernards:** Systematic screening and targeted treatment of *P. falciparum* asymptomatic carriers with artemether-lumefantrine in a community setting in Burkina Faso
MO 29 **Victor Chalwe:** The influence of mefloquine malaria prophylaxis on HIV disease progression: a randomized placebo-controlled trial
MO 30 **Kennedy Awuondo:** An opportunity to establish quality indicators and benchmarks for clinical laboratories supporting clinical trials in sub-Sahara Africa.
MO 31 **Rosemary Audu:** Characteristics of some quality essentials in clinical laboratories in Nigeria
MO 32 **Trudie Lang:** Using digital technology to support and enhance clinical trials in resource-limited settings

Cross-cutting

EDCTP-NACCAP Capacity building and networking session

Dr Eva Rijkers: Introduction NACCAP
Prof. Elly Katabira and Dr Joseph Ntaganira: INTERACT partnership programme
Dr Victor Mwapasa: CoMMAL partnership programme
Prof Tobias Rinke de Wit: ART-A partnership programme
Prof. Gibson Kibiki and Dr Reginald Kavishe: APRIORI partnership programme
Prof. Pontiano Kaleebu and Dr George Miiro: Building a sustainable Eastern Africa network for capacity strengthening and mentoring in research and health
Prof. Souleymane Mboup: The West African Node of Excellence for TB, AIDS and malaria
Prof. Francine Ntoumi: Central Africa at front stage through CANTAM
Dr Alexander Pym and Mrs Maerangis Rahmani: TESA: A model of clinical research capacity building in Southern Africa
Prof. Hannah Akuffo: ESSENCE – 'baby steps' in harmonizing policies and practices of research funders

CO 01 **Amber Abrams:** Pan African Clinical Trials Registry: an update on prospective clinical trial registration in Africa

CO 02 **Wenceslaus Kilama:** Emerging ethical and practical challenges for health researchers in Africa
CO 03 **Boitumelo Mokgatla-moipolai:** Mapping African research ethics review and medicines regulatory capacity
CO 04 **Jerome Ateudjieu:** TRREE online training project: mapping its first two years
CO 05 **Bornwell Sikateyo:** Understanding: Participants' consent in an entero-toxigenic vaccines trial in Misisi Township in Lusaka, Zambia.
CO 06 **Morenike Ukpong:** Training of layperson on ethics committees on how to review protocols
CO 07 **Rosemary Musesengwa Chekera:** Improving efficiency of ethics review in Zimbabwe through decentralisation
CO 08 **Liya Dubale:** Building effective and sustainable partnerships for global health research: the useful role of a partnership assessment tool
CO 09 **Mary Thiongo:** Data management in non-commercial north-south collaborative clinical research: lessons learned from some EDCTP funded trials
CO 10 **Palmer Netongo:** ISReCA: consolidating gains and setting new directions for longer term impact and sustainability in health research capacity building in Africa.

Presentations from EDCTP partners

PO 01 **Jean-Louis Excler:** International AIDS Vaccine Initiative (IAVI) collaborative network in Africa
PO 02 **Ambachew Yohannes:** UNITAID: Innovative financing for health
PO 03 **Val Snewin:** Wellcome Trust research capacity building initiatives
PO 04 **Siobhan Malone:** Strengthening research partnerships: the Bill & Melinda Gates Foundation perspective
PO 05 **Garry Aslanyan:** ESSENCE on health research
PO 06 **Stephan Duparc:** Partnering to develop the next generation of medicines to combat malaria
PO 07 **Vicky Cárdenas:** Aeras and EDCTP: Partnering to support TB vaccine clinical trials
PO 08 **Giorgio Roscigno:** African Society for Laboratory Medicine (ASLM): Advancing the laboratory profession and networks in Africa
PO 09 **Chidi Nwneka:** AAVP: Building partnerships for the common good
PO 10 **Trudie Lang:** Global Health Trials: Supporting clinical research by sharing practice, methods and knowledge.
PO 11 **Sheena McCormack:** Microbicides Development Programme (MDP): future plans
PO 12 **Alexander Ochem:** African Network for Drugs and Diagnostics Innovation (ANDI)

Colophon

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Page 4: Entrance of the United Nations Conference Centre (UNCC), in Addis Ababa, Ethiopia (Dayan Berhe, Ethiopia)
Page 12: The health centre at Sukuta, The Gambia (Tomáš Hanke, The Jenner Institute, University of Oxford, United Kingdom)
Page 22: Participant of the MVA85A clinical trial (Martin Ota, Medical Research Council, The Gambia)
Page 29: H.E. Jean-Pierre Ezin, the African Union Commissioner of Human Resources Science and Technology, at the Forum prologue session on Monday 10 October 2011 (Dayan Berhe, Ethiopia)
Page 30: Community educated about malaria and clinical trials (Fred Kironde, Makerere University, Uganda)
Page 41: Participants at the Cross-cutting Parallel Session on Wednesday 12 October 2011
Page 42: Participants of trial 'Assessment of the fixed-dose combination of Artesunate Mefloquine (ASMQ) as an alternative antimalarial treatment for children in Africa' (Nathalie Strub-Wourgaft, Drugs for Neglected Diseases Initiative, Switzerland)
Page 49: Poster presentations on cross-cutting issues at the Exhibition area (Dayan Berhe, Ethiopia)

Strengthening Research Partnership for Better Health and Sustainable Development