8-11 October 2006
Stockholm, Sweden

EDCTP

European and Developing Countries Clinical Trials Partnership

The Third European and Developing Countries Clinical Trials Partnership Forum

Partnership and African Leadership: Challenges and Opportunities

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The conference organisers acknowledge the generous support of:

- European Commission
- City Council of Stockholm, Sweden
- Swedish Society of Medicine
- Karolinska Institute, Sweden
- Netherlands and African Partnership for Capacity Development (NACCAP), Netherlands
- Instituto de Salud Carlos lll, Spain
- Medical Research Council, United Kingdom

European & Developing Countries Clinical Trials Partnership

Europe Office
P.O. Box 93015, 2509 AA The Hague,
The Netherlands,
Laan van Nieuw Oost Indië 334, 2593 CE The Hague
The Netherlands
Tel: +31 70 344 0880
Fax: +31 70 3440899

Africa Office
Francie van Ziji Drive, Parow,
P.O. Box 19070
Tygerberg, Cape Town
South Africa
Tel: +27 21 938 0819
Fax: +27 21 9380569

E-mail: info@edctp.org **Web:** www.edctp.org

Mr Kjell Erlandsson, of the Karolinska Institute, is acknowledged for some of the forum photographs.

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Britta Wahren

Diana Dunstan

PLENARY SESSION 1

Chair: Britta Wahren

Themes:

- **Building capacity in scientific skills and leadership in African strategies**
- **Networking within the partnership**

Welcoming Address and update since the second forum

Diana Dunstan, EEIG-EDCTP Chair

We have had many developments over the past year. Charles Mgone has joined us on behalf of Africa, and David Coles who is leading the north-north networking. Odile Leroy has left to join the European Malaria Vaccines Initiative (EMVI). On behalf of all of us, I would like to express my thanks for her tireless support and promotion of the EDCTP through a difficult time. She has left a gap, but we are working hard to recruit a replacement.

The EDCTP is a dynamic organisation, which has coped with problems and is now ready to progress further. This current forum has a role in forming an effective network of European scientists to work in partnership with Africa. It will be the African responsibility to ensure the sustainability of the programmes.

Among our many tasks has been to enforce ongoing lobbying for research in African countries by African researchers. It has become clear that African research priorities need a stronger voice through the Developing Countries Coordinating Committee (DCCC).

Nodes of excellence are needed to support weaker centres in Africa. This is important since we have access to little funding and resources in poorer countries. Here we can use the DCCC as a link.

We have kept in close touch with the European Commission (EC). The interactions with the EC have involved regular meetings with the Health Directorate. We have received a letter from the Commission extending the funding of EDCTP to 2010, conditional on approval of our roadmap. A September meeting with the Health Directorate and Commissioner's Cabinet suggested that co-funding should be across the whole programme and not on individual projects.

The main objectives of the Durban forum were networking between African and European scientists, promotion of the partnership and strengthening collaborations, and identifying common interests that could lead to joint activities through utilising EDCTP as an operational platform.

Regarding HIV/AIDS the Durban forum recommended that microbicide studies should be considered. Three projects were positively assessed involving sites from Kenya, Rwanda, Uganda, Tanzania, Mozambique and South Africa.

A further recommendation was that there should be studies on prevention of mother to child transmission (PMTCT) of HIV. A sum of €6,100,000 has been jointly allocated between EDCTP, Agence National pour la Recherche de la Sida ANRS (France), the Netherlands Organisation for Scientific Research (NWO), the Netherlands-African Partnership for Capacity Development and Clinical Interventions Against Poverty-Related Diseases NACCAP, Medical Research Council (UK), Instituto de Salud Carlos III (ISCIII) (Spain) and Irish Aid (Ireland) for this.

Recommendations in terms of tuberculosis included study of new diagnostics in context of definition of trial end-points together with studies of adjunctive therapy (e.g. steroids) in extra-pulmonary and other forms of tuberculosis (TB). Activities should be expanded to more adequately cover the available drug product portfolio. In addition, studies should be undertaken on co-infection and its implications for drug treatment including HIV with malaria and HIV with TB.

Important achievements were three calls for proposals that were launched in the fourth quarter of 2005. These were capacity building and site development for conduct of phase III trials of TB vaccines in high-risk populations (total budget €2,350,000); capacity building and site development for the conduct of phase III trials of TB vaccines in children under 1 year of age (total budget €2,350,000); and support of phase II/III trials to identify safe and efficacious ARV in combination with TB drugs in

TB patients with HIV infection (total budget: €2,500,000). Five projects were positively assessed in response to these three calls and contract negotiations are under way.

Malaria control remains an important area, and recommendations included studies on intermittent preventive therapy in pregnancy (IPTp). It was further recommended that sites be prepared in sub-Saharan Africa for forthcoming vaccine trials, and that synergy should be developed with partners on standardisation of end-points and assays.

Alternative therapies to quinine are required for treatment of severe *Plasmodium falciparum* malaria and more research investigations are needed on uncomplicated malaria and diagnostics.

Among the achievements are the currently funded projects evaluating four artemisinin-based combinations for treating uncomplicated malaria in African children involving sites in Burkina Faso, Nigeria, Zambia, Gabon, Uganda and Rwanda with a total budget of €1,999,990 and for evaluating intravenous artesunate in the treatment of severe malaria in African children, involving sites in Ghana, Gabon, Kenya, Gambia and Malawi (total budget of €5,000,000).

Recommendations were also made on capacity building, training and strengthening of regulatory capacity. EDCTP is now collaborating with the World Health Organisation (WHO) to support activities to strengthen the national regulatory environment of various African countries including training and development of a common regulatory framework for joint review of clinical trials applications, monitoring and trial site inspection.

EDCTP with additional funds from NACCAP contributed a total of €360,000 to support NRA (National Regulatory Authorities) training workshops for African regulators from 15 African countries namely Tanzania, Kenya, Uganda, Rwanda, Mozambique, Malawi, Zambia, Gabon, Ghana, Nigeria, Burkina Faso, The Gambia, Cote d'Ivoire, Mali, and Ethiopia. Other regulatory activities supported include funding for the first African Vaccine Regulators Forum that was held in Accra in September 2007 and the WHO Global Training Network course for African regulators in both English and French.

Other recommendations included the need to build laboratory capacity to investigate resistance to drugs for HIV/AIDS, tuberculosis and malaria, and to fund work on immunological correlates of protection for these diseases. Building regional reference laboratories will support these efforts, as will development of proficiency training.

Health ethics in Africa needs strengthening and to this end calls were launched with deadlines up to second quarter of 2006. Eight institutions, six of which are African, had successful applications to offer ethics courses and seminars. Three of these are already ongoing and the remaining five have contract negotiations underway. Applications from six African countries were successful and two of these are already funded, while the remaining four have contract negotiations underway. The Pan-African Bioethics Initiative (PABIN) had a successful application for establishing an African coordinating office for ethics. Contract negotiations are currently underway.

The important issue of training led to some important recommendations. Centres of excellence on data management and skill development should be addressed focusing on undergraduates. We should also stimulate growth of a research culture. Principle Investigators need to be encouraged to link their teams to networks, and furthermore we should develop links with industry for training in quality assurance and monitoring.

In addition to the on-going six senior fellowship projects, EDCTP has supported three senior and six career development fellowships, two MSc Studentships and seven PhD scholarships from African countries.

Networking requires support for meetings and networks across diseases, for instance through the DCCC. The EDCTP has sponsored meetings and workshops of sustainable networks on EDCTP-relevant subjects and provided incentives for joint capacity building programmes in Africa with two or more European institutions. Support has been provided to national networking of African scientists working on HIV/AIDS, malaria and tuberculosis in Africa and an MSc. course on clinical trials methodology has been developed.

Communication is of great importance and a quarterly EDCTP newsletter was launched in the first quarter of 2006 and is now running successfully.

EDCTP calls are widely advertised on the EDCTP

Dr Pascoal Mocumbi

website and with other collaborating organisations such as the Netherlands-African Partnership for Capacity Development and Clinical Interventions Against Poverty-Related Diseases (NACCAP) and African Malaria Network Trust (AMANET), our newsletter and the EDCTP listserv.

European and African partnership: Challenges and Opportunities

Dr Pascoal Mocumbi, EDCTP High Representative

Welcome to all participants at the Third Forum of The European and Developing Countries Clinical Trials Partnership (EDCTP). The Millennium Summit recognised the importance of good health as a prerequisite for reducing poverty and adopted the Millennium Development Goals (MDGs) as bench marks for initiatives and partnerships aimed at promoting sustainable development.

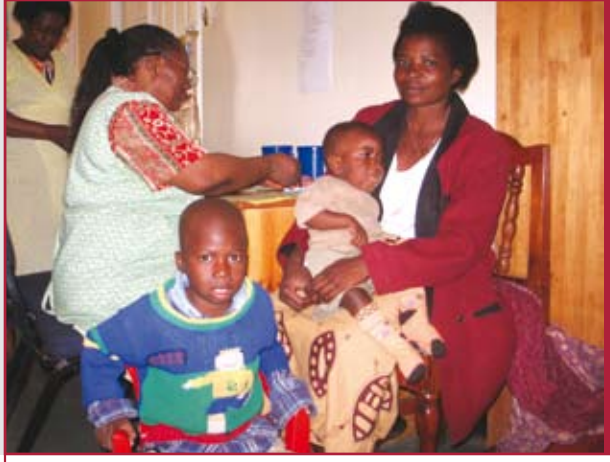
The purpose and objectives of this meeting have been spelled out by previous speakers. My role is to introduce the chosen theme: "Partnership and Leadership – Challenges and Opportunities". Indeed when a group of persons join together with the purpose of establishing a venture, they start by discussing the mission, goals and objectives, set a joint programme and establish the governing bodies before implementing the programme. That is what happened with our partnership i.e. EDCTP, which I prefer to refer to simply as – the Partnership. Why should we discuss leadership and partnership when we all know the governing structures of EDCTP? I presume that the choice of the theme was not chosen for us to review the joint decision by the Council and Parliament behind the EDCTP Economic Interest Grouping (EEIG); we are here to discuss something else. We are here to discuss what sort of partnership and leadership is needed to ensure full completion of the EDCTP mission based on the expected outcomes of EDCTP activities during the last three years in implementing its joint programme of action. In doing so we should identify the challenges and opportunities and draw recommendations on how best to organise ourselves to meet these goals.

How is EDCTP doing?

I can say that during the last one year, EDCTP has defined and established its structures, national programs and deepened the understanding of Article 169. The Executive Secretariat has an adequate research function and administrative management system. The ENNP has defined the national programmes and started to explore potential synergies; the PB developed a strategic view on scientific priorities and the DCCC has continued to actively identify gaps and needs in relation to capacity development. The ongoing activity of joint site visits by a team comprising of EDCTP Secretariat members and the High Representative (HR) confirms African government support for clinical trials activities through state assets used by the visited sites. This coupled with governments' support for salaries and subsidised rates for utilities such as water and electricity confirms commitment to participate in and support EDCTP-funded projects. Advocacy activities positioned EDCTP as a major partner in developing clinical trials among stakeholders as was demonstrated at the Brussels Stakeholders Forum "Connecting the chain". We are at the crossroads on our way towards achieving the two major objectives, namely contributing through integration of national research programs to accelerate the development of new and improved products against HIV/AIDS malaria and tuberculosis; and developing capacities for conducting high quality research.

Despite the progress made by EDCTP over the last year there is still a lot to be done to meet the benefits expected, namely a package of control interventions developed and deployed effectively against the three poverty related diseases and African sustainable institutions capable of initiating quality clinical trial studies on these diseases. To achieve this we need to recognise, nurture, support and strengthen the African leadership in the partnership. It is only through this leadership that we are going to guarantee successful and sustainable outcomes.

The outcomes of EDCTP ongoing activities in terms of sites distribution and scientists involved are known to all of us gathered here today. If the situation remains as it is now, what can we expect in 2010? A needs analysis of the existing sites and the need for testing candidate new



clinical interventions would help devise the challenges ahead. We have already identified gaps in sites visited so far. At this juncture I would like to draw your attention to the threat of drug resistance, the need to prepare alternative medication and the call by the Global HIV Prevention Working Group. Empirical studies have shown that antiretroviral treatment (ART) produces substantial changes in the viral dynamics in the host which translate into substantial changes outside the host system.[1] Similarly there are several reports of emergence of multi-drug resistant TB (MDR-TB).

A growing number of promising new HIV prevention approaches are in the late stages of clinical research and have the potential to dramatically reduce the burden of HIV around the world. Research on some of these approaches could show results within the next two years. However there are serious obstacles that could significantly delay or even de-rail critical prevention trials. These include inadequate resources and capacity to launch and complete trials and emerging ethical concerns. [2] The new HIV prevention approaches in development are male circumcision, cervical barriers and pre-exposure prophylaxis with antiretrovirals, herpes suppression, microbicides and HIV vaccines.

Challenges

The communication material portrays the partnership as guided by 11 principles:

- Decide the objectives together
- Build mutual trust
- Share information: develop networks, the power of sharing science
- Share responsibility
- Create transparency
- Monitor and evaluate the collaboration
- Disseminate the results
- Apply the results
- Share contributions and profits equitably
- Increase research capacity and
- Build on achievements.

1 María S. Sánchez, Robert M. Grant, Travis C. Porco, Wayne M. Getz, HIV Drug-resistant Strains as Epidemiologic Sentinels; Emerging Infectious Diseases Journal. 2006 Feb; Vol. 12(2): 191 – 7

2 Global HIV Prevention Working Group August 2006 – New Approaches to HIV prevention, Accelerating research and ensuring future access

EDCTP values are: Empowerment; Partnership based on mutual trust; Transparency; Innovation; Best practices and Responsibility.

Do we practise these principles and values? This will be the first of the challenges I have identified.

Continuing with other challenges - how can EDCTP address the following challenges?

Accelerated development of new clinical interventions needs a critical number of good clinical practice (GCP) compliant centres

Many players in the field - but leave critical gaps

Sustainability of the capacity of clinical trial sites (human resource and institutional capacity)

Financial capacity

Appropriate ethical and regulatory environment.

Opportunities

There are innumerable opportunities, but to start consider the following built on wisdom - how can EDCTP transform the challenges into opportunities?

- Contributing to development of capacities in Africa, working closely with African networks structured in different ways at national, regional and continental levels and based on three diseases (HIV/AIDS, malaria and tuberculosis), scientific skills and activities.
- Demand for Phase IIb clinical trials is increasing. We all know that this is real and if we do not act now, we may miss the opportunity to use the well established sites already receiving our grants.
- Build partnerships at all levels
- Establish collaborations and explore synergies and complementarities
- Networking.

Lennarth Hjelmåker

The way forward will require a strategy and an appropriate leadership. A strategy that takes into consideration capacity development as a long-term process, contributes towards developing countries having products, policies, institutions with capacity to conduct clinical trials and ability to diagnose and respond to our own health problems. I believe that despite recent difficulties, the partnership we are building is now on a much more solid foundation. Difficulties generate a response to protect our organisation like the antigen generates an immune response. To prepare an adequate response we need to agree on a strategy to build the leadership needed to accelerate the development of a critical mass of African principal investigators to lead the new clinical trial sites. The DCCC has prepared a concept paper on this; therefore you may wish to take the advantage of this gathering to prepare for constituencies meetings, making recommendations to the GA.

In summing up, may I remind you all that the Millennium Summit recognised the importance of good health as a prerequisite for reducing poverty and adopted the Millennium Development Goals as bench marks for initiatives and partnerships aimed at promoting sustainable development.

EDCTP is a true partnership between the European member states and developing countries in sub-Saharan Africa. It was established to step up cooperation and networking of European national programmes; accelerate clinical trials of new products, in particular drugs and vaccines in developing countries; help to develop and strengthen capacities in developing countries, including the promotion of technology transfer where appropriate; encourage the participation of the private sector; and to mobilise additional funds to fight HIV/AIDS, malaria and tuberculosis, including funds from the private sector. A significant part of the funding would be spent in the developing countries.

An assessment of EDCTP's three years' experience shows that a lot has been done implementing its joint programme of action. The governance structure and secretariat are already established, several projects have been approved and are being implemented in developing countries, including clinical trials, senior fellowships and training awards; moreover, capacity development in sites has started.

The third forum offers the opportunity to renew our commitments, discuss challenges and opportunities and make recommendations for the way forward.

As research on new clinical interventions to effectively control HIV/AIDS, tuberculosis and malaria advances, the need for additional sites to conduct clinical trials in endemic countries will increase sharply. For malaria alone, the portfolio of new artemisinin combination therapies and vaccine candidates largely surpass the already established sites and for HIV/AIDS and tuberculosis more candidates are undergoing preclinical investigation.

While calling for accelerating capacity to conduct trials in order to expedite development and testing of promising new interventions, I recommend that we should build on the achievements already made and the ownership demonstrated by participating countries in order to move forward in the implementation of our genuine partnership. From the established sites, EDCTP can maximise benefits by coordinating the development of regional nodes of excellence, building scientific African leadership and finding appropriate solutions to ethics and regulatory issues in developing countries, thus providing the appropriate environment for sustained interventions.

Official opening address

Lennarth Hjelmåker, HIV/AIDS Ambassador, Sweden

I was appointed AIDS Ambassador in 2003. Before that I headed the Department for Global Development and was previously Ambassador for Zimbabwe. My current focus is now very much on development at many different levels. I would describe myself as part of a package with high focus on HIV/AIDS and in this area I feel we need to be clearer on new developments. I feel like both a lobbyist and an activist with Global responsibilities (except in Sweden).

We know that there are three key diseases associated with poverty: HIV/AIDS, TB and malaria, and we need to address all of these in our fight against poverty, although most of my following remarks focus on HIV/AIDS.

Berit Olsson

Firstly, we need leadership in all areas and at all levels including national and international as well as all levels of society. We are going to have to take some difficult and challenging decisions. Secondly, we need to address HIV/AIDS with open minds. We know all about sexuality and human rights. But there are also rights to information, condoms, and people's own bodies and sexuality. We need to consider prevention, treatment and care. Of these, treatment and care tend to support each other. There is still a great need for further research. We have to overcome some of the problems of the society and do the right things in the right way; working together rather than against one another. We may not all work at the same speed, but we all have to work in the same direction with most effective countries willing to be in the driving seat.

We have prepared a global report, addressing various issues including:

- Empowering inclusive national ownership and leadership (private, societal, etc.)
- Alignment/harmonisation -- all involved must be prepared to align their activities with national systems and priorities
- Improve systems to enhance effectiveness and quality
- Oversight and accountability – lots of promises are being made; it is critical that we follow up on these.

Some of the recommendations that have been made are appropriate for all of the three key diseases. Our key words throughout have to be "long-term", "predictable" and "sustainable." There is no point on embarking on programmes without long-term and sustainable goals.

I shall conclude by coming back to progress with the EDCTP partnership. We need to develop real partners, not just consumers. We have to have a clear link with all of our objectives. The link between science, research and poverty has already been emphasised and we need to work together in all sectors and at all levels. Referring back to Dr Mocumbi's presentation and the stated objectives of the EDCTP, it is clear that a European voice can complement effectively what is being done at national levels.

Keynote Addresses
Chair: Britta Wahren and Charles Mgone

Research capacity building in Africa: learning from the Sida/SAREC experience

Berit Olsson, Sida/SAREC

In 2003, the Swedish government put forward important policies on shared responsibilities, involving the Swedish International Development Cooperation Agency (Sida) and the Department for Research Cooperation (SAREC), which is not just a vehicle to support Sida policies, but is a research funding organ within the development agency. This distinguishes SAREC from many other agencies. SAREC's mandate is assisting developing countries in their development of research capacity and the production of new relevant knowledge, as well as promoting Swedish research co-operation.

The 2003 Swedish Government bill "Shared Responsibilities" states:

'All areas of Swedish politics shall contribute to a fair and sustainable global development.''

'Swedish development co-operation shall contribute to an environment supportive of poor people's own efforts to improve their quality of life guided by perspectives of the poor and a rights perspective.'

Most money from Sida goes directly to developing countries, especially in Africa, supporting many health-related networks and initiatives. In 2005, support for research in developing countries amounted to 500 MSEK (Million Swedish Kroner), and of this total 320 MSEK went to Africa. A total of 300 MSEK was allocated for international research and 100 MSEK went to support Swedish development research.

Sida/SAREC provide support to a wide range of regional and international research programmes including:

- Democracy and conflict studies
- Environmental economy
- Drylands
- Coastal zone management

- Genetic resources
- Reproductive health
- Tropical diseases
- HIV/AIDS
- Epidemiology
- Environmental health
- Biotechnology
- Environmental technology
- Energy.

This means working with a number of health-related networks and initiatives in addition to the EDCTP, and covering a wide range of aspects concerned with African health.

It is clear that within national projects there can be a weak working environment, and this frustrates researchers. An individual who receives external research funding is all too often frustrated by problems that prevent smooth implementation of the project. But what alternatives do they have? Should they just give up or leave, find short cuts such as getting collaborators to purchase reagents, journals, etc, or tackle the problems and try to improve them? If we are to make progress it is necessary to address the environment and the systems which are bottlenecked in a holistic way.

Bilateral research cooperation already involves seven African countries, and of these there has been long-term support for more than 25 years in Tanzania and Mozambique. This support is often comprehensive, involving focus on research universities, supporting investments and national research systems. This bilateral research cooperation has been a prolonged learning experience

- 1975-1985 Research councils - grants
- 1980- Research training
- 1985- Research environments
- 1990- Universities/Institutions
- 1995- National research training
- 2000- Knowledge systems.

For Phase 1, SAREC initially started by supporting national research councils, which were assumed to be best placed to identify priority areas for research and allocated resources to these. Phase 2 involved the training of individual researchers. Following an evaluation in 1985, it was clear that few of the countries involved had sufficient capacity for the research council function and the training of individual researchers. The focus on capacity building and research training commenced with a project-based sandwich model, without individual scholarships. Supervisors came to the institution and PhD candidates went out for short courses on areas such as laboratory work. Training was accompanied by support for libraries, laboratory equipment and other materials.

In Phase 3, we concentrated on support for groups and creative environments with more support for infrastructure. This was still based on projects, but was more comprehensive. Phase 4 supported the build-up of a research university. From the 1990s, negotiated packages of support were provided to key institutions for research development including elements in line with the university's strategic plans, research training linked to staff development, and support for research management, laboratories, library and information and communication technology (ICT) connectivity.

Phase 5a involved support for local research training, where the capacity to award PhD degrees appears to be pivotal in capacity development for research. The involvement of groups of senior and junior staff members forms the basis for an academic environment, which may interact with the international research community, as well as regional networks. Phase 5b was to support for the research system at large, where it is timely to negotiate support in relation to national commitments for research development. Sida tries to support both national and regional infrastructure for research.

The university level support is a smörgåsbord whereby there is a no set format for university/national research support but dependence on needs. So how do we decide what to support within a university? The university selects from the smörgåsbord of possibilities, in line with the university's strategic plan. Specific research project areas are defined by the researchers and refined in collaboration with their (Swedish) collaborators but are reviewed on science and relevance (including relevance to Millennium Development Goals (MDGs). Depending on the level of research experience of the researcher, there may be different roles for the collaborator. Within the university

several faculties may have research projects, which may often involve a choice of different supportive actions to facilitate the research projects. Moreover, faculty needs may differ.

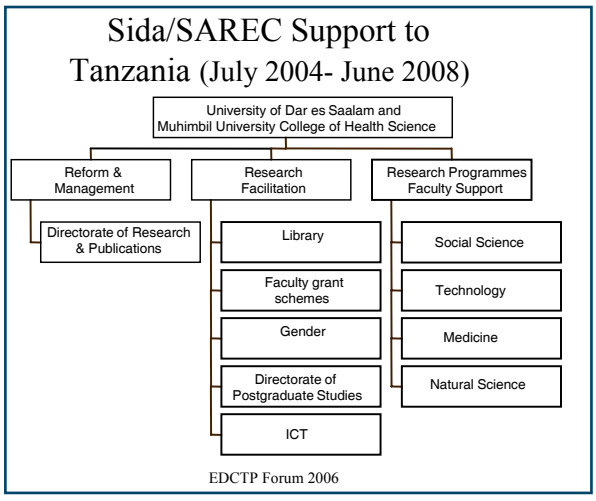
Makerere University (MU) is an example of such university support. In March 1999 problems were identified by MU about the weakness in research opportunities. These included a weak research culture, lack of scientific literature, lack of information on ICT, a weak and cumbersome administration, lack of research funds for those with PhDs to continue to do research and the policy that PhD was a prerequisite for lectureship while there were few opportunities for such training.

ICT was addressed starting in 2000 with the provision of funding to MU to devise a comprehensive IT master plan. Other donors including the Norwegian Agency for Development (NORAD). United States Agency for International Development (USAID) and African Development Bank (ADB) were asked to hold support until the master plans had been developed. In 2004 optical fibre cables were laid throughout the campus, a local area network installed and computers purchased. The results were a comprehensive network including intranet access, a library information system with electronic based cataloguing. Access to data included 7000 journal titles. The academic registry and financial management were also automated among other things.

