European and Developing Countries
Clinical Trials Partnership (EDCTP)

# SECOND ANNUAL FORUM

# HIV/AIDS, TB and Malaria in Africa: From Knowledge to Implementation

*A Strategy to do More, and Better*

EDCTP – European & Developing Countries Clinical Trials Partnership

International Convention Centre,
Durban, South Africa
3-5 October 2005

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AAVP | Africa Malaria Vaccine Programme |
| ART | Antiretroviral treatment |
| ARVs | Antiretrovirals |
| AU | African Union |
| CRFs | Case report forms |
| CT | Clinical trials |
| DCCC | Developing Countries Coordinating Committee |
| DFID | Department for International Developmen |
| DOTS | Directly Observed Treatment, Short Course |
| DSMB | Data and Safety Management Board |
| EANMAT | East African Network for Monitoring Antimalarial Treatment |
| EBA | Early bactericidal activity |
| EC | European Commission |
| EEIG | European Economic Interest Group |
| EMEA | European Agency for the Evaluation of Medicinal Products |
| EPI | Economic Policy Institute |
| EU | European Union |
| GCP | Good clinical practice |
| GLP | Good laboratory practice |
| HANMAT | Horn of Africa Network for Monitoring Antimalarial Treatment |
| HIV/AIDS | Human immunodeficiency virus/auto-immune deficiency syndrome |
| HTM | HIV/AIDS, TB and Malaria |
| IAEA | International Atomic Energy Agency |
| ICASA | Independent Communications Authority of South Africa |
| IPT | Intermittent preventive therapy |
| IPTc | Intermittent preventive therapy in children |
| IPTi | Intermittent preventive therapy in infants |
| IPTp | Intermittent preventive therapy in pregnancy |
| MDG | Millenium Development Goals |
| MDP | Microbicides Development Programme |
| MDR TB | Multidrug-resistant tuberculosis |
| MMV | Medicines for Malaria Venture |
| MRC | Medical Research Council |
| MTCT | Mother to child transmission |
| NEPAD | New Partnerships for Africa's Development |
| PDP | Professional development programme |
| PPP | Public-private partnership |
| PRD | Poverty-related disease |
| SATVI | South African Tuberculosis Vaccine Initiative |
| SCCC | Serial sputum colony counts |
| SOPs | Standard operating procedures |
| SP | Sulfadoxine-pyrimethamine |
| S-S | South-South |
| TB | Tuberculosis |
| WANMAT | West African Network for Monitoring Antimalarial Treatment |
| WBA | Whole blood assay |
| WHO | World Health Organisation |
| WHO AFRO | World Health Organisation Regional Office for Africa |

# EXECUTIVE SUMMARY

The main aim of the Second Forum of EDCTP held in Durban, South Africa, 3-5 October 2005, was to come up with considered recommendations as to how EDCTP can do more – and better – in terms of the theme of the meeting, namely 'HIV/AIDS, TB and Malaria in Africa: From Knowledge to Implementation'. An agreed strategy, hopefully, would also serve the broader objectives of partnerships that drive a global health agenda, and consequently would aim to promote prosperity and solidarity, ensuring long-term success and a better quality of life for future generations.

As Dr Odile Leroy, Executive Director of EDCTP, points out in her welcoming address, what will make a solid strategy is having very clear and implementable objectives and targets. "We need to map clearly the focus and the overall goal of EDCTP". She outlined the main objective of the Forum as an opportunity for:

- Networking between African and European delegates
- Promoting the Partnership
- Strengthening collaborations, or for identifying common interests that could lead to joint activity utilising EDCTP as an operational platform.

This, we believe, has been achieved. As Dr Pascoal Mocumbi said in his concluding remarks: "We are ending this Forum, knowing what is expected of us and how to proceed about achieving the goals suggested by your recommendations".

Following State-of-the-Art reviews on the status of drug and vaccine developments towards more effective interventions in the leading diseases of poverty, HIV/AIDS, tuberculosis and malaria, two round table discussions (each with three sessions) were conducted to formulate recommendations, statements on need, challenges, and priorities for EDCTP. Attended by some 200 delegates, mainly from Africa, lively interactive discussions led to practical and implementable suggestions as to how EDCTP can structure its programme of work for the next 5 years. Each session aimed to address bullet point statements and questions, with introductory presentations given by leaders in each of the areas (see Appendix II). The broad recommendations that came out of each and the overall recommendations of the Forum are given in the report on Plenary III: Summary and recommendations (page 35).

To further enhance an understanding of Africa's needs and to demonstrate the ability of African and collaborating scientists from the North to work together and to contribute to EDCTP's goals, two scientific sessions were conducted where original research projects were selected for oral or poster presentation by the Forum's scientific committee on the basis of prior submitted abstracts. It was clear from these sessions that there is a considerable depth of scientific skill and research knowledge in Africa, supported in many countries by good facilities that could form core sites for further expansion through networking and capacity building efforts.

## Overall recommendations of the Forum

Following general discussion of all of the recommendations that stemmed from the round table discussions, a condensed list of primary recommendations from the Forum was compiled. The EDCTP Partnership Board was charged with the responsibility to consider these points in the next revision of the Joint Programme of the Action, which is EDCTP's formal mechanism for translating Forum recommendations into action and into funding via calls for proposals.

## Overall recommendations – HIV/TB/Malaria

### HIV

- Microbicides studies
- Drugs for children and mother to child transmission
- Simplification of antiretroviral therapy
- Establishment of Centres of excellence for monitoring of resistance to available ARVs
- Vaccine clinical trials, with focus on mucosal vaccines

### TB

- New diagnostics in context of definition of trial end-points
- Studies of adjunctive therapy (e.g. steroids) in extrapulmonary and other TB
- Expand activities to more adequately cover the available drug product portfolio

### Malaria

- Intermittent preventive therapy in pregnancy (IPTp)
- Preparation of sites for vaccine trials in sub-Saharan Africa
- Synergise with partners on standardisation of end-points and assays
- Alternative therapies to quinine for severe *Plasmodium falciparum* malaria
- More research investigations on uncomplicated malaria
- Diagnostics?

### Cross cutting

- Studies of co-infection and implications for drug treatment (e.g. HIV-malaria, HIV-TB)
- Strengthen regulatory capacity
- Traditional medicine?

# Overall recommendations – Capacity and Training

## Laboratory capacity

- Build laboratory capacity to investigate resistance to drugs (HTM)
- Fund work on immunological correlates of protection (HTM)
- Link the development of capacity to clinical trials
- Develop proficiency training
- Build regional reference laboratories and repositories

## Networks

- Support meetings/networks across diseases (through Developing Countries Coordinating Committee)

## Training

- Establish centres of excellence on data management and developing skills
- Develop research culture (focusing on undergraduates)
- Encourage PIs to link their teams to networks
- Link with industry for training in quality assurance and monitoring

## Cross cutting

- Advertise more widely EDCTP calls and activities

# WELCOME AND INTRODUCTION

**Odile Leroy**,
EDCTP Executive Director

Delegates, members of the corresponding agencies, as well as visitors from Africa and overseas, I am very pleased to welcome you to this Second Forum of EDCTP.

Why are we here? We are here to design a strategy to do more, and better. This strategy should form the key element in the partnership of global health, and consequently for prosperity and solidarity. We need to ensure long-term success and guarantee a better quality of life for future generations. This strategy should reflect our vision of EDCTP – a vision of which it can be proud. This strategy needs to involve all the stakeholders from political representatives up to the citizens, non-governmental organisations, private sector and international organisations. We need your ideas, your opinions and your feedback.

EDCTP is a new instrument and I think for this strategy we need to develop innovative ideas and new instruments. EDCTP must keep moving towards and guarantee future success. We must set out our ideas for now and for the next 10 years from now. What will make a solid strategy? We need to have very clear objectives and targets. If you look at the example of capacity building for HIV or for any vaccine in Phase III, we need also to encourage the political decision-maker at the national and regional level to use this knowledge, to use the competency that has been developed through the clinical trial, to use the infrastructure generated by the vaccine trial. This is always for better health policy, advocacy and information to all the citizens. We need to map the focus of the final goal of EDCTP.

I have already said that EDCTP is a new instrument, but we also have in our package new instruments that we have to develop, and we have to be creative and to find innovative means of delivering objectives. I am very pleased to say that EDCTP is a new model of partnership, not only north-south partnership, but also in Europe it has made a lot of progress in this partnering between European countries.

We have to examine how to use the instruments at our disposal to work out the objectives more directly and more efficiently. We need also to clarify the implementation of the strategy – who does what? What can be done by EDCTP and what should be done by the other stakeholders? We definitely need to coordinate to advance in efficiency. We need to introduce guidelines to share the best practices on a wider scale. The successes are not only based on the work of the Secretariat but also on the full involvement of the stakeholders and the scientific community. We also need to monitor the strategy better. We need to set clear deadlines, to assess implementation of the strategy, to define and agree indicators. We also need to set up a decision process to better drive EDCTP work.

This Forum will certainly not be a leisurely conference, and I am sure that all of the participants will work hard to reach conclusions and recommendations. We are supporting nine subjects from institutions, and we have representatives from 31 different countries here, so I really think that we will achieve a great deal on these three days.

I would like to thank very much Bernard Fourie for the tremendous work he has done towards organising this Forum, as well as the South African Medical Research Council, and also acknowledge the support from the European Commission. I also thank all of you for your participation. I am very pleased to declare the Forum open.

# OPENING AND KEYNOTE ADDRESSES

**Chair: Anthony MBewu,** President of the South African Medical Research Council

## Official opening address: Opportunities for health research in Africa

**Keynote address to the Second Forum of EDCTP, presented on behalf of Luis Sambo, the Regional Director, World Health Organisation, Regional Office for Africa**
**by Dr Paul-Samson Lusamba-Dikassa, Director of Programme Management**

Mr Chairman,
Distinguished scientists,
Ladies and Gentlemen,

I am particularly honoured to deliver this keynote address on behalf of Dr Luis Gomez Sambo, the Regional Director for the World Health Organisation Regional Office for Africa. He has asked me to convey his wishes to all for a successful meeting.

Johann Wolfgang von Goethe said: "Knowing is not enough, we must apply; willing is not enough, we must act". It is true that without research, development cannot take place. It is equally true that biomedical discoveries cannot improve people's health without research to find out how to apply these within different health systems, population groups, and diverse political and social contexts.

It has been recognised that only 10% of health research funds are devoted to addressing health problems in the regions where 90% of the world population live. Furthermore, many research projects and offers for research in Africa are oriented by donors and their interests. Ethical concerns are neglected, even by researchers themselves, in a context of resource scarcity and lack of awareness on the part of communities.

At the Regional Committee meeting held last August in Maputo, the African Health Ministers urged Member States to promote operational research as a tool for improved planning, implementation, monitoring, evaluation and integration of national human African trypanosomiasis control programmes into the national health system. This serves as an example of the importance of health research for disease control and health development.

The 58th World Health Assembly took a resolution urging Member States to implement the recommendation made by the Commission on Health Research for Development to invest at least 2% of national health expenditures in research and research capacity strengthening. At least 5% of project and programme aid for the health sector from aid agencies should thus be earmarked for research and research capacity strengthening.

The resolution further called Member States to establish, implement or strengthen as applicable, national health research policies; to collaborate with other partners in health research; to promote activities to strengthen national health research systems; to strengthen mechanisms to transfer knowledge in support of evidence-based public health and health care delivery systems; and to encourage networking of national research agencies and encourage public debate on the ethical dimensions and societal implications of health research.

### Research and health development

Dr Jong-wook Lee, WHO Director General, stated that "in the continuing battle to deal with health challenges and meet the health-related Millennium Development Goals, we have an indisputable ally: science. There is a gap between today's scientific advances and their application: between what is known and what is actually being done." In order to address the 'know-do' gap, Dr Lee formally set up a Knowledge Management and Sharing programme, whose primary mission is to help bridge this gap and contribute to the achievement of the health-related MDGs and other internationally agreed health goals.

In its final statement, the Mexico Ministerial Summit on Health Research (16-20 November 2004) acknowledged that "Research has a crucial but under-recognised part to play in strengthening health systems, improving the equitable distribution of high-quality health services, and advancing human development." The Summit reaffirmed that "the culture of high-quality research, knowledge generation and its application are critical to (i) the attainment of health targets within the Millennium Development Goals; (ii) the performance of health systems, including human resources for health; (iii) the vitality of socio-economic development; and (iv) the achievement of health equity."

Scientific advances alone proved insufficient to tackle the world's most pressing health problems, particularly those in the developing countries. Indeed, during the last 50 years big strides have been made in biomedical research. However, important health problems still facing Africa have not been successfully tackled. Old and toxic medicines are still being used in the fight against the so-called 'neglected diseases', including African human trypanosomiasis, schistosomiasis and leprosy, to cite but a few.

Among the challenges facing health research are the issues of values and ethics, equity and excellence, and above all, the use of research findings. This implies the existence of sustainable health research policies and plans, efficient coordination mechanisms, and adequate funding.

### Opportunities for research in Africa

There are immense opportunities for health research in Africa. To date investments in research have been modest. Health systems are weak and research has been neglected. There is need to set research priorities, strengthen research capacities and address funding issues.

The meeting of the African Advisory Committee for Health Research and Development held in Mauritius in April 2002 recommended, among others, to enhance research in traditional medicine in the Region (legal framework, allocation of resources, evidence on safety and efficacy of traditional medicines, dissemination of information); to promote research

in training institutions (including health research initiatives in WHO country budget, supporting research coordination units and health research components in the curricula); and to stimulate research in non-communicable diseases (development of multi-country proposals).

The three big killer diseases, HIV/AIDS, tuberculosis and malaria, all offer an immense terrain to African researchers in several areas: prevention, treatment, public health measures, etc. Several endemic diseases are now neglected by the pharmaceutical industry, that does not find any interest in investing in research for these diseases of the poor. WHO is therefore encouraging African researchers to be involved in this area. The TDR programme, co-sponsored by the World Bank, UNDP and WHO, invests in training, proposal development and implementation as well as dissemination of research findings.

Africa is now facing a double burden of disease with a high burden of communicable diseases and a rapidly increasing burden of non-communicable diseases. African researchers should become more involved in studying the epidemiology of non-communicable diseases such as hypertension, cardiovascular diseases, diabetes, cancer, and mental disorders. Affordable and effective approaches for the prevention of these diseases need to be developed and implemented in order to avoid an epidemic of uncontrollable magnitude.

In the area of vaccine development, African researchers should contribute to ensure that the specificities of the continent are taken into account with regard to the pathogen type, the presentation and mode of administration of the products, cost implications, and logistical aspects that are particular to Africa. Researchers should explore how to apply biomedical discoveries in different health systems, population groups and political and social contexts.

There are knowledge gaps in the areas of human resources for health, health financing, health information and health service delivery. National health research should focus on priority health problems in the country concerned, on health systems challenges and on managing opportunities. The culture of research should be expanded beyond academic institutions and laboratories to include health service providers, policy-makers and civil society.

## Linking research to action

One major deficiency in health research across countries is that the research process and the policy process tend to exist in different worlds. The result is that research often has limited relevance to or impact on policy. Much of public decision-making and public health practices are neither based on evidence nor evaluated for effectiveness, efficiency, or equity.

Researchers and research institutions need the skills and resources to communicate with users in a more effective way. An environment must be created where the users of research can access and find relevant research to inform their decisions. The producers and users of research should work more closely together to shape the research agenda and to ensure that research is used to improve health.

## Roles and responsibilities

The researchers need to establish or strengthen linkages with existing research partnerships, networks and funding institutions. This will help them be updated on new knowledge, new developments and, most importantly, to seek funding opportunities.

The countries should create mechanisms for the coordination and strengthening of research activities. They need to gather information on areas that need further research and call for the contribution of researchers. Countries should also ensure the use of research findings for the improvement of health situation. They need to implement relevant recommendations.

The partners should give increased support to locally led health development research activities. They should facilitate the training of young researchers and the funding of research activities. Partners should also support the dissemination of research findings and their use.

WHO is engaged with several partners in health systems research to produce, share and utilise research for better health and health equity, and to integrate knowledge gained within all levels of health systems.

## What is the way forward?

There is a need to elaborate/revisit the national health research policies and plans, establish equitable access to published and unpublished information, and promote the culture and practice of health research.

All countries should undertake essential health research. Regional and international research partnerships should be set up and/or strengthened to tackle priority health problems. More financial resources for research should be mobilised. International mechanisms to monitor progress and generate support should be developed.

In order to strengthen health research one should keep in mind that leadership, funding, motivation of researchers and capacity building to design and implement research projects and apply research findings are of paramount importance.

WHO/AFRO applauds the European and Developing Countries Clinical Trials Partnership and particularly the organisation of this conference. The conference constitutes an important step on the way to the implementation of knowledge acquired through clinical trials in the areas of HIV/AIDS, tuberculosis and malaria. WHO/AFRO thanks the organisers for inviting the Regional Director to take part in the Forum and is looking forward to a successful meeting.

# Combating the major disease problems in Africa – the role of EDCTP

**Pascoal Mocumbi**, Haute Représentant, EDCTP

The heavy burden of diseases in developing countries, especially in Africa, seriously impedes economic development and causes unnecessary death and suffering.

Action to address this challenge is limited by weak health systems and limited access to drugs/therapeutics to fight poverty-related diseases, HIV/AIDS, malaria and tuberculosis. The situation is further aggravated by the 10/90-

gap disequilibrium between the global burden of disease and intervention research, or rather the 5/90 gap, to be more exact, for health research funding to research on health problems of developing countries. Between 1975 and 2000 just 13 drugs were developed for the WHO's list of 10 neglected diseases, which includes leprosy and dengue.[1]

The world faces enormous challenges, many of which disproportionately affect Africa, which registers the highest maternal mortality ratios and bears the double burden of communicable diseases and an increasing trend in morbidity and mortality associated with non-communicable diseases. In the African region the prevalence of HIV/AIDS and malaria show no sign of decline. Although by the end of 2004 23 African countries had changed their national drug policy and adopted artemisin-based combination therapies, a new and highly effective treatment against falciparum malaria, only a few have rolled out the programme. Although the recommended tuberculosis control, DOTS, has been adopted in all countries of the region, detection and treatment success rates are still below the targets of 70-85% set by the World Health Assembly in 1993.[2]

The final declaration of the 14-16 September 2005 Millennium Review Summit Meeting of Heads of State and Government states that Africa is "the only continent not on track to meet any of the goals of the Millennium Declaration by 2015".[3] We all know the enormous efforts deployed by our peoples and countries to combat major disease problems and promote development. Progress made in some countries shows that it is possible to do more. Despite the political will of our leaders translated into comprehensive African Union and New Partnerships for Africa's Development (AU/NEPAD), strategies and programmes that inspire mutually reinforcing actions to accelerate the self-sustaining growth of Africa and end dependency in the long term, lack of resources to invest in development limits our ability to move forward faster toward the realisation of the MDGs. The majority of African people are too poor to generate the savings and capital they require for their development. For that reason many people still face hunger and suffer from water shortages and the burden of preventable diseases. We also know well that it is not a matter of money alone. Beyond financial aid, what African people need is empowerment through transfer of knowledge and information to make appropriate use of technology.

Rapid progress made in science and technology during the last half of the 20th century was not used to find cures for malaria, tuberculosis and other diseases primarily affecting African peoples, considered less lucrative markets.

Taking the floor at the opening session of the Second EDCTP Forum, under the theme 'HIV/AIDS, TB and Malaria in Africa: From Knowledge to Implementation' I am optimistic. Why?

We are in fact living in an auspicious moment - characterised by a paradigm shift in the way of thinking and doing biomedical research partnerships. One year after the Rome Forum we are here in Durban to reflect on how best we pursue the implementation of the mission and objectives of EDCTP, exactly when the first grants are touching ground. We are also meeting at a moment when times have also changed in relation to R&D for neglected diseases. "At the end of 2004 over 60 neglected diseases drug development projects were in progress, including two new drugs in registration stage and 18 new products in clinical trials, half of which are already at Phase III."[4] The Scientific Strategic Plan published in January 2005 by the Global HIV Vaccine Enterprise Coordinating Committee identified clinical trials capacity as one of its priorities for development of a preventive HIV vaccine.

EDCTP aims to establish a new and sustained partnership between Africa and Europe in the area of research on HIV/AIDS, malaria and tuberculosis. The mission, as the Executive Director, Dr Odile Leroy has stated in her welcome address, is to accelerate the development of new clinical interventions to fight these diseases in sub-Saharan Africa and to improve the quality of research in relation to the target diseases through research integration in Europe and partnership with African countries. This is something new in the way of thinking collaboration and partnerships with Africa. EDCTP could also play a role as a network of clinical trials scientists and sites for HIV, tuberculosis, and malaria.

## How?

Our meeting in Durban offers us an opportunity for a real dialogue on how best we can use science and technology to contribute to poverty reduction and promote economic growth and human development. How can we seize the opportunity brought by the current paradigm shift in the way research is perceived by researchers, policy-makers and potential beneficiaries?

On one hand we have Africa at the start of a top-down process of building a Union and implementing a comprehensive strategic development programme under the NEPAD framework, on the other Europe is making the first experience of pooling relevant national research programmes to add value to the partnership. It is in this context that I would like to discuss the role of EDCTP:

1. First and foremost, partners share responsibilities in this venture. European and African commitment to EDCTP will be assessed through results and concrete examples of ownership initiatives in the implementation of the Joint Programme of Action. The partnership is essentially based on knowledge sharing and pooling of resources to develop clinical tools that are accessible and affordable.
2. The integration of European research makes EDCTP play a pivotal role demonstrating the application of Article 169 of the European Treaty as well of the AU/NEPAD bottom-up integrated development process.
3. EDCTP is expected to play a catalytic role in conducting controlled trials of the highest quality of new and improved drugs, vaccines and microbicides, tools against the three targeted poverty-related diseases identified for the initial phase. To that end it should be able to mobilise a variety of institutions and organisations, pool and coordinate their resources to accomplish more with less cost and without duplication of effort as they work focused on specific goals.
4. EDCTP's major contribution to capacity building in

1. Andrew Jack. *PPP An antidote to neglected diseases – Alliances of drug makers, governments and charities are reviving research into overlooked health problems.*
2. WHO/Afro Report to the 55th Regional Committee, 22-26 August 2005.
3. UN Summit 14-16 Sep 2005.
4. According to a report commissioned by the Wellcome Trust, the London-based medical charity*: The new landscape of neglected disease drug development.*

developing countries derives from its role in increasing capacity of scientists and institutions in African countries to undertake clinical trials to satisfy the needs for study of candidate HIV and malaria vaccines. To contribute continued research and development of new forms of therapy for HIV to address drug resistance, and to find new approaches to develop an effective preventive vaccine against HIV, Africa would need centres of basic research on the biology of HIV. Countries are interested in being involved at every level of scientific drug development, from concept to registration approval and beyond; they require institutional development going hand in hand with clinical trial expertise and related drug regulatory capacity. Community participation in clinical trials includes bringing information and informed cooperation to the communities. EDCTP is also aware that a sound ethical framework is a crucial safeguard to avoid possible exploitation of research participants from developing countries with limited institutional capacity to conduct their own clinical research, and undertakes to strengthen these ethical review capacities at both institutional and national levels.

5. EDCTP may also play a role as a network of scientists working on HIV, tuberculosis and malaria, and conducting trials for new drugs and preventive tools against the three diseases. The global dimension of EDCTP is illustrated by the working relations with other organisations, such as those present at the launch of the Cape Town office; collaboration of international initiatives involved in interventions for poverty-related diseases was discussed.

In conclusion, I invite you to participate actively in the search for solutions to the problems we face. Think of each issue as if it was your own. It is my hope that this Forum will help deepen ties of friendship and build trust between us as fellow human beings working to combat major disease problems in Africa, to eradicate absolute poverty and promote human development.

I look forward to a fruitful exchange of views.

## EDCTP – where are we now? Where are we going?

**Diana Dunstan**, Chair of EDCTP General Assembly

I'd like to add my welcome to those that you have already heard. I am very pleased to see you all here, and it is particularly good to have this year's conference in Africa.

The previous speakers have already admirably set the scene for the Forum, but it is my duty to tell you a bit about where EDCTP as an organisation is now.

I think you may have noticed that EDCTP has changed a lot over the last year. Most obviously, we have new faces – Odile Leroy as the new Executive Director, and other key new appointments in the Secretariat. In addition, I have taken up the position of Chair recently from Peter Lange, who had to give up the role as his duties in Germany were increasing. The new faces are one aspect of the change, but the other - that is most important - is that due to the energy and the efforts of the new Executive Director and the Secretariat, and thanks also to the work of the Interim Executive Director, we now have an organisation which is based on solid foundations, and has the skills and the energy to deliver our objectives.

We have made significant progress over the last year. First, we have done our best to solve many of the outstanding problems and also to try to repair any damage that dealing with those may have caused. We now have good-quality procedures in place for all our work, funds have been allocated, contracts have been signed, and as other speakers have already noticed, there are fellows already working towards the objectives of our programme. A new Call for Proposals was launched last week.

There is of course much more work to do. Most immediately, for example, some of the membership of the Partnership Board need to be replaced because they are leaving so that we have rotation in the membership. Similarly, the DCCC has members that need to be replaced. There are still people to appoint to the Secretariat. The responses to the new call need to be assessed, and the contracts awarded. Also, the progress on awards that we have made already will need to be monitored.

I want to emphasise to you that the Assembly understands that the most important thread running through all our work is the Africa-European Partnership. EDCTP's overall goals can only be achieved in the long term. It is the partnership between European and African clinicians and scientists, and our inks with the users of our research, which are key to reaching the goals.

We need to make a good case for funding beyond our first five years. Our progress in implementing our programme will be important, but the strength of the partnerships which underpin our work will be a key factor. I hope therefore that by the end of this meeting we will have forged more links, and put forward innovative and creative ideas which will be a sound basis for all the hard work and real commitment that we need in order to make progress over next year and those that follow.

## Mapping the framework – synopsis by Tony MBewu

We have so far heard described the process of developing potential tools that are both affordable and accessible to prevent the 3 million plus deaths from HIV, the 2 million plus deaths from tuberculosis and the 1 million plus deaths from malaria occurring annually in developing countries. We have heard about how EDCTP is already on track in terms of fellowships, whether developing capacity in developing countries, or in terms of another round of applications recently released.

We have heard about the integration that is occurring in the north in terms of European research in the areas of HIV, tuberculosis and malaria, and integration in the south in Africa in terms of efforts with the African Union, within NEPAD, with the WHO AFRO and many other networks of scientists. We have heard about the various drugs, vaccines, microbicides and other interventions that are being developed in Africa, and other parts of the developing world, and also the biomedical research that is being done in HIV, tuberculosis and malaria in

order to provide the prime for the development pipeline that will produce the new clinical tools.

We have heard of the importance of ensuring an ethical framework for the conduct of our research and clinical trials, and for ensuring equal partnerships between north and south scientists in these endeavours. We have heard about the remarkable sea change that is taking place in terms of developing drugs and clinical tools for neglected diseases, with only 13 new drugs developed between 1975 and 2000, but currently 63 projects under way. We have heard how public-private partnerships have played an important role in accelerating the pace of development. We have also seen how some of these PPPs involve US and European-based companies such as GSK, but now involve companies based in the south.

I have recently come from a meeting of the Global Forum for Health Research in Mumbai, India, where data were presented on what are called innovative developing countries. Examples were India, Brazil and South Africa in terms of the new knowledge that is being generated within those countries in areas of science and technology, including health. A recent publication showed that a country such as India in 2005 so far developed something like 388 US patents, compared with a country like South Africa with 93 US patents and a country such as Malaysia with 88 US patents. Increasingly as we move into the future we will see not only the practical testing of new drugs, vaccines and other interventions within developing countries, but also new knowledge generation for new clinical tools.

I arrived at this conference late because of the launch of the India-Brazil-South Africa trilateral in Cape Town, which is focusing on HIV and tuberculosis initially, and the current workshop is on HIV vaccine development. We are encouraged by the progress in new candidate development in India and also in South Africa where scientists in Cape Town are developing new candidates *de novo* which will be used in prime boost strategies and possibly using other technology platforms such as BCG or virus-like particles, with the possibility of clinical trials with some of these technologies beginning with Phase I possibly at the end of next year.

The theme of these three days is knowledge to implementation. Again we were reminded that it is not enough simply to discover new clinical tools, it is not enough to simply to develop those clinical tools, but we also during this phase of discovery and development have to remember that the challenge will also be to deliver those clinical tools. We must remember the message from the past with hepatitis B vaccine – which took 10 years from the time it reached market to the time it was widely available in developing countries – or the example of efluorhithine, a remarkable discovery that because of various market constraints, was slowed to reach those who needed it. These remind us that as knowledge workers we must redouble our efforts in developing new clinical tools, and remain mindful that we have to be aware of market conditions that will constrain delivery of clinical tools once developed.

Our speakers have set out the framework for our deliberations for the coming three days and all those issues, and I am sure that it will be a fruitful and productive workshop that will set EDCTP on a successful course for the future.

# PLENARY SESSIONS

## I Opening and State-of-the-Art

**Chair: Patrice Debré** (France)

- State-of-the-Art presentations on new developments in drugs and vaccines for HIV/AIDS, TB and Malaria, and the need for clinical trials in Africa
- Translating science into health service policy and practice

### Towards new drugs and vaccines for TB

**Bernard Fourie** (South Africa)

We cannot neglect to emphasise that tuberculosis (TB) is – and will certainly remain for some time to come – a major threat and a burden globally. Rates are increasing and control with current tools is suboptimal. The incidence rate of TB is increasing by 0.4% per year globally, but much faster in sub-Saharan Africa. Co-infection with HIV in the TB-infected is undoubtedly the most important cause of escalating TB incidence in sub-Saharan Africa.

Treatment success under DOTS for the 2000 cohort was 82% on average (slightly short of the WHO target of 85%), but substantially below average in the African region (72%). We look at new tools and their optimal application to at least assist with the control challenge, and hopefully to bring DOTS to meet the said target.

To start with, we need better drugs and vaccines. In summary one can say that of all the potential interventions, drugs that can reduce the continuation phase of therapy significantly would make a huge difference to the delivery of service and management of TB cases. Also, vaccines that can prevent the activation of dormant organisms, in the presence of HIV in particular, will have the greatest impact on the TB control programme.

So, for both drugs and vaccines, we are looking for new and better tools.

#### TB drug development priorities

Looking at TB drug development first, the main target is to shorten treatment for TB – currently stretching over a minimum of 6 months utilising at least four fairly potent drugs. We have almost forgotten the days when TB treatment ran over 18 months, and later down to 12. Then came the introduction of pyrazinamide in combination with rifampicin, that immediately made a huge difference and shrank the treatment period to 6 months. We are now looking for a similarly powerful intervention – treatment shortening or simplification that can bring it down to 3 months. There are scientists out there asking why can't it be even shorter – one month, or 2 weeks – what are the issues, do we understand the underlying mechanisms and the biology of the organism?

Huge efforts are required to address these questions.

What we have at the moment in terms of clinical trials is that treatment shortening or simplification is being organised around novel drug combinations with existing drugs, such as some of the third-generation fluoroquinolones (gatifloxacin, moxifloxacin). The reason for the inclusion of the fluoroquinolones is that some years ago a study with the drug ofloxacin, commonly used in MDR TB, showed potential in susceptible TB. It seems to sterilise much earlier than the conventional regimen, and the jump was made to what was already known to be more potent fluoroquinolones to act as substitutes of, for example, ethambutol.

There is also the long-acting rifamycins, of which there are several, such as rifapentine and rifabutin. Rifapentine has a significant half-life and its area under the curve is impressive. It is a drug that can easily be given once a week, but there are challenges. The main one with rifapentine is that, in HIV-positive individuals, the drug given at 600 mg might lead to the development of mono-resistance to rifampicin, as was shown in at least two different Phase III trials in different populations. Given the high burden of TB-HIV co-infection, this is not good news, and resulted in the licensed product in the US to carry a warning that rifapentine should not be administered to HIV positive individuals, which effectively cancels its utility in sub-Saharan Africa. We are hopeful that new studies with rifapentine, maybe in some innovative combinations with one of the quinolones, could lead to completely new thinking as to how the regimens might be constructed to good effect.

There are also some novel drugs around. Johnson & Johnson with partner Tibotec announced their diarylquinoline drug entering early human trials. There is also PA-824 from the Global Alliance for TB Drug Development, which has been approved for Phase I studies in the USA, and which is also a novel compound with very good activity against TB. So there are new possibilities on the horizon and we are looking forward to seeing these in clinical trials and for development programmes being processed rapidly.

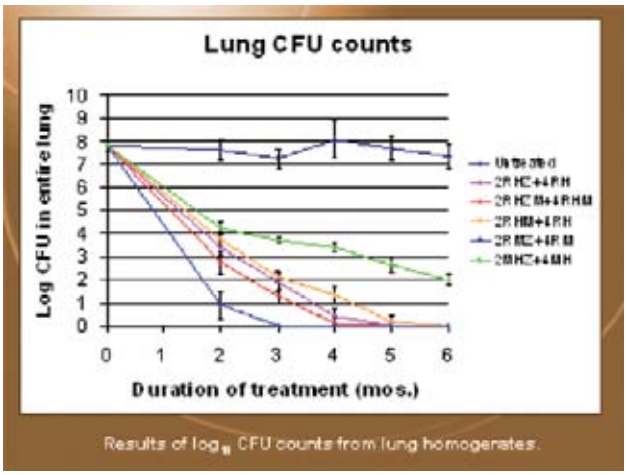
Back to the two fluoroquinolones. In terms of their pharmacokinetic characteristics, for both gatifloxacin and moxifloxacin the half-life is long, and the area under the curve is really significant, slightly greater for moxifloxacin than for gatifloxacin, but this is very immaterial given the interval that these drugs might be administered for. We will initially see administration twice a week rather than once a week.

Several of the fluoroquinolones have very good minimum inhibitory concentrations (MICs), with levofloxacin, in my opinion, a very underestimated drug – it has not been in clinical trials for TB. I think there needs to be a rethink about levofloxacin – it has very good characteristics and pre-clinical data.

**FEATURES OF NEW FLUOROQUINOLONES**
**Relevant to TB Therapy**

| Drug | Cmax | t½ | AUC | MIC 90 |
|---|---|---|---|---|
| Levofloxacin, 500mg | 6 | 7 | 34 | 1.0 |
| Sparfloxacin, 400mg | 1 | 20 | 41 – 54 | 0.5 |
| Gatifloxacin, 400mg | 5 | 8 | 29 – 40 | 0.25 |
| Moxifloxacin, 400mg | 5 | 12 | 45 – 51 | 0.25 |

AUC = area under the curve.



Results of $\log_{10}$ CFU counts from lung homogenates.

The above graph from Prof. Jacques Grosset's work shows some of the mouse experiments conducted with a variety of drug combinations, in a 6-month mouse-model which has been shown to be predictive of treatment response in humans. Conventional treatment is represented by the red line second from the left. Then there is a very interesting observation: where moxifloxacin was introduced, the graph leans quite significantly to the left. Furthermore, a remarkable observation was that an even more significant response was obtained in the absence of isoniazid, a drug that we thought could never be excluded from TB regimens. So with the exclusion of a key TB drug and introduction of a completely new agent, there is a dramatic response. This sort of thinking is introducing new paradigms around novel TB drug combinations.

Looking at experimental studies of once-weekly rifapentine regimens, we observe the following:

- increasing dose of rifapentine increases efficacy of treatment but may not prevent the selection of drug-resistant mutants;
- once-weekly regimens that are started after 2 weeks of daily treatment are effective only if supplemented by streptomycin or by daily isonaizid;
- moxifloxacin (or gatifloxacin) with its potent bactericidal activity and long half-life may be an excellent companion drug for some novel innovative regimens, instead of the experimentally applied streptomycin.

The list that we have here was discussed at the first EDCTP Forum, one year ago. There was general agreement on the importance of all of these study areas:

- Surrogate marker studies of drug efficacy
  - o Validation studies in context of clinical trials
    - – Early bactericidal activity (EBA)
    - – Serial sputum colony counts (SSCC)
    - – Whole blood assay (WBA) (for bactericidal activity)
    - – Drug tolerance
  - o Identification of new markers
    - – Biochemical/immunological
    - – Genetic
    - – Treatment of latent infection
  - o Trials of preventive therapy by HIV status (need better diagnostics)
- ARV combination treatment in TB patients
  - o Pharmacokinetics
  - o Optimal regimens and timing

Surrogate markers of treatment efficacy are desperately needed in order to enable shortening of the time it takes to conduct clinical trials of TB drugs or regimens. Some markers have already been proposed and are used, but most of them lack validation as recognised assays. Phase III TB clinical trials typically run for 5 years. In order to process a variety of options in new regimens and novel compounds, imagine the costs and the effort in trial organisation and patient recruitment – so we cannot make mistakes in the choice of drug or regimen to evaluate. We need to really come up with drug regimens and compounds with real potential. Therefore, we need validated surrogate markers for drug efficacy very soon. This is best done in the context of clinical trials, which is something that I believe EDCTP is very well positioned to undertake.

Firstly, early bactericidal activity is a surrogate whereby the fall in bacterial load over the first few days of single-drug treatment will tell us quite a bit about the killing ability of a particular compound. Within the first 2-5 days one can already make some prediction about the potential of some of these compounds. This technology has been established in clinical trial terms and several publications have resulted.

Another version of EBA is what we call serial sputum colony counts, whereby we extend the EBA principle to multi-drug regimens closely observed over the first 2 months of treatment. The end-point at 2 months is assumed to be predictive of the sterilising capacity of the regimen. Complete bacteriological negativity at 2 months is anticipated to correlate with absence of disease recurrence from the original infection post-treatment.

There have been other markers of efficacy suggested as well. These include the WBA proposed by Prof. Bob Wallis, whereby blood samples are collected at regular intervals from an individual during treatment, and the original infecting TB strain exposed to the drug concentration in the patient's blood sample.

Finally, antiretroviral treatment in TB patients is a big issue. Policy at the moment favours treating for TB first, and then introducing ART. However, with antiretroviral roll-out, patients have the right to insist on ART as soon as their status becomes known to them. We are not too sure about optimal combined regimens and timing thereof, and therefore more studies are needed, including accompanying pharmacokinetic assessments.

## Selecting the right studies: Vaccines

Here we are faced with a completely different kind of challenge. However, a lot of progress has actually been made in this field. We can safely say that a moderately effective post-infection vaccine (i.e. that blocks 50% of progression of infection to disease) could have a significant effect on reducing TB incidence. It has been held for a long time that decades are required before there will be a vaccine and it will not really make a difference to the epidemic, but there are fairly good models developed that show that this is not actually the case.

There is a big 'but' involved though. In populations with a high burden of both TB and HIV a significant effect is only likely to be attained if TB control is optimal, HIV transmission is significantly curtailed, and onset of AIDS is delayed. If that is present, TB vaccines are likely to make a big impact. There are several challenges to the development of new vaccines, though:

- Future vaccines will need to be effective in the face of prior BCG vaccination;
- Vaccination strategies would be best targeted at boosting the efficacy of neonatally administered BCG;
- It is unlikely that a pre-exposure vaccine before infection would have substantial impact – two-thirds of the world population are already infected with TB (**Editor's note:** See different opinion from Lawrence Geiter in his presentation during Plenary II);
- An effective therapeutic vaccine would have a significant impact on TB burden; and
- New vaccines would need to work under circumstances where BCG fails.

## Vaccination strategies

There are essentially two vaccination strategies proposed:

- Prime boost to protect against disease in infants - prime with BCG or rBCG or auxotroph mutant (live TB variant) initially, then boost with recombinant fusion protein in adjuvant, or vectored vaccine (e.g. MVA or adenovirus recombinants);
- Boost to protect against disease in adolescents/adults – we see a surge in the disease after the age of about 12 years until about 25 years. Choices here for further clinical studies are recombinant fusion protein in adjuvant and vectored vaccine.

## Candidate vaccines for TB

**Live vaccines:**

- Modified Vaccinia Ankara expressing Mtb Ag85 (Goonetilleke *et al. J Immunol* 2003)
- Recombinant live BCG expressing Mtb AG85 (Horwitz *et al. Proc Natl Acad Sci USA* 2000)
- Live attenuated Mtb (double deletion mutants) (Hondalus *et al. Infect Immun* 2000; Subandamurthy *et al. Nature Medicine* 2002)
- Recombinant live BCG expressing listeriolysin (Hess *et al. Proc Natl Acad Sci USA* 1998)

**Subunit vaccines:**

- 72f fusion protein subunit + adjuvant. (Reed *et al. Tuberculosis* 2003)
- Mtb multipeptide + adjuvant (Meister *et al. Vaccine* 1995)
- ESAT6-Ag85 fusion protein subunit + adjuvant (Weinrich *et al. Infect Immun* 2001)
- HSP65 DNA vaccine (Tascon *et al. Nature Medicine* 1996)
- DNA multigene vaccine (Delogu *et al. Infect Immun* 2001)
- Inactivated M. vaccae (Von Reyn *et al. CID* 2002)

This list represents an impressive pipeline of candidates. The big question then is: How far are we with the development of these candidates? Are they just concepts, are they still only being used in animals? The good news is that there are at least three already in Phase I clinical trials:

- UOXF viral vectored MVA-Ag85A
- GSKbio/IDRI in AS01/02 subunit Mtb72f
- rBCG30 overexpressing the 30-kDa Ag85B.

Advanced candidates are:
- rBCG lysteriolysin O
- SSI subunit Ag85B-ESAT6/LTK63 intranasal
- SSI subunit Ag85B-ESAT6
- Mtb72f in AS02A formulation (polyprotein recombinant).

## The road ahead

Short-term TB research priorities for vaccines are that we need to identify sites with the potential to be developed into clinical Phase II and III trial sites able to conduct large-scale studies at GCP standards. This is the major challenge for EDCTP, in my opinion. With these candidates coming forward and already three in Phase I, and more entering human clinical investigation over the next 2 years, there will soon be a major demand for communities where these vaccines could be tested in humans. We need to be prepared. Time is very short and there just are not enough organised clinical trial sites out there.