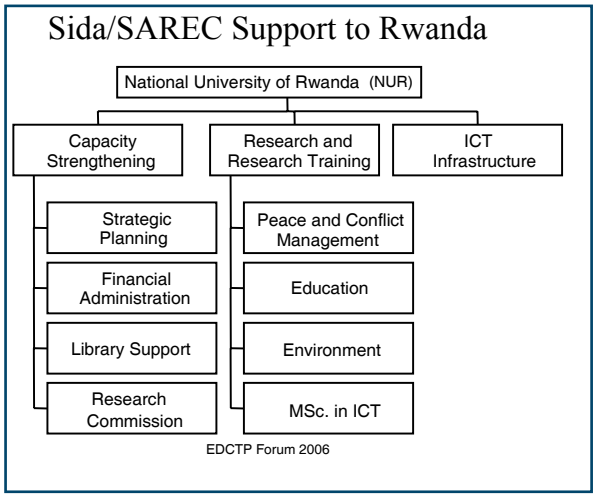
Lack of research funds also affects PhD holders and PhD aspirants. Support of faculty-based programmes was provided, aimed at supporting the supervisor to supervise. Collaboration was set up between senior Swedish researchers and their counterparts on projects of mutual interest with mutual PhD students registered at MU but with opportunity to spend time in Sweden and elsewhere. Funds were provided for the project on a needs basis. Further support was given for competitive university-wide and faculty-based research funds.

Other responses were the setting up of a Demographic Surveillance Site (DSS) at Iganga/Mayuge. This provides an opportunity for interdisciplinary research and continuous data that may be relevant for policy. PhD research courses were also supported (e.g. genes and genomes co-funded by the Karolinska Institute, where Swedish students undertake courses at MU). Support was provided to research administration in MU as well as in Sweden. A joint PhD degree agreement was signed in 2003 between the Faculty of Medicine and the Karolinska Institute. This was an historic achievement, though not SAREC's ultimate goal. Additional funding was encouraged for principal investigators supported by other agencies, thus giving an advantage to scientifically strong groups. 4-6% defined administrative costs were recognised, acknowledging that funding generates a need for increased resources. Opportunities were created for dialogue with the leadership, the university and the Ministry of Finance. MU was also asked to come up with its own comprehensive policy for encouraging research based on its research strategy which Sida could fund.

Collaboration with other funding agencies is also important, involving joint review and auditing, co-funding and liaison with stakeholder meetings, leading to possible joint reporting and rational procurement. Since no group or organisation can do this kind of work alone, we need to work with other countries and funding agencies and recognise the contribution of others. Examples of other country collaboration programmes include that of Tanzania and Rwanda as illustrated in the following charts.



Eric Buch



Discussion:

Question was raised about the relevance of e-learning programmes and the response was that many faculties could provide appropriate input, but that research learning is not based entirely on e-learning.

Another question was asked for elaboration of shortcomings found at MU in terms of research culture. It was then explained that MU requires PhDs for promotion, but that there is little real support for research programmes. Few African universities have built up a research culture in this way.

NEPAD strategies for developing regional capacity in combating diseases of poverty in Africa

Eric Buch, NEPAD

Primary objectives for New Partnership for Africa's Development (NEPAD) are to accelerate eradication of poverty in Africa and inequality with the developed world and to place African countries on a path of sustainable growth and development. Other objectives are to halt marginalisation of Africa in the globalisation process and to accelerate the empowerment of women.

This role for NEPAD was adopted by Heads of State of the African Union (AU) as its strategy for development of Africa, with United Nations (UN), Group of Eight (G8), (European Union) EU, and the World Summit on Sustainable Development (WSSD) backing. NEPAD is seen as a key facilitator at country level, helping to facilitate, mobilise, enable, leverage and build commitment for the programmes of the AU. The range of initiatives involved includes building African capacity, networks and centres of excellence.

NEPAD is unique in that it is Africa-determined and driven, and internationally positioned. It has the personal involvement of African presidents who undertake to adopt policies and strategies which include an African Peer Review Mechanism and Partnership Forum. This provides the potential to mobilise resources.The basis of the NEPAD health strategy is that there is a huge burden of preventable and treatable disease for which the response is growing, but which still needs massive scaling up. Africa is not on track to meet goals and targets. The NEPAD vision is of an Africa rid of the burden of unnecessary death and ill-health. Poverty drives ill-health; poor health leads to poverty and blocks development.

Reasons for the high burden of disease are many and varied. Poverty, marginalisation and displacement all contribute to this. Disease control in Africa is not adequate and health services remain weak and under-funded, with lack of support for health system development. In addition, African people are not sufficiently empowered and benefits are not distributed equitably.

The NEPAD strategy to address this situation was developed in 2002 and is currently being reviewed and updated. Originally some people were upset at pointing out that Africa still suffers, but analysis has shown that the factors outlined above are the main reasons for the burden.

Strategic directions have been identified as enhancing stewardship, building secure health systems and services and scaling up disease control programmes, especially those relating to childbirth. Individuals must be empowered to contribute to their own health and sufficient sustainable resources must be mobilised. These activities need to be both country- and region-specific. We are very committed to foundation building and investment is necessary to achieve this.

Piecemeal improvements will not work. Adequate funding and human resources are needed in order to progress. There is no point in asking for money when we know that this is not achievable. Our objectives must always be realistic.

Essential drugs remain widely unavailable, unaffordable, unsafe or improperly used throughout Africa. The challenges are to improve their distribution, production and pricing. We need to improve selection, purchase, cost, storage, distribution and their rational use. This means strengthened regulatory and quality assurance programmes. We also need to influence the pharmaceutical industry to make drugs and vaccines more affordable, particularly for HIV/AIDS, tuberculosis and malaria. Support is also needed for capacity for local production of essential drugs.

Although there are some important new initiatives, there is still lack of development of vaccines and more effective drugs for the treatment of HIV/AIDS, tuberculosis, malaria, trypanosomiasis and other communicable diseases, simply because the commercial opportunity is not good enough. This remains a blot on the record of the international community and the pharmaceutical industry.

So near, yet so far, is a reality regarding many of the new drugs and vaccines needed for the health problems of Africa, as a lack of research funding and potential profit stifles efforts. Though there have been some positive developments recently, we need to build on these. There is a need to advocate and leverage so that the capacity of the international pharmaceutical industry can be brought to bear on these challenges, backed up by government support on the continent and internationally.

Centres of excellence must be developed on the continent, within a sub-regional framework, as must south-south cooperation and more effective and relevant links with the north, which will continue to play an important role. Science and technology can be enhanced by utilising the framework adopted by the respective ministers, with priority initiatives and collaborating sites under development, including attention to biotechnology and traditional medicines.

The 2005 Abuja summit of the AU urged member states to take the lead in Trade-Related Aspects of Intellectual Property Rights (TRIPS) negotiations and in implementing measures identified for promoting access to affordable generic drugs. The Abuja Declaration also resolved to take all the necessary measures to produce with the support of the international community quality generic drugs in Africa, supporting industrial development. The Summit observed that one of the most intractable problems has been the unavailability of affordable drugs, coupled with the lack of demonstrable progress. Therefore the reality remains that many products remain too expensive and supply systems often unreliable. Moreover, although an increase to find appropriate new drugs and vaccines is needed, capacity is far from being harnessed for identifying urgently needed new formulations. Africa's ability to produce large volumes of quality generic drugs is a critical part of the solution. To achieve this will require African (and international) solidarity to preferentially purchase from African companies. It will also require action to remove poor quality drugs that are flooding the market, further loosening of international trade regulations, efficient registration of new products, industrial development support measures, investment in skills development and removal of trade barriers. The AU Summit had recommended that the multi-national pharmaceutical industry should increase research on the major burdens in Africa and price them more fairly at levels that reflect international solidarity. It also recommended that research into traditional medicines is scaled up and intellectual property is recognised, and that countries should speed up removal of tariff and non-tariff barriers. Additionally, it was recommended that regional Economic Community drug registration systems should be established and the AU Commission should take a lead in the development of a Pharmaceutical Manufacturing Plan for Africa.

EDCTP was launched in 2004 to focus on the need for new drugs and vaccines for the major burdens of disease in Africa, rather than leaving the continent hoping that there will be a lucky spin-off from multinational pharmaceutical research that focuses on the major burdens of the industrialised world. It seeks to bring the needed new drugs and vaccines to Africa's people.

A key factor inhibiting the development of new drugs for Africa has been the heavy investment that needs to be made, including the conduct of clinical trials, set against the limited potential profit and high financial risk. The creative use of niche funds to leverage opportunities that might otherwise be lost due to this, to facilitate a new kind of public-private partnership and support for the emergence of "global public goods" deserves all our support.

The mechanisms of the EDCTP are specifically structured to build African capacity, knowledge institutions and centres of excellence and to help stop us from bleeding experienced scientists and clinicians from the continent.

Indeed, we look forward to an extension of the Partnership beyond the three identified diseases to other major burdens on the continent, such as drugs against trypanosomiasis, leishmaniasis and vaccines against the strains of pneumococcus, meningococcus and rotavirus dominant in Africa.

In Africa we have accelerated development of new products, with price reductions of existing products and flexibility from industry. Though not quite at the required level, access to drugs (in particular ARVs) has improved with the support of government and philanthropic investment. Moreover in addition to introducing new products we need to address product registration and control, local manufacturing; cost and procurement; and the distribution and use of these products.

Registration and control are key elements. We need to develop ways to overcome delays and lack of expertise, and establish Research Ethics Committees (REC) and medicines control councils. It is necessary to control the "grey market" in poor quality drugs and to enable National Regulatory Authorities to take charge of the situation.

Manufacturing demands the development of specific skills. We need to overcome infrastructure, technology and skill gaps, and to ensure economies of scale to provide competitive prices. Important factors in our ability to break into the market are accredited regional suppliers, preferential purchasing by Africa and globally, tariff and tender advantages and the removal of tariff and non-tariff barriers. Together with government support, incentives and protection we should not have an unrealistic attitude towards pharmacoeconomics. India, for example, has taken many years to build up to the required scale. To catch up we need to fill the skills gap and to gain capital investment. Some African manufacturers are currently working at only half capacity, because they receive insufficient orders. Suppose Africa puts in place efficient local manufacturing, will the products meet the requirements and also be purchased, and how will we offset aggressive under-pricing by our competitors? For efficient procurement and use we need to further reduce costs and breakthroughs on intellectual property rights and licensing without scaring off development. Funding for research, development and drug manufacturing should be increased and transaction costs of global procurement capped while innovative and secure distribution mechanisms will help as our health systems are strengthened and expenditure grows to fill the gap.

In conclusion, let us all look forward to the EDCTP succeeding in bringing affordable new products to the market and growing African capacity. Also to it growing into other disease areas and using its base to support initiatives that see drugs reaching the poorest and most marginalised Africans.

Discussion:

A question was raised from the floor as to when solutions could be expected to the problems discussed. The response was that what we see with the EDCTP is African partners getting to know one another. NEPAD does not want to get involved in the merits of the proposals. NEPAD has a memorandum of understanding with EDCTP because it is the only real bridge between Europe and Africa, which will be supported as long as this supports NEPAD's objectives.

North-North networking: EDCTP as a vehicle for European member state collaboration and implications for partnership in Africa

Diana Dunstan, EEIG-EDCTP

Our mission in the EDCTP is to accelerate the development of new clinical interventions to fight HIV/AIDS, malaria and tuberculosis in developing countries, particularly sub-Saharan Africa, and to improve generally the quality of research in relation to these diseases. The outcome of EDCTP should be new drugs, vaccines, and enhanced research capacity (i.e. not funding mechanisms). These are areas where Europe already has strong research activities and global partnerships, but there are still major disease burdens, so we need to co-ordinate and do better.

EDCTP strategy includes integration of the existing National Programmes, listening to the needs of African scientists, identification of the gaps that EDCTP can fill, identification of opportunities to build on existing programmes and identification of partnerships for capacity strengthening in Africa. There is an opportunity to phase the strategy in line with roadmap thinking. The European portfolio addresses numerous European research activities and many in Africa across the three EDCTP diseases: AIDS, TB and malaria. There are overlaps and synergies between National Programmes (NPs) as well as gaps that EDCTP can fill. Various other programmes are best delivered through NPs.

Networking principles are activities which contribute to the integrated EDCTP programme, such as exchange of information, scientific workshops, training schemes and joint funding. However, the levels of networking do vary between funding agencies, institutions and individual projects.

The assembly established a European Network of National Programmes (ENNP), and each member state nominated a National Programme Networking officer (ENO). The objectives were to analyse and compare national funding mechanisms; identify national research activities relevant to EDCTP; identify gaps, overlaps and potential synergies between the national research programmes; develop strategies and proposals for harmonisation and European networking; advise on mechanisms for co-funding; help implement strategies approved by the General Assembly; and coordinate networking activities on behalf of the member states.

Several lessons have been learned. Scientists have already established good networks, and it takes time to create new research networks. Similarly, it takes time for funding agencies to merge schemes. EDCTP has initiated the process of integration during the first few years, but this is a long-term process. We cannot reach final objectives at the start. Integration is a process that takes time to evolve, which EDCTP can only achieve if there is future funding. Joint funding is an attractive option, but there are several barriers. There are different funding mechanisms; some are top down, others are bottom up. Legal structures vary, and there are different timings for decisions and different priorities. Research partnerships cannot be artificially created; they evolve.

How can we obtain oversight of the European portfolio? This is a question which EDCTP has not yet properly tackled.There are several potential solutions for the current situation. Networking grants are one option, but they can be slow to implement. Joint-calls are a proven technique, but need to be linked to existing activities. Brokered calls offer opportunities, but demand clear transparency and equal access. There are also other possibilities such as consortia, where existing partnerships combine their efforts. These are some of the things that EDCTP has done or can do – we have launched networking grants but have not had huge response from researchers.

The current strategy is for joint and brokered calls. Joint calls are driven by existing national funding programmes where new money is to be allocated through a call. The continuing role of the partnership board (PB) is to have a strategic perspective of National Programmes. The PB will define the EDCTP strategy in context of NPs and will work with the secretariat to develop the European landscape. There are many good existing research partnerships with Africa, linking with European networks and collaborating on clinical trial sites, training schemes and partner institutions. Several European research

institutions operate directly in Africa, such as the Medical Research Council (MRC) Gambia.

We can see several excellent opportunities for the EDCTP. We can open up new sites for partnership with Europe and promote science driven by needs of African people and scientists. We can also assist the DCCC to establish networks within Africa. It is clear that Africa needs to be directly involved in the process of integrating European NPs. However, there are still difficulties in making European funding available to African scientists. We need to remember that European partners will have other pressures, such as ensuring publication of studies and personal career development. However, we do have practical examples of successful collaborations. In order to maximise effectiveness in poverty related diseases (PRD) research, EDCTP seeks to work closely with and to both complement and supplement other bodies working in this area. One example is the EDCTP in partnership with African AIDS Vaccine Programme (AAVP). EDCTP also actively engages with the New Partnership for Africa's Development (NEPAD), including their Science and Technology Unit that deals with product development, as well as with the African Union Commission for Social Services.

EDCTP as partner of the Global HIV Vaccine Enterprise will launch a joint call with the Bill & Melinda Gates Foundation on capacity building for HIV vaccine clinical trials in 2006.

Some lessons have been learned from EDCTP efforts to strengthen sites in Africa. Creation of an enabling environment is essential, together with strengthening capacity of individuals and institutions. We need to involve all stakeholders such as communities, health-care providers, researchers and institutions in the context of on-going projects. Evaluation of research capacity development is essential, as is an integrated capacity development plan. There is a need to encourage capacity development to be driven by the countries, as defined by a sustainability plan.

Discussion

A question was raised whether EDCTP would still have open calls for proposals. The response was that EDCTP would use different approaches including joint calls and brokering and that this matter was to be resolved in the subsequently planned EDCTP constituency and stakeholders meetings.

Simon Agwale

ROUND TABLE 1

North-North networking: co-funding and supplementary grants in North-South partnerships

Simon Agwale

EDCTP was established in 2003 based on Article 169, which stipulated joint European research collaboration with €200 million contribution from EC, to be matched with funds from European National Programmes. North-north and north-south collaborations in joint programmes were established for the promotion of coordination and pooling of resources among EU member states, together with promotion of alliances between European institutes and African partners. There were also joint EDCTP and European National Programme calls for proposals. The expected benefits of partnerships in terms of co-funding were that different partners have different areas of interest, levels of resources to commit to partnerships and different lifespan of contributions. Co-funding can be taken as a sign of commitment (or condition) to the partnership.

Among the key lessons we have learned are that there is good willingness of partners to cooperate; EU states provide funds and expertise, while African states provide ownership of the programme including staff, infrastructure, expertise, study subjects, etc. However, coordinating EU states in pooling of resources remains a big challenge. There are undefined "national programmes"; coordination is a full-time staff activity; and there is diversity of interests in the three poverty-related diseases (PRDs) among different member states. Moreover, alliances between European institutes and African partners mostly follow colonial links, which makes the promotion of weaker institutions and scientists difficult and could weaken south-south networks.

So what should be the best way forward? Possibilities include continued advocacy for political support (the continuing task of the EDCTP High Representative), with intensified and sustained coordination of EU states. We need a strategy to involve and promote African institutes that are left behind because they have no historical European partnerships (e.g. establishment of regional nodes of excellence). At the same time we must facilitate south-south collaborations by working on the assumption that this is a feasible venture, and build capacity to initiate and sustain networks. We can use centers formed with northern influence and resources (usually referred to by our Northern partners as "our centers") as hubs for capacity building and support. Dependence on part-time experts should stop and we must address the need to alleviate financial constraints. Our Northern partners undoubtedly have many strengths. How can we leverage these to support our efforts? The answers lie in good and sustainable partnerships. What are these "true partnerships"? They need to be based on joint cause, planning, implementation, mutual trust, and other factors. This has to be the case in all joint-calls. A joint effort with more than one European partner is probably the best option. This addresses the diverse interests among the European states in the three PRDs. Delivery can be via a programme or a project. Programme delivery is probably best, as this will eliminate lack of funding due to preferences of donor states.

In Europe we have the requirements of Article 169; different partners have different areas of interest, different levels of resources to commit to partnerships and different lifespan of contributions. In Africa we have good willingness of African partners to own the programmes; sidelining of broader European-African and African-African partnerships due to emphasis of maintenance of colonial ties. Therefore, the way forward should be through continued advocacy for political support, with strong north-north, north-south and south-south networking strategies, coupled with implementation of the concept of regional nodes of excellence in Africa to support weak and emerging centres. This means investing in true partnerships involving all European Economic Interest Group states and emphasis on delivery at programme rather than project level.

Abdoulaye Djimde

Multicentre partnerships for clinical trials in Africa

Abdoulaye Djimbe, Mali

Recent progress has been made in several areas in the understanding of the immunology, pathogenesis and mode of transmission of the main poverty-related diseases. This progress, together with a sharp increase in interest and funding from the scientific community and various international funding agencies carries much hope for a brighter future in the fight against these diseases.

As a result several promising vaccines, drugs, diagnostics and devices have been discovered and carried to the phase of clinical testing. These have included new products; new-old products; old-new products; and combinations of these.

It is essential to conduct these trials in those very countries where the diseases are most prevalent. Yet, the basic infrastructure is often lacking. There may be a weak or inadequate, outdated legal and regulatory environment as well as scarce human expertise in Africa. In addition to these bottlenecks, ethical oversight is often absent or inadequate.

Some of the solutions to this situation are clear. We can address training of local scientists; we need to improve capacity development and empower local professionals. Probably the key is to develop multicentre partnerships. For example, multicentre clinical trials can be investigator-driven (e.g. some EDCTP projects), or can be pharma/sponsor driven. Support can come from a wide range of networked African institutions such as the East African Network for Monitoring Antimalarial Treatment (EANMAT), the West African Network for Monitoring Antimalarial Treatment (WANMAT), Multilateral Initiative for Malaria-Antimalarial Drug Resistance Network (MIM-ADRN), African Malaria Network Trust (AMANET), West African Consortium for Clinical Studies (WACCS) and the Malaria Clinical Trials Alliance/International Network of Field Sites with Continuous Demographic Evaluation of Populations and Their Health in Developing Countries (MCTA/INDEPTH) among others.

In order to proceed, we need to ask ourselves:

- Why do we need multicentre partnerships in Africa?
- What aspects of clinical trials should be covered in those partnerships?
- What can we learn from the existing partnerships?
- What needs improvement and how can we make these changes happen?
- How can we assess the impact of existing networks?
- What new types of partnerships are needed?

This makes it all the more indispensable for African institutions to team up and work together in close collaboration with their Northern partners. Multicentre partnerships are necessary at all stages of clinical trials in Africa, including planning, recruitment, conduct of trials, data management, ethics and dissemination of information. Several recent initiatives either driven from within Africa or inspired by the North are attempting to promote closer ties between African scientists and trial centers. These initiatives all need to be tested in the field in Africa.

EDCTP - the European Commission view

Octavi Quintana Trias, EC

The overall goal for the EDCTP is to reduce poverty in developing countries by improving the health of the populations. This will be done by developing new clinical interventions to fight HIV/AIDS, malaria and tuberculosis through European research integration, and in partnership with African countries. The European Commission (EC) attaches great importance to the successful implementation of the EDCTP initiative to alleviate poverty in developing countries (especially sub-Saharan Africa) through the control of malaria, TB and HIV and by co-ordination and integration of Member State National Programmes. EDCTP is a pilot initiative which has highly sensitive political issues for the EC, namely, development of a sustainable and genuine partnership between Europe and Africa and integration of research programmes of Member States towards a more structured and coherent approach.

The EC has supported the request for a cost-neutral extension of the Grant Agreement for 2 years. The EC recognises the nature and the scale of difficulties EDCTP has been faced with and acknowledges the efforts undertaken in the last year to improve the EDCTP structure and performance.

There are high international expectations from the EDCTP and the strong EC commitment towards the success of EDCTP is reflected in the agreement to extend funding to 2010, with some conditions. There are four key EC conditions in connection with this extension:

Focus on accelerated activities on clinical trials through effective implementation of Article 169 objectives

Request for a plan of activities demonstrating a clear increase of clinical trials and capacity building activities in Africa, with a timetable showing the disbursement of funds up to the agreed new contractual period of September 2010

Request for a Roadmap on coordination of NPs. This will be a detailed roadmap describing accelerated and concrete progress on the coordination of National Programme with recordable integration indicators

Member states will match the EC contribution at the level of EDCTP funded projects already foreseen in the last calls or by direct contributions. Co-funding will be one of the instruments to achieve the integration of National Programmes.

There will be an external evaluation of the progress of the EDCTP, commencing in November 2006. The conclusions will have important lessons for other projects based on Article 169. Therefore EDCTP faces some important challenges:

- Achieve promising results in the field of activities in Africa and in the integration of National Programmes
- Generate a real joint programme between member states, targeted to the South
- Mobilise industry for poverty-related disease (PRD) research
- Establish ownership of the EDCTP by African countries on all levels including political, scientific and institutional.

Discussion

A speaker from the floor noted that the forum has emphasised N-N partnerships, but asked what EDCTP has done to address relations with North America. The response was that the EDCTP is happy to collaborate with North America or other funding agencies.

Another speaker from the floor pointed out that every project must be assessed purely on scientific grounds and that there is a need to be imaginative in approaching this and avoiding conflicts of interest. Participation in projects is through member states not institutions, but different states have different mechanisms. For example, there are differences between Spain, Germany and United Kingdom.

Another speaker commented that those from Africa, particularly benefiting from cooperation, must think of the best ways to go into partnership using seed money to support cooperative institutional research with some form of legal binding and a legal institution. It is important that African leaders and new Senior scientists and researchers are seen to lead.

Concern was raised that co-funding could limit the active participation of African researchers as principal investigators and how would joint calls and brokering simplify African participation. It was also pointed out that joint-calls might be a double-edged sword, as they may hinder national requirements for funding. The Chair pointed out that everyone would agree that although it would be best for all funds to be available for all research, there are legal obligations to direct money in particular areas.

It was suggested that there is need to understand the need to stimulate research in other countries and agencies such as the Irish foreign affairs committee are looking for such opportunities to support. Capacity development would be valuable. Although each state has a legal right to apply directly for funding many people with good ideas do not know who to direct them to. Therefore, harmonisation will help. It was also pointed out that EDCTP is discussing with African countries and scientists to identify the most urgent problems for Africa. EDCTP guidelines are now available in English, French and Portuguese and countries and governments are realising the benefits of combining their efforts.

Wrap-up of Round Table I

Simon Agwale

Close the gap between the pilot experience and the need for quick actions: Speed up the process
Consider product approach versus project approach
Challenge European member states to be more creative and have less bureaucratic ways in getting funds to the EDCTP
New funding procedures at EDCTP must not lose transparency but ensure open competition. Moreover, this must not lose behind those who are not in established networks yet
Enforce ongoing lobbying for research in African countries by African researchers
African research priorities need stronger voice through DCCC
Nodes of excellence need to support weaker centres in Africa
Increase funding and resources in poorer countries through DCCC as a link.

Andrew Kitua

PLENARY SESSION 2

Chairs: Simon Agwale (Nigeria) and Laura Brum (Portugal)

Theme:
Making clinical trials run more cost-effectively and without unnecessary constraints.

Harmonising regulatory and ethics requirements, ensuring efficient trial/project management, networking, sharing of infrastructure and knowledge, sustaining clinical research capacity, centralising/standardising quality assurance and laboratory support.

South-South networking: need for nodes of excellence

Andrew Kitua, Tanzania

Africa bears 90% of the world burden of disease, yet has access to only 10% of funds to deal with this situation. We are challenged with major communicable diseases as well as poor or weak clinical services and high mortality caused by preventable conditions. We are further challenged by inadequate human resource capacity and weak infrastructure for research in support of clinical practices. Additionally, we have the challenge of upcoming non-communicable diseases to deal with.