There is also a great need for validation of genetic or immunological correlates of protection and prediction of response to vaccines as part of clinical trial activity. There is some good science being conducted here under major various grants, however, e.g. the EU FP6 programme for TB vaccine.

Nevertheless, we need to strengthen laboratory, clinical and administrative capacity as part of and in support of clinical trial site activities – this fits in particularly well with the EDCTP mandate.

We need also to demonstrate safety and immunogenicity of new vaccine candidates in infants or in adolescents/adults with latent TB infection, and we need to have the ability to select these individuals and follow them up in a well organised surveillance system.

We also need to evaluate rapid, field-friendly diagnostic tests for identification of latent TB infection - and that is a really tall order.

## Other developments in drug and vaccine delivery

There are aspects of drug and vaccine formulation that will in future allow pulmonary delivery or needle-free delivery, targeted cellular delivery, or timed-release. These technologies are new and in the developmental phase at the moment. Nevertheless, they promise new advances that might further enhance drug and vaccine development. Examples are:

- **Solid lipid particle-based anti-TB drugs:** Nebulisation of SLP microspheres containing anti-TB drugs to the lung in guinea-pigs improve drug bio-availability and reduce dosing frequency (Pandy and Khuller. *Tuberculosis* 2005). LPP technology in phase III clinical testing for inhaled insulin with Eli Lilly. This seems to be very promising in improving drug bio-availability and reducing dose frequency.
- **Large Porous Particles (LPP) and Porous Nanoparticle Aggregate Particles (PNAP)** (Edwards *et al. Science* 1997): This has been applied to TB at Harvard (Tsapis *et al.*, *Tuberculosis* 2003), is in stage III now and describes a convenient vector of delivery of nanoparticles and has recently been awarded the Gates Grand Challenge for development of inhaled TB vaccine. This is a new component that will optimise both the drug and vaccine arenas. PNAP is a convenient vector for delivery of nanoparticles engineered for targeting specific tissues.

## Conclusions

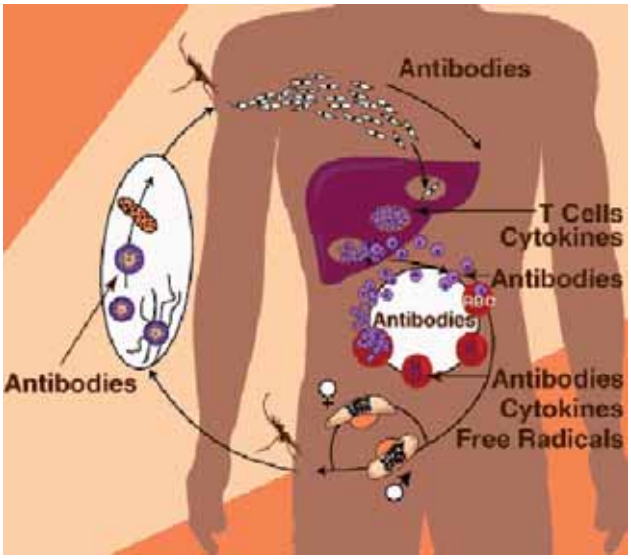
- It is likely that current drug treatment regimens for TB will begin to change in the next 3 to 5 years. We will not see a decade go by now without new TB drug regimens being proposed and maybe even introduced. There is a real possibility of treatment shortening and simplification based on new compounds or reconstructed drug combinations.
- There is mounting experience in prime boost strategies based on new TB vaccine candidates which will result in licensed new vaccine/s, affording significantly better protection against disease than BCG, within the next 7 to 10 years.
- New delivery options based on nanotechnology for both drugs and vaccines may revolutionise our approach to R&D in these fields in as little 2 to 3 years.

# Where are we with drugs and vaccines for malaria?

**Ricardo Thomson**, Scientific Director, National Institute of Health, Mozambique

This is a very complicated issue. I am just introducing the subject, and I am sure that we are going to discuss it further over the next few days. I am going to first talk about vaccines and move onto drugs.

***P. falciparum* life cycle**




This picture shows part of the life cycle of the most virulent of the parasites that cause malaria, and the reason for showing

this cycle is that it reveals that there are several points at which we can target the parasite – never pretending that we need to kill all the parasites at a given point in the cycle but preferably trying to kill a few parasites in each phase of the cycle, and then getting an impact.

When the mosquito inoculates the sporozoite, the sporozoite stays in the bloodstream for a few minutes and during that phase antibodies react and kill at least 5% of that population of sporozoites. Once the sporozoites penetrate the liver cells then cellular immunity is the only way to target those parasites in a better way. Those parasites that manage to go through the multiplication phase in the liver invade the red blood cells, and that is moment when the erythrocytic cycle begins. It is during this phase symptoms appear due to the release of toxins into the bloodstream. This is the point at which we could target the parasite, trying to kill it or at least trying to attenuate the symptoms of the disease. Finally, some parasites will transform into gametocytes, and these gametocytes will be sucked up by the mosquito. If antibodies against the gametocytes are present in the blood meal, they might block the development into sporozoites.

## Type of vaccine and candidates

So, what type of vaccine are we looking for? We know that this parasite is extremely complex and that it has thousands of antigens. However, only a few of them are capable of mounting an immune response that is meaningful in terms of protection. The other issue that we know very well is that immunity to malaria is likely to be the result of response to many antigens and not to a single one. This justifies even more the fact that we need to target the parasite in several sites – several places in the cycle – in order to reduce the levels of infection. It is also true that a good vaccine should induce long-lasting immuno- and cellular immunity – these two mechanisms together would definitely have a better impact against the parasite. One very important issue is that it should not be strain-specific. We don't want a vaccine that is going to select certain types of parasites that can break through the mechanisms of immunity caused by the vaccine. Ideally – but not so easy – a cocktail of antigens would be the best solution.

Which vaccine candidates are currently under development? Again, if we look at the image of the life cycle of the parasite, number one we have sporozoites penetrating in the bloodstream and for that we have several candidates against the Circunsporozoite Protein (CSP). I am currently one of the co-investigators in the trials that are taking place in Mozambique, testing the RTS,S/AS02 vaccine candidate. Here I would like to make a small comment – it is very interesting that sometimes we think so long about things related to the cycle of the parasite, and we try to find the most difficult explanations, and once we do the trials and we see the results, we see that the explanations are relatively simple. It was very interesting to participate in this trial.

It is not only the RTS,S/AS02 vaccine candidate that targets the sporozoite, there are other groups and formulations aimed at reducing the number of sporozoites penetrating the liver cells and later the red blood cells. If those sporozoites manage to penetrate the liver cells, we need to be able to target them at that point. Using DNA and viral vectors we have several candidates looking at the possibility of creating a good cellular immune response to target these cells, destroying these cells but not causing any harm to the host. But of course, because things are not perfect, some of the parasites will definitely be able to go through, and then we have to target them when they are multiplying in the red blood cells. There are several antigens, some on the surface of the merozoite, that can be the target of vaccines.

Finally, an interesting approach is the development of a vaccine to try to block the fertilisation of the gametes in the mosquitoes. Such types of vaccine wouldn't protect the individual but would protect the community, because the transmission of malaria would be reduced.

**Vaccine Candidates under development**

| Group (field collaboration) | Vaccines (type) | Target |
|---|---|---|
| Apovia, USA; New York University, USA | ICC-1132 (protein) | Pre-erythrocytic |
| GlaxoSmithKline Biologicals, Belgium; and WRAIR, USA (Medical Research Council [MRC] Laboratories, The Gambia; Centro de Investigacao em Saude de Manhica [CISM], Mozambique) | RTS,S (protein) | Pre-erythrocytic |
| Malaria Vaccine Development Unit, National Institutes Of Health, USA | Pvs25, AMA-1 (protein) | Transmission blocking, blood stage |
| Naval Medical Research Center (NMRC), USA; Vical, USA | Pf-CS, Pf-SSP2/TRAP, Pf-LSA-1, Pf-EXP-1, Pf-LSA-3 (DNA vaccines) | Pre-erythrocytic |
| New York University, USA | CS (synthetic polymers, MAPs, polyoximes) | Pre-erythrocytic |
| Oxford University, UK (MRC Laboratories, The Gambia; Wellcome-Kenya Medical Research Institute [KEMRI] collaboration, Kilifi, Kenya) | DNA ME-TRAP, MVA ME-TRAP, FP9 ME-TRAP, MVA-CS (DNA and recombinant viral) | Pre-erythrocytic |
| Statens Serum Institut (SSI), Copenhagen; Institut Pasteur; Institute of Lausanne, Switzerland | GLURP, MSP-3, CS (synthetic peptide) | Pre-erythrocytic, blood stage |
| Walter and Eliza Hall Institute of Medical Research, Melbourne; Queensland Institute of Medical Research (QIMR), Brisbane; Swiss Tropical Institute; Biotech Australia Pty (Papua New Guinea Institute Of Medical Research) | MSP-1, MSP-2, RESA (protein) | Blood stage |
| Walter Reed Army Institute of Research (WRAIR), USA (KEMRI, Kisumu, Kenya) | FMP-1 (protein) | Blood stage |

EXP=exported protein. LSA=liver stage antigen. MAP=multiple antigen peptide. Pvs=Plasmodium vivax surface protein. AMA-1=apical membrane antigen-1. RESA=ring infected erythrocyte surface antigen. SSP2 and TRAP are synonyms: sporozoite surface protein 2 and thrombospondin-related adhesion protein. Only vaccines being tested in clinical trials as of May, 2003, are listed. Field collaborations are only listed if field trials of the candidate had begun as of May, 2003.

This table gives an idea of the multiplicity of institutions and groups working around the issue of malaria vaccines, from institutions in Europe, the United States, Australia, France – there are many candidates looking at different stages of the lifecycle of the parasite.

DNA subunit vaccines are one way of trying to get a vaccine that is effective against malaria. We know that live attenuated or inactivated vaccines are not practical for many diseases and malaria is one of the cases. The history of malaria has shown

that that was tried with no much success. In DNA subunit vaccination, part of complete antigens are identified from the pathogen, but unfortunately they vary greatly in their capacity to raise antibodies. We need to increase understanding of the antigen processing; which adjuvants are better as a way to improve the immunogenicity of the candidates. Another problem is insufficient duration of induced immune response. This is clearly a great difficulty. There are several trials in which there is a raise in antibody titres, but that is not long-lasting and so doesn't protect the individuals for long enough.

DNA vaccines are composed of sequences of *Plasmodium falciparum*, inserted in a plasmid and then introduced into the human body as a way of inducing immunity against the proteins that these DNA sequences code for. The DNA could also be inserted in virus vector and in that way through its multiplication an immune response could be induced. DNA and recombinant viral subunit vaccines can induce cellular immunity, but it is apparent that there is a poor humoral response to that kind of vaccines.

As I said in the beginning, the ideal objective would be to stop the sporozoites from invading and multiplying in the liver cells and then penetrating the erythrocytes. So an ideal vaccine for this stage should induce a good humoral response against the sporozoites and should also induce a potent cellular immune response against the liver stage. RTS,S, which is a recombinant protein vaccine, is currently the most advanced candidate in that sense. Being the most advanced doesn't mean that we are very close to the solution, but that we are encouraged by the results that are available in order to get a vaccine that is at least partially protective, and this partial protection could have a major impact on malaria in endemic countries.

There are also those candidates based on the liver surface antigen 1 and 3 that are expressed by the parasites when they are in hepatocytes. LSA3 is expressed by both erythrocytic and blood stage parasites, seems to be conserved and immunogenic, being something that could be looked at.

The technique using prime-boosting with vaccines to try to induce a potent immune response is another approach by several groups in the world, by priming the DNA or viral vectors and boosting them again with viral vectors. DNA modified vaccinia virus Ankara (MVA) and attenuated poxvirus FP9 can be used in such process. An insertion is made in the virus to this effect. This approach has induced high T-cell responses, but the level of protection was low.

For blood stage vaccines there are two possible classes – vaccines that will block the invasion of the erythrocytes by the merozoites released from the pathocytes, or vaccines that will attenuate the complications of the disease, reducing the symptoms. For those blocking the invasion of the merozoites, the most promising candidates are MSP1, the best characterised antigen involved in invasion, and MSP2, another antigen on which some vaccine candidates are based and undergoing clinical trials. GLURP and MSP3 are also candidate antigens that are under development in Europe as candidates that can be used against the blood stage of the parasite lifecycle.

Anti-complication vaccines are conceptually new. In recent years it is increasingly accepted that one doesn't really need to kill all the parasites, what one needs to do is to reduce the impact of those parasites on disease by acting against the parasite toxins, or targeting those parasites that cause complications such as cerebral malaria, or adhesion of the parasite to the placenta. *P. falciparum* glycosyl phosphatidyl inositol (GPI) molecule is the lead candidate for the "malaria antitoxin vaccine".

Sexual-stage vaccines are based on the principle that antibodies against gametocyte antigens can prevent transmission. *P. falciparum* gametocyte recombinant protein, Pfs25, is under clinical assessment in the US, but this kind of vaccine would not protect vaccinated individuals from disease.

A vaccine that would block infection would be the ideal solution to tackle the effects of the disease, but being aware that a vaccine would never be 100% protective, we also need to address those that can protect us against the parasites that penetrate the erythrocytes and then cause the symptoms of the disease.

## Where are we with drugs for malaria?

I think we need to revisit the story of those old drugs that we are now trying to forget about, to understand the mistakes we might make in the future with the new drugs. I think the example of chloroquine which was introduced some 50 years ago is a good example of what we shouldn't do with drugs. I understand the pressure to treat malaria at the community level, but I also believe that a very rational approach should be used. A very rational approach means using the drugs rationally. There are not many opportunities in the future concerning antimalarial drugs and therefore, we need to treat the disease with those drugs we have currently, very carefully.

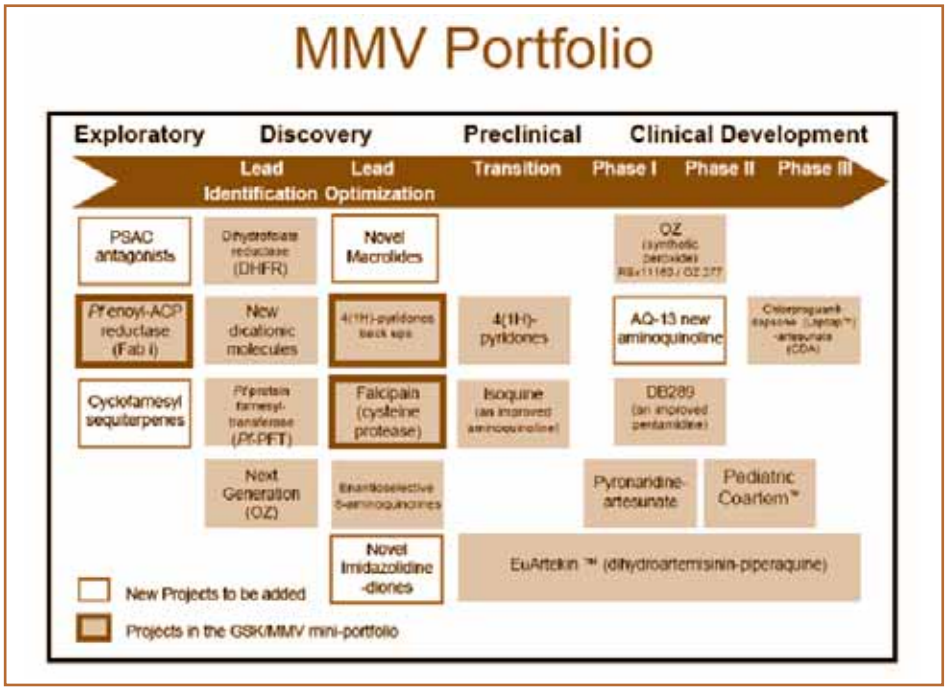
Chloroquine was used for a few decades before resistance first appeared in Asia and then later in Africa, and these days this drug is now usable only in very few parts of Africa. There are some attempts to rescue the drug by using other compounds that can probably reverse the resistance of the parasites, or other antibiotics that combined with chloroquine can have a good efficacy in treating the disease.

Amodiaquine is a drug related to chloroquine that interestingly was used and tried in some other countries in combination with other drugs, and seemed to have good efficacy – but when you go to the field you find that the use is difficult, for reasons that are not always very easy to understand. Clinical trials showed that the drug has a good efficacy, but then you send the drug to the field and for several reasons, some related to side-effects, others related to the fact that people are not used to the drug, its use is difficult. In some countries amodiaquine is used in combination with sulfadoxine-pyrimethamine, but in some amodiaquine is dropped from the combination therapy after a few months. As an example – we in Mozambique have adopted amodiaquine-SP as the first line drug, but after 6-7 months a number of the physicians don't want to use it, claiming the occurrence of side-effects and that people don't like it. With monotherapy, one might be able to treat one patient and solve that patient's problems, but one might not be doing much good to the community as a whole.

Quinine is still there – a drug that has been around for a long time and is not very pleasant, but that has been saving lives and is still one of the main drugs used to treat severe malaria. It can sometimes be applied in combination with an artemesinin derivative. Mefloquine, we all know, is a compound related to quinine, with a long half-life that could be used for prophylaxis. But there are side effects that are not pleasant

and this long half-life somehow could be the reason for the rapid emergence of resistance in some parts of the world.

Sulfadoxine-pyrimethamine in combination with sulphonamides is a drug combination that is in use in several parts of Africa to treat malaria, especially so in the last few years. There are different approaches: in some places it is used as monotherapy, which is naturally a mistake, and some people in this room have experienced this situation. For all combination therapy regimens with SP, even those including chloroquine or amodiaquine, experience from some parts of the world show that compliance is very difficult, resulting in the drug being used alone and then resistance emerging very fast.




Atovaquone is a good antimalarial but unfortunately very expensive and therefore it is difficult to consider its use in endemic areas.

Then we have the ACTs, based on the combination of artemesinin derivatives and other drugs. It is my personal view that it is a very good way to treat malaria, but there is an emerging tendency to use the ACTs just the same way we did with chloroquine – there are as yet no reports of high resistance to these combinations, but we have to be aware of the issue and be a bit more careful than just going for it without control.

My country a few years ago opted for the combination of SP and amodiaquine. Many global institutions in the world are advocating the use of ACTs, and we agree that we should go for ACTs – but we should do that carefully. Being careful does not mean that we neglect lives that are at risk – but we don't want to neglect lives that could be at risk in the future. The issue of treatment with ACTs is one that needs to be looked at very carefully, especially in countries where health care coverage is very low and access to health services and treatment is very difficult.

There is a lot being done to find new treatments for malaria. We are definitely being faced with a very big challenge. It is a big challenge and we never know if we are going to get to the end of the clinical development of some antimalarials or combinations of antimalarials. This brings me back to the fact that we need to be careful with what we have available now. We must not think that we have some drugs so close in the near future that we can neglect those that are available now. This is the message that I want to get across – and that mistakes cannot be repeated. We have very few opportunities in the future, and we need to be careful and to be rational. Physicians in the field need to think rationally and not only think about the moment or the context in which they are working. It is understandable that their main objective is to treat the patient they are dealing with, but we also must make sure that by treating one, we are not harming everybody.

# Global progress on the development of HIV vaccines and vaginal microbicides

**Salim Abdool-Karim**, Pro Vice-Chancellor (Research): University of KwaZulu-Natal; Director, Centre for the AIDS Programme of Research in South Africa; Professor in Clinical Epidemiology, Columbia University; Adjunct Professor in Medicine, Cornell University

## Introduction

The prevalence of HIV infection in pregnant women, using anonymous testing, in a rural South African community provides a harsh reminder of why we need an HIV vaccine and microbicide.

**Temporal trends in HIV infection in pregnant women in a rural district**

| Age Group | 1992 | 1995 | 1998 | 2001 |
|---|---|---|---|---|
| 20-24 | 6.9% | 21.1% | 39.3% | 50.8% |
| 25-29 | 2.7% | 18.8% | 36.4% | 47.2% |
| 30-34 | 1.4% | 15.0% | 23.4% | 38.4% |
| 35-39 | 0.0% | 3.4% | 23.0% | 36.4% |

*Source: Wilkinson D, Wilkinson D, Abdool Karim SS, Williams B, Gouws E. JAIDS 2000; 23: 405-9*

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It can be seen that from 1992 to 1995, the prevalence in 20-24-year old pregnant women trebled from 6.9% to 21.1%. In the next 3-year interval, from 1995 to 1995, again it almost doubled. What we are seeing is how the prevalence

of HIV has grown rapidly in this youngest group - this gives you some idea of the rapidity with which the HIV epidemic has been affecting those in the youngest age group.

This table also gives you some idea of the cohort effect. In other words, if you took the 'class of 1992', and they had a class reunion every 3 years, you can get some idea of what the birth cohort effect would be. The prevalence rates in the diagonal in this table show an increase from 6.9% in 1992 to 18.8% in 1995, 23.4% in 1998 to 36.4% in 2001. This indicates the rapidity with which the HIV epidemic is growing, particularly in young women and across the birth cohort as seen in the table.

## HIV vaccines

Where are we in terms of devising an HIV vaccine to try and stem the tide of the HIV epidemic? In the vaccine field we have two broad thrusts – one looking at preventive vaccines and the other looking at therapeutic vaccines. The area of therapeutic vaccines is still highly experimental and I am not going to touch on that to any great extent as I am going to focus on preventive vaccines.

The primary goal that has been set for a vaccine is to try and prevent HIV infection from becoming established – commonly referred to as trying to establish 'sterilising immunity'. The second goal, which is probably the more realistic goal at this time, given the candidate vaccines that we are working with, is the attempt to prevent progression to AIDS from occurring after the onset of HIV infection.

The vaccine arena has been growing in fits and starts, and has been going through different waves over the last 10-15 years. It started off with a strong focus on humoral immunity, focusing on antigens being recognised by specific lymphocytes which lead eventually to the creation of antibodies.

In the last 8 years or so, there has been a shift in the vaccine arena to vaccines that instead of focusing on antibodies, focus on T lymphocytes and cytotoxic T-cell killing. This particular group of vaccines initially looked at developing CTL responses to epitopes that focused on the core of the virus and therefore may be effective across different clades. The main reason for the failure of antibody-based vaccines has been the inability of any vaccine to develop antibodies that neutralise primary HIV isolates. We have not up to this stage been able to find an antigen that would simulate an antibody in a human that would lead to a primary isolate being neutralised. So there has been a shift away from vaccines looking at antibodies, most of which followed the failure of the Vaxgen trials to show efficacy of vaccines which intend to stimulate antibody production predominantly. There has been a steady shift towards looking at CTL-based vaccines.

The more than 30 HIV vaccine candidates in human trials are mostly subunit vaccines, vector-based vaccines, and naked DNA vaccines, and the most prominent of these classes are the vector-based vaccines. There have been several trials looking at the different pox vectors, and there is now a steady shift towards adenoviral-based vaccines, and the Ad5 vaccine in particular – the Ad5 vector is proving to be the most popular in terms of progression through to the different stages of clinical trials. There are two broad streams of Ad5 vaccines that are being developed – those based on gag antigens and those based on multiple components of HIV.

### HIV Vaccine classes

| | Vaccine type | Example |
|---|---|---|
| 1. | Whole attenuated vaccines | none |
| 2. | Live attenuated vaccines | Live attenuated vector |
| 3. | Subunit vaccines | Peptides, Proteins, Lipopeptides |
| 4. | Vector-based vaccines | Canarypox Vectors, Fowlpox Vectors, Modified Vaccinia Ankara Vectors, Non-Replicating Adenovirus Vectors, VEE Vectors, Yeast Vectors |
| 5. | Naked DNA vaccines | DNA Plasmid Vaccines |

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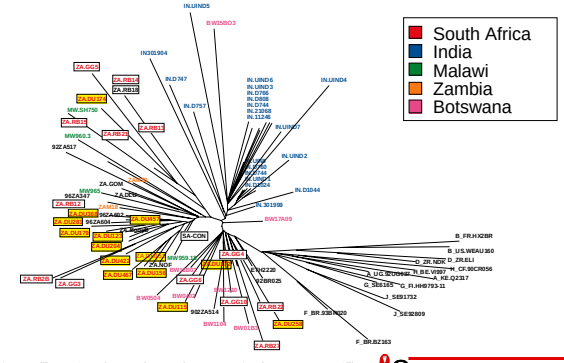
Broadly speaking, the thrust in the HIV vaccine field has been moving away from using a single vaccine to using what is broadly termed as a 'prime boost' strategy, where the immune system is primed with one particular vaccine, usually a DNA vaccine, and then is subsequently boosted with another vaccine, often a vector-based one.

## Challenges and major issues in HIV vaccines

What are the challenges facing vaccine development and some of the big issues that we are trying to grapple with? This phylogenetic tree shows the relationship and diversity of the different viruses. Viruses listed as 'ZA' are South African strains, and the tree shows that the South African strains have quite a wide dispersion. If you compare the South African viruses those that have been sequenced from neighbouring countries, you can see that the SA strains are similar to the strains from all our Southern African neighbours. This gives you some idea of the diversity of the viruses across the different parts of Southern Africa. The difficulty in developing a vaccine is the need to include epitopes that would be common to the full spectrum of all these viruses.

### Challenges in choosing antigens




Source: Williamson C, Morris L, Maughan MF, Piug L-H, Dryga SA, Thomas R, Reap EA, Cilliers T, Van Harmelen J, Pascual A, Ramjee G, Frelinger J, Johnston R, Abdool Karim SS, Swanstrom R. Characterisation and selection of HIV+ subtype C isolates for use in vaccine development.

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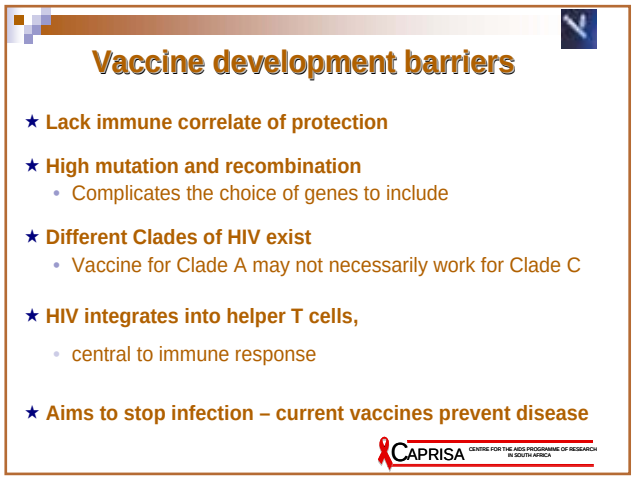
Despite the challenge, we have been able to make some progress and to date there has already been at least one Phase

III trial that has been undertaken using a subunit protein vaccine, AIDSVAX 101, developed by a company called Vaxgen. This trial was conducted in The Netherlands, and in the US and it showed no protection against primary HIV infection. However, what it has done is give us a range of clues about what we might be looking for. To better understand this, there are now studies that look at what the immune escape mechanism has been among those subjects who became infected in the course of this trial.

What we are looking at now is an expanded pipeline that for quite a while was reduced to a few new candidates each year, but is now a steady flow of several new candidates. Indeed, the Phase II and Phase IIB pathway involves new candidates that are either beginning trials right now or will be by the middle of 2006. Most of them are focusing on some kind of combination of naked DNA together with adeno- or other viral vectors.

What have been some of the most major development barriers that we have had to deal with? Probably the single most important barrier has been our inability to identify any immune correlates of protection. The only marker we have on which to base a decision of whether we should be progressing with a particular candidate or not is human efficacy data – we have no other basis with which to determine whether a product should move forward or not. It is unlike the situation with measles, where we know if you produce antibodies, you would have a degree of protection – in HIV we don't know what kinds of immune correlates we are trying to achieve.




The second big challenge has been the high mutation rate and the different clades that exist. Since we are dealing with such a diversity of viruses, we may make a vaccine against one particular strain of virus, but it may not have cross-immunity against the full spectrum of viral diversity. Further, in the presence of a vaccinated population, the virus may mutate and escape the immune response, so that what you would have in a vaccinated population would be a strain of virus that is an escaped mutant.

A point which has really challenged the vaccine field is one of trying to understand whether it is really possible at all to prevent the integration of HIV into resting T cells. It is optimistic to believe that any of the current vaccine candidates will be able to prevent the establishment of HIV infection in perpetuity, within an individual. At this point none of the candidates tested in animal models and in humans have been able to prevent this early integration of HIV into the human genome. So what we have had in effect are vaccines that are not able to stop HIV infection; rather we have vaccines that try to prevent disease by slowing progression to AIDS.

## Microbicides

Microbicides are chemicals that are intended for use in the genital and anal tracts for prevention of HIV infection. They come in different types of formulations - cream, suppository, gel and film - and the most popular currently is the gel.

One type of microbicide works by enhancing the natural defences of the human body. The vagina is naturally strongly acidic, and if there was a way in which we might be able to protect that natural acidic environment, it would present a natural barrier for HIV infection. In the course of sexual intercourse semen acts as a strong alkaline, and when it enters the vagina it neutralises the pH and creates an environment where the original protection of the low pH of the vagina has now been lost. There are products that are being developed that try to buffer that alkaline capacity of semen, and maintain the low pH in the vagina. There are also approaches that try to engineer Lactobacilli so that they will grow in the vagina and thereby produce lactic acid and thereby keep the pH of the vagina at a low (acidic) level. Examples of this type of microbicide are Buffergel; Engineered lactobacillus; and Hydrogen peroxide/peroxidases

The first-generation microbicides were the surfactants. They are essentially products that act by disrupting cell membranes, similar in their mechanism of action to what you would see in a soap. They kill or inactivate the organisms by disrupting the membrane or envelope or adjusting it so that they become more porous. Examples of first generation surfactant microbicides are Nonoxynol-9, Octoxynol-9; Benzalkonium chloride; C31G - Savvy; and Chlorhexidine zinc gel.

This was the first group of microbicides tested in humans, and the reason they were popular 10 years ago is that they were already widely used in the field of reproductive health, largely as spermicides, either on their own or in conjunction with diaphragm. It was thought that these products may have the potential to prevent HIV infection because they have other non-specific activity. They have been tested in various trials and there have been three large effectiveness trials. The last trial, which was conducted in Africa, showed the potential for harm that these products might lead to - so these products have lost favour in terms of future development, although there are still one or two products in this class that are still currently in human testing, like C31G.

Second-generation microbicides are long-chain polymers that work by inhibiting the steps of pathogen entry into mucosal cells. They create a protective layer within the vagina that prevents the virus when it enters in semen from attaching to cells within the vagina. Examples of these microbicides are Carraguard; PRO 2000 gel; Cellulose Sulfate, and Emmelle/ Dextrin-2-Sulfate. This class of microbicides is the one that is furthest advanced and currently in a whole range of microbicide efficacy trials in the USA, Africa and Asia.

The third-generation of microbicides are even more narrowly focused in terms of their mechanism of action, and

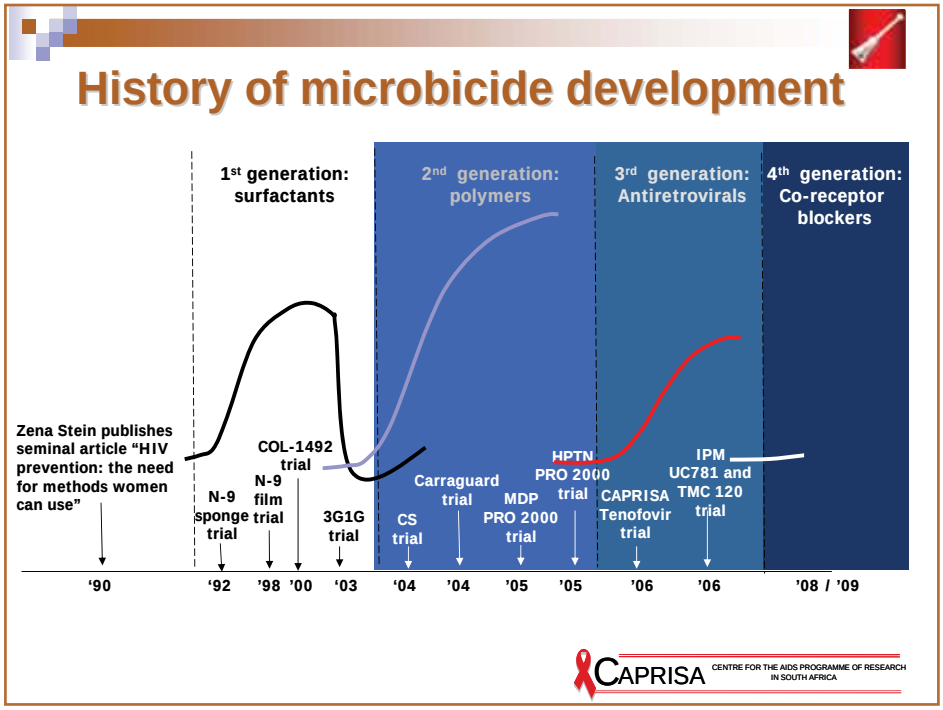
these are essentially antiretroviral drugs, often those that have shown poor absorption and therefore have not progressed further as part of the treatment programme and have been moved into the microbicide arena. Their mechanism of action is by inhibiting post-fusion replication. Examples of these are Nucleoside reverse transcriptase inhibitors (PMPA); NNRTIs (UC-781); and Protease inhibitors (WHI-07).

The one that is the furthest developed at this point is a drug called Tenofovir, which is used quite widely as a therapeutic oral formulation and there is also a gel formulation that is quite advanced in terms of proceeding now into efficacy trials. These antiretroviral drugs work at the level of the initial stages of infection - at the point at which they prevent the virus from replicating. They don't prevent the initial entry of the virus into the host, but rather they focus on replication and on preventing the replication cycle and preventing the establishment of HIV infection within the clinical trial.

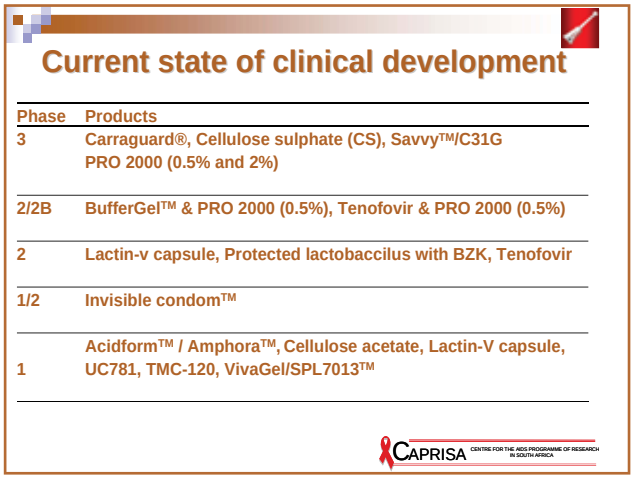
The fourth-generation microbicides – co-receptor blockers – act by preventing fusion between the pathogen and the mucosal cell. At this point the furthest developed is PSC-Rantes which is a blocker of the co-receptor CCR5.

## Progress with microbicide trials

The first-generation microbicides - the surfactants have lost favour after the results presented at the International AIDS Conference presented here in this very room in 2000.




At this point most of the subjects that have been enrolled in human efficacy trials are for second-generation products, the polymers, and there are very large numbers of these subjects, and this number is going to grow very rapidly as the large MDP studies come on stream. With the third-generation studies, which you see at the red line, trials of UC781, TMC 120 and Tenofovir will start soon. There are several studies of Tenofovir gel in humans and we anticipate that efficacy trials are likely to start sometime next year. The last white line is the fourth-generation products, with which there have been no human studies undertaken to date. The current state of clinical development is shown below.




The invisible condom is a product I have not yet described in any detail. This works as a polymer and also by becoming a mechanical barrier because it is thermal dependent. It is in gel formulation at low temperatures, but at 35-37°C it hardens in the vagina to become almost like a condom in the way in which it covers the vagina and the cervix. This product is already proceeding to Phase I trials.

## Conclusion

In conclusion, in both vaccines and microbicides, we are dealing with two major obstacles:

1. Lack of correlates of protection – we have surrogate markers that indicate actual protection. So we are not able to do studies that would look at these correlates and give us some idea of whether this product is likely to go forward and be efficacious.
2. Similarly, we have no animal models. For example, if one tries to look at animal models for microbicides, it is inappropriate to use monkeys because the monkey vagina has a neutral pH and there are few correlations between monkeys and humans for microbicides.

In the absence of having correlates and in the absence of having validated animal models we have no option but to do human clinical trials. There is a huge need for human clinical trials capability and a range of organisations working on building this kind of capability.

In both the area of HIV vaccines and vaginal microbicides the Gates Foundation has taken quite a lead role in terms of

bringing the various players together. In the field of HIV vaccines they are currently a major sponsor of the vaccine enterprise; in the area of microbicides they are currently sponsoring a global initiative known as the Microbicide Development Strategy that brings together a whole range of players to try and map out what the major thrust of research in microbicides should be.

Based on what we have seen to date, in both microbicides and vaccines, we have real potential to influence the course of the epidemic. With the additional clinical trial capacity, we can make real progress in this field and with it transform the level of obstacles from being mountains to molehills.

## Acknowledgement

I would like to acknowledge the Alliance for Microbicide Development, Rockefeller Foundation's report on Mobilisation for Microbicides - The Decisive Decade, and Cheryl Baxter for assistance with the slides.

# II North-South and South-South research partnerships – Current status and opportunities for initiating and strengthening collaborations

**Chairs: Odile Leroy** (France/Netherlands) and **Thomas Egwang** (Uganda)

- Potential partnerships/collaborations in Africa
- Capacity building, training and networking – needs for and examples of successful North-South and South-South research partnerships

## Engaging African partners in European research programmes

**Arnd Hoeveler** (Belgium) European Commission, DG RTD – Health Research

Infectious diseases are one of the priorities of the 6th Framework Programme of Research of the European Commission which addresses the following areas: HIV/AIDS, malaria, tuberculosis (TB), neglected diseases, BSE/TSE, HCV, antimicrobial resistance, pandemic influenza and SARS. I will focus only on the three major poverty-linked infectious diseases: HIV/AIDS, malaria and TB.

There are some general principles of EC research policy on poverty-related diseases (PRDs) which I would like to underline. Research on HIV/AIDS, TB and malaria requires a more long-term-oriented strategy for sustainability, with the development of partnerships also with the private sector. The focus in PRDs is not only on HIV, but also on TB and malaria, and the objective is to exploit and build upon the synergies between the three diseases. There is also the need to develop an overall framework for the different development phases for candidates, so that the EC programmes are focusing not only on discovery, but also on more downstream clinical research. There is a shift in the focus of the EC to evoke directly high disease burden areas into the research consortia.

Under the 6th Framework Programme PRDs have a budget of €400 million for 4 years over the period of 2003-2006. There are two pillars through which the EC funds the three poverty-related diseases. Each pillar is funded with €200 million:

- **Project funding**, which comprises (a) the funding of large consortia (for basic and preclinical research up to early testing (€5-25 m, 10-50 partners, 4-7 years)); and (b) funding of small-scale, high-risk projects (maximum €1 m, 2 years, young researchers).
- **Programme funding** through EDCTP, which has a separate legal entity external to the EC and its own implementation structures. EDCTP is independent of the Commission although funded with €200 million by the EC. I focus here only on the first pillar of project funding.

The overall aim of FP6 is to structure and integrate European research into a pipeline of projects ranging from early discovery to early clinical testing of drug and vaccine candidates for each of the three diseases. The EC research portfolio (STREP+IP) in HIV/AIDS, malaria and TB after 3 years of FP6 is as follows:

| | Discovery projects | Translational research | Clinical development |
|---|---|---|---|
| **FP6 instrument** | STREP | IP | EDCTP |
| **Total budget** | €56 M | €123.1 M | €400 M |
| **EU contribution** | €43.8 M | €94.8 M | €200 M |
| **Participating research groups** | 158 | 170 | N/A |

Concerning the participation of institutions in FP6: there are 220 EU institutions participating and 67 non-EU, giving a total of 287. Concerning developing countries participation in FP6: total EU contribution €138 million; total EU contribution to DC €8.6 million, total EU contribution to Africa €7 million; number of African countries – 12; number of DC – 16.

I would like to focus now on some concrete examples of how African institutions and researchers are participating in some of the EC projects.

**Example 1: OFLOTUB - a TB clinical Trial coordinated by C. Lienhardt**

The objective of this project is to evaluate the efficacy of a 4-month duration gatifloxacin-containing drug regimen for treatment of pulmonary TB. It concerns a multicentre randomised open-label controlled trial with a total of 2000 patients involved. The following African counties are participating: Benin (Cotonou), Guinea-Conakry (Conakry), Kenya (Nairobi), Senegal (Dakar) and South Africa (Durban).

The EU partners in this project are France, Belgium and the UK. For these projects there is a partnership between the EC Consortium and WHO-TDR (MoU in process).

**Example 2: TB-VAC - an integrated project for the design and testing of vaccine candidates against TB, coordinated by J. Thole Lelystad**
*Objective:* To identify, develop and evaluate in preclinical and clinical Phase I trials new and improved TB vaccines.
Three components: vaccine discovery; strategic research; and downstream development.
Consortium with 27 European + 3 African partners (Senegal, Gambia, Ethiopia); total budget: €20.8 M; EU funding: €16.8 M. Duration 5 years, starting January 2004.
The African partners are mostly involved in setting up the microbial and immunological laboratory capacity to conduct the Phase I trials of three promising candidates in the later phase of the project.

**Example 3: BIOMALPAR www.biomalpar.org**
This is a network of excellence on the biology and pathology of the malaria parasite, coordinated by Dr Artur Scherf of the Institut Pasteur. The EU contribution is €15.5 million over 5 years. Research teams were made up from 21 institutes (44 groups) from 11 countries plus 3 African partners (Sudan, Uganda, Mali) after a joint call between BIOMALPAR and MIM TDR (€1 million).

Involvement of Africans: Level 1: Executive Committee: African included; level 2: additional African partners during lifetime of projects, joint call BIOMALPAR/MIM TDR – re-entry grants only for Africans to African institutions; level 3: integrative PhD programme in cooperation with EMBL, 'sandwich' PhD, collaborative research projects between 2-3 institutions, 16 PhDs, one-third go to African students; other programmes: EU Marie Curie Fellowships (Henry Vial, M. Lanzer), 'training networks', 10 additional PhD students (3-4 have to be Africans).