So how would African nodes of excellence address this situation? There is an urgent need for deliberate efforts to mitigate these diseases. Our purpose should therefore be to create and maintain sufficient capacity within Africa to formulate and conduct clinical research with the focus on poverty related diseases of African relevance in order to accelerate the creation of new drugs and tools for treatment and to raise the quality of clinical practices. The objectives will be to create and/or strengthen identified institutions to become specialised research and training centres in clinical research, ensuring that such centres have strong capacities in basic required skills for clinical research such as good clinical practice (GCP), good clinical laboratory practice (GCLP), data management and research ethics. There is a need to identify and strengthen centres of higher learning to host quality training courses in essential basic and applied sciences related to the study and control of major poverty related diseases and to enhance research collaboration and networking by creating fellowships and exchange programmes between African institutions coordinated by the identified centres.

The strategy to achieve these objectives is to identify and strengthen the capacities of selected African institutions to conduct and host training in specific, but fundamental areas of clinical research on poverty related diseases. EDCTP will accredit the centres as regional hubs or nodes of excellence for training.

The nodes will be linked to smaller centres, increasing the scope of networking. EDCTP will not actually own any of the centres, but have an important coordinating function between them.

Regional research methodology workshops will be conducted to identify talents in the fields identified above and support them to develop research proposals for their MSc or PhD, and sponsor them to train in the identified nodes.

EDCTP will require and support the identified nodes of excellence to establish fellowships and exchange programmes in partnership with other institutions within their region. These strategies will be implemented by the ECTCP Secretariat and local institutions assessing the institutional capacity, followed by an invitation to apply for accreditation as EDCTP nodes of excellence. Centres with insufficient capacity can apply to increase capacity in identified areas such as GCP, GCLP, data management, quality control, ethics and others. Training, support, exchange programmes, scholarships, etc., will be coordinated via the EDCTP. A training programme for PhD and MSc in specialised areas will be established and supported by the EDCTP.

The outputs from this process will include increased production of PhD and MSc graduates who are linked with their institutions and who have been trained in relevant areas within their working environment. It will foster the establishment of strong regional networks in clinical research fields linked to EDCTP stimulate enhanced capacity to access global funds.

What are the advantages from this approach? It will

maximise effective use of limited resources and accelerate production in numbers and quality of clinical research scientists. It will increase career opportunities and enabling environment and incentives leading to retention of better trained scientists while attracting those in the Diaspora. There will be better participation and ownership of the means for solving Africa's own health problems, allowing for more equitable partnerships with northern institutions.

This strategy needs to be implemented through an institutional base, to ensure integration and long-term sustainability of the process. Moreover, it will be easier to get government recognition and funding commitments on this basis. An institutional base will be better suited to create generations of scientists links in research and training, thus broadening career opportunities and development.. The key strengths of this proposal are that African research and training institutions already exist at different levels of competence. There is political will to succeed, and African Governments have committed to achieve Millennium Development Goals in the Abuja Declaration. The suggested approach fits well with the New Partnership for Africa's Development (NEPAD) strategy of creating centres of excellence within sub-regional framework and strengthening south-south cooperation which will enable south-south partnerships to access other funding. It also accelerates the capacity building component of EDCTP.

In conclusion, we suggest the creation of strong networks around nodes of excellence among southern academic and research institutions to accelerate the generation of quality scientists in sufficient numbers to mitigate the high disease burden. It will provide the required enabling environment offering better career opportunities and incentives that prevent brain-drain. The south and Africa in particular, will have better active participation and ownership of the means of solving its own health problems. It will furthermore raise the professional quality and capacity of southern institutions to forge better and equal partnership with northern institutions.

Discussion

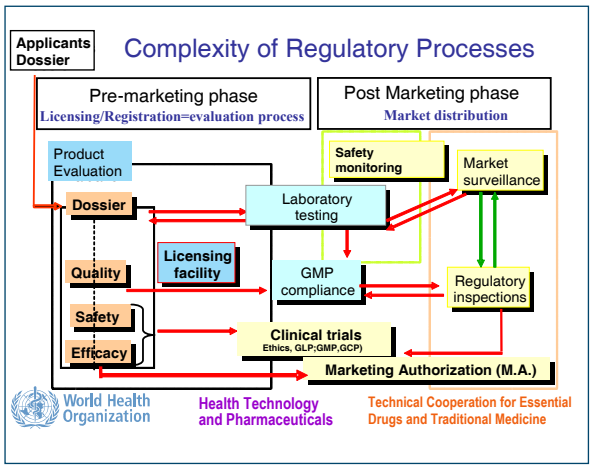
In response to a question from the floor, It was noted that although there may be efforts to set up similar initiatives, these would not have the vision of the current proposal. One way to maximize resources is to make an inventory of similar initiatives. Another speaker pointed out that training is important, especially in the field of epidemiology and that perhaps one or two universities could concentrate on such an area.

Harmonising drug regulation in Africa

Precious Matsoso, World Health Organisation

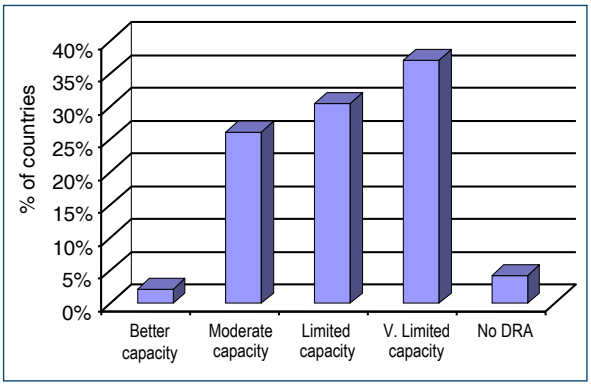
Growth in biomedical science and technological advances include in the case of science growth from innovative chemistry (serendipity), to molecular drug design (empiricism) and genetics (prediction); medicine from art to experience to evidence; and technology, from manual to automation and computer-controlled operations.

This has meant that the complexity of the regulatory processes and requirements has increased.



There are still significant regulatory gaps. Of the World Health Organisation 192 member states, 1/6 have

developed regulatory systems; 1/2 have varying levels of development and operational capacity and 1/3 have limited or no capacity. This situation is reflected in the status of African Medicine Regulatory Authorities.



In terms of clinical trials in sub-Saharan Africa, 1179 eligible randomised controlled trials have been conducted over the past 50 years. 154 trials had over 500 participants and 79 trials over 1000. Almost half of these trials were conducted in South Africa (n=565). Four other countries accounted for another quarter (Nigeria 98, Kenya 89, Gambia 56 and Tanzania 50). Only 19 countries had more than one trial per million population.

South Africa accounted for over 90% of all trials on malignant, respiratory (31/33), digestive (69/76), musculoskeletal (27/27) and congenital (2/2) diseases. It also accounts for 75-90% of trials on diabetes (10/13), endocrine (9/10), cardiovascular (75/99), and genitourinary (29/34) diseases and injuries (26/31), but for only 14% of trials on infectious and parasitic diseases (74/150).

The absence of national directories of research activities in most African and other developing countries means that the magnitude of research is underestimated.

Integration between regions means that regional and sub-regional approaches and global initiatives are considered for pooling resources to deal with capacity challenges, reducing duplication of effort and redirection of resources. As an example of this, the Gulf Cooperation Council (GCC) and Pan-American Health Organisation (PAHO) have good experiences in procurement). It also means standardising requirements and setting up legal mechanisms for joint negotiation as well as streamlining regulatory processes.

We have seen progress in integration among African countries. Countries have removed barriers to trade (e.g. tariffs). It may be appropriate to advocate for removal of taxes and tariffs for essential medicines. Interconnectivity has improved in terms of transport links and telecommunication. The Economic Community Of West African States (ECOWAS), the Southern African Development Community (SADC) and Communauté Économique et Monétaire de l'Afrique Centrale (CEMAC) are good examples.

There have, however, been some drawbacks to the process including conflicts, a high disease burden, a multiplicity of regional economic communities (leading to duplication, overlaps and waste of scarce resources). Transport costs are still very high and the integration process proceeds at a slow pace. This is a strong case for harmonisation. There are regional and subregional approaches and global initiatives that are considered for pooling resources to deal with capacity challenges. There are numerous current regional medicine regulatory initiatives:

- AFRO (East African Community (EAC), ECOWAS, CEMAC, SADC, and Union Economique et Monétaire Ouest Africaine (UEMOA)
- AMRO (PAHNDRA, ANDEAN, MECOSUR)
- SEARO/WPRO (ASEAN)
- EURO (EMEA,NIS, CADREAC)
- EMRO (GCC).
- In addition there are major global initiatives:
- WHO prequalification (supports procurement, but has strong regulatory focus)
- DCVRN (Developing Countries Vaccine Regulatory Network of 9 countries established by WHO)
- EU Article 58, Scientific opinion for medicines exported from EU but not for sale in EU, partnership with WHO
- FDA Tentative approval of the President's Emergency Plan for AIDS Relief (PEPFAR) linked products, confidentiality agreement with WHO
- International Conference on Harmonisation/Global

Cooperation Group (ICH GCG) - Participation of some sub-regional blocs, SADC, ASEAN, PANDRA

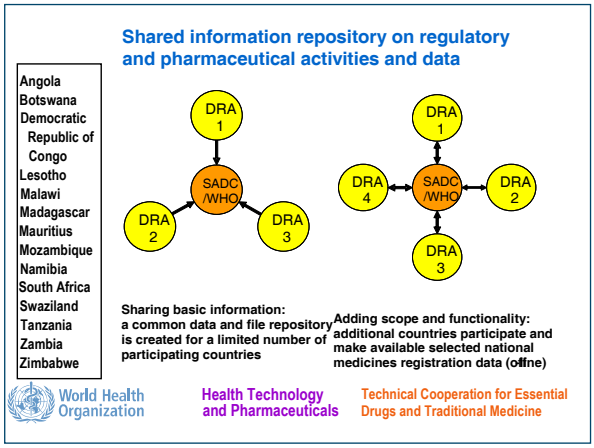
The anticipated benefit from harmonisation is that it will improve approval and review processes to match the increasing complexity of applications (biotechnology products, priority medicines and those derived from rapidly evolving technologies, new drug and vaccine delivery technologies and devices)

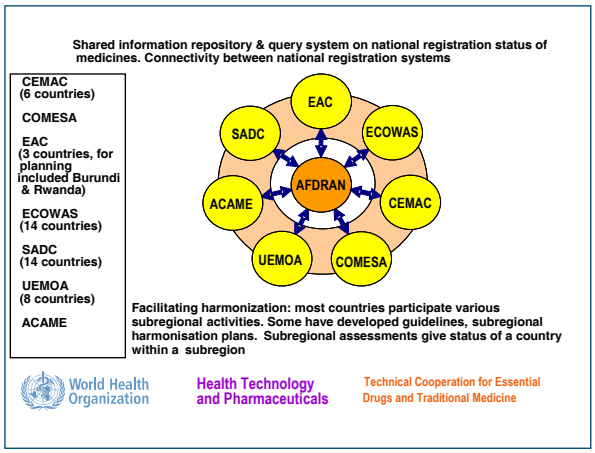
There are still challenges. Global initiatives are a good start but not a complete solution for resource-constrained settings. Adaptation is needed to help developing countries deal with technical complexities and capacity challenges they face. This depends largely on the successful implementation of a model, which acknowledges and incorporates the sharing of regulatory burden between participating countries.

There are strategic harmonisation problems in the Eastern Mediterranean region which include the five chronic emergency countries; GCC is only for 6 countries; production capacity exists, with strong industry; regional pooled procurement for Gulf States is well established; and most countries use pricing as part of regulatory approval.

In terms of medicine registration, the situation is that the regional median time for approval of new medicines differs, shortest being in Bahrain and that GCC has centralised procedure for registration of medicines in Arab states of the Gulf.

There are also strategic issues in the AFRO region including the AFRO strategic frameworks on local production, medicine regulation and procurement; legal instruments present in some of the sub-regions and the high disease burden such as HIV/AIDS, malaria and tuberculosis. Medicine regulation, regional median approval of medicine registration differs from 3 months to 2 years (study involving 3 countries and the Middle East countries). There is maximisation of WHO prequalification benefits, FDA tentative approval and Article 58. SADC; EAC and ECOWAS, have Regional medicines regulatory plans developed for 5 years.





Opportunities for exist for engagement including exchange of information and regulatory issues such as joint assessments, inspections and dossier evaluation. Twinning arrangements can be organised with more stringent authorities.

There are opportunities with legal issues, where we can address intellectual property rights and TRIPS flexibilities, as well as strengthened patent searching capacities of national and regional offices (the African Intellectual Property Organization (OAPI), the African Regional Intellectual Property Organization (ARIPO)). Policy issues lead to further opportunities. We can review economic policy objectives in the regions, utilise spare capacity and ensure economies of scale, and review industrial and infrastructural requirements for technology transfer and clinical research. Pooled procurement is another opportunity. We can share resources and expertise, remove taxes and tariffs barriers, improve local delivery structures and strengthen management and administration of regional structures.

Leen Rigouts

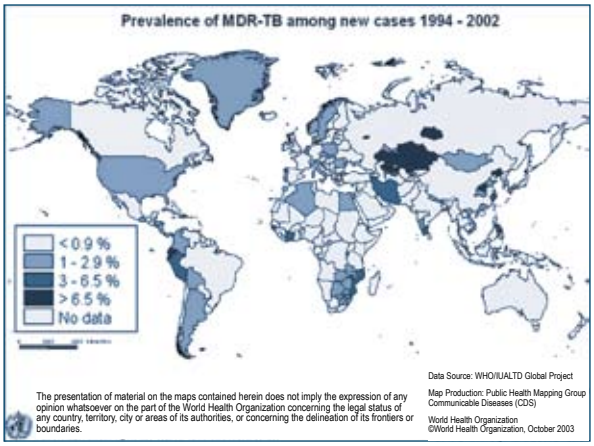
Discussion

A question was asked whether pharmacovigilance is a prerequisite for WHO opening the approval process, when a product is not marketed in Europe. The response was that a package was being formulated to address this situation. A decision has to be made on how to measure the benefit profile for that product, especially bearing in mind that most of the data is usually collected in the north.

The WHO/IUATLD Supra-National Reference Laboratory Network for Tuberculosis

Leen Rigouts, Belgium

The Supra-National Reference Laboratory was created in 1994 to support global drug resistance surveillance (DRS). The objectives of this global project in terms of anti-TB drug resistance surveillance were to estimate the magnitude of drug resistance globally and to determine trends. The project would evaluate the progress of TB programmes and provide data to inform policy decisions and strengthen laboratory networks. Various publications have recorded progress: guidelines for surveillance of drug resistance in tuberculosis (1997/2006); Reports 1-3 (1997-2004). Surveys between 1994 demonstrated the prevalence of multi-drug resistant tuberculosis (MDR-TB) among new cases of infection.



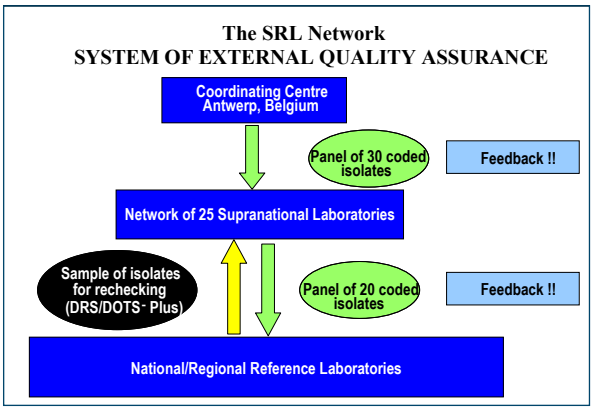
The principles followed by SRL include accurate sampling of population under study, differentiation between new and previously treated cases and quality assured laboratory results.

The original project work was undertaken with 16 laboratories as selected by WHO, the exclusive source that financed the project. Work was concentrated in Europe, although there were 2 laboratories in India. There was an extreme scarcity of good laboratories. There are now 26 laboratories.

The Supra-national Laboratory Network (SRLN) 2005 now has links with more than 150 countries. Among these are include 2 in Africa, 5 in the Americas, 1 in the Middle East, 11 in Europe, 2 in South Asia and 5 in Western Pacific.

The terms of reference of the SRL are that it is a permanent functional laboratory, with commitment to support at least two countries, providing proficiency testing (PT), quality assurance (QA) of surveys/DOTS-Plus and training where necessary. There is a commitment to participate in meetings and studies, with 5 annual network meetings and 2 ongoing second-line drug (SLD) studies. SRL is also committed to participate in annual External Quality Assurance (EQA) PT and fulfil performance criteria.

The coordinating laboratory for organisation of proficiency testing for rounds 1 to 5 was in Ottawa,



Canada. This succeeded in standardisation of techniques, validation of methods and improved precision. For rounds 6 to 11 the coordinating laboratory was in Antwerp, Belgium and continuation of previous efforts now involved expansion to 24 laboratories.

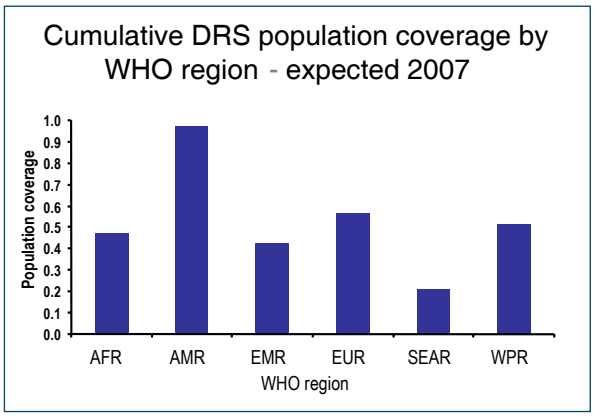
We are now dealing with 20 strains; 10 of those in duplicate. These have attained significance after two successive rounds Lot Quality Assurance Testing (LQAT). With no errors, 95% efficiency is reached; with maximum

2 errors, 90% efficiency is reached. The panel targets are: 50% prevalence of resistance (any drug); non-MDR subset; various combinations of resistance; clinically well documented.

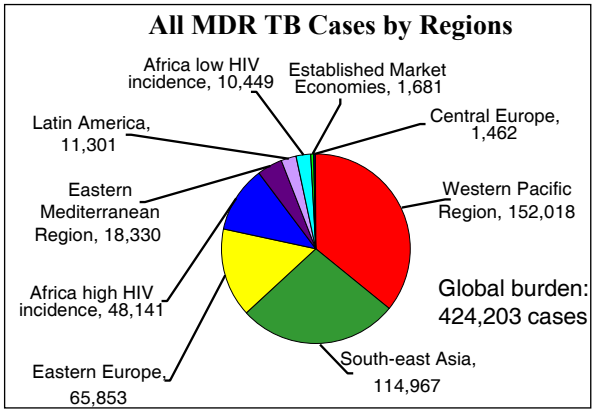
SRL proficiency looks good. Over time persistent excess errors were isoniazid, none; rifampicin, one laboratory; streptomycin, one laboratory; and ethambutol, two laboratories. Excess errors were not linked to specific methods and were periodically seen in several laboratories. However, these errors may be over-estimated possibly due to exclusion of some problem strains.

There are limitations on samples for re-checking of drug resistant strains (DRS), such as problems with international transport of TB strains, lack of funding and within Africa, links with SRL are not clearly defined or are scattered over different SRLs.

The Network contribution to TB control is terms of drug resistance surveillance is better standardisation of testing, quality assurance of surveys and availability of more reliable data from new cases is continuously being collected, leading to forecasts for 2007 as shown in the following chart.



Almost 45% of African countries have carried out at least one baseline drug resistance survey, but not without great difficulty. Poor performance and restricted capacity of National Reference Laboratories has been the primary obstacle in organising baseline surveys. Overburdened national TB control programmes (NTPs) and lack of human resources necessitates a prioritisation of other activities before repeat surveys. This has resulted in very few trend data in the region.



The contribution of the network to TB control is in strengthening TB laboratory services, which are, however, still limited with focus activities only among the TB high-burden countries of Eastern Europe, Central Asia and the Far East, but hardly in Africa.

The Network has also broadened the scope by support of the Acid Fast Bacilli (AFB) microscopy network and strengthening and expansion of the use of culture for diagnosis. For phase I (1994-2002), the first and second reports noted that MDR-TB is widespread, with localised and severe epidemics, especially in the former Soviet Union and China. This led to policy recommendations for the start of DOTS-Plus/Green Light Committes (GLC), expansion of pilots, evaluation of projects, and increased access. For phase II (2002 to the present), the third DRS report noted that we must evaluate category II in some settings, as well as category I in areas of high drug resistance prevalence, and look at both Drug Resistance Surveys (DRS) and HIV. It was recommended that the treatment guidelines be updated.

In terms of policy development, population based first line drug surveys are important for trend analysis (reliable drug susceptibility testing (DST) for isoniazid and rifampicin). There is a clear need to supplement population based DRS with small cohort studies relevant for DOTS-Plus, with small surveys combined with history of treatment and antibiotic use to inform DOTS-Plus regimens. Second line DST is much less reliable and lab capacity for second line is not well developed locally.

Challenges remaining include improvement of drug resistance testing and capacity building in terms of reliability and clinical significance in low and middle

Jelle Thole

income countries and investigation of the relative priority of DRS versus AFB-microscopy. Our role in general TB research is not yet defined. It was not our original objective and is still limited to some SRLs.

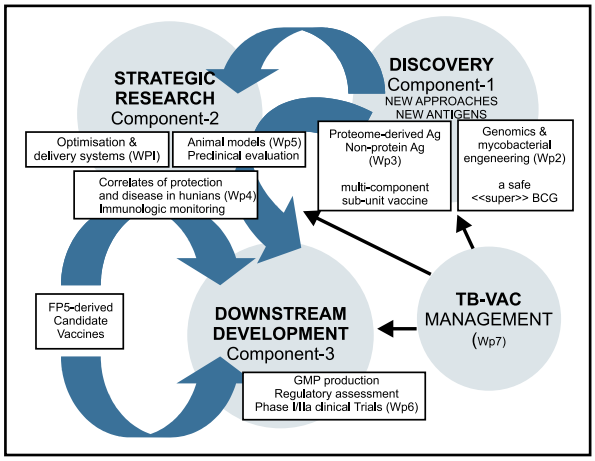
An integrated project for the design and testing of vaccine candidates against tuberculosis: identification, development and clinical studies

Jelle Thole, the Netherlands

TB-VAC is an integrated project which aims to discover, develop and clinically test new TB vaccines, and may harbour some of the new vaccines that may be developed in the later clinical stages by the EDCTP partnerships. Tuberculosis is a worldwide problem. It is caused by an acid fast bacterium with which 30 % of the world population is infected and at risk of developing TB. There are 8 million new cases per year, 2 million deaths, 1 million of which are due to HIV and TB co-infection and drug resistant forms.

BCG vaccine is not effective in the young adult population. In the context of the European Union (EU) frameworks, initiatives have been developed to design new vaccines that might replace or improve BCG. In the sixth Framework Programme of the European Commission (FP6) a project was funded as TB-VAC. The main goals of TB-VAC are to discover, optimise and clinically test vaccines. This means the discovery and optimisation of vaccine candidates and identification of correlates of protection and disease. Further goals are capacity building for clinical evaluation of phase I trials in developing countries and evaluation of lead candidates in small clinical phase I trials. There is liaison with other consortia such as the Mucosal Vaccines for Poverty Related Diseases (MUVAPRED), Aeras Global TB Vaccine Foundation and EDCTP to enable further large clinical trials in African countries. We are dealing with 29 European and 4 African research institutions and 2 major vaccine producers. The project budget is approximately €20 million over five years.

The project is divided into three parts, from discovery, to strategic research to downstream development of



vaccines and correlates. In all, there are more than 60 activities.

Discovery has led to a whole series of project that include:

Work package 2 (WP2) -- Live vaccines and immunmodulatory ligands (Carlos Martin, UNIZAR, Zaragoza, ES)

Improved BCG and attenuated TB strains as live vaccines

Identification and effects immunomodulatory ligands (LAM, granuloma formation).

This project focuses on discovery of new live vaccines base on BCG/Attenuated TB; A small part is devoted to immunodulatory effects of ligands of mycobacteria tuberculosis that may induce granuloma formation, may play a role in pathology and perhaps should be avoided in new vaccines.

Work package 3 (WP3) -- Antigen discovery (Stefan Kaufmann, MPIIB, Berlin)

Novel antigen components with a focus on genus/ strain specific and latency associated antigens

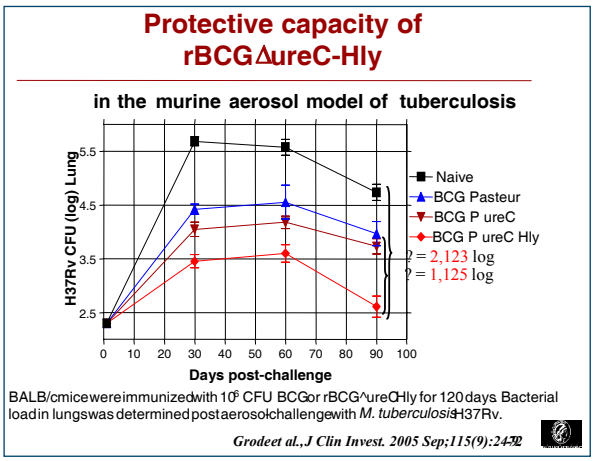
Prime boost strategies

Murine latency models.

This focuses on discovery of new subunit antigens (focus on antigens from Beijing clade, and those associated with latency); and on developing models for latency, with the aim to design vaccines against latent bacteria, a goal that may well go beyond the time frame of the current project.

Vaccines for strategic and downstream development: S.Kauffman group: BCG to listeriolysin of listeria

monocytogenes that enables BCG to enter into cytoplasm and access other APC pathways; Second mutation in urea to increase PH to improve effectiveness of HLY.



Strategic:

Work package 1 (WP1) -- Optimisation of existing vaccine candidates (Peter Andersen, SSI, Kopenhagen, DK)

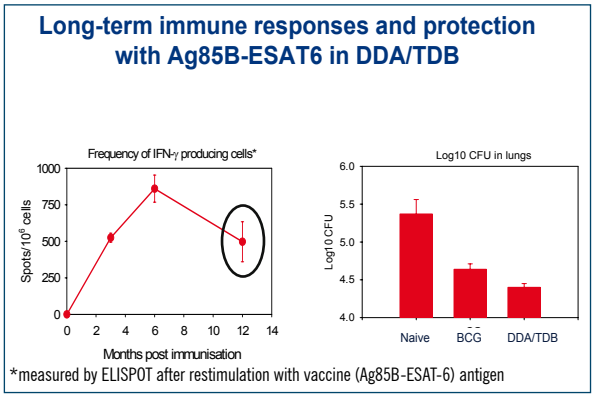
- Optimisation of delivery and composition of subunit vaccines (HYB1 Ag85B-ESAT6 fusion)
- Delivery: liposomes, niosomes, microspheres, viral vectors
- Adjuvants, immunomodulators: mycobacterial lipids, CpG-oligodeoxynucleotides (ODN) etc.
- Post-translational effects (E.coli vs. Mycobacterium produced)
- Effect on protection, memory/maintenance, pathology, Th1/Th2

This is a second generation vaccine candidates for downstream development in phase I trials.

DDA/TDB is a novel adjuvant for the efficient induction of both cell-mediated and humoral immune response. It is a stable formulation based on cationic liposomes plus an immunomodulator.

PA group Kopenhagen

Cationic liposomes Dimethyl dioctadecyl ammonium bromide containing liposomes containing immunomodulator TDB (LipoVAC) – DDA was unstable but with mixing a stable component was formulated.



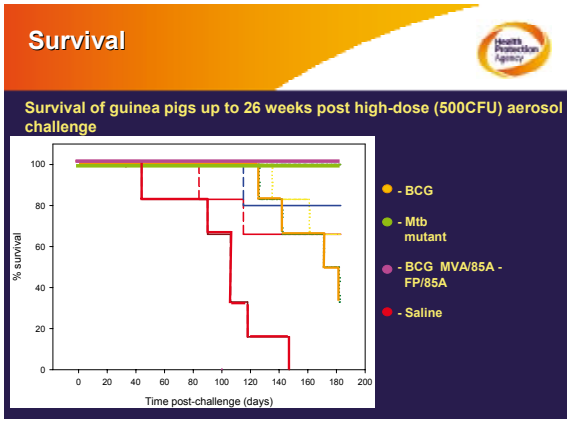
Work package 5 (WP5) Preclinical evaluation and selection of vaccine candidates

Ann Rawkins, HPA-PD, UK

This project is a preclinical model for evaluation of safety, immunogenicity and protective efficacy, using guinea pigs, macaques and specific mice models. Small part of the project is devoted to non-protein components of mycobacteria. These are second generation vaccine candidates for downstream development in phase I trials.

Experiments are conducted to allow head-to-head comparison of lead candidates. Candidates are selected based on pre-set criteria such as evidence of efficacy in other models, safety and clinical relevance.

Survival:



Survival curves of a recent experiment (example is combined with pathology) evaluate improved vaccines or vaccine strategies as compared to BCG.

Optimisation of existing vaccine candidates towards phase I trials

Strategic research: WP4 (WPL Tom Ottenhoff, LUMC, Leiden)

To identify and develop correlates of protection and markers of TB disease and TB immunopathology.

Classically restricted CD4 and CD8 T cells specific for *M. tuberculosis*

Unconventional T cells specific for *M. tuberculosis*

Surrogate markers, new assays and gene expression profiling of in vivo host immunity

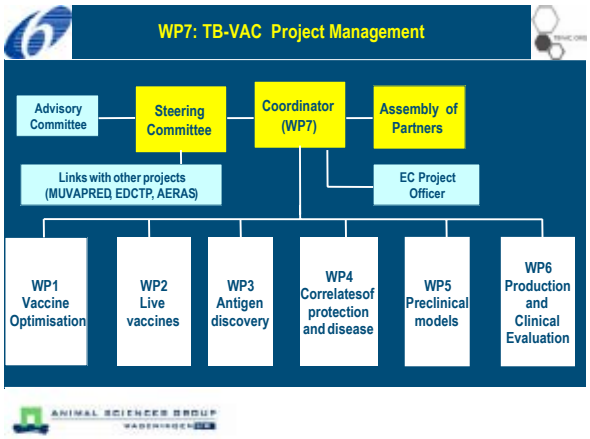
An important aspect is impact on time and resources for evaluation of vaccine candidates in future clinical trials and early identification of the most effective vaccines. Many candidates are being identified and further optimised. Validation may be the next step which in part may go beyond time frame of TB-VAC. However, still this is an important issue and we keep this firmly on board. An example of a candidate correlate may be HBHA (Locht, Mascart).

Clinical development

WP6 Optimisation of existing vaccine candidates towards Phase I trials (WPL, Paul-Henry Lambert, Geneva)

- GMP production
- Regulatory aspects of vaccine development including pre-clinical files
- Phase I clinical trials, in TB endemic and non-endemic areas.

EDCTP will be involved in selection of candidates for further trials. Several vaccines are being clinically developed. FP5 and FP6.



The management of the consortium involves detailed consideration of legal and ethical issues. Communication is an important component of management. Internal communications involve a reporting tool via the website, with details of activities and expenditure. Steering committee meetings are summarised via teleconference or in face-to face meetings. WP meetings are held twice each year, and there is an Annual Assembly. For external communication, there is a 12 month report plus new implementation plan to EC, together with specific meetings and press conferences. External communications are supported by a web site (www.tb-vac.org) and by various publications.

Ensuring quality, safety and efficacy of vaccines - Vaccine regulatory issues in African countries

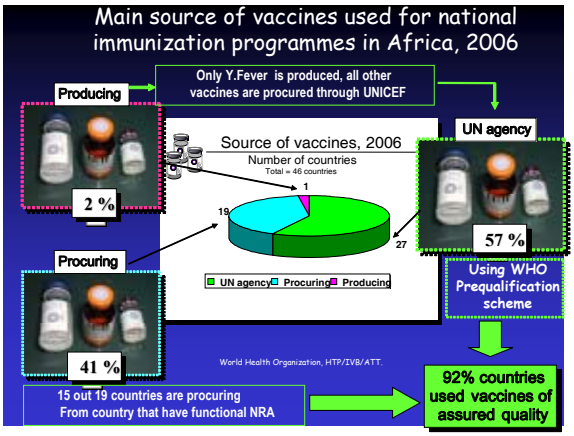
Lahouari Bergharbi

There are many issues and challenges which need to be met by regulatory systems in Africa. Regarding scientific issues there is limited expertise in new vaccines science (combination vaccines, DNA, adjuvant, preservative, vector, etc.); huge viral diversity (HIV, Rotavirus) and complex geographic distribution; weak registration and licensing process when dealing with biologicals; inadequate immune response to natural infection; immune correlates of protection are difficult to establish; vaccine response is not always better than natural

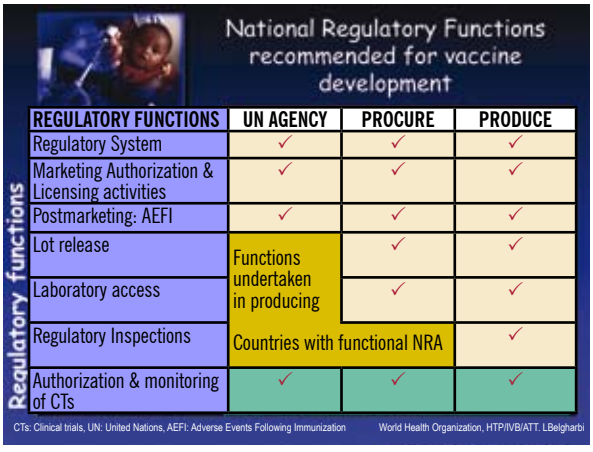
infection; lack of appropriate models indicating that human trials are key to develop research; definition of efficacy and end points are key in clinical trial protocol. Similarly, there are numerous regulatory issues which need to be addressed. These include lack or weak regulations which may not be consistent with international standards (lot release, GMP, GCP, GLP, etc.); overlapping of roles of parties (National Regulatory Authorities (NRA) and ethics review committees); limited knowledge of foreign-sponsored regulations; absence of provision for expedited reviews; regulations/guidelines in place require updating (article 58, ECBS guidelines); no inspection of clinical trials sites; lack of procedures to assess, authorise and monitor clinical trials; and limited or lack of pharmacovigilance and laboratory capacity.

The challenges also encompass managerial issues such as limited human resources for regulation; lack of funding to develop NRA oversight; no or limited local manufacturing capacity; limited exchange or sharing of regulatory information to guide decision making; sponsors and manufacturers influence decision making that is not consistent with international standards.

Assured quality sources of vaccines procured through WHO prequalification, 2006 include 14 industrialised countries and 6 developing countries which include only Senegal from Africa. Globally 24 manufacturers produce 65 pre-qualified vaccines which are used in 112 countries on 53% of the total population.



WHO's goal to ensure quality, safety and efficacy of vaccines is to be assured that 100% of vaccines used in all national immunisation programmes are of assured quality. The definition of "Assured quality vaccines" for a vaccine producing country is that the National Regulatory Authority (NRA) is independent from vaccine manufacturer and or procurement system; the NRA is fully functional with the system in place and the six regulatory functions implemented; there are no unresolved reported problems with the vaccine. These requirements are guided by the Experts' Committee on Standardisation of Biologicals (ECBS) recommendations on safety, efficacy and quality issued in WHO Technical Report Series (TSR).



The Global Training Network (GTN) has trained 1200 staff from 100 countries since 1996 with support from World Bank (WB), Japan International Cooperation Agency (JICA), UK Department for International Development (DFID), Australian government's overseas aid program

(AusAid), World Health Organisation (WHO), European Union (EU), International Development Bank (IDB), Asian Development Bank (ADB), The United Nations Children's Fund (UNICEF) and recently the European and Developing Countries Clinical Trials Partnership (EDCTP).

Activities planned and implemented:

By the end of 2010 : 37 out of 46 countries will have developed appropriate critical regulatory functions:

2006: 6 countries
2007: 6 countries
2008: 8 countries
2009: 8 countries
2010: 9 countries

A range of activities is recommended to strengthen vaccine regulatory systems in Africa:

Sensitisation of country and stakeholders
Development of Institutional Development Plans (IDP)
Joint inspection of clinical trials (CTs) sites
Networks and forum to exchange and share regulatory information
Development of appropriate regulations and procedures
NRA assessment and follow up visits to monitor impact
Training on critical regulatory functions
Joint review of clinical trials applications (CTA)
Building centres of excellence and roster of regulatory/ scientific experts.

Current progress in strengthening vaccine regulatory systems in Africa

Activities conducted	Status
1.Fund raising plan	Completed
2. Three NRA planning workshops countries with IDP* for 28 countries	Completed
3. Meeting of Developing Countries Vaccines Regulatory Network (DCVRN)	Completed
4.Joint review of CTs applications for MeningoA + Workshop on regulatory procedures for clinical evaluation of vaccines+forum for the evaluation of clinical data of rotavirus vaccines for registration purposes	Completed
5. Sensitisation/advocacy workshop for all country stakeholders	1 out 3 completed
6. GTN training provided to AFR countries on vaccine regulation	9 out of 28 countries completed
7. GTN Training provided to AFR countries on PMS/AEFI	15 out of 28 completed
8. GTN training provided to AFR countries on clinical evaluation	6 out of 28 countries completed

Regional initiatives 2004-2007 – objectives and expected outcome:

- Planning NRA activities through development of Institutional Development Plans (completed in 28 countries)
- Promote communication among NRAs and raise awareness on regulatory changes and challenges (Developing Countries Vaccine Regulatory Network (DCVRN) input, African Vaccine Regulators Forum (AVAREF), Joint review, Joint inspection of CTs, sensitization workshops, Uganda)
- Promote communication between sponsors/ regulators/ethics committees/ research centres to determine specific needs for different types of vaccines (same as point 2)
- Provide expert support to assess suitability of clinical data for registration : DCVRN, AVAREF, training on clinical evaluation
- Facilitate capacity building activities and availability of expertise for regulatory review of clinical trial applications and monitoring of clinical trials: NRA assessment, follow up visits, meeting of regulators and training on relevant regulatory functions. Joint review of CTAs, joint inspection, AVAREF
- Plan and organise training on relevant regulatory functions that are critical for African NRAs: Clinical evaluation, post-marketing surveillance (PMS)/adverse events following immunisation (AEFI) and regulation. DCVRN on regulatory inspections of CTs.

WHO/EDCTP activities planned and conducted to support the development of a harmonised regulatory framework in Africa, 2005-2007 (Planning Phase 2005)

January, May and December 2005:

Three NRA planning workshops for 28 countries (Addis, Ouagadougou & Gaborone): The main outcome is 28 Institutional Development Plans (IDP) to implement a harmonised/common regulatory framework to ensure quality, safety and efficacy of vaccines and relevant clinical trials conducted in Africa. Involved countries were Ghana, The Gambia, Ethiopia, Kenya, Uganda, Senegal, Mali, Central African Republic, Togo, Guinea, Chad, Benin, Cameroon, Niger, Rwanda, Angola, Botswana, DRC, Malawi, Namibia, Rwanda, South Africa, Tanzania, Zambia & Zimbabwe (EDCTP / WHO funding)

March 2005:

Training course on authorisation/approval of clinical trials (Pretoria, South Africa). The main outcome was provision of knowledge to regulators and vaccine experts about principles of vaccine clinical evaluation relevant to authorisation and monitoring of clinical trials. Involved countries were Ghana, the Gambia, Uganda, Kenya, Nigeria and Ethiopia (WHO funding)

September 2005:

Workshop on Regulatory Procedures for clinical evaluation of Vaccines (Addis, Ethiopia). The main outcome was development of templates procedures for submission/review of clinical trials applications and integration of activities and importation/release of clinical batches. Countries involved were Botswana, Ghana, Cameroon, Ethiopia, The Gambia, Uganda, Kenya, Mali, Nigeria, Senegal, Tanzania, Zambia, South Africa (WHO funding)

December 2005:

Regulatory forum on clinical evaluation of rotavirus vaccines (Botswana 12/05) The main outcome was: (a) Presentation and discussion of scientific information on issues that may affect the efficacy and safety of rotavirus vaccines; and (b) Allow countries to make a final decision with regards to registration of rotavirus vaccines. Involved countries were Botswana, Ghana, Gambia, Zimbabwe, Malawi, Cote d'Ivoire, South Africa, Zambia, and Cameroon through WHO funding.

The implementation phase began during 2006.

January-May 2006:

EDCTP/WHO agreement was developed and signed. The main outcome was support of €360.000 for 18 months (June 2006-December.2007). Involved countries were Ghana, Uganda, Tanzania, Nigeria, Malawi, The Gambia, Mozambique, Rwanda, Gabon, Mali, Burkina Faso, Kenya, Ethiopia, Zambia, Cote D'Ivoire (EDCTP funding).

June 2006:

Joint review of clinical trial activities of Conjugate Meningitis A vaccine (Banjul, The Gambia). The main outcome of the meeting was a Review of clinical trials applications for Phase II conjugate meningitis.A vaccine by Mali and the Gambia national regulatory and vaccine experts on relevant gaps/missing information concerning meningitis A vaccine clinical trials. Involved countries were The Gambia, Mali, Ghana, Senegal (WHO funding).

July and August 2006:

Country workshop in Uganda & Senegal to sensitize all stakeholders for implementation of IDP recommendations. The main outcome was updated institutional development plan (IDP) and coordination plan to involved all stakeholders in follow up implementation of recommendations. Involved countries were Senegal and Uganda (WHO funding).

September 2006:

African Vaccine Regulators' Forum (AVAREF), Accra, Ghana, 19-22 September completed as planned with funding from EDCTP.

Development and translation of training material

for the Benin (French) and Ethiopian (English) courses on authorisation and monitoring of clinical trials – completed.

Planned activities for 2007

January 2007:
Joint inspection of clinical trials of conjugate meningo A vaccine (EDCTP funding)

March 2007:
Workshop on regulatory inspections of clinical trials (tentative) (EDCTP funding)

April and October:2007:
AVAREF meeting

September.2007
Training for 10 countries (French speaking) on authorisation and monitoring of clinical trials (EDCTP funding)

February and June 2007:
Training for 20 countries (English speaking) on authorisation and monitoring of clinical trials (Addis, Ethiopia) (EDCTP funding)

January-December:
Follow up IDP and monitoring activities in 5 countries

Progress and impact on vaccine regulatory systems

68 NRA assessments concluded (October 1998-December 2005); 220 regulatory experts recruited by April 2006.

Changes documented to improve regulatory oversight of vaccines

- Plan developed and implemented for all countries involved
- Training planned and conducted for all countries involved
- Template procedures to evaluate CTs applications
- Amended regulation to involve NRA in evaluation of CTs
- Clarification of roles and responsibilities to authorise CTs
- Focal point and training requested for staff
- Guidelines discussed, amended for endorsement by MoH
- Coordination among NRA/Ethics Committee to authorise CTs
- First African Vaccine Regulators' Forum held (Ghana, Accra, September 2006).

First African Vaccine Regulators' Forum (AVAREF), September 2006
Participants - 19 Countries, NRA and ethics committee
Experienced NRAs – European Agency for Evaluation of Medicinal Products (EMEA) & US Food and Drug Administration (US-FDA)
Product sponsors - GSK, MVP-PATH, WRAIR, US NIH
Themes - selected disease of importance: HIV, malaria, Meningitis A and Rotavirus, regulators
Funded by - WHO, EDCTP; MVP-PATH and AAVP
Issues - Low funding for NRAs, conflict of interest because of limiting resources, lack of confidence in IRBs, separate institutions, access epidemiological data, laboratory capacity, ADR investigation, information sharing network.
Recommendations from the Forum:

- Need to expand and sustain capacity building in vaccine trials oversight
- Joint review of clinical trial application should be expanded
- Strong interest in conducting joint inspection of clinical trials sites
- Increase training opportunities to develop regulatory capacity
- Develop guidance for clarification of roles of NRA & ethics committees
- Pharmacovigilance provision re article 58 should be flexible for implementation
- Develop clinical trials case definition of efficacy for malaria vaccines
- Secretariat's forum is hosted in WHO/AFRO.

Next steps are to plan for the second phase and identify

resources to sustain the WHO/EDCTP initiative (initial phase was granted €300.000, to be completed by December 2007). In addition we shall put in place support in priority coordination and monitoring of initiatives (forum, networking, African experts in regional coordination mechanisms/institutions). We will support training, coordinate curriculum development and expand to all relevant institutions (NRA, ethics, research, pharmacovigilance centre) and expand networking among key international leaders and country partners. IT will also be expanded and utilised to advocate and publish best practices, experience and develop online training.

Experiences in the conduct of clinical trials

Kalifa Bojang

When considering clinical trials, we must consider the key elements. These are firstly, personnel. For successful trials we need adequate numbers of trained personnel and trained support staff. In terms of facilities and equipment we need appropriate field sites and clinics, as well as a laboratory. We need to consider epidemiology and the disease to be studied, as well as the population. We must also operate within an ethical code of conduct. Above all we must consider the options for capacity building in all that we do.

We operate from several MRC field sites in The Gambia, but for this example, we will look at Basse. The Basse Field Station is located 373 km from the coast. It is used to conduct several clinical trials on malaria and acute respiratory tract infection (ARI). The Basse Field Station offers excellent accommodation and laboratory facilities. Communications are good including internet connectivity and access to mobile and land phones. This is a rural community in which the study area has been thoroughly mapped. The ward at the Basse Health Centre has an inpatient facility with 18 paediatric beds and a 24-hour nursing staff. The OPD facility has a clinical examination and treatment room. Major renovations took place in 2001. A back-up generator is available and an ambulance for referral to Bansang hospital is also available. The study population is characterised by the mapping of the study area, census of the target population, data on migration and occupation, birth rate, age-specific deaths and prevalence of other diseases that might alter responses to the disease of interest.

Epidemiological studies are influenced by geographical and seasonal distribution of the disease of interest, including prevalence, expected incidence by age, effect on morbidity, mortality and clinical manifestation as well as interaction with other diseases. This process may require several years of study.

Transportation in this rural area is based on motor cycles, which are very convenient; on all-terrain motor vehicles to transport study subjects and investigators; and other forms of transport as needed.

Diagnostic facilities are available for common medical conditions. Facilities at the local health centre may require upgrading. We collaborate with other institutions to assist in diagnosis in selected cases. Our criteria for choice of instrumentation are that it must be user-friendly, easy to troubleshoot, repair and service and the supplier must offer customer support.

Detection and investigation of serious adverse events is a very important factor. The most appropriate method will depend on local circumstances. In rural areas will need a mortality surveillance system, which can be based of a village reporter, on verbal autopsy. The disadvantage of verbal autopsy, however, is that it is difficult to standardize and validate.

Internet connectivity is important for effective communication, providing access to Information and research tools, facilitating training, and offering an increased sense of membership and involvement in the global scientific community.

Information about the trial is disseminated by distribution of flyers, community meetings, drama performances, radio and television. Good community relations and full participation are essential. We discuss with all stakeholders - not just with the study subjects or parents. We build relationships with the community; never promise what we cannot deliver. We also give prompt feedback to the community, and discuss post-trial expectations.

Ethical conduct of research means obtaining informed consent, and working with the Institutional Review Board,

Tumani Corrah

with oversight by Data Safety Monitoring Board (DSMB), local safety monitors, etc. as well as setting up an efficient mechanism for adverse event reporting. Informed consent is not straightforward. The consent forms may be too long and technical, and it is possible to overemphasise benefits and minimise risk. The doctor/investigator has a dual role, and this can lead to a therapeutic misconception on the part of patients. We regard informed consent as a process rather than as a document.

Oversight is provided largely by the MRC Scientific Coordinating Committee (SCC). Members comprise senior staff of the Unit, meeting monthly to review proposals for research projects and debate wider scientific topics. Approved projects are submitted to the Ethics Committee for review. The Gambia Government/MRC Laboratories Joint Ethics Committee judges all projects that have been reviewed and approved by the SCC. The main considerations are safety and well-being of the participants, issues of personal intrusion and real or potential benefit that the trial or project offers to the Gambian people. The Committee has guidelines that deal with informed consent, volumes of blood samples to be collected, incentives for participation, and such matters. The local safety monitor acts as an advocate, providing clinical advice on any illness to study subjects, especially in circumstances in which treatment might influence the course of the trial. The monitor also provides advice to the investigators on whether a set of clinical circumstances in a study warrants formal notification to the DSMC. The Independent Data Safety Monitoring Committee (IDMC) has the overall responsibility to protect the ethical and safety interests of research participants. Specific responsibilities may include making recommendations for safety monitoring procedures, providing guidelines related to stopping or putting a study on hold due to an increased risk, and reviews analyses safety data collected during the trial. Risk management needs careful consideration. Contingency plans are necessary in case of political upheaval, currency devaluation, natural disasters, health and safety hazards such as road traffic accidents and possible deterioration in access to the study site.

Capacity building is a process supporting all trials. It involves assessment of existing trial sites; GCP and GCLP; clinical facilities; follow-up capacity; data management; sample storage; statistical support. In terms of training, we need to develop short-term courses and workshops, including GCP training workshops; project management training; Institutional Review Board (IRB) Training; bioethics workshops. Training awards can be linked to ongoing research programmes. We need leadership and management training; training for local researchers for principal investigator positions; strengthened financial accounting in institutions; specialised training in academic institutions on clinical trials design and execution, epidemiology, immunology etc.

The key lessons we have learned are that developing a trial site takes a lot of time and requires resources and that maintaining the site is difficult and time consuming. In addition, community-based trials need community partnership.

Sustaining trial capability: strategies for building and retaining skills

Tumani Corrah, The Gambia

The key question for science in Africa is why good people are lost and the main challenge is how to reverse this. The science gap between Africa and the rest of the world is widening and under business-as-usual this gap will continue to grow. A significant number of centres of research excellence in Africa are largely expatriate-run organisations. Whilst the commitment, output and contribution of the expatriate scientists at these centres to the African development agenda are evident, the long-term sustainability of these institutions will require leadership from within the continent. In most cases, the prospects for a talented, young African physician or scientist returning to Africa with a postgraduate degree from a prestigious foreign university are bleak; low and insecure salaries from weak, under-equipped institutions and few prospects for obtaining sufficient internal or external resources to conduct competitive research. Not surprisingly, many do not return home.

A two-pronged approach is suggested to address some of these problems:

Identify, nurture and develop talent from the earliest possible stage, through an attractive and well-supported

development and professional pathway.

Remove economic and career obstacles to re-entry for expatriate African researchers wanting to return to the continent.

According to the Commission for Africa Report, specific action is needed for strengthening science, engineering and technology capacity. Currently, overall scientific capacity is limited and restricted to a few regions, and the science gap between Africa and the rest of the world is widening.

In summary, the present situation is of inadequate training environments, under-resourced institutions, few development opportunities and low salaries. The challenge, therefore, is to build and sustain internationally competitive, cost-effective centres of scientific excellence on the continent, and to empower African scientists to develop and lead these centres.