## How to participate in EU programmes

- Consult the PRD brochure: *Poverty-related diseases, HIV/AIDS, Malaria and Tuberculosis*;
- Visit the PRD website: http://europa.eu.int/comm/research/health/poverty-diseases/index_en.html
- Visit the specific websites of projects, e.g. www.Biomalpar.org, www.Embro.org.uk
- In order to find a partner: http://partners-service.cordis.lu/
- Contact the National Contact Points: http://www.cordis.lu/lifescihealth/ncp.htm

**Key principles of FP6 participation rules:**
- at least three participants from three different countries (EU, candidate or associated countries);
- additional partners from almost anywhere ('3 plus 1'); and
- African partners cannot be the administrative coordinators, but should be the 'scientific head'.

Specific topics were given to apply for the 4th call (deadline 9 November 2005). However, since the deadline will be past when these proceedings are published, they are not elaborated upon here. Other opportunities for African researchers to participate in EC-sponsored actions are the following:

**A. Advanced Course of Vaccinology (ADVAC) www.advac.org**
A 2-week training programme on vaccination strategies and vaccination policies; EC sponsors 20 participants from developing countries (minimum 10 from sub-Saharan Africa). Dates: 23 May to 3 June 2006; Deadline for application: 15 November 2005.

**B. European fellowships**
European Training Networks, deadline 2006
http://europa.eu.int/research/fp6/mariecurie-actions/opportunities/proposals_en.html

Call for proposals for Marie Curie Fellowships for Early Stage Training, deadline 2006
http://europa.eu.int/research/fp6/mariecurie-actions/opportunities/proposals_en.html

Incoming International Fellowships, deadline 18 January 2006
http://europa.eu.int/research/fp6/mariecurie-actions/opportunities/proposals_en.html

Pan-European Researcher's Mobility Portal
http://europa.eu.int/eracareers/index_en.cfm

## Conclusion

There are several opportunities for African researchers to participate in different EC research programmes (PRDs, Marie Curie, Fellowships, International Cooperation programme) which are, however, not sufficiently used. In some cases new partners can be integrated in already running consortia (e.g. BIOMALPAR). The EC PRD programme is focusing on discovery and preclinical and early testing clinical trials, whereas EDCTP is focusing on Phase II/III clinical trials in sub-Saharan Africa. While it is requested to have at least 3 European partners in the EC programme (http://fp6.cordis.lu/lifescihealth/calls.cfm), 2 partners are sufficient for the 2nd call of EDCTP (http://www.edctp.org/default.asp?CID=93). In addition, EDCTP has the advantage that principal investigators from Africa can also be the financial administrator. This is not possible in EC programmes, although the scientific head of a project can be African and this is heavily encouraged by the EC.

Take home a lesson from the Durban Forum: **Please network!**

## New calls see www.edctp.org

**Cynthia Naus**, EDCTP Operational Manager

EDCTP Grants fall into four schemes: Clinical Trial grants; Capacity Building; Training Awards; and Networking. New calls for proposals were launched on 27 September 2005, and more calls will follow this year and next year.

In terms of clinical trials, requirements are as follows:
- participation of at least two institutions for EDCTP-EEIG member states and one African institution;

- two-stage procedure – Letter of Intent and Full Proposal;
- partners from EDCTP-EEIG member states have to provide 50% co-funding in cash or in kind. You can ask your local European Networking Officer about co-funding. Where such funding is provided in kind it can include the following: personnel, durable equipment, travel and subsistence, subcontracting, consumables, training and financial and administrative assistance.

Below follow slides outlining the various new calls

**Clinical Trials**

Deadline 12 December 2005

| *Topic* | *Total available EDCTP budget* | *Max EDCTP contribution per grant* |
|---|---|---|
| Capacity Building for microbicide trials | 7,000,000 | 2,500,000 |
| Capacity building for TB vaccine trials in high risk populations and children under 1 year of age | 2,350,000 for each topic | 2,000,000 |
| Clinical Trials for the treatment of TB in HIV infected individuals | 1,833,333 | 1,000,000 |

More topics will follow this and next year

**Capacity Building**

Deadline: 5 December 2005

| *Topic* | *Total available EDCTP budget* | *Max EDCTP contribution per grant* |
|---|---|---|
| Support for African coordinating office for ethics | 1,800,000 | 1,800,000 |
| Support for courses and seminars on ethics | 700,000 | 100,000 |
| Support for the establishment of ethical review boards | 500,000 | 50,000 |

**Training Awards**

Deadline Fellowships: 28 November 2005

Deadline PhD/MSc: 21 November 2005

| *Award* | *Number of awards for this year* | *Duration* | *Budget per grant* |
|---|---|---|---|
| Senior Fellowship | 8** | 2 years | 200,000 |
| Career Development Fellowship | 7** | 2 years | 100,000 |
| PhD Scholarship | 7** | 3 years | 75,000 |
| MSc studentship* | 15 | 1 year | 21,000 |

•Only available for staff of EDCTP funded sites

•** 2 awards will go to staff of MRC-UK in Africa

In terms of 'Networking', there are many different types of grants. Networking requirements differ per grant. Most request EU and African participation. Some grants require co-funding from EDCTP-EEIG member states. The deadlines are 1 November 2005 and 1 May 2006.

EDCTP networking managers can help find partners for networking grants as well as for clinical trial grants.

**Networking**

| *Topic* | *Total available EDCTP budget* | *Maximal budget per grant* |
|---|---|---|
| Joint capacity building projects in Africa | 1,000,000 | 100,000* |
| Support for network of training facilities for clinical monitors | 75,000 | 30,000 |
| Sponsorship of meetings of sustainable relevant networks | 100,000 | 25,000 |
| Coordination of research activities in Africa | 200,000 | 50,000 |
| Support of networking of African Scientists working on HIV, TB or malaria** | 400,000 | 50,000 |

•* 50% Co funding required from 2 EU institutions

•** Should involve either EDCTP grantees and/or DCCC member

Another Networking opportunity is Development of an M.Sc. course in Clinical Trials Methodology. Stage 1: deadline for application for organisation costs 28 November 2005. A budget of 10 000 Euro will be awarded to a maximum of five consortia. Stage 2: deadline for full proposals 31 January 2006. Available budget: 450 000 Euro.

## Call for experts

We are also looking for people who are willing to serve as reviewers, either as a member of a review board or as external reviewers.

# Establishing and managing collaborative networks for tuberculosis drug trials – challenges for long-term studies: The OFLOTUB TB drug trials Consortium

**Christian Lienhardt** (France/Senegal), Tuberculosis Research Group, IRD - Dakar

## Rationale

Despite a treatment of proven efficacy, TB rates continue to increase in resource-poor countries, with persistence of high treatment default rates, spread of multi-drug resistances, and high impact of HIV infection. There is therefore a great need to improve access to and delivery of treatment, and to decrease duration of treatment, both for new drugs and new combinations of drugs.

Below are features of some of the new drugs being looked at.

**Ofloxacin**

- Proven bactericidal activity against *Myco. tuberculosis* (Garcia-Rodrigues, 1993 ; Gillespie, 1998).
- Rapidly absorbed.
- High concentrations in respiratory cells, secretions and macrophages.
- Low cost, included in the WHO essential drug list.
- Several clinical trials (Tsukamura, 1986; Hong Kong Chest Service/MRC, 1992)
  TRC Chennai 2001: various 4-month duration regimens – sputum-smear conversion at 2 months 90-95%, relapse rate 6 months after treatment 3-12%.

**Gatifloxacin**

- 8-methoxy-fluoroquinolone active against Gram+ and Gram- organisms.
- Used for the treatment of commune infections (pneumonia, acute bronchitis, sinusitis, skin infections, UTIs and SRDs).
- *In vitro* and *in vivo* experiments: more active than ofloxacin against susceptible and resistant *Myco. tuberculosis* isolates, anti-TB activity similar to moxifloxacin (Tomioka, 2002; Alvirez-Freites, 2002).
- Relatively benign toxicity profile.
- Free of many of the class effects of quinolone antibiotics (e.g. phototoxicity).
- Potential cardiotoxicity (QT enlargement), although of minor degree compared to other fluoroquinolone compounds (class effect).
- Reported early effect on glucose homeostasis with severe hypo- or hyperglycaemia.

## Towards a combined gatifloxacin-containing 4-month duration regimen for treatment of TB

### Development workplan

1. Pre-clinical toxicology studies
2. Phase I pharmacokinetic study
3. Phase II trial
4. Phase III RCT

**Phase II trial**

Serial sputum colony counts (SSCC) study to assess the sterilising activity of a gatifloxacin-containing regimen compared with other FQ-containing regimens in TB patients (2 months duration): GHRZ vs OHRZ vs MHRZ vs EHRZ.

**Phase III RCT**

Phase III multicentre open-label RCT of a 4-month gatifloxacin-containing short-course regimen vs standard 6-month regimen for the treatment of pulmonary TB.

***Methods***

- Open-label RCT
- Non-inferiority
- Treatments
  - test: 2 months GHRZ/2 months GHR
  - control: 2 months EHRZ/4 months RH
- Sample size: 1035 patients/arm
- Followed-up for 2 years after completion of treatment.

***Preparing the trial***

- Identify sites for the conduct of the trial
- Conduct rigorous site assessment for evaluation of needs
- Identify reference institutions
- Develop standard operating procedures
- Develop standard CRFs
- Develop a standard data base and data management system
- Conduct appropriate training
- Identify and train external clinical monitors.

***Site assessment***

Multidisciplinary team (clinician, epidemiologist, micro-biologist, statistician/data manager):

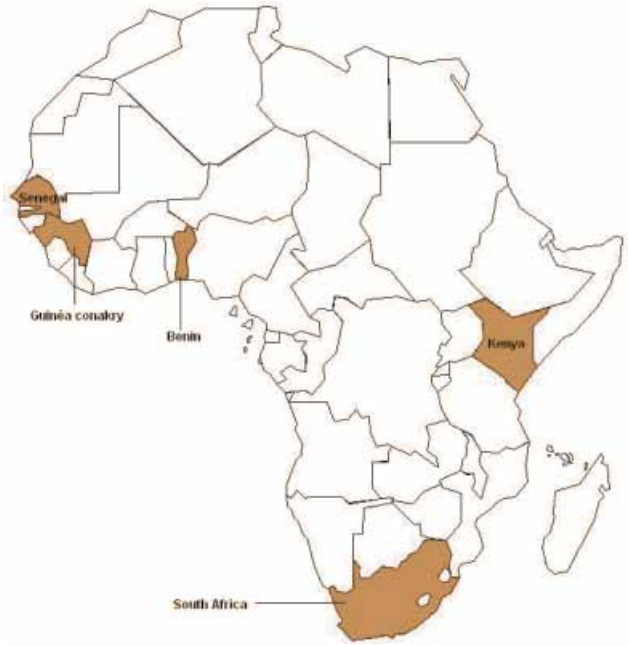
- description of the site (institution, national programme)
- TB epidemiological indicators
- access to patients
- presence of suitable clinical structure + equipment
- availibility of a well-functioning lab (decription, techniques, qualification of lab technicians, ...)
- data management possibilities (suitable human resources + equipment)
- administrative aspects (delegation and management of funds)
- willingness to participate.

- Establishment of a list of needs in terms of :

- human resources
- training needs
- technology transfer
- equipment needed
- requests for site 'upgrading'.

- Development of a specific work-plan per site.

**OFLOTUB African sites**



***OFLOTUB African collaborators***

- National TB Control Programme, Senegal (Dr M. Ndir, Dr C. Seck).
- National TB Control Programme, Benin (Prof. M. Gninafon).
- Pneumology Unit, University Teaching Hospital Ignace Deen, Conakry, Guinee (Prof. O. Bah-Sow).
- MRC South Africa (Dr B. Fourie).
- Kenya Medical Research Institute (Dr J. Odhiambo).

***European collaborators***

- IRD France (C. Lienhardt): design of the trial, epidemiological expertise and trial coordination.
- Infectious Diseases Unit, University Teaching Hospital, Garches, France (Prof. C. Perronne): clinical expertise.
- Institute of Tropical Medicine, Belgium (Prof. F. Portaels): Supra-National Reference Laboratory and coordination of microbiology aspects.
- LSHTM, London, UK (Dr K. Fielding): data management oversight and statistical analysis.
- St George's Hospital Medical School, London, UK (Prof. D. Mitchison): microbiological assays, sterilisation studies.

***Consortium Agreement***

- Development of a Consortium Agreement linking the 10 partners (5 African and 5 European institutions).
- Defines common goals and objectives, timelines, respective partners' roles and responsibilities, managerial activities and administrative aspects, IP rights and publication policies.

***Development of SOPs***

- Written on the basis of the Master Protocol.
- Follow GCPs/GLPs requirements.
- Finalised on the basis of situation in sites.
- Detailed training plan indispensable to upgrade sites and labs to suitable standards, compatible with GCP/GLP requirements
  - before trial starts
  - while trial is conducted.

***Training***

- Good Clinical Practise:
  - introduce/reinforce GCP concepts
  - ensure that research conducted in each site satisfies these recommendations (ongoing).
- Good Laboratory Practise: train lab technicians involved in all laboratory aspects on the need and practise of GLPs.
- Microbiology: train microbiology lab staff on the needs and practicalities of regular and efficient internal quality control.
- Data management: train data managers in setting-up and managing rigorously established database.
- Epidemiology: strengthen knowledge in epidemiology and provide PIs with the tools to create and develop further research projects.

***Establishment of an independent structure to supervise the trial – the Data and Safety Monitoring Board (DSMB)***

This fully independent committee provides advice to the trial coordinator on all aspects of the trial, recommends and supervises interim analysis, and makes specific recommendations on the continuation of the trial, particularly on ethical and safety issues.

## Conclusion

The creation of a network of sites to conduct clinical or vaccine trials on TB responds to the need to address specific methodological issues (large sample size, long duration of follow-up, definition of rigorous outcomes, geographical variability, etc.).

This gives an excellent opportunity to create and promote a group of sites of excellence to carry out clinical trials in Africa and constitute a real and solid network. Upgrading structures and providing training is an *essential* component of research projects in Africa.

Conjugated efforts are definitely an asset. The OFLOTUB Consortium was created to respond to a specific question, but through the establishment of a network of sites of excellence linked with dedicated reference institutions, can serve as a basis for other investigations.

## Acknowledgements

Thanks to all colleagues who permitted this vast effort to take place:

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- KEMRI, Kenya: J. Odhiambo, W. Githui, E. Amukoye
- LSHTM, London, UK: K. Fielding, B. Sismanidis, C. Merle, S. Bennett
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- WHO/TDR.

# AMANET – capacity strengthening and networking of malaria R&D in Africa

**Wen L. Kilama** (Tanzania), Managing Trustee, African Malaria Network Trust

***Please note:*** This presentation appears on www.edctp.org

# The Malaria Vaccine Initiative

**Melinda Moree** (USA), Director

***Please note:*** This presentation appears on www.edctp.org

# The Microbicides Development Programme (MDP)

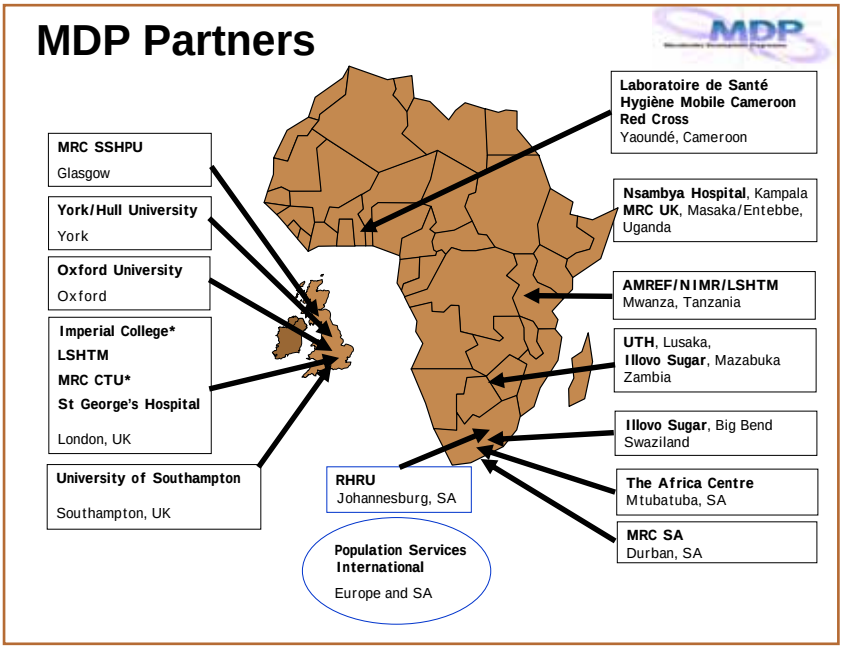
**Richard Hayes** (UK) on behalf of all MDP investigators

The Microbicides Development Programme (MDP) is a partnership between UK/MRC and six African academic sites in four countries, supported by DFID and MRC.

The aim of the MDP is to provide an effective, affordable, accessible microbicide for those that need it most.

The history of the MDP is as follows:

- It began in 2000 when the UK Department for International Development (DFID) was asked if it would be willing to support an enlarged programme of research on vaginal microbicides.
- The next year, 2001, the MRC peer-reviewed a 5-year programme grant proposal, and DFID agreed to fund it.
- This year DFID and the MRC approved supplementary funding for MDP up to 2009 for completion of a Phase III trial of Pro2000.




## Objectives

The objectives of the MDP are:

- to determine the scientific mechanisms underlying the activity of agents;
- to conduct preclinical evaluation of potential microbicides in *in vitro* models;
- to undertake early clinical studies of new products (including combinations) in UK and African populations;
- to conduct early exploration of the distribution and retention of products and formulations;
- to assess sites for their suitability for inclusion in a Phase III trial and to prepare them for such a trial through feasibility studies; and
- to undertake a multinational, randomised, double-blind, controlled trial of candidate compounds in Africa.

In parallel with the feasibility studies, a multidisciplinary group of behavioural and social scientists, social marketers, health economists and mathematical modellers was established to work with the sites to:

- collect data to optimise the tools and procedures used in the Phase III trial, and to understand the way in which the products are used within the study and the broader population; and
- provide economic and epidemiological support to facilitate the delivery of any product shown to be effective in a trial.

## An overview of the MDP Phase III trial

This is a randomised double-blind placebo-controlled trial with three arms: 2% Pro2000, 0.5% Pro2000, and placebo. Around 12 000 HIV-negative women will be recruited and followed up for 1 year. Detailed safety evaluations will be undertaken in a subset. The primary analysis will look at effects on HIV incidence during the first 9 months of follow-up; secondary end-points will include HSV2 sero-incidence, and the prevalence of gonorrhoea and chlamydia.

Feasibility studies in the African study sites started in mid-2002 and continued through 2004. The feasibility studies were designed to assess:

- HIV incidence/prevalence in the target population;
- ability of the site to recruit and retain in follow-up HIV-uninfected women; and
- relevant social science research to inform the Phase III trial.

Objectives also included assessment of condom usage, demographic and behavioural characteristics of the population, acceptability of pelvic examination, and acceptability of microbicides. Social science activities were carried out in parallel to the feasibility studies. In each site the social science team conducted focus groups and in-depth interviews to:

- validate instruments being used to collect behavioural data;
- assess the role of coital logs; and
- estimate the frequency of anal sex.

### Target populations

**South Africa**

Durban: women attending two health clinics at Tongaat and Verulam (50 km north of Durban); Johannesburg: women attending primary health clinics in Soweto and Orange Farm; Africa Centre (KwaZulu-Natal): women attending community clinics.

**Tanzania, Uganda and Zambia**

Mwanza, Tanzania: women working in bars and other food and recreational facilities in Mwanza City, recruited and

followed up through special mobile clinics; Masaka, Uganda: sero-discordant couples identified and recruited through population-based sero- surveys; Mazabuka, Zambia: women living on a sugar plantation and entitled to access health care on the estate, and women recruited at a clinic in a nearby town.

## HIV incidence

| Populations | Clinics & communities | | | | Bar/food Facilities | Discordnt Couples |
|---|---|---|---|---|---|---|
| | A | B | C | D | E | F |
| Recruitment period (m) | 14 | 15 | 12 | 18 | 14 | 2 |
| Person yrs FU | 499.2 | 531.4 | 86.2 | 356.4 | 717.4 | 31.2 |
| Sero-conversions | 37 | 21 | 16 | 13 | 25 | 4 |
| HIV incidence | 7.4 | 3.9 | 18.6 | 3.6 | 3.5 | 12.6 |
| 95% CI | 5.4, 10.2 | 2.6, 6.1 | 11.4, 30.3 | 2.1, 6.3 | 2.4, 5.2 | 4.8, 34.1 |

**...hence decision to use 4% in sample size calculation**

Based on data from the feasibility studies, HIV incidence in the study sites ranged from 3.6 to 18.6 per 100 person-years. This supports the assumption of 4 per 100 person-years for the sample size calculations.