The haemorrhage of African talent can be seen in the Gambia experience, where there will have been 60 years of MRC laboratories by 2007. However, to date only a few Gambian-African scientists have scaled the heights. MRC Gambia has the following training manifesto:

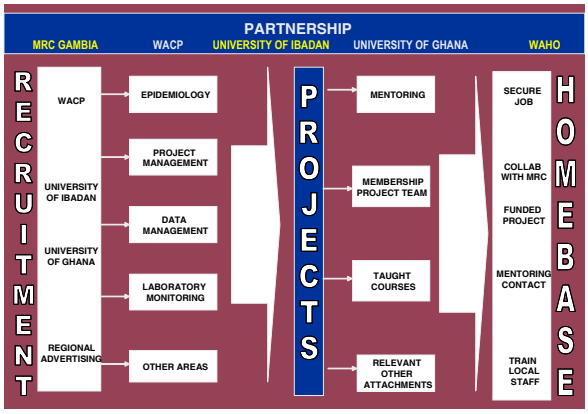
Quality, cost-effective training to facilitate the mission of the Unit to produce science of the highest quality in a Unit of the highest quality, which has strong local, regional and international links and is making an impact on health locally and globally.

Note that capacity building has always been on the agenda; however, it is time for a change in direction. In the past, within Medical Research Centre there has always been strict division of labour. In the 1980s there were a senior research nurse (SRN) and two postgraduates. In the Greenwood era things improved. There were laboratory technicians, access to the Open University and by 2000, 7 Gambian PhDs including other West Africans, and numerous MScs.

The current situation is that we have a fledgling university which can award certificates, distance-based learning diploma (University of Westminster); distance-based learning BSc (University of South Africa) and PhDs. Moreover there is a dedicated training department with two international staff posts. School leavers can be entered in a one-year MRC programme, and three to four years fast-track UK BSc programme. So far, two have graduated with first class honours; however, only one full-time studentship can be supported at any one time. The University of The Gambia has an MRC-funded head of Paediatrics. The University is also supported by lectures given by MRC scientists and internships and electives for students. Overseas postgraduate training is undertaken, together with students from West Africa and elsewhere on the continent.

MRC Gambia provides excellent facilities in Africa, with research and collaborative projects and research methodology training:

An excellent environment is provided for post-doctoral



fellowships together with an ongoing successful PhD programme. However, there is still a lack of post doctoral funding. Four-year fellowships, can be offered, with links to an overseas collaborator and the experience of working in a top institution overseas. In this way we can promote the acquisition of technical skills, attract post-doctoral Gambians and other Africans back from abroad.

We hope that our graduates can compete for international positions and become involved in multi-country studies. There is now an opportunity for infectious and tropical diseases training for UK and EU students. We propose making available four post-doctoral positions per year. In addition, GCP/GCLP competence will be increased with appropriate training.

Funding issues can be addressed by EDCTP-funded MSc, PhD, and post doctoral and career development fellowships. Other opportunities for funding include the Gates Grand Challenges and the European Commission.

In conclusion, we are developing structured training with well-defined professional development pathways supported by functional laboratory facilities. These factors, together with appropriate compensation will eventually provide a critical mass of staff. Our ultimate objective is that Africa becomes as the continent of choice for our most promising scientists.

ROUND TABLE II

Introductory presentations: Capacity building for clinical trials in Africa

Kalifa Bojang, MRC Gambia

Development of new interventions against infectious diseases involve phased sseries of studies designed and executed according to scientifically rigorous and appropriate ethical standards so as to demonstrate safety, optimise dose and schedule and demonstrate efficacy. Clinical trials are important steps in this process and must be conducted in such a way as to assure the integrity of the process and validity of the outcomes. In order to undertake such trials countries must have in place capabilities and infrastructure needed to ensure proper conduct of studies, including ethical review of the protocol, volunteer recruitment, protocol adherence, documentation, quality assurance and control, and data management.

There is currently a mismatch between disease burden caused by infectious diseases and the technical and human capacity of many African countries to conduct clinical trials of new interventions to combat these diseases. The number of people affected, infected or dying from HIV/AIDS, malaria and TB is on the increase, but few people in developing countries have access to effective malaria interventions and anti-retroviral drugs. There is a lack of appropriate resources to tackle these diseases and insufficient capacity to carry out clinical trials of new interventions to combat them. It is therefore important to build research capability of African researchers so they can undertake clinical trials in their own local settings. Building indigenous research capacity will enable African scientists to contribute to the development of appropriate control strategies in their countries and translate results of studies carried out elsewhere into their individual national settings. Eventually results of such clinical trials will contribute to finding appropriate solutions to health problems in Africa.

The objectives of such a programme are to train leaders in science and public health and establish centres of excellence to facilitate outstanding scientific research. We need to facilitate trainees in assuming positions of responsibility and authority and attract and train new researchers and managers, while facilitating leveraging of resources for added support through competitive processes. More effective clinical trial management means addressing control and accountability; effective communication; ethical conduct; and planning and execution of clinical trials. Our strategies to implement improvements in these factors include establishing clear institutional goals and objectives with clear mission statements as well as carrying out a comprehensive situation analysis which will identify major gaps in capacity and define the competencies required. Based on this, we can design a comprehensive capacity programme to enhance competence. The integrated development plan will include training of scientists, technicians and other cadres as well as infrastructure development and proposals writing for funding. Key elements of capacity building are obtaining adequate numbers of trained key personnel and support staff; adequate facilities including equipment and supplies; an ethical framework for research; and funding.

Severe challenges are faced by scientists in resource-poor settings, notably limited financial resources and infrastructure to support research; absence of administrative and political support, and poor remuneration and limited career prospects. In this setting, personnel need training in many relevant disciplines, which include clinical, biostatistics, immunology, epidemiology, data management, molecular biology, social science and financial management among others. What are the strategies to employ to achieve these ends? Short-term training can take the form of workshops, short courses, re-entry grants, while longer-tem grants will support degree courses. Partnerships are valuable in providing technical assistance, and technology transfer, while networking means bringing together information exchange, scientific conferences, exchange programmes and mentorship.

Developing trial infrastructure involves assessment of existing trial sites. This must also be supported by provision of internet connectivity, which is now an

essential tool for the scientific community. Finally, we need to ensure effective planning and execution of clinical trials, with all of the detail that this involves. The formula for success in capacity building will be a capable and committed leadership, supported by adequate and consistent funding, with appropriate remuneration and career structures for staff. An appropriate and supportive infrastructure is needed, with modern services, working in a stable political, economic and social environment.

In conclusion, capacity building is a long term effort that requires visionary leadership and resources. Individual capacity building is a continuous process essential for sustained capability in research and control. To achieve these set of goals, support from multiple agencies is often required

Discussion:

A speaker from the floor observed that data from African clinical trials is analysed elsewhere, and that addressing this situation would be an important part of capacity building.

Another speaker asked how trial findings were translated into policy in the Gambia. The response was that there are regular meetings with the Ministry of Health who are kept well updated of the findings, and the treatment policies have changed as result of this.

One speaker commented that in Europe volunteers are paid while in Africa this is not done. The response was that although compensation of volunteers is an important issue it must be noted that researchers should not provide anything which could be seen as an inducement to participate in research.

A question was raised regarding the role of the African Union (AU). The AU is currently pulling together money from various international funders.

A participant from the floor proposed that EDCTP should not concentrate on long postgraduate training of up to 5 years because there are many graduates to be trained but rather should concentrate on short- and medium term programmes.

A DCCC member observed that we have different forms of training in different institutes, and we need to learn from examples in a systematic way.

Another questioner asked how the model could cope with increased funding to build centres of excellence. The response was that with the coordination of EDCTP, both regions and centres are being looked into. The issue of national versus regions has to be considered. Based on capacity it is possible to group together, choose and invite appropriate northern partners and funds.

Concerned was raised on the criteria that would be used to select centres of excellence. Ownership is an important concept for Africans, and one needs to be clear about where to draw the line between the sponsors and the researchers. EDCTP has not yet established the criteria.

A question directed to Dr Bojang concerned supplementing of funding. How do researchers sustain a clinical trial site in the absence of a sponsor interested in studies on a particular new compound? The response was that sites require people and skills to attract funds from multiple sources. These capacities and competences need to be developed at the sites. Capacity planning needs to be embedded in the long-term planning of projects. .A number of factors need consideration. One obvious threat is the question of time. Leadership often comes from people who have excelled academically but may not have ample time dedicated to research activities..

It was observed that a centre, rather than a site, will usually have more than one function. After completing a trial, what then? We are forced to provide a site maintenance fund. This could mean switching from e.g. a vaccine study to drug studies. The centre can be networked, with shared facilities and expertise.

It was pointed out that staff are often recruited from the public sector to join a research project. Caution should be taken not to undermine the public sector.. In The Gambia there is an agreement with the government that staff cannot be employed from the public sector without agreement from their line managers. Another speaker asked how to maintain a site once the trial is over, and how to maintain talent in Africa? The solution is to raise sufficient funds. We need creative financing which could build up into something like a pan-African trust fund, as in

Steve Wayling

ethics, where there is an overhead devoted to the subject. This could be a sustainability tax to feed into the trust fund, with money distributed on the basis of scientific excellence.

Another speaker remarked that while he greatly empathised with the principle of capacity building, he remained to be convinced about the role of the EDCTP phase II trials. There is a limited number of such trials to be performed though ideally he would like to see the EDCTP funding a series of rolling phase II studies. Following this line of reasoning, there are limited number of African trials that could be funded. Should EDCTP spread its money, or target a small number of high quality studies? The response was that one might use a portfolio approach which would hopefully deliver a project. The EDCTP wants to build capacity to make sure that outcomes are of top standard. The EDCTP should be able to both build and retain capacity. EDCTP's approach is not to build capacity in isolation, but to build capacity in the context of clinical trials and coupling it with utilisation.

Framework for career development in clinical trials

Steve Wayling, WHO Geneva

Based on the principle that people are the foundation of research, TDR continues to invest in developing the skilled human resources needed to address the prevention, treatment and control of tropical diseases. The Career Development Fellowships which TDR initiated in 2000 are intended to better target training to priority areas and to develop local resources that TDR could draw upon in the future. The goal of these fellowships is to train individuals in situ with relevant partners in order to develop specialised skills not readily taught in academic centres. On completing their fellowships, the individuals return to their home institutes to add to the local capacity and become a valuable resource for TDR and their region. TDR has now completed five years of collaboration with Glaxo-SmithKline Biologicals in training, through doing, in clinical research and development. In addition, TDR has partnered with other groups as placement for career development fellowships including Serono Biotech, Wellcome-Trust and the WHO Regional Offices. Other partners have included Pfizer, the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) and the Infectious Diseases Institute.

Major lessons have been learned over the past 15 years, and it is clear that there is a need for harmonisation of the status of researchers in their respective settings. We need to create enabling and attractive research environments and improve sustainability of staff retention by allowing researchers to pay themselves. Sustainability will also be improved by creation of interest in pursuing a clinical trials career at student levels in schools. Later in their careers, we need to discourage senior researchers from keeping young scientists at lower levels for a long time.

We should reduce over-emphasis on developing MDs only, and provide start-up funding for creation of conducive research environments. A pool of monitors is needed to cover non-pharmaceutically funded research. Training should be broadened to include financial know-how, negotiation skills, etc., to create independent scientists. Re-entry grants should be introduced, and MSc funding should be maintained. Finally, we should Introduce attachment programmes to clinical trial sites and create a comprehensive database of existing training opportunities.

Scientific leadership and development in Africa

Francine Ntoumi, EDCTP

The background is that any indicator of global science shows the high level of discrepancies between advanced economies and developing countries. Constraints to building research capacity in Africa are present at biomedical, clinical and operational level. In addition, many deficiencies have been identified at the policy and regulatory levels. The most serious challenge is, does Africa have what it takes to provide the lead in addressing

directly, in the most specific manner possible, the mission of the EDCTP? Are we in a position to develop new clinical interventions to fight poverty-related diseases of HIV/AIDS, malaria and tuberculosis? Can we do this by integration of European research efforts in partnership with Africa, and if so, how should we approach the challenge?

We need to be able to define African leadership by clarifying the roles of principle investigator (PI) and other investigators and develop a system for measuring scientific leadership in Africa. Project leaders should manage the funds and be paid fairly. We should be inspired by the US leadership programme and learn from the experience of Drugs for Neglected Diseases Initiative (DNDi) in relation to African country PI and site PIs. The EDCTP should develop an inventory of scientific African leaders and fake partnerships put together for the sake of grant application. We therefore propose the following process for demonstrating African scientific leadership. We should bring together EDCTP Stakeholders (scientists, pharmaceuticals, developers, funding agencies) in a meeting(s) in Africa under the auspices of NEPAD/AU and the EC/EDCTP in order to:

- Consolidate the African partnership
- Identify the research priorities
- Insist on the integration of the European effort for research in Africa on the required interventions
- Declare the support of governments and scientific institutions for the effort, both financially and in kind
- Agree to a plan of work for implementation in the short-term in accordance with the broader EDCTP plan of work.

Joseph Odhiambo

PLENARY SESSION III

Chairs: Richard Adegbola (Gambia) and Peter Kremsner (Austria)

Theme:
Partnership and African Leadership for conducting clinical trials: experiences from the field and reports from EDCTP projects.

Keynote addresses

Partnership and African leadership in tuberculosis drug and vaccine research

Joseph Odhiambo, Kenya

Africa's tuberculosis epidemic is driven primarily by HIV and poverty, targeting the most productive age group. Over and above present TB/HIV interventions, new TB drugs and vaccines are urgently needed. The reason TB persists as a killer is that treatment takes up to 8 months and missed doses, in turn, fuel multi-drug resistant tuberculosis (MDR-TB). Yet the only new TB drugs in the last 4 decades are variations of those already existing. Innovative new drugs must improve patient compliance through shorter and simpler TB treatment regimens, address the needs of HIV+ persons, treat MDR-TB and eradicate latent infection. New and more efficacious TB vaccines could be pivotal adjuncts to new drugs, especially if proven effective in high HIV populations. BCG prevents only 5% of potentially vaccine-preventable TB deaths.

New TB drugs need to have a short and simple regime, leading to improved compliance. They must also suit the needs of managing TB/HIV co-infection, as well as treating MDR-TB and extensively drug-resistant tuberculosis (XDR-TB). In addition, they need to eradicate latent TB infection and must be affordable for people most in need. Any new TB vaccine must have high and consistent efficacy, especially against adult pulmonary tuberculosis (PTB), leading to multiplicative benefits with TB treatment. It must also be affordable, and should not interfere with skin tests.

These needs were underscored at the Stop TB Partnership's meeting in Versailles, France, in 2005, where recommendations highlighted:

The importance of enabling and promoting research
An urgent need for new TB diagnostics
The quest for new anti-TB drugs
The need to invest in young professionals for TB research and programme management
The need for new TB vaccines – candidates on the way.

New interventions need commensurate investment in research, a position that puts Africa at a crossroads given her greatest need against the weakest economic base. Under the ambits of African Union (AU) and New Economic Partnerships for Africa's Development (NEPAD), African leaders have identified TB and HIV control among key priorities for poverty reduction.

Several important initiatives are addressing the current problems. The Global Alliance for TB Drug Development was conceived in South African in 2000 to create better TB drugs and register a new compound within 10 years. The Alliance enlists global expertise through networking, which this has led to PA-824, the first promising compound, moving through the R&D pipeline. The Tuberculosis Research and Development Coalition enlist the participation of TB endemic regions in Africa, Asia and Latin America. The South Africa TB Vaccine Initiative (SATVI), launched in Capetown in 2002, has a mission to develop new and effective TB vaccines. SATVI has a strong South African leadership and international partnerships as well as dedicated accredited clinical and immunology research laboratories.

The multicentre, randomised, control trial of Ofloxacine-containing, short-course regimen for the treatment of pulmonary tuberculosis (OFLOTUB project) is an ongoing study involving Senegal, S Africa, Benin, Guinea and Kenya, designed to simplify and shorten TB treatment from six to four months. It is funded jointly by WHO and EC, and coordinated by IRD in Senegal. All principal investigators and staff are Africans from respective countries - an example for leadership and partnership. Local capacity building (training in Good Clinical Laboratory Practice (GCLP) and Good Clinical Practice (GCP), infrastructure, data management, and other personnel training) is an important aspect of this

trial. The benefits for nurturing existing talents in Africa have been demonstrated.

Dr Valerie Mizrahi, of Witwatersrand, 2003, discovered mechanisms for development of TB drug resistance (published in Cell). She identified a protein essential to survival of the TB bacilli. Her subsequent work has focused on leads for new TB drugs and vaccines.

There is already strong African political leadership in TB control and TB research. The African Union made a commitment on universal access to HIV/AIDS, TB and malaria services by 2010 (Abuja, 2006), and the EDCTP's response fits neatly into NEPAD's principles and objectives. The TB Emergency Declaration (Maputo, Aug 2005) advanced the TB agenda. There is strong political pressure; the High Representative provides high political visibility for the EDCTP; Nelson Mandela is a strong advocate for TB treatment (AIDS Conference, Bangkok, 2004). There is also strong country-level political commitment.

In terms of TB, the EDCTP priorities are to select new candidate tools for evaluation, and help to establish strong north-south clinical trial collaboration and capacity for clinical trials in southern Africa. The EDCTP supports state-of-the-art TB clinical sites and TB laboratory infrastructure in South Africa, and provides supplementary funding to existing African sites for drug and vaccine trials, building support for capacity building and networking. The primary foci of the EDCTP TB portfolio are to find new TB drugs/drug regimens that shorten and simplify treatment, and to develop innovative regimens that meet the needs for treatment and prevention of TB in HIV positive persons. Newer, more efficacious TB vaccines are needed in high HIV settings; surrogate markers of TB treatment response are required, together with more sensitive and specific TB diagnostics.

Several needs and gaps (adaptable to TB) have been identified by the DCCC, including upgrading trial sites and health delivery systems; setting up a comprehensive inventory of programmes, clinical sites and institutions; appointing training monitors; improving networking; encouraging nodes of excellence; mentorship; enhanced infrastructure; collaboration with WHO AFRO; and better data management. Potential African sites to be developed as (TB) nodes of excellence include Clinical and Biomedical Tuberculosis Research Unit, MRC, S Africa; Kenya Medical Research Institute (KEMRI); Research Institute for Development (IRD), Dakar and various others.

At the Clinical and Biomedical Tuberculosis Research Unit, MRC, South Africa. (Director: Dr Roxanna Rustomjee), current projects include:

- OFLOTUB study
- TB/HIV interaction studies
- TB Treatment and HAART
- Early Bactericidal Activity (EBA) studies on new TB drugs
- Immune responses to TB/HIV treatments
- WHO/TDR survey of TB diagnostic test prices, practices and preferences in 7 high burden countries
- Bioavailability studies of Fixed Dose Combination (FDC) TB drugs
- Studies in surrogate markers of drug efficacy, disease activity and relapse in TB.
- At the Kenya Medical Research Institute (KEMRI) (Director Dr Davy Koech), the vision is to be a centre of excellence in health research - nationally, regionally and internationally:
- Participated in British Medical Research Council (BMRC)-led TB trials (1970s)
- Participated in EBA studies (1990s)
- Evaluated a PCR TB diagnostic tool (1990s)
- WHO/TDR TB isolates bank project
- Launched the OFLOTUB project (2005)
- TB laboratory with Drug Susceptibility Testing (DST) and Polymerase Chain Reaction (PCR) facilities
- 40-bed research hospital
- Capacity for drug isolation, analysis and pharmacokinetic studies
- New production, training units, animal house
- EDCTP-supported TB vaccine trial site in pipeline
- Product with in-vitro anti-TB activity identified.

African leadership in EDCTP is already assured. EDCTP Secretariat includes leading African scientists and the High Representative; in the DCCC, leading African scientists

Sodiomon Sirima

set Africa's agenda, identifying needs and gaps. In the Partnership Board there are four members from Africa. Among EDCTP-supported TB projects are training awards (Mukthar–Sudan, Hanekom-RSA, seven applications under review); TB therapeutic clinical trials (Jindani, Helden, Gillespie, Merry); TB networking grants; capacity building in scientific skills, ethics, leadership; vaccine trial sites development (10 African countries).

The power of leadership, networking and partnership must be harnessed. Achievement of the goals of TB control calls for stronger leadership of African scientists and S-S networking. N-S partnerships must prioritise the need to nurture and support present and emerging talents in Africa: to achieve success, strategic N-S partnership and sustained African political and financial commitment are essential. The EDCTP provides a good catalyst to these processes.

Partnership and African leadership in malaria drug and vaccine research

Sodiomon Sirima, Burkina Faso

Malaria is a weapon of mass destruction. The most recent estimates suggest that Plasmodium falciparum infection causes 300 to 500 million clinical episodes of malaria each year, with over 1 million deaths, of which more than 90% occur in sub-Saharan Africa. In 2000, approximately 100 million African children lived in areas where malaria transmission occurs and an estimated 800,000 died of malaria. Children less than five years of age and pregnant women are the most vulnerable.

The current global strategy for malaria control places most emphasis on the early diagnosis and prompt treatment of cases. However, the spreading of P. falciparum resistance to affordable antimalarials represents a major challenge to these strategies. Vector control is of limited effectiveness due to insecticide resistance and environmental concerns. In order to restore hope there is an urgent need to develop effective vaccines and affordable drugs. Usually the early development of new malaria drugs or candidate vaccines takes places in the North and the later stages in the South. A partnership between Northern and African scientists is then necessary to develop new drugs or vaccines. We are looking at south-south partnerships between research institutions; north-north partnerships between research institutions and the community, and of course, the north-south partnerships.

There is a need for joint partnership to encourage early development of new candidate vaccine or drugs, screening for new antigens or new drug compounds, and late development of new candidates vaccine or drugs. But what do we actually mean by "partnership"? As defined in a dictionary, partnership is a "type of business **entity** in which partners **share** with **each other** the **profits or losses** of the business undertaking in which they have **all invested**."

Partnerships also require leadership, and we can define this as "The **ability** of an individual to **influence**, motivate and enable others to contribute toward the effectiveness and success of the organisations of which they are members."

There are some important guiding principles for effective research partnerships

- Common decision on objectives
- Building of mutual trust
- Sharing information and responsibility
- Creation of transparency
- Equitably sharing of profits
- Increase research capacity.

In such partnerships, common decisions need to be made on objectives and leadership. All the partners must be involved in the decision if the objectives are to be achieved during partnership: the research priorities must fit in with the interest of each partner. African leadership can provide more vision, which is necessary to influence the group for the achievement of the objectives.

Building up of mutual trust and leadership can be difficult, because many prejudices are based on the historical and "cultural differences" often seen between the partners. However, the creation of trust between partners contributes to development of a good working environment. In these circumstances, African leadership demands more motivation and the self –assurance necessary for a leadership.

Souleymane Mboup

Sharing of information also demands leadership. As the partners are often geographically distant, it is necessary to have a well-functioning communication system, and ideally the partners should have a comparable level of information. African leadership means being empowered to influence and motivate the group. Shared scientific responsibilities and technical leadership of the project means sharing of management responsibilities. African leadership requires ownership, acquisition of experience and motivation, together with the abilities necessary to influence and motivate the group.

Full transparency is essential, and it is important to declare openly to all partners the sources and amount of all resources, especially funds, and the way these resources are being used. As far as possible, financial decisions should be taken by all partners and double standards in remuneration of the partners should be avoided. Profits must be shared equitably, with all partners taking part in the dissemination of the results at conferences and in publication of scientific papers. Similarly, there should be equal sharing of benefits such as licence and commercial values resulting from the partnership. Effective African leadership means recognition of the leader at a national and international level which in turn leads to establishment and strengthening of the leadership.

Research partnerships are formed to strengthen the total capacity of the involved partner at the individual and institutional level. This means improvement of the infrastructure, equipment and human capacity development. For African leadership, gaining of expertise and abilities is necessary for the leader to influence and motivate the group for the achievement of the objectives.

The infrastructure and equipment supporting effective African leadership include:

- Clinical trials facilities
- Clinical laboratories
- Functional patient care facilities
- Transportation (vehicles, motorcycles etc.)
- Communication equipment.

This partnership should be an opportunity for the emergence of a real African leadership. This can only be possible if African scientists are well-trained, have their institutions well-equipped and if they have been given the opportunities to be involved at all steps of the clinical trials, preferably as principal investigators. The funding agencies like EDCTP should play a major role to make this happen.

Malaria is a complex disease and the development of a vaccine or new drug by a single northern or southern institution or country is quite impossible. A partnership is needed and if implemented according to its guiding principles, a strong partnership could well establish Africa's leadership in malaria research. As local experts, these leaders should play a dynamic role in the development of new and effective control tools of malaria in Africa. Funding agencies like EDCTP, World Health Organisation (WHO), National Institutes of Health (NIH) and the like are expected to act as catalysts.

Partnership and African leadership in HIV/AIDS drug and vaccine research

Souleymane Mboup, Senegal

In 2005, 13 new trials of preventive AIDS vaccine candidates began in nine countries around the world. Two of these involved vaccine candidates that entered phase II trials, an intermediate stage of clinical evaluation. Several of those newly initiated trials involved novel vaccination strategies. Participation by Africa in those trials is continuously increasing. Rwanda started its first AIDS vaccine trial and South Africa began the country's first phase II AIDS vaccine trial. In 2000, only one African country participated in vaccine trials; by 2006 this had grown to eight countries in East Africa, operating from a number of clinical trial sites. Others are pending and further countries in West Africa are preparing for vaccine trials. Five trials have been completed, and a series of preventive trials are enrolling or pending. The first "test of concept" trial, in fourth quarter of 2006, was of the MRKAd5 Trivalent Vaccine.

The first "test of concept" study of HVTN 503 was a South African Study to test subtype B vaccine (Ad5 gag, pol, nef) in subtype C region (similar to STEP HVTN502 in

MSM in USA). This study will examine if subtype B vaccine is efficacious against subtype C heterosexual infection. It is expected to markedly enhance the information on efficacy in women, will refine the assessment of the impact of pre-existing Ad5 titers, and will more than double the number of endpoints in order to enhance the evaluation of correlates of protection.