## Trial design: RCT

**Women years required:**

| incidence/ 100 pyrs | 40% reduction 90% | 40% reduction 80% | 35% reduction 90% | 35% reduction 80% |
|---|---|---|---|---|
| 4 | 7875 | 5880 | 10607 | 7970 |
| 4.5 | 7000 | 5227 | 9429 | 7040 |
| 5 | 6300 | 4704 | 8486 | 6336 |

**...if FU 9m in majority, and assume 15% LTFU**
**11,920 women needed**

The trial was designed to provide 90% power of detecting a 40% reduction in HIV incidence, and 80% power to detect a 35% reduction.

## MDP approaches to collaboration

### North-South-South partnership

There is joint decision-making with representation on committees and MDP working groups. Information flow in the working groups is through emails and also via telephone conferences.

During the trial preparation phase, MDP working groups were established covering laboratory, clinical trial, social and community activities. These working groups operated on a 2-monthly cycle, discussing specific sets of design issues according to a timetable of tasks. During each cycle, a list of questions was emailed to working group members by the coordinating group. Responses were returned by email, and used to prepare a document setting out a suggested position on each issue. This was circulated by email, and formed the basis for a teleconference to reach an agreed consensus.

Investigator workshops are held annually, rotating between the African MDP sites. An important aspect of MDP is that there is flexibility to allow for varied study populations and local context.

**Capacity building in MDP** is tailored to the differing needs of individual sites. This may include:

- Research infrastructure, for example in IT equipment, data management or laboratory capacity.
- Staff training: e.g. on-site training in GCP, GLP, monitoring and data management. There are currently no specific MDP funds for MSc/PhD training, and EDCTP funds may be sought for this.
- South-South exchange is an important aspect of the MDP partnership: this includes between-site visits to share expertise in various areas; and co-monitoring whereby site investigators have been trained in monitoring and visit other sites to assist with monitoring activities.
- Another important aspect of MDP is that data-management is carried out at each site, and sites will be encouraged to carry out statistical analysis of site-specific data with support from MRC/CTU.
- Preparation for the Phase III trial has provided a clear focus for the capacity building initiatives.

## Acknowledgements

The participants.
The staff.
Durban: Gita Ramjee, Shamantha Naiker, Neetha Morar Johannesburg: Helen Rees, Sinead Delaney Moretlwe, Jonathan Stadler, Jocelyn Moyes
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PSI: David Nowitz, Jayne Rowan

# African AIDS Vaccine Programme (AAVP)

**Carolyn Williamson** (South Africa), Chair: AAVP Biomedical and Clinical Sciences Working Group, Institute for Infectious Diseases and Molecular Medicine, University of Cape Town
for **Pontiano Kaleebu**, Chair: AAVP Steering Committee, Assistant Director, Uganda Virus Research Institute, Entebbe, Uganda

## History of the AAVP

By 1999 Africa had the biggest HIV burden in the world (two-thirds of an estimated 34 million people with HIV). The first HIV vaccine trial was held in 1987 in the USA, and by 1999 more than 70 Phase I vaccine trials had been undertaken, but only one trial was to start in Africa. There was no vaccine based on the African subtype in trial, and capacity was limited.

The Nairobi meeting of the WHO/UNAIDS Vaccine Initiative held in June 2000 had two major outcomes:

- the Nairobi Declaration: An African Appeal for an HIV Vaccine; and
- the African AIDS Vaccine Strategy: An outline describing vision, goals, principles, milestones and activities framework.

**http://www.who.int/vaccine_research**

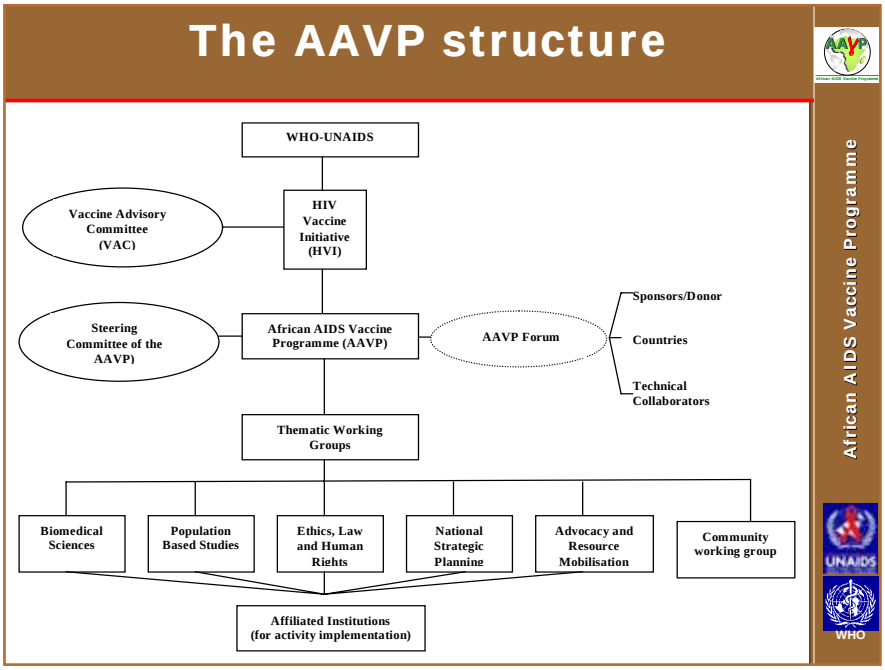
The AAVP was established in September 2000 out of the above meeting, and is a network of African scientists, institutions and communities working together to promote and facilitate HIV vaccine research and evaluation in Africa through capacity building and international collaboration.

The vision of AAVP is to advocate and support a coordinated effort to ensure global HIV vaccine development of appropriate and affordable vaccines for Africa in the shortest possible time. Its objectives are:

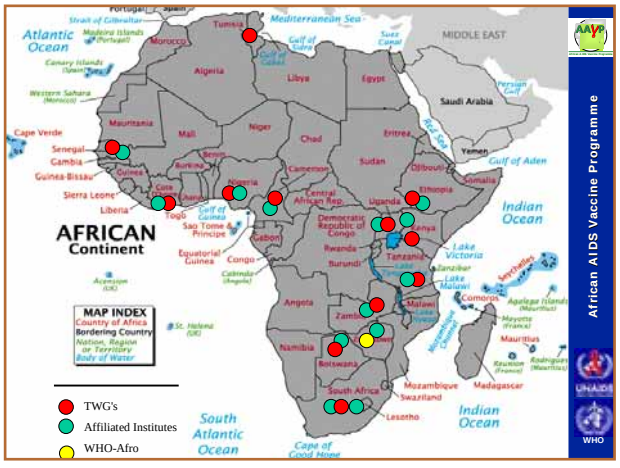
- to develop advocacy strategies and communication tools;
- to network people and institutions;
- to promote the development of appropriate candidate vaccines for Africa;
- to facilitate the preparation for clinical trials through capacity building; and
- to develop plans for future access.

## The AAVP structure

The structure of the AAVP is shown in the diagram below.




The activities of the AAVP are implemented by the thematic working groups (TWGs), with the assistance of the secretariat, and under the guidance of a steering committee.



## Achievements of the AAVP

The achievements of the AAVP in various sectors are briefly outlined below.

### Advocacy and mobilisation

Communication tools have been developed (booklets, posters, newsletter, web-page), and three forums organised in Cape Town, Addis Ababa and Yaounde. Satellite meetings were held at ICASA and Vaccine Conferences. Three workshops were held with the media, in Nairobi, Dakar and Bamako, and a media network is being established.

### Biomedical sciences

To help determine the training requirements, an inventory of laboratory capacity was completed in 2002 and a follow-up survey is under way. One of the main activities of this working group is to provide short-term training through support given to 12 technical workshops on virological and immunological characterisation (>130 scientists trained). Two good clinical practice workshops have been held and support given to 9 projects on virus isolation and characterisation. An IAEA/WHO-funded research project is under way to establish a laboratory network in 5 countries (Cameroon, Ethiopia, Kenya, South Africa and Uganda).

### Ethics law and human rights

A database of existing Research Ethics Committees has been established and 3 training workshops held on ethics, in Lagos, Kampala and Dakar. Research reports have been compiled on legislation and regulation of health research in 5 countries (Uganda, Kenya, Tanzania, Ethiopia and Botswana).

### Population-based studies and community preparedness

A workshop on strategies for the development of HIV vaccine trial sites has been held and an inventory made of existing cohorts and sites in Africa. A training workshop for community groups was held in Nairobi, and consultation with community groups to develop a strategy for AAVP in Tunis and Cape Town. A satellite meeting for community groups was held in Dakar.

### National strategic planning: AIDS Vaccine Plans

Guidance for National Vaccine Plans has been developed to be used by countries and support given to 10 consensus workshops in countries including Nigeria, Tanzania, Zambia, Cote d'Ivoire, Ethiopia, Uganda, Botswana and Kenya. Support has been given to regulatory capacity building - 3 National Regulatory Authority strengthening workshops have been held in Addis Ababa, Ouagadougou and Zanzibar, and establishment of an AAVP Regulatory Advisory Panel is under way.

### Publications and policy documents

Policy document on the importance of HIV subtypes for HIV vaccine evaluation (in preparation); Obstacles for enrolment of women and adolescents in trials (in preparation); Access to care and treatment; Guidance for National AIDS Vaccine Plans; Research Ethics Committees (in preparation); Ownership of data.

### Other achievements

There is formal collaboration with IAVI (Community, National Plan, Training, Regulatory, Media) and collaboration with SAAVI (Ethics, Regulatory, Community). Other collaborations include ICASO and AfriCASO. Consultations are under way for further collaborations with HVTN, CDC, US DOD, Global HIV Vaccine Enterprise, ANRS, AVAC and EDCTP.

Funding is provided by the following bodies:

- CIDA Canada
- SIDA/SAREC Sweden
- WHO/UNAIDS
- Netherlands
- IAVI
- CDC, DoD, SAAVI (Co-sponsor specific activities).

An external review was held in June 2005, with the objectives of assessing progress, efficiency, effectiveness and impact, and examining the governance and management structure of AAVP, and proposing options for structural and functional improvements.

This review noted that AAVP had achieved significant progress, but that it needs more funding, needs to reprioritise, and needs to further develop key indicators and identification of its unique added value.

## Opportunities for collaboration

The comparative advantages of AAVP/WHO/UNAIDS are that it includes all member states of AU, has experience and credibility, is linked with all partners (has neutrality), does not develop products (has no vested interest), and has experience in ethics (UNAIDS), regulatory and policy issues (WHO)

Potential areas of collaboration include training fellowships, supporting capacity building (GCP, regulatory, ethics, scientific, etc.), and site development, including support of other trials (e.g. malaria or TB) which could have benefit to HIV vaccine trials. Other areas include supporting targeted research via institutional and regional collaboration, implementation of National Vaccine Plans, and working together on policy and community issues.

## Acknowledgements

Steering Committee Members: Pontiano Kaleebu – Chair, Alash'le Abimiku - Vice-Chair, John Nkengasong, Dawit Wolday, Shenaaz el Halabi, Sinata Koulla-Shairo, and Coumba Toure Kane.

Chairs of Thematic Working Groups: Malaki Owilli, Ibou Thior, Roy Mugerwa, Carolyn Williamson, and Doug Wassenaar.

WHO/AAVP Secretariat: Marie-Paule Kieny, Saladin Osmanov, Madani Thiam and Coumba Touré.

# The Aeras Global TB Vaccine Initiative: Strategies in TB vaccine research and development with a focus on site development

**Lawrence J. Geiter**, Ph.D., Aeras Global TB Vaccine Initiative, USA

## About Aeras

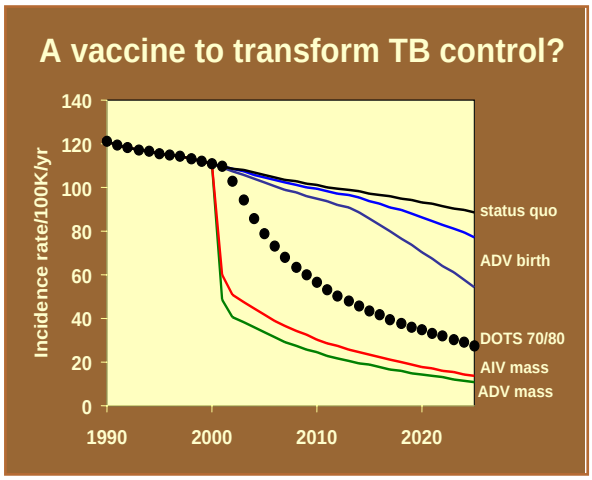
Aeras is an international non-profit organisation with 14 current partners, among them:
Crucell NV (Netherlands), Statens Serum Institut (Denmark), GSK (Belgium), Max Planck Institute (Germany), UCLA (USA), University of Cape Town (South Africa), and St John's Medical College (India). It is organised and tries to function very much like a pharmaceutical company with a focus on product development, but we also a have the need to promote capacity development. Most of our partners in terms of producing products are from Europe, and the two that we are working on capacity development with are in South Africa and India.

**Mission:** To develop new TB vaccines and ensure their availability to all who need them.

Aeras forms joint development teams with partners to develop promising TB vaccine candidates – currently there are two leading candidate regimens and a third we hope to announce shortly.

The goals are to obtain regulatory approval and ensure supply of a new TB vaccine regimen to prevent TB in the next 7-10 years, and to introduce second-generation vaccines with improved product profiles and efficacy against latent TB in 9-15 years.

Primary funding provided by the Bill and Melinda Gates Foundation with additional funding from CDC, NIH, and Danida.




Source: Chris Dye, WHO, from: *Clinical Tuberculosis*, 3rd edition, pp. 21-42, Chapter 2, Epidemiology, P.D.O. Davies (ed.). London: Arnold, 2003.

I take issue with my good friend Bernard Fourie that the vaccine we need to focus on is the one that acts against latent infection. This graph was done by Chris Dye of WHO. The top line shows the status quo – if we change nothing in the way we deal with TB. The black dots are if we achieve the DOTS goals of 70% and 80%. The blue lines are if you gave a vaccine that prevented infection at birth, and that was your only strategy. The green line is the best case, and that is if you give a vaccine that prevents reactivation of latent infection. The red line is the projection of what would happen if you gave an anti-infection vaccine to the entire population. Having discussed this with Chris, the belief, and there is a lot of epidemiological evidence, is that most of the TB in high-burden countries comes from more recent infection and not reactivation of latent infection. So in fact a vaccine that is effective in producing protection against infection would have a very important and very dramatic impact on the epidemiology of TB.

## Prime boost strategies – recombinant modified BCGs

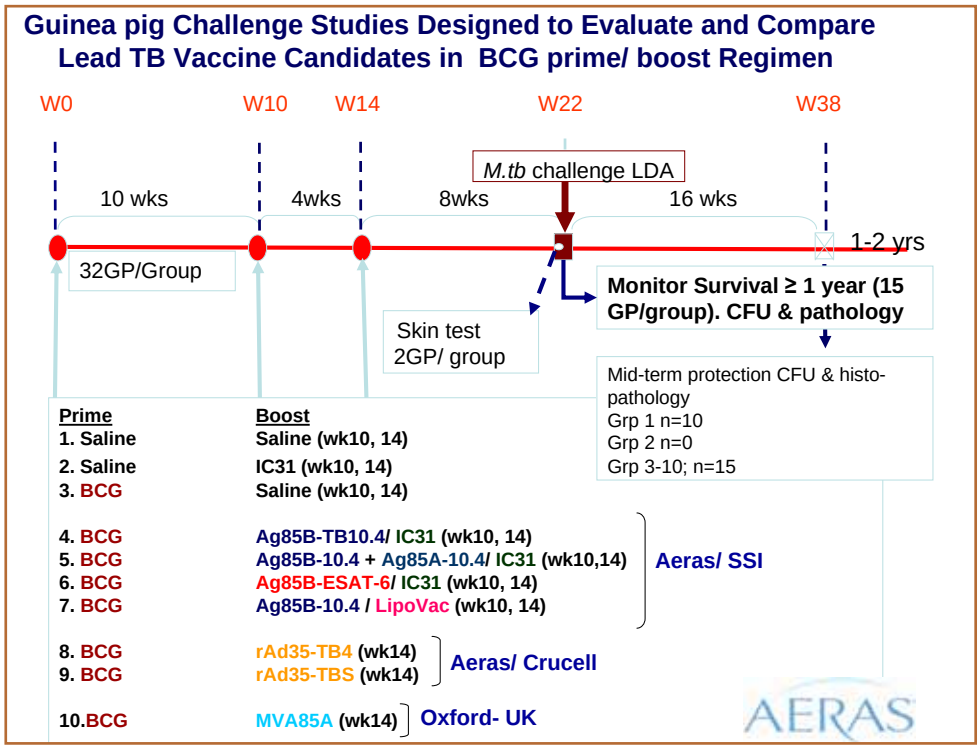
As others have mentioned, we have to deal with the fact that BCGs are going to be given at birth. However, there are a number of recombinant BCGs:

- rBCGs over-expressing TB antigens: Horwitz at UCLA (well tolerated in a Phase I trial);
- rBCGs escaping the endosome: Kaufmann at Max Planck Institute;
- rBCGs mutated in superoxide dismutase expression: Kernodle at Vanderbilt;
- rBCG with RD-1 region replaced: Cole at Institute Pasteur;
- Aeras rBCG strain AFV112 – combines the Horwitz and Kaufmann discoveries.

***Candidates for boosting infants and adolescents***

- Recombinant fusion proteins in adjuvant
  - Mtb72f (well tolerated in Phase I) GSK
  - Ag85B::ESAT6 SSI/TBVAC
  - Ag85B::10.4 fusion SSI/Aeras
- Vectored vaccines
  - rMVA-Ag85A (safe and immunogenic in multiple Phase I trials) Oxford
  - rAd35-Ag85A::Ag85B::TB-Y fusion Aeras/Crucell
  - Oral Shigella dsRNA Aeras

This is a rather complicated slide (overleaf) about guinea-pig challenge studies under way – about 3 months into post-infection follow-up, but the main point is that one of the things Aeras brings to vaccine development for TB and part of its value is to bring different products and technologies together under one platform. In this experiment we can look at immunogenicity and technical effectiveness in a single animal model of all three vaccine approaches above. The next step will be to take the winners and use them in combination with rBCGs, eventually seeing which will be the best one to move forward to human clinical trials. Our approach is to take on a lot of risk – and risks that other vaccine companies that are working for profit usually would not. This type of risk that




## Lessons learned and questions raised from the BCG clinical trial

It is indeed possible in this setting to obtain specimens for TB culture from very young infants and PBMC for banking. We also learned that there is very little information on hospitalisations or death, and we are probably going to have to set up independent systems to try and determine cause of death. The rate of confirmed TB is very high (+2%) whereas severe TB was almost eliminated in the BCG trial cohort, but this may be due to a surveillance effect and has to be examined further.

we are taking on is that we are going to be starting Phase I trials of various products while still doing preclinical work to help select and determine which of the vaccines that make it through will go to Phase II trials. These are things that would usually be done in series and not in parallel.

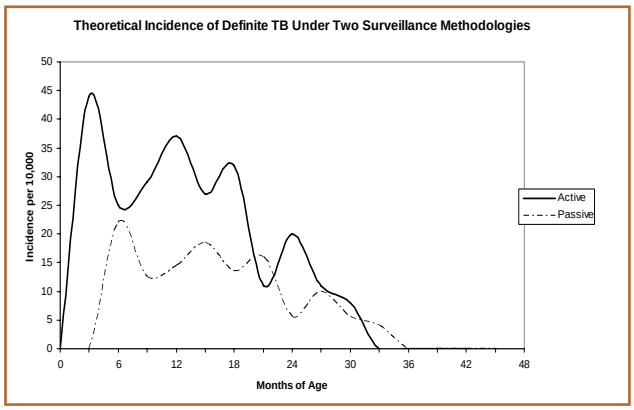
## Site development and capacity building

We very much take the approach 'To learn by doing' – you learn to do community-based TB vaccine trials by *doing* community-based TB vaccine trials. We need to do this by learning how to do a trial – we haven't done such large trials, to try and enroll thousands of people, with the high degrees of follow-up that are going to be needed. Similarly, we need to learn about TB. As another presenter pointed out – there a lot of things we 'knew' about TB that turned out to be wrong.

In terms of the South Africa site, it is centred on a large community in Worcester, about and hour and half from Cape Town on the highway, and the other major centres are Ceres, Robertson and Montagu. The other area we were working in is Palamaner in Southern Andhra Pradesh, in collaboration with St John's Medical College of Bangalore, India.

Ongoing and planned studies in South Africa are a BCG randomised controlled trial and an adult prevalence study; and in both South Africa and India an adolescent cohort study and neonatal cohort study.

## Neonatal cohort studies, India and South Africa




The dark line above shows the risk of culture-positive TB every 3 months that was actually observed in the BCG trial that is finishing up in South Africa. The dotted line shows the incidence that might be observed if there was a strong surveillance effect and if under passive surveillance half the cases resolved and the reporting of the remaining cases was delayed 6 months. Our need to resolve the effect of surveillance has led us to undertake a neonatal cohort study. In India this will also provide an opportunity to build needed capacity and learn about the incidence of TB in infants in that community.