Another key study is the VRC DNA Prime RAD5 boost. This is currently the largest trial concept being tested in Africa. Enrollment is into 3 trials in 6 countries in Africa, with more than 600 participants. It involves 3 major vaccine initiatives and networks:

HIV Vaccine Trials Network (HVTN); US Military HIV Research Program (USMHRP); International AIDS Vaccine Initiative (IAVI), PAVE 100 (in planning for 2007/8) will be the next proof of concept trial in Africa, planning to enroll ~12,000 globally and ~8,000 in Africa.

Therapeutic vaccine concepts are also enrolling in African trials while other vaccines are being planned: PAVE 100: DNA /Ad5; ~12 000 participants; 8 000 in Africa; multiple sites; multiple partners; Mrk Ad5: Adolescent trial in SA (HVTN/DAIDS); SAAVI DNA /MVA: Phase I trial in SA (SAAVI / HVTN /DAIDS); EuroVac (NYVAC); Chiron (Subtype C Env); Tat Vaccine (AVIP /ISS).

There is increasing participation in Africa. In initial studies in 2000, there were 50 volunteers from only one country. In 2006, there were 400 volunteers from 8 countries, in studies involving 15 trial sites. By 2008 more than 4,000 volunteers are expected, probably from 12 countries, and by 2010 the number of volunteers is expected to rise to more than 10,000.

Some of the scientific challenges are specific to Africa

The vaccine pipeline is too narrow; there may be pre-existing immunity to vaccine vectors; genetic diversity may cause complications.

ARV therapy in sub-Saharan Africa involves complicated combination regimens and is expensive and dangerous because of severe side effects. In addition, there can be rapid development of drug resistance in the community. So, instead of promoting expensive and dangerous ARV therapies, prevention is the logical solution.

A short-term evaluation on the first 175 patients showed virological and immunological results similar to Western countries, with excellent adherence and good Accessibility and Acceptability

- Clinical trials in Africa have involved:
- First trial in Africa of a simplified regimen
- Effective through treatment period among severely immunocompromised individuals in resource-poor settings
- ARV clinical trial in resource-poor settings is feasible
- Introduction and validation of a new ARV Drug in Senegal.

An ongoing trial is taking place on ANRS 1207/IMEA 025 once daily. This contains tenofovir, emtricitabine and efavirenz as separate tablets. Marked reduction in viral load has been achieved in preliminary results, with good virological and immunological efficacy and good adherence to treatment. This study also addresses a more simplified dosage, using two tablets or a single combination tablet.

In conclusion, there is,

Increased African participation in vaccine trials
Increased funding to address scientific questions
Increased partnerships to accelerate the field.

These factors will increase the success rate at an accelerated pace, though the results of the first Phase IIb trials in Africa are still 3-5 years away. Other considerations are ARV scaling up in developing countries; host, viral, environmental factors such as logistical and operational. An affordable second line regimen is required, and there is still a need to increase African participation in ARV clinical trials. Such studies will have an impact in both developing and developed countries.

Discussion

A question from the floor noted that in 2000 there was only one site, and that by 2006 this had increased to eight East African countries operating from multiple sites. But what is still missing are the results. In response it was noted that research on HIV/AIDS in Africa started very slowly. The first studies in Uganda took up to seven years

Diarmuid McClean

from start finish in order to provide results. Many of these studies follow on from Phase I, and will already have been commenced in the country of the developer. Involved agencies have very strict regulations about their conduct, and what is done in Africa is exactly what happens in Europe and Asia.

Another question related to the variation between sites in East and West Africa and whether it was possible to close the developmental gap between these centres. The response was that southern Africa has the highest prevalence of HIV/AIDS and therefore that is the reason so many trials are conducted there. One speaker who also agreed with the concept of nodes of Excellence, wanted to know what EDCTP's priorities were. He mentioned that there are strong candidates for drugs and vaccines, developed in the North. But should EDCTP get involved in the discovery and development process? The current scope of EDCTP activities is mainly Phases II and III clinical trials and this may be broadened in future.

A panellist pointed out that we must acknowledge the great differences between AIDS, TB and malaria. Malaria is actually 'owned' by Africa, therefore if we do not take leadership in malaria studies, we will not solve the problem.

Partnership and African leadership from funder's perspective

Diarmuid McClean, Ireland

Irish Aid is not a scientific institution but a small agency, deeply engaged at country level with health. The heart of our mission is poverty reduction and accelerated progress towards Millennium Development Goals (MDGs). Improving health outcomes is a critical task, and the focus is technically justifiable. Africa merits priority attention, and we strongly support harmonisation of both assistance and donors. For all of this, African leadership is absolutely vital, in health and beyond. Health is multi-sectoral.

Irish Aid is a European donor and is involved in antiretroviral drugs (ARV) scaling up in developing countries. Through this involvement it is clear that an affordable second line regimen is required. There is also clear need for increasing African participation in ARV clinical trials.

The expanding budget of Irish aid is not matched by a corresponding increase in the staff size. There is a shift from projects and programmes towards pooled mechanisms, budget support (including Sector-Wide Approaches (SWAPS) and grant management entities. These are a more effective use of aid, despite some problems. However we know that a mix of modalities is the best way.

So why is Irish Aid interested in clinical trials? Lack of new and better products is a fast-growing obstacle to progress, especially in Africa. And for the main part the R&D is neglected. Public money is needed – this is new for us. But is African leadership interested in this? Why should they be? The Commission on Health Research for Development recommended that at least 10% of external assistance should go to health related research. But the money is either not there or is well hidden. Why? There has been a shared failure. Research has been afforded low priority in health development by donors and government partners. An important factor behind this is that health research leadership and influence has not been effective and is mostly absent. It is most important now to provide money for SWAPS and Direct Budget Support (DBS). Health research needs supportive and effective leadership from the Ministries of Health and Finance, research bodies (authorities, oversight bodies, institutions) and domestic (Irish) parliamentarians and Ministers.

The environment for our work is now improving and there are many new opportunities that include NEPAD, strong national plans with good buy-in to lead AIDS response and health sector development, together with an accelerated research activity at country level and donors getting together for health research. So we who are concerned with health research have to get behind NEPAD, engage with its structures and support delivery of its projects. We need to engage with the top table – to use what works and find a way do some basic politics that will achieve our ends. We need to put national AIDS research and health sector plans and budgets when engaging with donors to assist with country level strategies for health

research. As donors, we must address our domestic research agenda, collaborating with the Irish Health Research Board. Here assistance is needed from EDCTP to promote better appreciation of EDCTP in Irish institutions and to help the person responsible for the National Programme. With a strong, WHO direction like-minded donors that support health research have to convince purse-string holders of the value of health research.

At global and EU levels, it is important to promote harmonisation with donors and funders supporting Product Development Partnerships (PDPs) – Donor Coordination Groups. PDP country level studies must go through country-led coordination forums and include capacity building. We also need to track the impact of Global Health Partnerships (GHPs) on Human Resources for Health (HRH). This also involves the Support Global Health Workforce Alliance and Human Resources for Health Resources (HR-HR). We must support the EDCTP and participate in governance (could we see an African head of the EDCTP?).

Engaging the Ministry of Health and Ministry of Finance and Planning can assist. Leadership can be strengthened for stronger stewardship of the wider health sector in order to bring in outliers. This involves strong harmonisation between donors; a solid sectoral plan; and a soft game where we can name and shame non-players. The same attitude can apply to health research. It is not so much where you get but how you get there. In this connection we know that some health researchers have remarkable access and considerable influence, so we should use them. This takes time and we need to draw these influential people in as soon as possible to participate in research planning. Building a culture of demand for evidence and research is key – supported by effective leadership and visible research activity.

How can health research accelerate progress versus alternatives? Certain types of research make more immediate sense when we are dealing with scarce resources – systems, coverage surveys, etc. In these circumstances, clinical trials come later. However, none of the above is possible without HR-HR and supportive systems for:

- Research prioritisation and approval
- Sourcing funds and fund management
- Networking – including regional
- Proper links with health development
- Institutions that are integral to these systems.

Donor options at country level can be directed away from individual projects to systems development and planning. Institutional support, leadership support and networking, both national and regional, require similar support. A joint strategy harmonised with other donors will probably address regional aspects. HR-HR merits special attention beyond the development of competency. The key is to reward and promote performance; research leadership will develop from the stem cell of young talent. Like other HRH, this requires a multi-level strategy. We must be sure that support to GHPs such as EDCTP sustains and builds HR-HR and this young talent.

Why do clinical trials need MoH national leadership? Core budget support is essential, and products and evidence need to be linked to policy. Access has to be provided for successful products. We need to utilise the resources of MoH staff, facilities and systems without undermining them, and we need to be able to cope with setbacks – huge fallouts are not uncommon and can destroy an entire project. What do clinical trials bring to the MoH? Firstly, we can see a shift from extractive research to positive contribution and benefit. The associations with prestigious projects have some valuable political currency. We can expect regulatory capacity to be built and as this capacity is built, pharmacovigilance should follow. Access issues will receive early attention, and there will be "spill over" of benefits for quality of care (QoC). And of course there will be strengthened research capacity.

Coordination of initiatives is important for African leadership. How does the EDCTP work link with other clinical trials – including PDPs? Some of the initiatives presented in this forum could be coordinated for enhanced benefit, such as Supra-National Reference (SNR) laboratories, regional regulatory options and hubs and nodes of excellence.

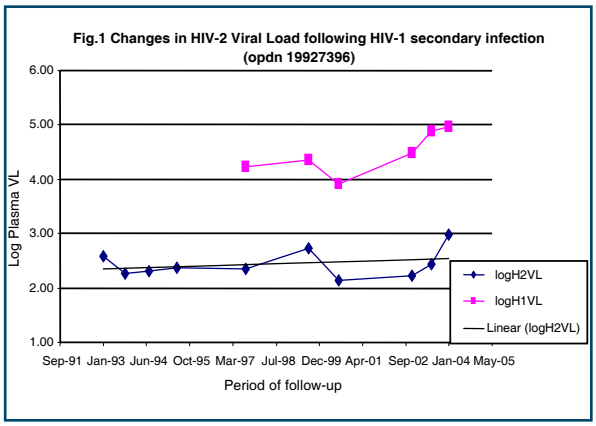
Abraham Alabi

Report from the First EDCTP investigators' meeting

Viral load dynamics as an insight to the therapeutic vaccine efficacy in HIV dual infections

Abraham Alabi, The Gambia

The objectives of this study were to investigate viral load (VL) dynamics in HIV-1 and HIV-2 dually infected individuals, and to examine the possible effect of HIV viral load on the efficacy of therapeutic vaccines in dually infected individuals. Individuals in our clinical cohort include those who were infected with both HIV-1 and HIV-2. Those infected with a single HIV type (HIV-1 or HIV-2) were identified and followed up on a quarterly basis, during which the acquisition of a second HIV type occurred. Viral load was measured in patient's sequential plasma samples using an in-house colorimetric HIV RNA assay, and CD4 was measured by flow cytometry using FACScallibur.



Viral load dynamics in HIV dually infected patients appears to be complex and possibly depends on a number of host and viral factors such as virus strain, virus fitness, etc. Efficacy of HIV therapeutic vaccines may depend on the susceptibility of the different virus types in patients dually infected with both HIV-1 and HIV-2.

Fig.4 Changes in HIV-2 Viral Load following HIV-1 superinfection (opdno. 19896277)

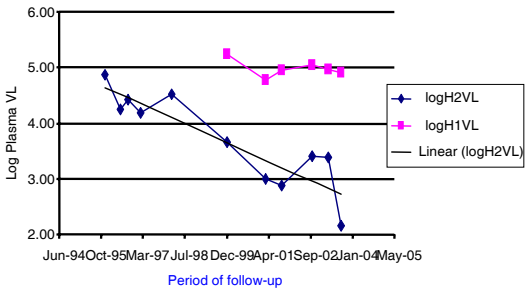


Fig. 5. Changes in HIV-2 Viral Load following HIV-1 superinfection (opdno. 19813502)

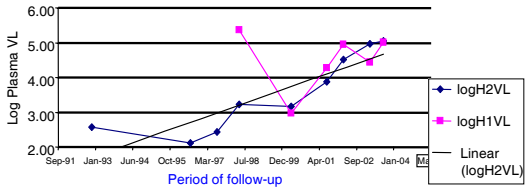
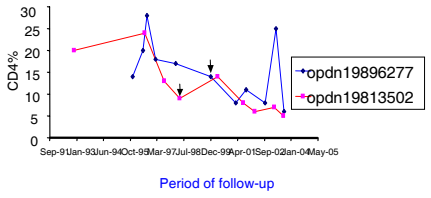
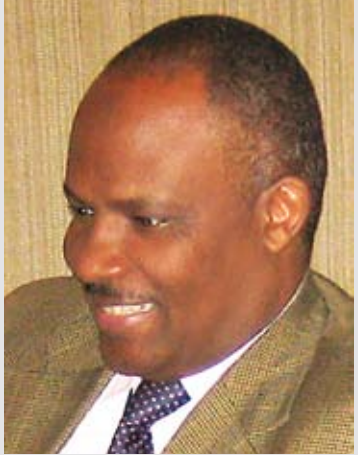


Fig. 6 CD4 changes in HIV-2 patients following HIV-1 secondary infection



Future perspectives include the need to enroll more HIV-1 & HIV-2 dually infected patients for follow-up studies, and to undertake more virological and immunological studies focusing on such patients in order to better understand the viral dynamics and possible implications for future vaccine trials.



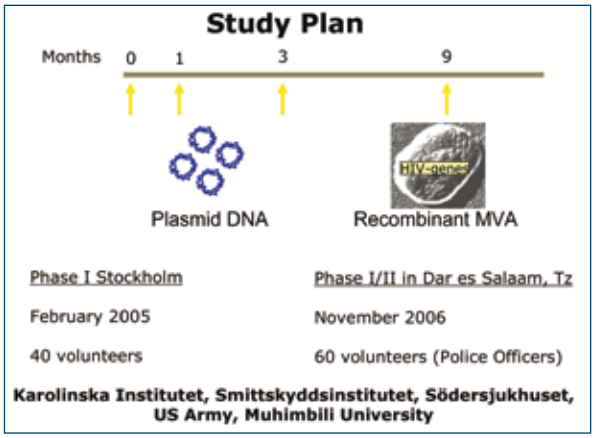
Muhammed Bakari

The HIVIS project is a north-south collaborative study of the safety and immunogenicity of a multigene, multiclade HIV-1 plasmid DNA prime and MVA vaccine boost

Muhammed Bakari, Tanzania

Objectives of this study were to optimise the immunisation schedule for HIV-1 DNA vaccine, priming with HIV-1 MVA vaccine boosting, in the development of an HIV-1 preventive vaccine and to develop expertise and capability to study HIV-1 vaccines in Tanzania.

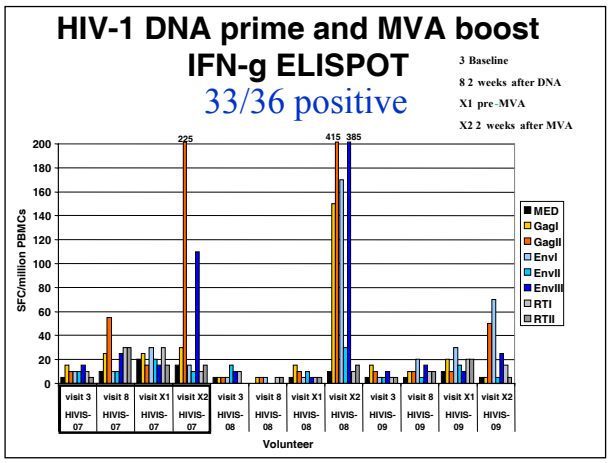
The study involved a 7 plasmid HIV-1 DNA multigene/ multiclade vaccine developed by the Karolinska Institute and produced by Vecura, and MVA / CMDR developed by the NIH and produced by Walter Reed Army Institute of research.



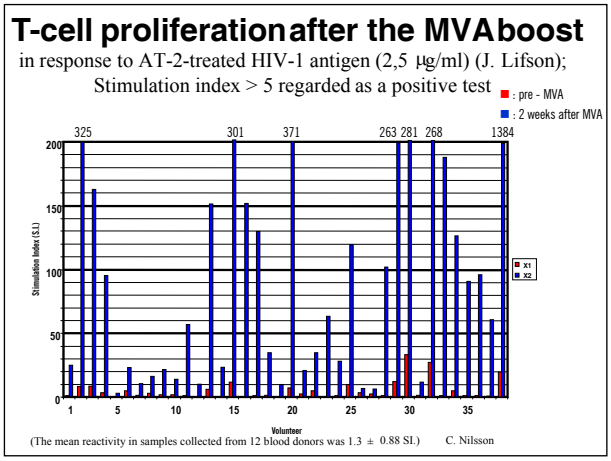
The HIV-1 DNA prime was given as three immunisations into the deltoid muscle or the skin above.

Results in Sweden were that by the end of June 2006, all 38 eligible volunteers had received three DNA and one MVA immunisations. The immunisations were generally well tolerated and there were no safety laboratory abnormalities. Administration of rGM-CSF was associated with influenza-like adverse events.

33/36 (92%) vaccinees fullfilled the criteria of IFN-g ELISPOT reactivity to HIV-1 peptide pools. Another two vaccinees had invalid ELISPOT results due to high background reactivity.



37/38 (97%) vaccinees showed HIV-1 specific T-cell proliferative responses. The study is still blinded.



The situation in Tanzania is that HIV/AIDS was declared a national emergency by the President. Tanzania's National HIV/AIDS Policy (2001) incorporates research on HIV vaccines and the Tanzania National Framework for the conduct of HIV vaccine trials has been in place since February 2005.

The study protocol incorporating advice and inputs from the WHO-UNAIDS and from the African AIDS Vaccine Programme (AAVP) that was and largely developed by Tanzanians, has already received national as well as institutional ethical clearances. Tanzania's Food and Drugs Authority (TFDA) has granted approval for the randomised, double- blind, placebo-controlled study to be conducted.

60 volunteers (45 men, 15 women) have been recruited so far, with a further 250 ready to be screened. These

volunteers are primarily from a cohort of police officers (POs). The rationale for recruiting from this group is that this is a relatively stable population which is easy to follow up. There has been a supportive stance from the Ministry of Home Affairs and highest Police authorities. Almost all volunteers have attained secondary school education level, hence are relatively better than most of the population in terms of informed consent and understanding of study related procedures. The voluntary nature of participation was emphasised at all levels.

A group of police officers was formed from among those interested in HIV/AIDS prevention activities. We conducted workshops with them and provided more information on HIV/AIDS and the HIV vaccine study. Those interested were invited to list their names and provide addresses for further contact. More educational training workshops will be conducted with them for more details of the study. Those willing will be invited for screening at the site after a further one-to-one educational session.

Clinical and laboratory personnel involved include senior investigators with extensive research experience who oversee the study; and younger scientists in training or who have completed PhD training through Sida/SAREC funding. Multiple institutions are involved including Muhimbili University College of Health Science (MUCHS), Muhimbili National Hospital (MNH), police force and the University of Dar es Salaam, Sociology Department.

The majority of key personnel were trained in good clinical practice (GCP) and good clinical laboratory practice (GCLP) through courses facilitated by World Health Organisation (WHO), African Malaria Network Trust (AMANET), African AIDS Vaccine Programme (AAVP), International AIDS Vaccine Initiative (IAVI) and HIV and AIDS management. A further GCP training course is planned. Senior participants have been exposed to the HIV vaccine trial setting in Sweden. In-country networking is an important aspect, and HIVIS staff visited the Mbeya Medical Research Programme to review their experiences with the Phase I/II HIV vaccine trial.

Medical and HIV care will be available at the Muhimbili National Hospital (MNH) HIV clinic. HIVIS investigators are already aligned with the HIV clinic, and are of multiple sub-specialties. The HIV clinic at MNH offers HIV counselling and testing, free ARVs and co-trimoxazole prophylaxis. Being at MNH, it will be relatively easy to handle other non-HIV related illnesses. MUCHS, Tanzania, will be responsible for safety tests and most of the immunogenicity assessments, including T-cell responses (ELISPOT, FASCIA, LPA). SMI, Sweden will conduct tests for neutralizing antibodies, CTL assay and HLA typing. HIV strain characterization will initially be processed at MUCHS, followed by sequencing in South Africa by Carolyn Williamson. Remaining challenges include financial resources: we are operating with very modest budget. EC extension of funding is promised, and availability of additional funding will be crucial for successful completion of the trial in Tanzania. The Tanzanian government has been generally very supportive, but we are exploring further opportunities for assistance. Staff attrition may become an issue. We also need to address important bureaucratic procedures at national and institutional levels.

Our interim conclusions are that three injections with HIV-1 plasmid DNA as prime with a single HIV-1 MVA boost are safe and gave strong IFN-gamma Elispot reactivity 2 weeks after the last injection in over 90% of healthy Swedish volunteers. Preparations for the conduct of the Phase I/II trial in Tanzania are at an advanced stage and the trial is expected to start in November, 2006. Additional financing will be crucial to realise the trial to completion in Tanzania and pave the way for more trials.

Discussion

A question was raised as to whether the research participants included senior police staff members and if there were evidence of influence from such staff on other participants as well as sufficient women among the participants and what was the effect of transfers out of the area? The response was that few of the collaborators were senior officers, but that no coercion took place. It was noted that few women participated, but this was not a problem. The issue of transfer of officers has been discussed with the authorities, who have agreed not to transfer any of the participating officers.

Paul van Helden

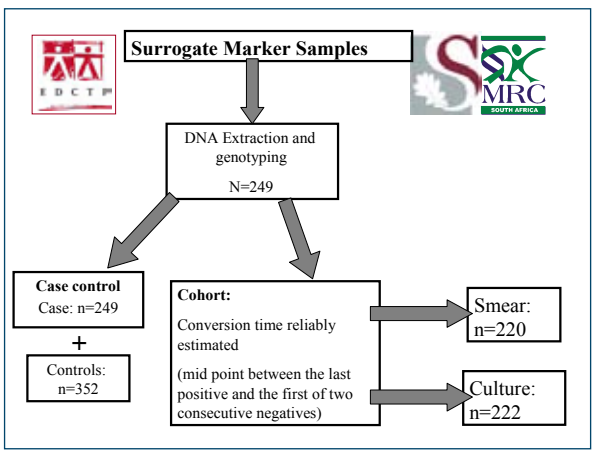
Surrogate markers to predict the outcome of antituberculosis therapy

Paul van Helden, South Africa

The objectives of this study were to identify host biomarkers which predict successful cure or identify the risk of recurrence during early treatment. These markers could be host or bacterial. The study involved recruiting a cohort of uncomplicated smear positive, first-episode TB patients and placing them on standard DOTS treatment. They were followed up carefully and a variety of samples were collected (>90 000) during repeat visits at up to 30 months. Sample analysis included blood parameters, serology, immunology, bacteriology and genetics.

313 patients were recruited, some excluded and the rest followed to 30 months. Of the more than 90 000 samples collected, there was only 75% smear conversion at 2 months. There was 6.6% recurrence (reinfection + relapse). Promising markers for slow or non-conversion or recurrence included smoking, certain vitamin D receptor (VDR) alleles, some blood parameters and soluble serum markers.

In the course of the study, it was found that time-to-detection (TTD) of *M. tuberculosis* could be distinguished, even as early as 1 week. Use of BACTEC cultures appears to be a viable alternative to colony counting in evaluating early bactericidal activity (EBA). This leads to the question can TTD be used to predict responses to TB treatment? Time-to-detection of BACTEC cultures increases with duration of treatment, and increase vary between patients. These differences become apparent early in treatment.



Fastest resolution of *M. tuberculosis* infection was associated with a low extent of pulmonary involvement, non-smoking, low WBC count and low absolute neutrophil count. Similarly, short height was a factor in fast resolution, together with ApaI "AA" genotype and TaqI "T" containing genotype.

A pilot study of host serum surrogate markers for week 8 sputum culture outcome led to identification of new markers. Chest X-ray findings (presence of multiple cavities), CD3dim NK T cells in peripheral blood, soluble intercellular adhesion molecule (ICAM) and soluble tumor necrosis factor (TNF) receptor II, used in a general discriminant analysis model predicted negative week 8 sputum culture with 88% accuracy and positive cultures with 92% accuracy.

The use of support vector machine classification techniques identified suPAR, sTNFRII and CD3dim/CD56+ NK T cells as contributors to a predictive model with 100% accuracy.

A further study by JA Verschoor (University of Pretoria) was briefly discussed, which examined anti-mycolic acid antibodies as surrogate markers for active TB. This utilised the Mycolic acid Antibody Real-Time Inhibition-test (MARTI-test), where the endpoint measured is the degree of inhibition of binding of anti-mycolic acid antibodies to a mycolic acid coated gold surface of an SPR-biosensor upon pre-incubation of patient serum with liposomes containing mycolic acid. The inhibition gives a more specific account of anti-mycolic acid antibody activity in patient sera than direct binding to the biosensor surface. The antibody activity correlates with active TB, falling away when the patient is cured.

In the current study, gene expression profiles in whole blood RNA stored during treatment will be defined using Affymetrix GeneChip microarrays. Key genes and biological pathways which are differentially expressed between patient groups will be identified and the results used to formulate a predictive test of outcome using these gene expression biomarkers.

It was encouraging that bacteriology and genotyping provided a basis for dividing patients into well-defined groups for further analysis. The initial results suggest that this approach holds promise, as we are able to find

Maowia Mukhtar

markers with good predictive value. This needs further investigation, as no single marker has 100% sensitivity yet or specificity in large numbers.