### Study objectives

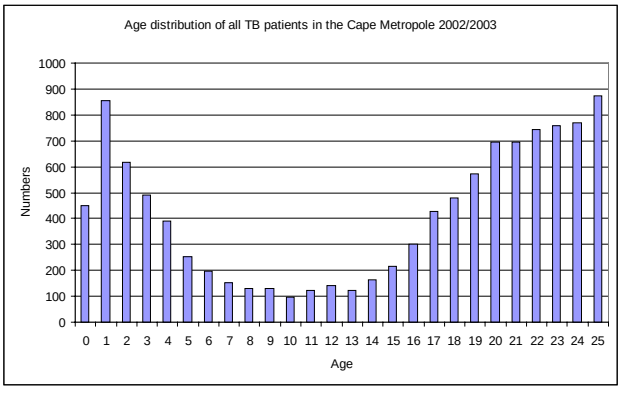
- Compare rates of disease in active and passive groups to evaluate surveillance effect.
- Estimate incidence of TB during first 2 years of life in India and compare with South Africa.
- Establish capacity to vaccinate at or near birth in India.
- Establish capacity to conduct autopsies to determine cause of death.

## Adolescent cohort studies, India and South Africa

The diagram below shows the age distribution of TB cases in the Cape Metropole of Western Cape Province, but the same general distribution would be observed in most TB-endemic countries. The increase in risk of developing TB in the early teenage years makes this an important potential population for TB vaccination to prevent infection and disease. Cohort studies in this population are planned in India and South Africa and will provide our first opportunity to learn about TB infection and disease incidence in these populations and to build capacity to organise a cohort and ensure high rates of follow-up in this population.

### Study objectives

- Estimate TB incidence in 12- to 18-year-olds in India and South Africa and compare.
- Compare rates of disease in active and passive groups to evaluate surveillance effect.
- Establish capacity to form adolescent cohort and follow-up, conduct autopsies to determine cause of death.
- In India, obtain and bank blood specimens.
- In South Africa, characterise risk of TB given a positive QuantiFERON.®




Aeras

## Professional Development Programme (PDP)

This is a collaborative initiative with SATVI in South Africa to develop a model programme that builds and sustains capacity of the entire clinical research team – from community outreach workers to nurses and drivers. Those members of the clinical research team with greatest patient contact have the least opportunity for education – they should understand why they are doing something and not just what and how they are doing it. They have the greatest impact on the study participants. The motivation comes from a statement overheard by an outside monitor of the BCG trial, hearing one of the community counsellors saying that: "The study vaccine comes from the bark of a special tree that grows only in Tokyo, Japan". We were using Tokyo BCG as the study vaccine. The statement to the person being asked for consent indicated some understanding but a profound lack of knowledge about what the study was, and what BCG and vaccines are.

The Aeras Professional Development Programme is designed to provide a solid background in the rationale and implementation of clinical trials, and career opportunities. It is offered to all levels of staff, including drivers, community counsellors, nursing staff, laboratory technicians and managers. There are three different levels, and everybody has to take the introductory level.

Level 1, Introduction, comprises: Clinical Infectious Disease 1, Infectious Disease Epidemiology & Biostatistics 1, Clinical Research Practice 1, Clinical Research Organisation and Management 1, Good Laboratory Practice 1.

Level 2, Intermediate, comprises: Clinical Infectious Disease 2, Infectious Disease Epidemiology & Biostatistics 2, Clinical Research Practice 2, Clinical Research Organisation and Management 2, Good Laboratory Practice 2.

Level 3, advanced, comprises: Clinical Infectious Disease 3, Infectious Disease Epidemiology & Biostatistics 3, Clinical Research Practice 3, Clinical Research Organisation and Management 3, Specialised Good Laboratory Practice.

The PDP is a process and simply a series of modules. A skills audit is made of each individual's work experience, education and training, and present areas of responsibility. A Personalised Development Dossier is developed for the individual comprising PDP but also other courses the individual might need; the individual career advancement path is outlined and attainment of new competencies is chronicled. Aeras offers a core curriculum for staff at three levels (assistant, officer and manager), and the PDP is evaluated by independent assessors who will look at the strengths and weaknesses of components and overall programme.

## Acknowledgements

University of Cape Town: Greg Hussey, Tony Hawkridge, Willem Hanekom, Hassan Mahomed, about 70 others on the South African TB Vaccine Initiative Study Team.
Public Health Research Institute: Gila Kaplan.
KNCV Tuberculosis Foundation: Suzanne Verver, Martien Borgdorf.
St John's Medical College, Bangalore: Anura Kurpad, Mario Vaz, Rajini Macaden, Nelson Jessuraj, and host of others soon to be hired.
Professional Development Programme: Sylvia Silver (GWU), Jen Page (Aeras), M. Buchanan, M Geldenhuys.

# The Global Alliance for TB Drug Development

**Khisimuzi Mdluli** (USA), Ph.D., Project Leader, Research, Global Alliance for TB Drug Development, New York, USA

One-third of the world's population is infected with *Mycobacterium tuberculosis* – or around 2 billion people, and 8-9 million develop active disease annually. Two million deaths occur each year – 1 person dies every 15 seconds. There are 400 000 cases of multidrug-resistant tuberculosis (MDR-TB) each year.

Tuberculosis is the leading cause of death in HIV-positive people – 12 million people are TB/HIV co-infected.

Current TB drug therapy comprises the following:

- Active TB
  - Standard therapy – 4 drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) for 2 months, followed by isoniazid and rifampicin for 4 months.
- Latent TB
  - Standard therapy – isoniazid for 9 months.
- MDR-TB
  - Individualised, prolonged therapy; there are few available drugs, and they are poorly tolerated and difficult to administer.
- TB/HIV co-infection
  - Drug interactions with antiretroviral agents - simultaneous therapy difficult.

There is hence a need for new TB drugs since the existing drugs are complex and the disease currently requires 6-9 months' treatment. There has been no new anti-TB drug in over 30 years. However, we have a situation where TB/HIV co-infections are fueling each other and MDR-TB is on the rise. Yet it remains an unattractive market for the private sector.

## History of the TB Alliance

What is the Global Alliance for TB Drug Development, and how did we come about? The Alliance was born at a meeting in Cape Town in February 2000 hosted by the Rockefeller Foundation and South African Medical Research Council, attended by over 120 organisations (health, science, philanthropy and private industry). As a result of this meeting a Declaration was made in Cape Town of the need to support the goals of the Stop TB Initiative, create a scientific blueprint and develop a pharmaco-economic analysis, and the TB Alliance was born. This is an International Public-Private Partnership, a non-profit organisation based in New York, Brussels and Cape Town. We focus solely on developing drugs and do not develop capacity unless we specifically need clinical trial centres for performing specific studies; however, we do not have a mandate to train scientists in the developing world.

The Alliance operates according to an entrepreneurial, virtual R&D approach, outsourcing R&D to public or private partners and undertaking pro-active fund-raising.

The TB Alliance Mission is to:

- develop new, better drugs for TB;
- ensure affordability, access and adoption (AAA); and
- conduct, coordinate and catalyse TB drug development activities worldwide.

## AAA strategy

Affordability – appropriate pricing in developing countries
Adoption – ensure that new drugs are incorporated into existing treatment programmes
Access – procurement and distribution to those patients who need them most.

What should a new TB drug look like? A new TB drug should:

- Shorten the duration of TB treatment or otherwise simplify its completion
- Be effective against MDR-TB
- Be compatible with HIV treatment
- Improve the treatment of latent TB

Our objective is first to shorten treatment for TB, and then to simplify it. We planned our attack in two forms, a near-term vision and a long-term vision.

## Near-term vision

In terms of the near-term vision, we believe that the objective of shortening and simplifying treatment is feasible, and we believe this because it has already been done: treatment has historically already been shortened from 24 to 6 months – there is therefore a general road map available. Preclinical models predict that drugs currently in the pipeline could shorten therapy to 2-3 months. Clinical trials of current drugs have demonstrated that most patients are cured in 3-4 months – but have no way to identify which ones. Two to three-month regimens should be achievable with new, more effective drugs. The aim is also to simplify from daily to weekly dosages.

In terms of HIV, the objective is to provide safer and more effective TB drugs that can be used simultaneously with antiretroviral therapy, and the approach is to test for and prioritise compounds without P450 interactions. Even compounds that do not shorten treatment of active TB disease may be safe for co-therapy with ARVs. Success will be a consequence of efforts for treating active disease.

In terms of MDR-TB, the objective is to provide safer and more effective therapy. The approach is to prioritise novel mechanisms of action, and screen MDR-TB strains. Even compounds that do not shorten treatment of active disease may be efficacious for MDR-TB. Again, success will be a consequence of efforts for active disease.

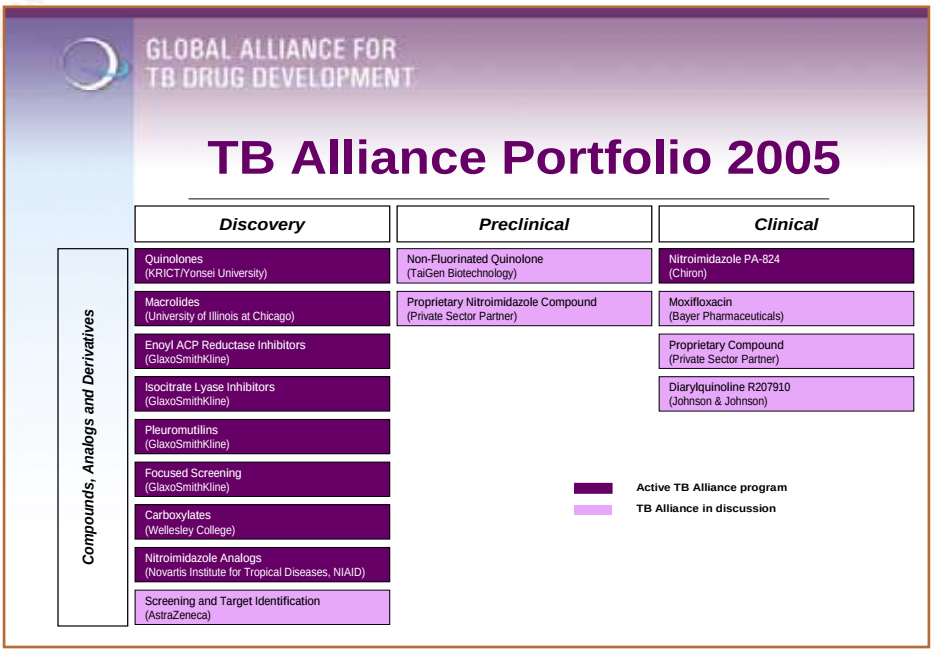
## Long-term vision

Our long-term vision is to reduce treatment of active disease to 7-10 days of treatment, instead of months. However, this will be very difficult to achieve without advances in the understanding of the biology of 'persistence'.

## TB Alliance portfolio 2005

Taking a closer look at a few of the projects:

PA-824 is a novel nitro-imidazole, and has potent activity against both active and slow-growing *Myco. tuberculosis*. It possesses both bactericidal and sterilising activity. Phase I clinical trials began in June 2005.




The Alliance works with GlaxoSmithKline on a joint drug discovery programme at GSK's Diseases of the Developing World facility in Tres Cantos, Spain, and has four different projects with them: enoyl ACP reductase inhibitors; isocitrate lyase inhibitors and pleuromutilins – both of which are pharmaceutically naïve products and have never been used in man before; and focused screening.

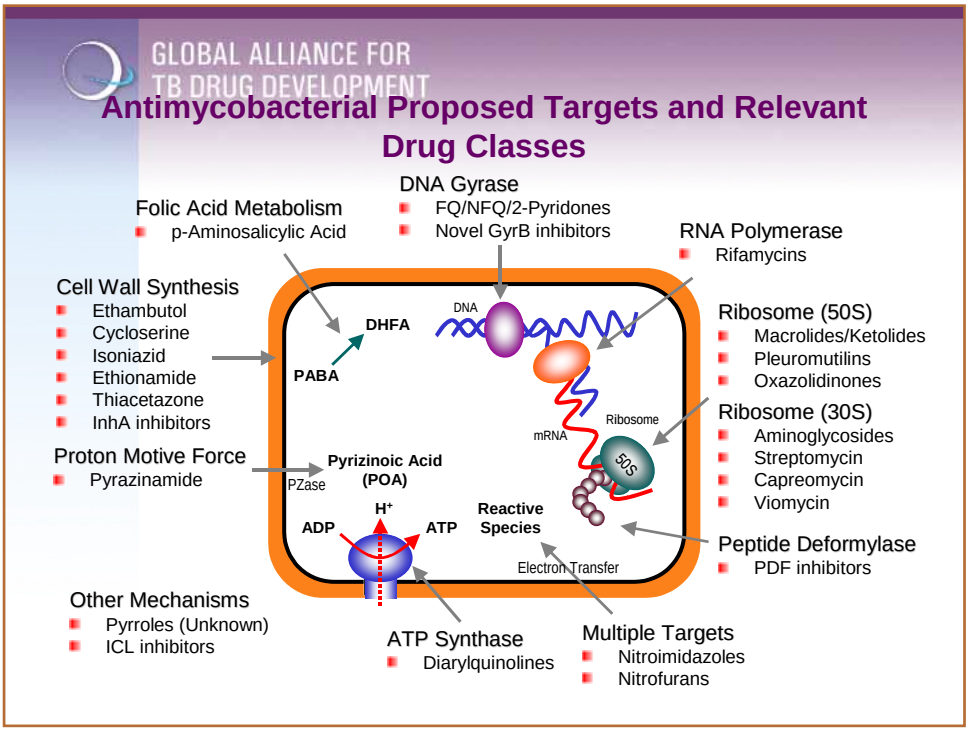
We are also working with the University of Illinois at Chicago's College of Pharmacy – Institute for Tuberculosis Research, seeking to discover macrolide antibiotics with potent activity against *M. tuberculosis*. The current two-year joint research programme includes chemical synthesis of novel analogues, as well as *in vitro* and *in vivo* biological testing.

With the Korea Research Institute of Chemical Technology (KRICT) in Daejeon, South Korea, the Alliance is conducting a two-year research programme geared to the chemical synthesis of novel quinolones, pyridones and quinolizines. *In vitro* and *in vivo* biological testing of the KRICT compounds is done at Yonsei University College of Medicine in Seoul, South Korea.

As shown in the figure below, just like in any antibiotic discovery programme, we are targeting all the biological processes that are vital for maintaining the life of the mycobacterium. The only difference is that we try to emphasise those processes that are not targeted by currently used drugs so that we may be able to combat MDR-TB, and those processes that seem to be important for *in vivo* growth, like energy production, so that we may be able to treat persistent, and maybe even latent infections.

We have one goal only – and that is to produce new, more effective and affordable drugs against TB. We are willing to partner with anybody who shares our goals and can contribute to their achievement.

**More information about the Global Alliance for TB Drug Development may be found at www.tballiance.org**



# Developing trial site capability for TB vaccine testing in Africa: The South African Tuberculosis Vaccine Initiative

**G. Hussey, T. Hawkridge, W. Hanekom**, SATVI

The first point we would like to make is that research does not occur in a vacuum, it occurs in various contexts. One important context to acknowledge is the political context. In this country although we are now 10-11 years post-democracy, we are still struggling to correct the imbalances of the past. The legacy of apartheid lives on, and research is not immune to that. Poverty and unemployment are rife. But on the positive side we have initiatives such as NEPAD.

The second context that is important is the research context itself. It is true that there is limited funding for research – there is only so much cake to go around. There are also limited human resources, with a continuing brain drain. Whatever the relations are between researchers and funders, there will inevitably be some powerplay in terms of decision-making and the research agenda.

## The South African Tuberculosis Vaccine Initiative

The mission of SATVI is to contribute to the development of new and effective tuberculosis vaccines. Our focus is on translational research. Our activities are as follows:

### Clinical trials

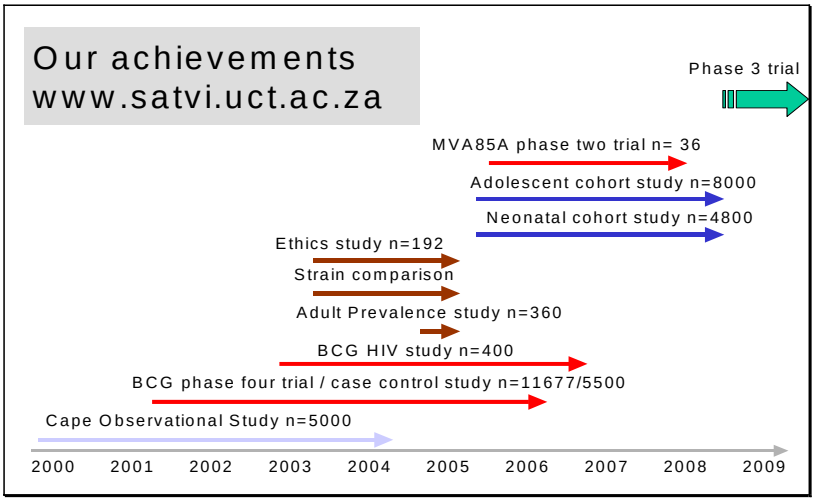
- To develop the capacity of the site to do Phase I to Phase IV vaccine trials.
- To identify important epidemiological characteristics that are of relevance to tuberculosis in the area.
- To identify clinical, microbiological and immunological endpoints of key importance to all stages of vaccine trials.

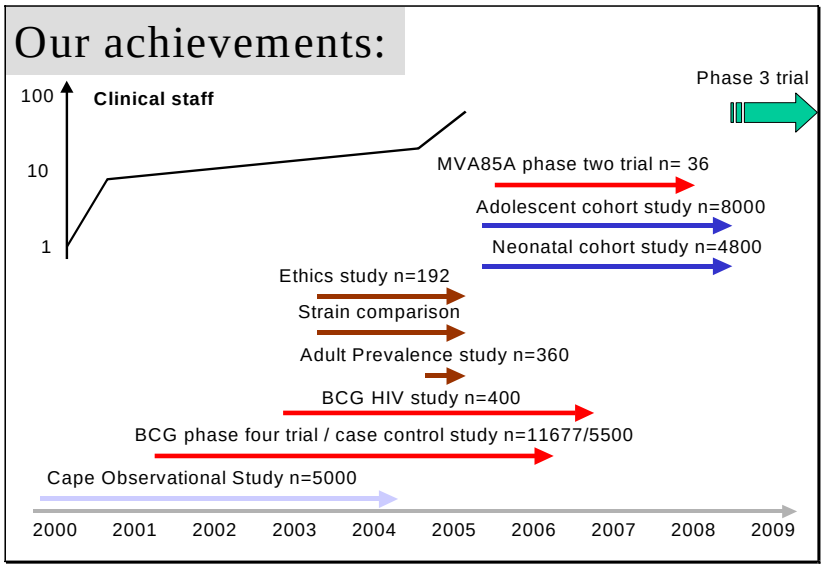
### Immunology studies

- Aim to characterise the human host immune response to TB and BCG vaccination.
- To identify immune correlates of protection against TB induced by BCG vaccination.
- To determine if BCG vaccination is safe and immunogenic in HIV-positive children.

Our facilities include Brewelskloof TB Hospital in Worcester, 100 km from Cape Town, the SATVI Research Centre in Worcester, and the Institute of Infectious Diseases and Molecular Medicine at the University of Cape Town (UCT).

## Our achievements




I emphasise our 'flagship programme', which is the Phase IV trial in 11 677 newborns, because it demonstrates that we have capacity to vaccinate and follow up large cohorts of participants in a developing country setting. I also refer you to Dr Geiter's and Prof. Hanekom's talks which cover aspects of our work in some detail.

## Partnerships

None of these achievements would have been possible without partnerships. We have heard a lot about these. Important partnerships include those between researchers and funders. It is not a cheap exercise to set up a basis to conduct clinical trials, and I would like to acknowledge our funders who have made this possible. Another very important partnership is

that between researchers and the health services. Others include partnerships with the community – community-based organisations and non-governmental organisations, and with academic institutions, both local and international.

Our international partners include the following:

- Aeras Global TB Vaccine Foundation
- KNCV, The Netherlands
- Max Plank Institute
- Statens Serum Institut
- Oxford University
- PHRI, New Jersey
- Case Western University
- George Washington University
- McGill University/University of Montreal
- Tokyo BCG laboratory
- WHO Stop TB Vaccine Working Group
- EDCTP

These are the principles that we think are very important when establishing any successful partnership. Firstly, ownership of the research should reside with the organisation doing the work. There should be joint decision-making, and no research unless the sponsoring partner is committed to investment and to capacity development. These are really the non-negotiables. Other things that are important in maintaining good relationships are good communication, information sharing, transparency, trust, and mutual respect.

In terms of community partnerships, this for us is 'work in progress'. I don't believe that we have a perfect model of getting the community involved in research. One must consult, consult and consult here. We have a Community Advisory Board, and have managed to collaborate with trade unions/ employers, parent and teacher organisations and NGOs, as well as using press and radio to disseminate information. It is an ongoing challenge to elicit meaningful participation from poor and disempowered communities. A recent paper from the Africa Centre in KwaZulu-Natal, South Africa, proposes a model for achieving this.