We are now preparing to test the models based on the most promising markers in large cohorts of patients with different outcomes of TB treatment at week 8 and week 26. Analysis of the stored samples will lead to identification of candidate predictors for cure, which can then be tested in future trials on large numbers of samples.

Discussion

In response to a query asking if a single marker could provide accurate identification, the response was that it was unlikely that a single marker would be 100% accurate. Probably a model will be developed based on several markers since it is expensive to measure all parameters in all patients. On differentiating between recurrence and reinfection, the response was that they type all isolates, with multiple genotyping probes. In the 14 recurrences, 10 were reinfection, and 4 were classified as relapses. But in the long-term, around 70% are reinfections, and these patients are far more likely to progress to the disease.

Epidemiological patterns of pulmonary TB in eastern Sudan

Maowia Mukhtar, Sudan

Objectives of the study were to investigate the epidemiology of pulmonary TB in eastern Sudan and to identify a new site for future TB clinical trials.

Clinical surveys were conducted to identify TB patients, using cross sectional surveys to determine the cough rate. Observational surveys were used for identification of possible risk factors. The study sites were Kasalla (nomadic population) and Gadarif (established settlements).

Cough rate and clinical survey results

Kassalla state had 30 villages, in which 14,118 individuals were screened and 284 of these had cough representing a cough rate of 2%. Of the 284 individuals with cough, 108 were clinically suspected to have tuberculosis. In comparison, Gadarif state had 50 villages in which 16,080 individuals were screened and 904 of these had cough, representing a cough rate of 5.62%. Of the 904 individuals with cough, 10 were clinically suspected to have tuberculosis.

Additionally, the population of Kassalla state is 1.4 million, with a male to female ratio (M:F ratio) of 1.1, all age groups affected, treatment seeking history greater than year and a default rate of greater than 20%. In contrast the population of Gadarif state is 1.6 million, with a male to female ratio (M:F ratio) of 3.1, 15-40 age groups mainly affected, treatment seeking history less than year and a default rate of less than 20%.

It was concluded that two distinct epidemiological patterns exist in eastern Sudan. Kassalla state is inhabited by nomadic tribes with a mobile life style, different socio-economic structure and a weak health system. On the other hand, Gadarif state is inhabited by tribes with seasonal farming, stable communities and better health system and these differences are reflected by the rates of coughing that we measured.

Our future objectives are to improve access to effective TB diagnosis and treatment, strengthening of the health system and effective TB control by vaccination and health education.

Discussion

A question from the floor asked if TB was identified in infants. The response was that infants were not included in the study because of the difficulty of diagnosing them in the field.

Charles Mgone

PLENARY SESSION IV SUMMARY AND RECOMMENDATIONS FROM ROUND TABLE DISCUSSIONS

Chairs: Bernard Fourie and Patrice Debre

Capacity development for the conduct of clinical trials: the EDCTP approach

Charles Mgone, ES

The main goal of EDCTP is to accelerate Research & Development of intervention tools against HIV/AIDS, malaria and tuberculosis through the conduct of rigorously high quality clinical trials following best practices, good clinical practice, ethical principles and applicable regulatory guidelines. Health research capacity development is a process which involves inculcating and nurturing a culture of research and building and enhancing research capacity. It means optimal utilisation of research capacity as well as retention and sustaining of research capacity, in an enabling and conducive environment

The main players we have to consider are:

- National governments (South and North) and their planners and policy makers, as well as political leaders
- Scientific community
- Funding agencies
- Civil society.

There are many potential pitfalls which we need to recognize and avoid, such as fragmentation, duplication, redundancy, unfulfilled or missed gaps, misdirection, incompleteness and overlapping efforts.

The EDCTP attitude is that capacity development should be an integral part of a programme. This ensures:

- Customised capacity development
- Optimal capacity utilisation
- Learning by doing (practical experience gain)
- Successful outcomes
- Credibility to the capacity development process
- Sustainability of activities and capacity.

Networking provides added value to capacity development because it leads to creation of a critical mass able to cope with the demands of complex programmes while removing isolation and allows sharing of common advocacy. South-south mentorship can be coupled with south-north collaboration and technology transfer and synergy can be facilitated. Networking also means sharing of scarce facilities, expertise and knowledge.

An enabling environment is pivotal. It should address the ethics review, approval and monitoring, regulatory framework, clinical trials registry and best practices, including GCP and GCLP. The enabling environment also includes career development paths, with career development awards, senior fellowships, equitable salaries, incentives and other rewarding systems. Infrastructure development encompasses many parts of the enabling environment.

The ethics review includes establishment and support of Ethics Review Committees (ERCs)/Institutional Review Boards (IRBs), coordination of the ERCs and support for training, using e-based learning and workshops. The EDCTP capacity development in the regulatory framework in Africa include support of the regulatory pathway, with review of clinical trial applications and monitoring of clinical trials, African Vaccine Regulators' Forum (AVAREF) and the global network training for francophone (Benin) and anglophone regions. (Ethiopia).

Some valuable new approaches and ways forward have been proposed in this forum. These include development of a roadmap, joint calls, brokering, consortia and establishment of nodes of excellence or collaboration.

Stefan Wagener

Christine Manyando

RAPPORTEURS' REPORT – ROUND TABLE I

North-North Networking: Co-funding and supplementary grants in North-South Partnerships

Stefan Wagener, Germany

Recommendations are that EDCTP should work on the gap between the pilot function for an Article169 initiative and the urgent need for prompt and appropriate delivery of activities in the field. This will need creativity and flexibility from all parties involved. EDCTP should no longer dwell on its difficult past but be even more focussed on the needs for developing and implementing effective and reliable new drugs and vaccines. The processes and mechanisms for the funding of these measures need speeding up. However, the development of a new funding scheme must continue to be transparent to the scientific community. We need to discuss again the proposed new strategies such as joint calls, brokered calls and the consortia approach and if these are introduced the rules must observe transparency and competition in order not to lose the scientific expertise, which was not part of the already established structures. EDCTP Member States need to be more creative and less bureaucratic in getting funds for the EDCTP. We need to challenge the European funders in order to overcome administrative hurdles since lack of co-funding can be a limiting factor for excellence.

Integration of National Programmes (NP) as one central task for European member states also involves those partners who are the targets for joint interventions and who know the needs in their countries. We must involve African partners in the discussions and the integration approach of the European NPs.

Due to the urgent need for intervention, available products must be more seriously considered and brought forward for new clinical trials. We need a product approach vs. the existing project approach.

African researchers must enforce ongoing lobbying for research in African countries on a scientific and political level in order to raise more awareness and support and to secure grants. African health ministers have committed themselves to spend 2% of their budgets on research. African research priorities need a stronger voice based on DCCC as the central voice. Africans also have the responsibility to make themselves heard at home. Poorer countries with little resources need to approach DCCC if this has not yet been done and try to make a difference via this committee's activities.

Existing African excellence needs to be strengthened by setting up nodes of excellence (NoE), so that weaker centres can grow under the leadership of these NoEs.

Multicentre partnerships for clinical trials in Africa

Christine Manyando, Zambia

A number of fundamental questions have arisen from this forum. For example, why do we need multicentre partnerships in Africa? What aspects of clinical trials should be covered in those partnerships? What can we learn from the existing partnerships? What needs improvement and how to make these things happen? How can we assess the impact of existing networks? What new types of partnerships are needed?

In terms of multicentre partnerships, our discussions included ethics and regulatory issues, data management issues, diagnostics, variations in institutional strengths vis-à-vis capacity for conducting clinical trials, areas needing emphasis in partnerships and the role of the EDCTP including its funding approach.

The following suggestions and recommendations were made:

Regional ethical bodies should be formed. This should not preclude national regulatory and ethical bodies nor the strengthening of the institutional bodies.

We need to foster cross-country recognition in the area of ethics, with harmonisation of standard operating procedures, guidelines and joint reviews.

Areas of emphasis in partnerships and networks should be at institutional level rather than at individual or project related level. We need to improve south-south interaction and to involve partners from protocol writing stage through to data dissemination. We also need to have qualified staff who are highly motivated, and develop mutual respect, with all having the same level of knowledge and access to information. Partnerships and networks need to be formed based on disease-specific issues, but must be GCP compliant even if disease areas are not considered.

Sustainability can be maintained by involvement of government, utilising the NEPAD platform where possible

Funding can be optimised by encouraging co-funding into a common pot and not at project level. We have to avoid fragmentation and territorialism such as European versus American or influences on colonial links

Sponsorship issue: the EDCTP should consider providing access to liability insurance

We need to promote partnerships based on scientific collaboration and strength rather than historical linkages

Effective data management will mean full access and sharing of data generated

Transparency among partnerships should be encouraged

We must foster state of the art training in GCP and GCLP, addressing drug trials, vaccine development and diagnostics and devices.

Michael Makanga

RAPPORTEURS' REPORT - ROUND TABLE II

Capacity building and scientific leadership development

Capacity building for clinical trials in Africa

Michael Makanga, SEC

Key elements of capacity building were reviewed and considered as follows:

- A critical mass of properly trained and motivated key study personnel is essential, with an adequate number of well-motivated support staff
- Facilities, equipment and supplies (main and field/satellite sites) need to be considered. Administrative and financial services need consideration, together with clinical and laboratory facilities, including sample storage
- Internet connectivity provides access to scientific information and is a valuable research tool, providing better communication, networking, project coordination and offering membership of the global scientific community. E-learning can be an important part of training
- Conduct of clinical trial should include site preparation such as good clinical practice (GCP) and good clinical laboratory practice (GCLP) training, study subjects follow-up capacity, project planning and management, financial management, data management
- Ethical capacity strengthening
- Regulatory capacity strengthening
- Raising of funding necessary to develop and maintain clinical trials capacity and to address bridging activities and staff retention between projects.

The recommendations of the round-table included:

Clear institutional goals and objectives which must address training, research and service delivery as well as patients' management.

Situation analysis must identify major gaps in capacity, define the competencies required and design a comprehensive capacity programme to enhance competence.

An integrated development plan should be prepared including training of scientists and technicians (with a career development plan); details of infrastructure development (capacity building and utilisation) and funding.

It is necessary to encourage well structured multidisciplinary training tailored to institutional requirement. These will include short-term training in workshops and short courses; long-term training for Masters and PhDs (locally relevant, sandwich approach); partnerships, providing technical assistance and technology transfer; networking, with information exchange, scientific conferences, exchange programmes and mentorship programmes.

Encourage development of strong and committed leadership and utilise these leaders as role models and mentors for young researchers.

Improve staff retention by better salaries and creation of an enabling environment. Institutions should develop creative financing mechanisms that build up a 'trust fund' (e.g. diversification of research work done, overheads); stimulate local staff to seek funding from different funding organisations and advocate for research funding from African governments.

Strengthen the national health systems including the Expanded Program on Immunization (EPI) system and discourage undermining of the public sector by aggressive recruitment of local staff for clinical trials.

Encourage pharmaceutical industry involvement in clinical trials to invest in capacity development.

Capacity sustainability can be supported by involving African governments in the long-term strategic plans for projects, and by promoting research and training in African research training institutions (networking of African universities). Networking of highly specialised laboratories can also improve sustainability (when they evolve as reference

Francine Ntoumi

Thomas Nyirenda

laboratories). Sustainability is also supported by encouraging local staff competitiveness for funding from different funding organisations.

Improved transparency with sharing of information and accountability.

Active involvement of all partners (North and South) at all stages of planning including proposal writing, conduct of clinical trials, data analysis and report writing.

Ethics and regulatory capacity strengthening.

In view of large number of generics in use, there is some regulatory concern. There is a need for bioequivalence study capacity in Africa.

Improved capacity for community participation.

Development of scientific leadership in Africa

Francine Ntoumi, SEC

The main components of the background to scientific leadership are:

Many indicators of global science show high discrepancies between advanced economies and developing countries.

The constraints of building research capacity in Africa have been identified at biomedical, clinical and operational level.

Many deficiencies have been identified in policy and regulatory aspects.

The challenge for the EDCTP is to develop new clinical interventions to fight HIV/AIDS, malaria and tuberculosis, by integrating European research efforts into a partnership with Africa. But does Africa have what it takes to provide the lead in addressing the problems directly, in the most specific manner possible? How should we approach this challenge?

How can we define or propose African scientific leadership? We need to consider the principal investigator from the north versus co- investigator from the south issue. We have to develop a system for measuring scientific leadership in Africa, taking account of experience, publications and management of research activities and contribute to the integration and coordination of the European research effort in Africa. We can also draw on the experience of DNDi, with African country PI and site PIs. We should be inspired by the US leadership programme. The EDCTP needs to develop an inventory of African scientific leaders, and should be cautious about true versus fake partners. Finally, the scientific leader should manage the funds and be paid fairly.

We need to have a clear and comprehensive definition of African scientific leaders, because African participation does not necessarily mean African leadership. This should be based on a comprehensive inventory of African scientific leaders through the ongoing efforts of the Developing Countries Coordinating Committee (DCCC) and the Africa Office (AO) and involve those parts of Africa that are currently neglected.

African health ministers have committed 2% of their health budgets to research. This should be put in a common pot to support African sites.

The partnership can bring together stakeholders including scientists, pharmaceutical manufacturers, developers, funding agencies, etc in meetings in Africa under the auspices of NEPAD/AU and the EC/EDCTP. In order to create efficient partnerships in Africa, we must integrate the European research effort in Africa and select late-stage products with high relevance to Africa, then prioritise and promote their investigation in as comprehensive an effort as possible.

Scientific leadership: career development for clinical trials

Thomas Nyirenda, SEC

The mission of WHO/TDR and some of the partnerships it fosters have already been reviewed in this forum and focussed on many lessons that have been learned over the past 15 years.

Round table discussions centred on several areas of concern as follows:

- Differences in status among researchers
- Unattractive research environment
- Inadequate remuneration systems
- Poor paths for young scientists

Bernard Fourie

- Limitation on the scope of cadres to be trained
- Lack of residual funding to keep centres going in absence of grants
- Lack of an adequate pool of monitors
- Limited training in research e.g. financial management
- Inadequate number of re-entry grants
- Lack of adequate information on training opportunities.

To address these issues, the following recommendations were made:

Country and institutional levels

We need to harmonise the status of researchers and allow them to work in an enabling and attractive research environment, while creating clear career paths for young scientists. We can allow researchers to pay themselves through grants and to ensure a future generation of scientists We need to stimulate interest in a clinical trials career in schools.

Funding

We should reduce the current overemphasis on developing MDs only. Start-up funding should be provided for the creation of conducive research environments. Moreover we should create a pool of monitors to cover non-pharmaceutically funded research and training should be broadened to include financial know-how, negotiation skills, etc.

In order to create independent scientists we need to introduce re-entry grants and maintain other training awards. We also should introduce attachment programmes to clinical trial sites and we can stimulate sustainability by creation of a database of existing training opportunities.

Discussion

A speaker from the floor noted that each country has institutional centres as well as individual centres. How should these be best coordinated for maximum impact?

According to Dr Kitua, it is ownership that is the real issue. If an institution is run by another country, then it is owned, and is not an African institution. We should work more together, sharing all of the results and benefits. Building expertise in Africa is a combination of people and institutions. Could EDCTP accredit both institution and scientists, perhaps acknowledging their progress and topping up their salaries? If the EDCTP accredited in this way, could they renegotiate with the governments for access to the 2% from the African Health Ministries? Accreditation gives confidence to third-party funders, who may grant greater autonomy..

An institution has to grow, and it grows around individuals as human capacity and infrastructure increase and may progress into a centre of excellence. Some institutions however are either growing very slowly or not growing and are heavily dependent on a single senior scientist. Loss of senior scientists may result in total collapse of such institutions and this kind of situation should be avoided in African institutions.

Some key statements that served as a firm background for discussion during the Round Table sessions

Session Chair: Bernard Fourie, South Africa
Pascoal Mocumbi, EDCTP High Representative

"EDCTP can maximise benefits by coordinating the development of regional Nodes of Excellence, build scientific African leadership and find appropriate solutions to ethics and regulatory issues; thus providing the appropriate environment for sustained interventions"

Diana Dunstan:

"Africans need to enable Europeans to achieve the objectives of Article 169"

Quintana-Trias:

"There can be no doubt as to the exact mission of the EDCTP and of the expected outcome: develop new clinical interventions to fight HIV/AIDS, tuberculosis and malaria in the context of the integration of European research efforts and in partnership with Africa"

Key issues in partnership and networking were north-north relationships, co-funding and supplementary grants. We need to speed up the partnership and networking

process – the focus must be primarily on European research integration and on achieving the principles of Article 169.

We need to shift to a product approach rather than project approach – we have to move available, promising products into trials but must hear Africa's opinion on priorities using DCCC as the bridge. We also need to activate creative co-funding options, removing barriers for investigators but observe transparency. A move on setting up nodes of excellence could deliver the output as well as acting as training centres for weaker research institutions.

Multicentre partnerships for clinical trials in Africa can promote a regional and subregional framework for ethics and regulatory bodies, aiming for harmonised policies and cross-country recognition, and building on existing initiatives – we can also involve WHO as a stakeholder. We should engage institutions rather than individuals towards sustainable partnerships, utilising NEPAD as a platform for confirming government commitment to the process. We need to involve all partners at all levels of the process, recognising the multi-party nature of the collaboration. We at the same time need to formulate clearly how foreign partners and funding could/should be factored into EDCTP-funded projects. The sponsorship issue has been raised, and we need to consider - is product liability cover the actual issue here?

Regarding capacity building for clinical trials in Africa, we must network specialised skilled sites and provide funding to serve as training nodes for future trial staff and project leaders – also maintain infrastructure and equipment. It will be necessary to promote diversification of scientific skills, ensuring cost-effective application of time and infrastructure across these multi-disciplinary projects. Other factors associated with capacity building for clinical trials in Africa include enabling access to training programmes for financial and project management; the critical need for data management structures; the need for trust and bridging funds to guarantee salaries and remuneration of scarce skills, without undermining public services; sustaining research capacity; and engaging the pharmaceutical industry in skills development.

Scientific leadership in Africa can also be stimulated. We can develop definition for and an inventory of scientific leaders in clinical and biomedical research in Africa and structure this into a resource for optimal utilisation and transfer of skills to future scientists in whole of Africa. We can promote the true principal investigator identity and legitimate African stakeholder status in proposals for funding, including full responsibility for management of funds.

A stakeholders meeting should be organised in Africa in early 2007, where a response could be formulated regarding Africa's consortium role as applicable to the core mission of the EDCTP, i.e. optimally engaging the available technical skills and infrastructure in Africa, and also for structured development and expansion. We also recommend pressure on African governments regarding the promised 2% of African health budget, which could be allocated to a common research fund.

A clear need has been identified for development of a framework for career development in clinical trials. As a foundation for this, we can promote biomedical and clinical research as a career amongst students in science and medical faculties, together with compiling and maintaining a widely available catalogue of training programmes and courses, as well as offering access grants. As part of career development we can introduce and support attachment programmes in clinical trial sites, with broad exposure to trial conduct and management, financial know-how, negotiation skills and grant-writing.

We can make greater efforts to retain and sustain our scientists. We need start-up funding for attractive and efficient working environments that are conducive to innovative activity, re-entry grants and job security after foreign training, harmonised salary structures and recognition in different settings and promotion opportunities.

We have identified other key issues which need following up and/or further discussion; notably brokered and joint calls, African consortia (where we need a better definition), nodes of excellence, and some special issues such as a NEPAD/AU platform, sustainability and retention of skills.

CONCLUDING REMARKS

Pascoal Mocumbi, EDCTP High Representative

Over a period of three days we have heard political and scientific leaders giving advice and commitment on a wide range of subjects:

- Capacity building in scientific leadership in Africa
- Networking within the partnership
- Making clinical trials run cost-effectively
- Partnership and African leadership for conduct of clinical trials
- Experiences from the field and reports from EDCTP projects.

What have we learned?

In Africa there is great commitment for the EDCTP programme. There has already been project implementation and more still needs to be done. This African involvement can be used to foster integration of research programmes in the North. There is great need for sustainable capacity building, networking through strong structures and coordination of the networks.

In Europe there is progress in mobilising national programmes to achieve Article 169, though more needs to be done. The need for true partnership with Africa is evident.

At donor/funder level more and more partners are expressing the importance of EDCTP structure for delivery of new tools to Africa. However, there is need to engage policymakers at an earlier stage in the process.

What is the way forward?

From the presentations at the forum it was clearly demonstrated that we are making very good progress in achieving our objectives. It was demonstrated that we have commitment from both north and south partners. The challenge we face is to scale up our activities, in implementing the recommendations from this forum.

LIST OF PARTICIPANTS

Abdoulaye Djimde
University of Bamako
P.O.Box 1805 Bamako, Mali
Tel: +223 2228109
adjimde@mrtcbko.org

Abdullrahman Orosanya
Creating for life Initiative
12 Balogun Kuku Street Aguda Surulere
Lagos, Nigeria
Tel: +234 014334310
concern_conscience@yahoo.co.uk

Abebola Orimadegun
University College Hospital
P.O.Box 29914 Ibadan, Nigeria
Tel: +234 8058266882
beorimadegun@yahoo.com

Abraham Alabi
MRC Laboratories
P.O.Box 273 Banjul, Gambia
Tel: +220 4495442
aalabi@mcr.gm

Alawai Shaaban Swabury
Europe SADC States Bridge (ESSB)
Askanischer Platz 4
10963 Berlin, Germany
Tel: +49 3039788185
a.swabury@essb.de

Alfred Brima Bangura
Organization for Poverty Alleviation and Development
Rue 54 x 59 Medina
B P 28249 Dakar, Senegal
Tel: +22 15759546
infoopoad@yahoo.com

Alfred Tiono
Centre National de Recherche et de Formation sur le Paludisme
Ouagadougou, Burkina Faso
Tel: +226 50324695
t.alfred@fasonet.bf

Al-Hassan Al-Ansary
TB Research Centre Kassala University
Sudan Kassala, Sudan
Tel: +249 411820996
alansaryalansary@hotmail.com

Alioune Dieye
Institut Pasteur de Dakar
P.O.Box 220 Dakar, Senegal
Tel: +221 8399242
dieye@pasteur.sn

Alphonse Ouedraogo
Centre National de Recherche et de Formation sur le Paludisme (CNRFP)
Ouagadougou, Burkina Faso
Tel: +226 50324695
alphonse.ouedraogo@yahoo.fr

Amadou Tidiani Konate
Centre National de Recherche et de Formation sur le Paludisme
Ouagadougou, Burkina Faso
Tel: +226 50324695
a.konate.cnlp@fasonet.bf

Andreas Heddini
Swedish International Development Cooperation Agency (Sida)
SE-105 25Stockholm, Sweden
Tel: +46 086985420
andreas.heddini@sida.se

Andrew Yona Kitua
National Institute for Medical Research
Luthuli Road/Sokoine Drive 2448
P.O.Box 9653
Dar-Es Salaam, Tanzania
Tel: +255 222121400
akitua@nimr.or.tz

Anna Papa-Konidari
Aristotle University of Thessaloniki
School of Medicine
Thessaloniki, Greece
Tel: +30 2310999006
annap@med.auth.gr

Armand van Deun
Institute of Tropical Medicine
Antwerp, Belgium
Tel: +32 32476548
avdeum@itg.be

Arnd Hoeveler
European Commission
CDMA 03/49
1049 Brussels, Belgium
Tel: +32 22956801
arnd.hoeveler@ec.europa.eu

Asim Ahmad
Ministry of Health
Khartoum, Sudan
Tel: +249 912880500
asigamaz@hotmail.com

Bankole Nehemiah Amoo
Ibadan South East Local Government
P.O.Box 20395 Ibadan, Nigeria
Tel: +324 8052181520
kolexdamic@yahoo.com

Beatrice Namutangula
Makerere University
P.O.Box 6240 Kampala, Uganda
Tel: +256 772426484
bnamutangula@gmail.com

Bernard Fourie
Medicine in Need (MEND)
P.O.Box 749, La Montagne
Pretoria, South Africa
Tel: +27 123398547
bfourie@medicineinneed.org

Bjørg Halvorsen
Directorate for Health and Social Affairs
P.O.Box 7000 St. Olavs Plass
Oslo, Norway
Tel: +47 24163323
bha@shdir.no

Boitumelo Semete
Council for Scientific and Industrial Research
Building 14c Brummeria
Pretoria, South Africa
Tel: +27 128412366
tumisemete@yahoo.com

Britta Wahren
Karolinska Institute
SE-171 82Stockholm, Sweden
Tel: +46 84572300
britta.wahren@smi.ki.se

Bruno Gryseels
Institute of Tropical Medicine
Nationalestraat 155
2000Antwerpen, Belgium
Tel: +32 32476200
bgryseels@itc.be

Bruno Kilunga Kubata
Biosciences Eastern and Central Africa Network
P.O.Box 30709 Nairobi, Kenya
Tel: +254 204223204
b.kubata@cgiar.org

Catherine Royce
Drugs for Neglected Diseases Initiative
1 Place Saint Gervais
1201 Geneva, Switzerland
Tel: +41 229069230
croyce@dndi.org

Charles Makassi
National Institute for Medical Research (NIMR)
P.O.Box 9653 Dar es Salaam,
Tanzania
Tel: +255 272641915
rectocap-kilosa@kickeko.com

Charlotta Nilsson
Karolinska Institute
SE-171 82 Solna, Sweden
Tel: +46 94572612
charlotta.nilsson@smi.ki.se

Chifumbe Chintu
University of Zambia
P.O.Box 50110 Lusaka, Zambia
Tel: +260 1254681
cchintu@zamnet.zm

Christiane Druml
Medical University of Vienna
1090 Vienna, Borschkegasse 86
Vienna, Austria
Tel: +43 1404002147
christiane.druml@mediuiwien.ac.at

Christina de Carvalho Nicacio
Swedish International Development Cooperation Agency (Sida)
SE-105 25 Stockholm, Sweden
Tel: +46 86984020
christina.de.carvalho@sida.se

Christine Manyando
Tropical Diseases Research Centre
P.O.Box 71769 Ndola, Zambia
Tel: +260 2621732
manyando@zamnet.zm

Chukwuemeka Nwachukwu
University of Calabar
P.O.Box 5615 Calabar, Nigeria
Tel: +271 14030490
dremeka31@yahoo.com

Claire Newland
Medical Research Council
20 Park Cresent
W1B 1AL
London, United Kingdom
Tel: +44 2076365422
claire.newland@headoffice.mrc.ac.uk

Claudia Herok
Federal Ministry of Education and Research
Hannoversche Strasse 28-30
10115 Berlin, Germany
Tel: +49 18885296
claudia.herok@bmbf.bund.de

Dario Zanon
EC Commission
Rue de Cheup de Mors 21
BE-1049Brussels, Belgium
Tel: +32 22980250
dario.zanon@cec.eu.int

David Olufemi Olaleye
University of Ibadan
Ibadan, Nigeria
Tel: +234 22412457
ibvirology@yahoo.com

Desta Getachew Aderaye
Addis Ababa University
P.O.Box 2380 Addis Ababa, Ethiopia
Tel: +251 0115510653
getadera@yahoo.com

Diana Dunstan
Medical Research Council
20 Park Crescent
W1 London, United Kingdom
Tel: +44 2076365422
diana.dunston@headoffice.mrc.ac.uk

Diarmuid McClean
Irish Aid
Bishop's Court, Redmond's Hill
Dublin, Ireland
Tel: +353 1 4082401
dairmuid.mcclean@dfa.ie

Dirk van der Roost
Institute of Tropical Medicine
Nationalestraat 155
2000 Antwerpen, Belgium
Tel: +32 32476212
dvdroost@itg.be

Dominic Dery
Kintampo Health Research Centre
P.O.Box 200
Kintampo, Ghana
Tel: +233 6127304
Bon-ereme.dominic@ghana-khcr.org

Egeruan Babatunde Imoukhuede
European Malaria Vaccine Initiative
12 Bell House, Ewen Crescent
London, United Kingdom
Tel: +44 02086748318
ebimoukhuede@hotmail.com

Eileen Hoal
Stellenbosch University
Faculty of Health Sciences, Box
19063 Tygerberg, South Africa
Tel: +27 219389412
egvh@sun.ac.za

Elly Katabira
Makerere University Medical School
P.O.Box 7072 Kampala, Uganda
Tel: +256 41530020
katabira@imul.com

Emeka Emmanuel Micah
Youth Awareness Campaign AIDS (YACAA)
46A, LSDPC Ogudu Road
Lagos, Nigeria
Tel: +234 18908855
youthawareness_aids@yahoo.com

Eric Sandström
Karolinska University Hospital
Venhälsan, Södersjukhuset
118 83 Stockholm, Sweden
Tel: +46 86162571
eric.sandstrom@karolinska.se

Eveline Geubbels
Project Ubuzima / IATEC
Rue Akagera 716
P.O.Box 4560 Kigali, Rwanda
Tel: +250 503431
e.geubbels@iatec.com

Fabio Zicker
World Health Organization
Avenue Appia 20
CH-1211 Geneva, Switzerland
Tel: +41 227913805
zickerf@who.int

Francisco Moises
National Institute of Public Health
CP 3665 Luanda, Angola
Tel: +244 222393247
moisesfrancisco@hotmail.com

Franklin Weria Mosha
Kilimanjaro Christian Medical Centre
P.O.Box 3010 Moshi, Tanzania
Tel: +255 272753909
fwmosha@kcmc.ac.tz

Friday Odey
Institute of Tropical Disease Research and Prevention
PMB 1278 Calabar, Nigeria
Tel: +234 8037135417
awhobe@yahoo.com

Genesis Nana Boateng
Omanbapa Professional Institute
P.O.Box TF 218
New Tafo, Ghana
Tel: +233 243965466
kingboata@yahoo.co.uk

George Ademowo
Postgraduate Institute for Medical Research and Training, College of Medicine
PMB5017 Ibadan, Nigeria
Tel: +234 241270
Ademowo_g@yahoo.com

Georgina Njideka Odaibo
University of Ibadan
Ibadan, Nigeria
Tel: +234 22412457
foreodaibo@hotmail.com

Gernard Msamanga
Muhimbili University Collega of Health Sciences
P.O.Box 65015
Dar es Salaam, Tanzania
Tel: +255 222150503
gmsamanga@muchs.ae.tz

Getnet Ali
Addis Ababa University
9842 Addis Ababa, Ethiopia
Tel: +251 115511211
getnetyimer@yahoo.com

Gloria Omosa-Manyonyi
University of Nairobi
P.O.Box 60399 (00200)
Nairobi, Kenya
Tel: +254 2022717694
gomosa@kaviuon.org

Gunilla Källenius
Karolinska Institute and Swedish Institute for Infectious Disease Control
SE-171 82 Solna, Sweden
Tel: +46 84572430
Gunilla.kallenius@smi.ki.se

Gunnel Biberfeld
Karolinska Institute and Swedish Institute for Infectious Disease Control
SE-171 82 Solna, Sweden
Tel: +46 84572660
gunnel.biberfeld@smi.ki.se

Hannah Akuffo
Swedish International Development Co-operation Agency (SIDA)
10525 Stockholm, Sweden
Tel: +46 86985053
Hannah.akuffo@side.se

Hannah Kibuuka
Makerere University-Walter Reed Project
P.O.Box 9630 Kampala, Uganda
Tel: +256 41534588
hkibuuka@muwrp.org

Hassan Mahomed
University of Cape Town
Cape Town, South Africa
Tel: +272 14066697
hassan@rmh.uct.ac.za

Herman Parfait Awono Ambene
O.C.E.A.C.
P.O.Box 288 Yahounde, Cameroon
Tel: +237 2232232
hpaawono@yahoo.fr

Hulda Swai
Council of Scientific Industrial Research (CSIR)
P.O.Box 395
Pretoria, South Africa
Tel: +271 28412366
hswai@csir.co.za

Isabel Noguer
Instituto de Salud Carlos III
Sinesio Delgado 6
Madrid, Spain
Tel: +34 918222108
inoguer@isciii.es

Issa Nebie
Centre National de Recherche et de Formation sur le Paludisme
01 BP 2208 Ouagadougou 01
Ouagadougou, Burkina Faso
Tel: +226 50324695
issanebie.cnlp@fasonet.bf

Jane Maina
World Vision International South Sudan
P.O.Box 9704 Nairobi, Kenya
Tel: +254 204441777
jane_maina@wvi.org

Janneke van de Wijgert
Academic Medical Center
Pietersbergweg 9
1105 BM Amsterdam, Netherlands
Tel: +31 203149355
j.vanderwijgert@iatec.com

Jean – Jacques Moka
OCEAC
P.O.Box 288 Yaounde, Cameroun
Tel: +237 2232232
moka_jean_jacques@yahoo.fr

Jeanne – Françoise Mucomwiza
OCEAC
P.O.Box 288 Yaounde, Cameroun
Tel: +237 2232232
jf_muco@yahoo.fr

Jelle Thole
Animal Sciences Group
Edelhertweg 15
8219 PH Lelystad, Netherlands
Tel: +31 320238508
jelle.thole@wur.nl

John Kebaso
African Population and Health Research Center
P.O.Box 10787 Nairobi, Kenya
Tel: +254 202720400
jkebaso@aphrc.org

John Shao
Kilimanjaro Christian Medical Centre
P.O.Box 3010 Moshi, Tanzania
Tel: +255 272754377
jshao@kcmc.ac.tz

Joseph Babadi Johns
Masianday Foundation and Cenpad-Opad Bajito Onda
Rue 22 x 27
BP 28249 Dakar, Senegal
Tel: +223 5167922
prdirector5@yahoo.com

Joseph Odhiambo
Kenya Medical Research Institute
P.O.Box 606-00621 Village Market
Nairobi, Kenya
Tel: +254 0202713008
jodhiambo@ke.cdc.gov

Joseph Vyankandondera
Centre Hospitalier Universitairede Kigali / Project Ubuzima
P.O.Box 655 Kigali, Rwanda
Tel: +250 503431
vyankajo@yahoo.fr

Judith de Kroon
NWO-NACCAP
P.O.Box 93120 2509 AC
The Hague, Netherlands
Tel: +31 703440553
kroon@nwo.nl

Juhani Eskola
National Public Health Institute (KTL)
Mannerheimintie 166
FIN-00300 Helsinki, Finland
Tel+ 358 947448502
juhani.eskola@ktl.fi

Kalifa Bojang
MRC Laboratories
P.O.Box 273 Banjul, Gambia
Tel: +220 5668108
kbojang@mrc.gm

Kamija Phiri
College of Medicine
P.O.Box 360 Blantyre, Malawi
Tel: +265 1674628
kamijaphiri@gmail.com

Kashongwe Munogolo
Catholic University of Bukavu
P.O.Box 2 Bukavu, Congo
Tel: +243 813178240
zkashongwe@yahoo.fr

Klaus Winkel
Statens Serum Institut
Artillerivej 5
2300
Copenhagen, Denmark
Tel: +45 32683670
win@ssi.dk

Lahouari Belgharbi
World Health Organization
Avenue Appia 20
CH-1211
Geneva, Switzerland
Tel: +41 227913925
belgharbil@who.int

Laura Brum
National Health Institute Dr. Ricardo Jorge
1649-016 Lisboa, Portugal
Tel: +35 1217519236
laura.brum@insa.min-saude.pt

Lawrence Yamuah
Aranauer Hansen Research Institute
P.O.Box 1005 Addis Ababa, Ethiopia
Tel: +251 113213763
yamuahlk@yahoo.co.uk

Leif Bertilsson
Karolinska Institute
Stockholm, Sweden
Tel: +46 858581071
leif.bertilsson@ki.se

Luis Guerra
Instituto de Salud Carlos III
Sinesio Delgado 6, Madrid, Spain
Tel: +34 918222108
inoguer@isciii.es

Lynn Zijenah
College of Health Sciences University of Zimbabwe
Mazoe Street
P.O.Box A178 Avondale
Harare, Zimbabwe
Tel: +263 4791631
sodai@mweb.co.zw

Maarten Schim van der Loeff
Academic Medical Center
Pietersbergweg 9
1105 BM Amsterdam, Netherlands
Tel: +31 203149300
m.schim@iatec.com

Malebona Matsoso
World Health Organization
Avenue Appia 20
CH-1211 Geneva, Switzerland
Tel: +41 227911452
matsosom@who.int

Mame Aissatou Toure
Institut Pasteur Dakar
36 Av Pasteur
BP 220 Dakar, Senegal
Tel: +221 8399241
atoure@pasteur.sn

Manuel Romaris
European Commission
Office 3/35
BE-1049 Brussels, Belgium
Tel: +32 22998733
manuel.romaris@ec.europa.eu

Maowia Mukhtar
Institute of Endemic Diseases, University of Khartoum
P.O.Box 11463 Khartoum, Sudan
Tel: +249 183779712
mmukhtar@iend.org

Maria de Lourdes Spencer Lopes dos Santos
Independent Consultant HIV-AIDS
CP 108 Mindelo, Rep. Cabo Verde
Tel: +238 2311465
marialouspencer@hotmail.com

Maria Isaguliants
Swedish Institute for Infectious Disease Control
Nobels v 18
17182 Solna Stockholm, Sweden
Tel: +46 84572609
maria.isaguliants@smi.ki.se

Mark Palmer
Medical Research Council
20 Park Cresent
W1B 1AL London, United Kingdom
Tel: +44 2076705355
mark.palmer@headoffice.mrc.ac.uk

Mathieu Ndounga
Centre d'Etudes sur les Ressources Végétales (CERVE)
Rue de l'Auberge de Gascogne, Enceinte ex-ORSTOM, Makélékélé
Brazzaville, Congo
Tel: +242 5260503
ngoualandounga@yahoo.fr

Maurice Bucagu
National University of Rwanda
BP. 5229 Kigali, Rwanda
Tel: +250 585166
mbucagu@yahoo.com

Mbaraka Amuri
Ifakara Health Research & Development Centre
P.O.Box 53 Morogoro, Tanzania
Tel: +255 232625164
amuribaraka@gmail.com

Michel Klein
ETNAXVAX
54 Strathgowan Avenue
M4N 1B9 Toronto, Canada
Tel: 1 416 481 3549
michel.klein@umontreal.ca

Mike Chaponda
Tropical Diseases Research Centre
P.O.Box 71769 Ndola, Zambia
Tel: +260 2640204
mikechapozy@yahoo.com

Mohamed Sillah Sesay
Young Leaders-Sierra Leone Organization
16 Richard Street
Freetown, Sierra Leone
Tel: +232 76712338
sl_youngleaders@yahoo.co.uk

Mohammed Lamorde
Infectious Diseases Institute
P.O.Box 22418 Kampala, Uganda
Tel: +256 41307228
mohalamorde@yahoo.co.uk

Monique Wasunna
Drugs for Neglected Diseases Initiative
25700 Lavington, Nairobi, Kenya
Tel: +254 202730076
africa@dndi.org

Muhammad Bakari
Muhimbili University College of Health Sciences
P.O.Box 65001
Dar Es Salaam, Tanzania
Tel: +255 748387328
mbakari@muchs.ac.tz

Mulenga Modest
Tropical Diseases Research Centre
P.O.Box 71769 Ndola, Zambia
Tel: 260 026202402
clinsciences@zamtel.zm

Nelson Sewankambo
Makerere University Faculty of Medicine
P.O.Box 7072, Kampala, Uganda
Tel: +256 41530020/1
sewankam@infocom.co.ug

Nienke Veldhuijzen
IATEC Foundation
Pietersbergweg 9
1105 BM, Amsterdam, Netherlands
Tel: +31 203149300
n.veldhuijzen@iatec.com

Niresh Bhagwandin
South African Medical Research Council
P.O.Box 19070, Tygerberg
Cape Town, South Africa
Tel: +27 219380207
niresh.bhagwandin@mrc.ac.za

Olivier Basenya
National Institute of Public Health
P.O.Box 6807, Bujumbura, Burundi
Tel: +257 217565
basenya@yahoo.fr

Osman Sankoh
INDEPTH Network
P.O.Box KD 213 Kanda
Accra, Ghana
Tel: +233 21254752
osman.sankoh@indepth-network.org

Patrice Debre
Hopital Pitie Salpetriere
Bät C.E.R.V.I. – 83 bld de l'Hòpital
Paris, France
Tel: +33 142177482
patrice.debre@psl.ap-hop-paris.fr

Paul van Helden
Stellenbosch University and MRC SA
P.O.Box 19063
Tygerberg, South Africa
Tel: +27 219389401
pvh@sun.ac.za

Pembe Issamou Mayengue
Medical Research Unit of the A. Schweitzer Hospital
B.P. 118, Lambarana, Gabon
Tel: +241581099
pmayengue@yahoo.fr

Peter Gottfried Kremsner
Institut für Tropenmedizin
72074, Tübingen, Germany
Tel: +49707129987179
peter.kremsner@uni-tuebingen.de

Peter Ndumbe
Faculty of Medicine University of Yaounde
1 Melan Street
BP 8445, Yaounde, Cameroon
Tel: +237 2312730
pndumbe@yahoo.com

Peter Smith
London School of Hygiene and Tropical Medicine
Keppel Street
WC1E 7HT, London, United Kingdom
Tel: +44 2079272246
p.smith@lshtm.ac.uk

Rachel Kotila
University of Ibadan / University College Hospital, Ibadan, Nigeria
Tel: +234 2110088
taiwokotila@post.com

Ramatoulie Janha
Medical Research Council Laboratories
P.O.Box 273, Banjul, Gambia
Tel: +220 4495442
rjanha@mrc.gm

Rebecca Kivumbi - Mayanja
Makerere University Medical School
P.O.Box 1202, Kampala, Uganda
Tel: +256 41570386
beckymayanja@hotmail.com

Reem Bairam
University of Khartoum
Khartoum, Sudan
Tel: +249 183793263
rimta_22@yahoo.com

Richard Adegbola
Medical Research Council (MRC)
P.O.Box 273, Banjul, Gambia
Tel: +220 4494491
radegbola@mrc.gm

Sacra Tomisawa
State Secretariat for Education and
Research, Hallwylstrasse 4
3003, Berne, Switzerland
Tel: +41 313229693
sacra.tomisawa@sbf.admin.ch

Sian Roberts
Liverpool School of Tropical Medicine
Pembroke Place
Liverpool, United Kingdom
Tel: +44 151 7053212
s.roberts@liv.ac.uk

Simon Agwale
Innovative Biotech LTD
P.O.Box 30, Keffi, Nigeria
Tel: +234 8032900355
sagwale@innovativebiotechng.com

Sodiomon Bienvenu Sirima
Centre National de Recherche et de
Formation sur le Paludisme
Ouagadougou, Burkina Faso
Tel: +226 50324695/6
s.sirima.cnlp@fasonet.bf

Soren Jepsen
European Malaria Vaccine Initiative
c/o Statens Serum Institut
Artillerivej 5, DK-2300
Copenhagen, Denmark
Tel: +45 32683188
sje@ssi.dk

Sossanna Kolyva
General Secretary for Research and
Technology, Ministry of Development
Mesogeion 14, 11521 Athens, Greece
Tel: +30 2107458113
skolyva@gsrt.gr

Souleymane Mboup
Dakar, Senegal
Tel: +2218216420
mboup@nanslbr.org

Stefan Svenson
Karolinska Institute and Swedish Institute
for Infectious Disease Control
SE-171 82 Solna, Sweden
Tel: +46 705322471
stefan.svenson@vmm.slu.se

Stefan Wagener
DLR Project Management Agency on
behalf of the Federal Ministry of Education
and Research
Heinrich-Konen-Str. 1
D-53227, Bonn, Germany
Tel: +49 2283821648
stefan.wagener@dlr.de

Stefano Buttò
Istituto Superiore di Sanità
Viale Regina Elena 299
00161, Rome, Italy
Tel: +39 0649903248
stefano.butto@iss.it

Steven Velabo Shongwe
East, Central and Southern African
Health Community (ECSA-HC)
P.O.Box 1009, Arusha, Tanzania
Tel: +255 272504106
sshongwe@crhcs.or.tz

Steven Wayling
World Health Organization
Avenue Appia 20
CH-1211, Geneva, Switzerland
Tel: +41 227913909
waylings@who.int

Takafira Mduluza
University of Zimbabwe
P.O.Box MP 167, Mount Pleasant
Harare, Zimbabwe
Tel: +263 4308047
mduluza@medic.uz.ac.zw

Tamirat Gebru
Alemaya University
P.O.Box 70226 Addis Ababa, Ethiopia
Tel: +2510113205582
tamiratgw2002@yahoo.com

Teresa Maguire
Health Research Board
3rd Floor, 42-47 Knockmaun House
Lower Mount Street, Dublin, Ireland
Tel: +35 316761176
tmaguire@hrb.ie

Thomas Peto
National Institute for Medical Research
(NIMR)
P.O.Box 9653,
Dar es Salaam, Tanzania
Tel: +255 272641915
rectocap-kilosa@kickeko.com

Tumani Corrah
Medical Research Council
P.O.Box 273, Fajara, Gambia
Tel: +220 4496715
tcorrah@mrc.gm

Ulrich Fruth
World Health Organization
Avenua Appia 20
CH-1211, Geneva, Switzerland
Tel: +41 227912678
fruthu@who.int

Veronique Estico
Ministry of Health
Mont Fleuri Mahe Seychelles
Victoria, Seychelles
Tel: +248 241852
faestico@yahoo.co.uk

Videlis Nduba
Kenya Medical Research Institute
P.O.Box 614-40100, Kisumu, Kenya
Tel: +254 572021036
vnduba@kemri-ucsf.org

Walter Jaoko
University of Nairobi
Kenya AIDS Vaccine Initiative, Medical
Microbiology Dep
P.O.Box 19676, Nairobi, Kenya
Tel: +254 202727694
wjaoko@kaviuon.org

Zakayo Mrango
National Institute for Medical Research
(NIMR)
P.O.Box 9653
Dar es Salaam, Tanzania
Tel: +255 232623228
rectocao-kilosa@kickeko.com

Zeinab Elmahdi
Institute of Endemic Diseases
102Khartoum, Sudan
Tel: +24 9912380977
hibamahd180@hotmail.com

GLOSSARY OF ABBREVIATIONS

AAVP	African AIDS Vaccine Programme
ADB	Asian Development Bank
AFB	Acid Fast Bacilli
AMANET	African Malaria Network Trust
ANR	National Agency for Research
ARIPO	African Regional Intellectual Property Organization
ARV	Anti-retrovirals
AU	African Union
AusAID	Australian Government's Overseas Aid Program
AVAREF	African Vaccine Regulators Forum
BMRC	British Medical Research Council
CEMAC	Communauté Économique et Monétaire de l'Afrique Centrale
CTA	Clinical trials applications
DBS	Direct Budget Support
DCCC	Developing Countries Coordinating Committee
DCVRN	Developing Countries Vaccine Regulatory Network
DFID	Department for International Development
DNDi	Drugs for Neglected Diseases Initiative
DOTS	Directly observed treatment, short course
DRS	Drug Resistance Surveillance/Strain
DSMB	Data Safety Monitoring Board
DSS	Demographic Surveillance Site
DST	Drug Susceptibility Testing
EANMAT	East African Network for Monitoring Antimalarial Treatment
EBA	Early bactericidal activity
EC	European Commission
ECBS	Experts' Committee on Standardisation of Biologicals
ECOWAS	Economic Community Of West African States
EDCTP	European and Developing Countries Clinical Trial Partnerships
EEIG	European Economic Interest Group
EMEA	European Agency for the Evaluation of Medicinal Products
EMVI	European Malaria Vaccines Initiative
ENNP	European Network of National programmes
ENO	European Networking Officer
EPI	Economic Policy Institute
EQA	External Quality Assurance
ERC	Ethics Review Committees
EU	European Union
FDC	Fixed Dose Combination
GCC	Gulf Cooperation Council
GCP	Good Clinical Practice

GHP	Global Health Partnership
GLC	Green Light Committee
GLP	Good Laboratory Practice
GTN	Global Training Network
HIV/AIDS	Human immunodeficiency virus/auto-immune deficiency syndrome
HR	High Representative
HR-HR	Human Resources for Health Resources
HVTN	HIV Vaccine Trials Network
IAVI	International AIDS Vaccine Initiative
ICAM	Intercellular adhesion molecule
ICH/GCG	International Conference on Harmonisation/Global Cooperation Group
ICT	Information and communication technology
IDB	International Development Bank
IDMC	Independent Data Safety Monitoring Committee
IDP	Institutional Development Plan
IRB	Institutional Review Board
JICA	Japan International Cooperation Agency
IPTp	Intermittent preventive therapy in pregnancy
KEMRI	Kenya Medical Research Institute
LQAT	Lot Quality Assurance Testing
MCTA/INDEPTH	Malaria Clinical Trials Alliance/International Network of Field Sites with Continuous Demographic Evaluation of Populations and Their Health in Developing Countries
MDG	Millennium Development Goals
MDR-TB	Multi-drug resistant TB
MIM-ADRN	Multilateral Initiative for Malaria-Antimalarial Drug Resistance Network
MoH	Ministry of Health
MRC	Medical Research Council
MSEK	Million Swedish Kroner
MUVAPRED	Mucosal Vaccines for Poverty Related Diseases
NACCAP	Netherlands-African Partnership for Capacity Development and Clinical Interventions against Poverty-Related Diseases
NEPAD	New Partnership for Africa's Development
NoE	Nodes of Excellence
NORAD	Norwegian Agency for Development
NP	National Programme
NRA	National Regulatory Authorities
NTP	National TB Control Programme
OAPI	African Intellectual Property Organization
OFLOTUB	Ofloxacine-containing, short-course regimen for the treatment of pulmonary tuberculosis
PABIN	Pan-African Bioethics Initiative
PAHO	Pan-American Health Organisation
PB	Partnership Board
PDP	Professional Development Programme
PEPFAR	President's Emergency Plan for AIDS Relief

PI	Principal Investigator
PMTCT	Prevention of mother-to-child transmission
PRD	Poverty-related disease
PT	Proficiency testing
QA	Quality assurance
QoC	Quality of care
REC	Research Ethics Committee
SATVI	South African Tuberculosis Vaccine Initiative
SADC	Southern African Development Community
SCC	Scientific Coordinating Committee
SIDA	Swedish International Development Co-operation Agency
SIDCER	Strategic Initiative for Developing Capacity in Ethical Review
SLD	Second-line drug
SRL(N)	Supra-National Reference Laboratory(Network)
S-S	South-South
SWAPS	Sector-Wide Approaches
TB	Tuberculosis
TRIPS	Trade-Related Aspects of Intellectual Property Rights
TSR	WHO Technical Report Series
UEMOA	Union Economique et Monétaire Ouest Africaine
UK	United Kingdom
UNICEF	The United Nations Children's Fund
USAID	United States Agency for International Development
USMHRP	US Military HIV Research Program
VL	Viral load
WACCS	West African Consortium for Clinical Studies
WANMAT	West African Network for Monitoring Antimalarial Treatment
WB	World Bank
WHO	World Health Organization
WHO AFRO	World Health Organization African Region Office
WSSD	World Summit on Sustainable Development
XDR-TB	Extensively drug-resistant tuberculosis