There are many ways that one can collaborate with the health services in order to do research: by providing technical advice and support, consultancy services, training of health workers, support of education programmes, infrastructural development, and by paying attention to their research needs. I would like to emphasise employment policies and practices: not 'poaching' health services staff. You cannot have a good relationship with the health services if you are constantly taking their staff. We have a policy whereby our salaries are on a par with the provincial packages, so there is no financial incentive for someone to move across from the health services, and in addition we will not offer a post to anyone currently employed by the health services.

In terms of research team partnerships with our academic partners, around the world and in South Africa, we insist that research proposals are devised and worked on jointly and that there is a commitment by collaborators to capacity development at our site. An example of this, which Dr Geiter spoke at some length about in his presentation, is the Professional Development Programme which Aeras have sponsored and have been involved in delivering at our site. We encourage our staff to submit their work for presentation and publication to both national and international audiences. It is important that we publish and attend conferences and present both nationally and internationally.

## Our professional development programme (PDP)

This recognises that there is a need for development of all research staff, not just at investigator level, and a need for a comprehensive development programme, not just short courses in GCP/GLP. The PDP was put together in partnership with Aeras GTBVF and currently looks at three levels: assistant, officer and manager. There are currently five modules at each level:

- Clinical research practice
- Clinical research organisation and management
- Epidemiology and biostatistics
- Clinical infectious diseases
- Good laboratory practice

The programme also incorporates needs assessments and individual development plans.

## Conclusion

In conclusion, these are the things about partnerships that we think are important: they should be non-exploitative, there should be mutual recognition of worth, and no partnership can happen without investment in technology transfer and capacity development.

The table below illustrates models of doing research in developing countries (Costello & Zumla, 2000), categorising them into 'semi-colonial' or true partnerships. We would hope that we have developed true partnerships, or that we are indeed moving in that direction.

Models of doing research in developing countries (Costello and Zumla, 2000)

| Characteristic | Semi-colonial model | Partnership model |
|---|---|---|
| *Setting of research agenda* | Dominated by outsiders | Negotiated with insiders |
| *Links with national institutions and training programs* | Peripheral | Integral |
| *Management* | Line management by foreigner | Line management by national or insider |
| *Staff costs* | Predominantly foreign salaries; over-inflated local salaries | More balanced investment and more sustainable in the long term |
| *Dissemination* | Heavily oriented to international journals and conferences | International dissemination balanced by outputs in national and regional journals and media to reach a wider audience |
| *Emphasis on sustainability and generalizability of research findings* | Low | More likely |
| *Influence with local policy makers* | Low | High |
| *Effect on national institutions* | Negative: attracts best and brightest away from national research institutions | Positive: builds up local academic infrastructure |

## Site identification and development for microbicide trials in resource-poor settings: The experience of the International Partnership for Microbicides

**Paul Coplan** (USA)
***Please note:*** This presentation appears on www.edctp.org

# Forum Dinner

On the evening of day 2, 4 October, Drs Odile Leroy and Bernard Fourie welcomed the Guest of Honour, South Africa's Minister of Health, Dr Manto Tshabalala-Msimang, and the other guests to the official Forum Dinner.

## Address by the Honourable Minister of Health of South Africa

**Dr Manto Tshabalala-Msimang**, on the occasion of the Dinner at the Second Forum of EDCTP

Important representatives and distinguished guests, Dr Odile Leroy, the Executive Director of EDCTP, members of the academia, ladies and gentlemen

Let me start off by congratulating EDCTP Developing Countries Coordinating Committee on their decision to pick new members to ensure a broad member ownership by the African scientific community. I trust that you will go a long way in ensuring that our science sharing power will play a significant role in the presentation of resolutions of the Partnership. It is pleasing to note that there is a focus on capacity building, training and networking.

From the time that EDCTP was officially launched in 2004, representatives from African government, the European Commission and other important stakeholders have deliberated on a number of issues, and I am happy that the focus for this year is on the implementation of the outcomes of those deliberations.

The main objective of clinical research is to develop knowledge, to improve health and to understand human biology. I wish to emphasise that it is an obligation of all investigators to ensure that research participants are not merely used as a means to an end, but actually have the respect for what they contribute to the research as a whole.

South Africa provides a unique environment for research. The former advantaged areas of our country have good infrastructure, serious researchers, and well equipped research institutions comparable to many developed countries. On the other hand, the rest of the population is affected by the burden of diseases common to many developing countries, particularly in sub-Saharan Africa. All these have attracted many international institutions to develop and tap their data in our country. As you know, increasing research activity, competition and attractive research environments may sometimes result in disorder and fraudulent practice. That is why we are making an effort to ensure that research is conducted in an ethical manner and that the interests of the participants in the research are also protected. We want to ensure that the researcher-participant relationship is well regulated and sets out the specific responsibilities of the researchers and the rights of the participants.

I am happy to inform you that South Africa is finalising the revision of its good clinical trials guidelines for the conduct of clinical trials in human participants, and trust that all clinical interventions coordinated under the direction of this organisation will conform to the norms and standards that apply in the guidelines in our country. I am also pleased to inform you that the process of registration of clinical trials in South Africa is under way. The South African National Research Register is available for sponsors and investigators to register all clinical trials before they commence in our country. This will ensure transparency in the conduct of clinical trials and will also inform the public of trials that are under way. These are some of the measures that we have put in place in ensuring that the rights, dignity and safety of human participants are considered at all times during the

planning and implementation of any clinical intervention.

The rights of patients and participants in research are now entrenched in the National Health Act of South Africa which was promulgated earlier this year. The Act also makes provision for the establishment of the National Health Research Committee, which will assist in identifying health research priorities for the country. These priorities should be determined based on the burden of disease, the cost-effectiveness of the intervention, availability of resources and the health needs of our community.

I trust that appropriate research – not only on clinical interventions, but also on health systems in general, will provide too for better policy development as well as new technology. Also critical for our organisations I hope is to align our research approaches to those countries for whom this research has been conducted. South Africa in particular adopted the National Research and Development Strategy in 2002 which should guide our activities in agriculture, education, health, science and technology, that are involved in the area of research. The Department of Science and Technology is responsible for cross-cutting institutions and cultural or scientific and natural research and the Human Sciences Research Council, line function departments like agriculture and health, who have to set research goals and budgets for institutions reporting to them or working in a specific line function area. It is critical to understand here these local dynamics to ensure synergy and proper coordination of programmes to maximise our impact. We have to ensure that research priorities are relevant and respond to local needs.

Therefore I hope that this second Forum of our organisation will live up to its theme of translating knowledge into implementation. We need evidence-based interventions that should assist us in strengthening our health research and in responding to the major health challenges affecting our population. I hope that you will be able to use the three days you are spending here to take us from knowledge to implementation.

# III Summary and recommendations from round table discussions

**Chairs: Bernard Fourie** (South Africa) and **Marie-Paule Kieny** (WHO Geneva)

## Overview of the objectives of the Forum and of EDCTP priorities for clinical trials, capacity building, training, and networking

**Odile Leroy,** Executive Director, EDCTP

Dr Leroy gave a brief overview of the above, setting the scene by outlining the objectives of the Forum as the following:

- **Networking**
- **State of the art**
- **Recommendations.**
  - How can EDCTP translate the available knowledge into actions?
  - Are the current priorities for EDCTP fitting the needs of African research and health policies?

In terms of **African (south-south) networking**, objectives are as follows:

Creating a network of African scientists and institutions engaged in EDCTP-relevant activities:
- to create an inventory of their activities,
- to exploit the potential synergies, and
- to identify the needs and strategies for capacity strengthening.

Securing the support of the scientific, clinical and political authorities in the African countries and regional organisations, and in general the co-ownership by Africa of EDCTP.

Ensuring that EDCTP effectively addresses the needs and priorities of the researchers, health systems and the populations.

Strengthening the regulatory environment for clinical trials in Africa.

Developing a network of Reference Laboratories in Africa.

In terms of **clinical trials**, she outlined EDCTP priorities to be as follows:

### Malaria drugs

Treatment of uncomplicated and drug-resistant falciparum malaria.
Treatment of severe malaria.
Treatment of malaria in pregnant women.

### Malaria vaccines

Protection of young children.
If becoming available, protection of pregnant women.

### Tuberculosis drugs

New drugs or regimens, which shorten or simplify tuberculosis treatment.
New regimens for treatment and prevention of tuberculosis associated with HIV.
Surrogate markers of treatment response.

### Tuberculosis vaccines

Effective tuberculosis vaccine/s, including those for use in patients co-infected with HIV/AIDS.

### HIV/AIDS drugs (antiretroviral treatment (ART))

Simple and standard ART for adults and children.
New treatment.
Prevention of mother-to-child transmission.

## AIDS vaccines

Clinical development of prophylactic and immunotherapeutic vaccines.

## Microbicides

Conducting Phase II and Phase III trials.
Collecting safety data in uninfected and infected adolescent age group.

**In terms of capacity building, EDCTP priorities were described as follows:**

### Individual training

Training of trainers.
Training in the context of trials and site development.
Research and exchange fellowships to build individual scientific leadership.
Development of joint courses between EU and African institutes.

### Institutional capacity strengthening

Improving infrastructure of (potential) clinical trial sites.
Prepare and strengthen selected sites in Africa for Phase I/II trials.
Developing methods and capacity for Phase II/III trials in African sites.
Strengthening human resources in sites and institutes.
General scientific, logistic and managerial support to African institutes.
Enhancing capacity for GCP, GCLP and ethics.
Capacity development of information and data management in African institutions.

# Introductory comment by Dr Bernard Fourie about the round tables

The round tables aimed to formulate recommendations, statements on need, challenges, and priorities for EDCTP. This Forum has been brought together to assist with this process. Each session's facilitator and rapporteur was asked to ensure that the predefined key discussion points were adequately addressed, also in the context of the introductory presentations given by leaders in each of the areas; abstracts are reproduced in Appendix II with no additional narrative and the actual presentations appear on www.edctp.org. The broad recommendations that came out of each and the overall recommendations of the Forum are listed below, and form the basis for further discussion and action by EDCTP constituencies in defining future EDCTP priorities and activities.

# Report from Round Table I: Conducting clinical trials in Africa towards evidence-based interventions for HTM control

## HIV/AIDS

Facilitator/Rapporteur **Britta Wahren** (Sweden), **Simon Agwale** (Nigeria)

**Main topics for discussion:**

- **HIV and AIDS, drugs**
- **HIV and AIDS, microbicides**
- **HIV and AIDS, vaccines**
- **HIV and AIDS, drugs**
- **HIV and AIDS, microbicides**
- **HIV and AIDS, vaccines**

### HIV and AIDS, drugs

**Issue:** HIV drug treatment
**Discussion:** Complex treatment difficulties of adherence and monitoring
**Recommendations:** Fund studies to achieve simplification of ART regimens
Fund studies related to treatment of children

**Issue**: Transmission of HIV from infected mother to child before, during and after birth.
**Discussion**: Means to reduce transmission, drugs, non-toxic intervention to the child, reasons for increased transmission during mixed feeding.
**Recommendations**: Fund studies to prevent MTCT
Fund projects aimed at reducing HIV transmission during breast feeding

**Issue**: Results of antiretroviral treatment
**Discussion**: Many programmes with ART are ongoing; problems with drug resistance will become prevalent. Not necessary to establish full-blown vload and sequencing competence everywhere
**Recommendation**: Establish regional Centres of Excellence on monitoring ART treatment and resistance

### HIV and AIDS, microbicides

**Issue**: Support of microbicide trials
**Discussion**: EDCTP competence and economic power to support Phase III trials
**Recommendation**: Identify and fund preparatory trials

### HIV and AIDS, vaccines

**Issue**: Vaccination of children against HIV
**Discussion**: Difficulties in acknowledging the need; think about side-effects
HIV genes inserted in BCG, measles vectors

**Recommendation**: Think about ways to associate HIV vaccination with the childhood vaccine programmes

**Issue**: HIV vaccine candidates in Europe
**Discussion**: 9 Phase I HIV vaccine candidates in Europe; Critique for not having issued any HIV grants. Around 10? applications for the first vaccine call. Bottlenecks: GMP production
**Recommendation**: Calls for HIV vaccines
Use the presently available Phase I tested candidates

**Issue**: To develop mucosal vaccines
**Discussion**: Which type of delivery induces good and long-term immunity at mucosal surfaces cf effective vaccines for cholera; Virus-induced cervical cancer.
Evaluate licensed/ongoing other mucosal vaccines (6 exist)
**Recommendations**: Call for mucosal HIV vaccines, combine with microbicide call

**Issue**: Vaccine testing in early HIV infection
**Discussion**: Means to provide read out of vaccine potency (dendritic cell immunisation).
Do HIV vaccines provide clinical benefit in infected individuals?
**Recommendation**: Calls for small immunotherapeutic trials. Should be combined with drug trials.

### HIV and AIDS, drugs

**Issue**: Efficacy of ART
**Discussion**: Viral load during treatment. Expensive and complex monitoring of drug efficacy
**Recommendation**: Fund studies that identify surrogate markers for monitoring HIV-infected patients on ART

### HIV and AIDS, microbicides

**Issue**: Assessing HIV incidence
**Discussion**
**Recommendation**: Capacity building, validation of HIV tests

**Issue**: Regulatory issues in Phase III trials
**Discussion**: Ways to simplify assessment
**Recommendation**: Support regulatory reviews, in an EMEA-like fashion, with expedited reviews, registration and standardised ethical reviews

### HIV and AIDS, vaccines

**Issue**: To discover correlates of protection
**Discussion**: Do interesting studies on small cohorts in order to discover pathogenic events of importance for vaccines, such as events in primary infection, LTNP, early mucosal events
**Recommendation**: Should be supported by basic research grants

## Summary of HIV recommendations

- Fund studies to achieve simplification of ART regimens
- Fund studies related to treatment of children
- Fund studies to prevent MTCT
- Fund projects aimed at reducing HIV transmission during breast feeding
- Establish regional Centres of Excellence on monitoring ART treatment and resistance
- Identify and fund microbicide preparatory trials
- Think about ways to associate HIV vaccination with childhood vaccine programmes
- Call for HIV vaccines (use the presently available Phase I tested candidate)
- Call for mucosal HIV vaccines (combine with microbicide call)
- Call for small immunotherapeutic trials (combined with drug trials)

## Tuberculosis

(Facilitator/Rapporteur **Alwyn Mwinga** (Zambia), **Voahangy Rasolofo** (Madagascar))

**Main topics for discussion:**

- **Past experiences in TB drug and vaccine clinical trials permitted the identification of different obstacles:**
  - **treatment**
  - **outcome;**
  - **diagnostic tools for children, extrapulmonary TB and TB/HIV;**
  - **lack of correlates of protection against TB;**
  - **data management;**
  - **treatment of MDR TB.**
- **Need to develop (to create) new collaborations, new partnerships for new TB clinical trials. Need to have information about existing clinical trials, trial sites and networks.**

### Recommendations

TB vaccine clinical trials

- Different models should be considered for site selection or focus
  - Either specialised (for type of trial, preventive or therapeutic vaccine) or with the ability to do both
- Investment should be made in surveillance systems (demographic); set up and maintenance of these systems is a requirement for a trial site
- To consider support for development of data management, administration, ethics review
- More research required in the identification of immunological markers and correlates of protection
- EDCTP should fund research in development of SAE detection systems

TB drug clinical trials

- Investment is required in building lab capacities for the development of assays in research institutes where ongoing research could maintain the lab (sustainability)
- EDCTP should support trials of TB diagnostics (tools for diagnosis of paediatric TB, extrapulmonary TB and TB/HIV, MDR-TB)

- Trials are required for extrapulmonary TB in the presence of HIV
- MDR-TB should be a focus for clinical trials but first priorities for Phase IV (programmatic trial) of MDR-TB treatment regimens
- EDCTP should develop capacities in terms of regulation requirements for using second-line TB drugs and running clinical trials on MDR-TB.

New collaborations and networking
- EDCTP should play a brokerage role in providing information on existing trial sites and facilitate the development of networks and partnerships.
- EDCTP should partner with other agencies for funding.
- EDCTP should support capacity building for epidemiological surveillance.

Networking of sites
- EDCTP should identify 2-3 big sites, with different TB epidemiological regions (rural, urban, high HIV, low HIV) to develop into centres of excellence for clinical trials:
  - Identify smaller sites to collaborate with these big centres.
  - Provide capacity building for smaller sites in a network.
  - Big centres transfer skills (data, research findings, good diagnosis criteria) to other centres with high disease burden.

## Malaria

Facilitator/Rapporteur **Ricardo Thompson** (Mozambique), **Thomas Egwang** (Uganda)

**Main topics for discussion:**
- **Networking**
- **IPTi and IPTp**
- **African leadership in multinational grants**

### Recommendations:

- Networking
  - Multicentre approach covers a range of epidemiological settings
  - Provides on-job training using limited resources
  - Provides technical support: standardised protocols
  - Supports policy review/change
  - examples: EANMAT, WANMAT, HANMAT
  - Networking with existing networks e.g. AMANET
- IPT
  - Validated intervention in infants and pregnancy
  - Alternative drugs to SP need to be evaluated
  - impact on drug resistance needs to be investigated
  - EPI approach not useful in children > 1 year old
- African leadership
  - EU and other funders e.g. Gates should emphasise leadership roles for African investigators – financial, scientific: capacity in leading big consortia.

### Summary of TB recommendations

**TB vaccine clinical trials**
- Consider different models for site selection or focus (either specialised for preventive or therapeutic trials or with the ability to do both)
- Invest in surveillance (demographic)
- Support development of data management, administration, ethics review
- Fund research on identification of immunological markers and correlates of protection
- Fund research in development of SAE detection systems

**TB drug clinical trials**
- Invest in building lab capacities for development of assays
- Support trials of TB diagnostics
- Support trials for extrapulmonary TB in the presence of HIV
- Focus on MDR-TB
- Develop regulatory capacities for using second-line TB drugs and running clinical trials on MDR-TB.

**New collaborations and networking**
- Play a brokerage role in providing information on existing trial sites and facilitate the development of networks and partnerships.
- Support capacity building for epidemiological surveillance.

**Networking of sites**
- Partner with other agencies for funding
- Identify 2-3 big sites, with different TB epidemiological regions (rural, urban, high HIV, low HIV) to develop into centres of excellence for clinical trials

### Summary of malaria recommendations

**Networking**
- Multicentre approach covers a range of epidemiological settings
- Provides on-job training using limited resources
- Provides technical support: standardised protocols
- Supports policy review/change
- Examples: EANMAT, WANMAT, HANMAT
- Networking with existing networks, e.g. AMANET

**IPT**
- Validated intervention in infants and pregnancy
- Alternative drugs to SP need to be evaluated
- Impact on drug resistance needs to be investigated
- EPI approach not useful in children > 1 year old

**African leadership**
- EU and other funders, e.g. Gates should emphasise leadership roles for African investigators – financial, scientific: capacity in leading big consortia

# Report from Round Table II: Capacity building, training and networking: Practical approaches to strengthening capability and developing research partnerships

## Developing laboratory capacity/ collaboration

Facilitator/Rapporteur **Karin Weyer** (South Africa), **Francine Ntoumi** (Congo)

**Main topics for discussion:**
- **Gaps in laboratory capacity**
- **Invest in existing laboratory structures or develop new ones?**
- **South-South networks**
- **Opportunity for interdisciplinary (HTM) cooperation?**

**Issue**: Gaps in laboratory capacity
**Discussion**:
- Lack of database on laboratory capabilities
- Lack of linkage/involvement with existing services
- Lack of accreditation systems
- Country differences (infrastructure, capacity, etc.)

**Recommendations**:
- EDCTP to fund audit of laboratory capacity
- Proposals to show linkage with national lab services
- Fund uniform systems for accreditation
- Harmonise protocols and procedures

**Issue**: Invest in existing laboratory structures or develop new ones?
**Discussion**:
- Need for regional networks of Reference Laboratories, based on disease burden
- Sustainability a major concern

**Recommendations**:
- Look at existing models (e.g. HIV endpoints networks, IAAE, WHO SRL)
- Fund networks according to needs assessment
- Fund (small) ancillary studies between trials to maintain laboratory proficiency

**Issue**: South-South networks
**Discussion**:
- Methodology training
- Student and technician exchange
- Standardised protocols, procedures, reagents
- Quality control and quality assurance

**Recommendation**:
- EDCTP call for establishing S-S Laboratory Networks

**Issue**: Opportunity for interdisciplinary (HTM) cooperation?
**Discussion**:
- Difficult and not feasible
- Different technical requirements (e.g. biosafety)
- Separation necessary, e.g. between bacteriology and immunology

**Recommendation**:
- Retain focus on specific clinical trial questions

### Summary of laboratory capacity recommendations

- EDCTP to fund audit of laboratory capacity
- Proposals to show linkage with national lab services
- Fund uniform systems for accreditation
- Harmonise protocols and procedures
- Look at existing models (e.g. HIV endpoints networks, IAAE, WHO SRL)
- Fund networks according to needs assessment
- Fund (small) ancillary studies between trials to maintain laboratory proficiency
- EDCTP call for establishing S-S Laboratory Networks
- Retain focus on specific clinical trial questions

## Networking and health services capacity development

Facilitator/Rapporteur **Getachew Aderaye** (Ethiopia), **Thomas Nyirenda** (Malawi)

**Theme: Developing research networks – how to do it and sustain them**

**Main topics for discussion:**
- **Practical approaches to developing research networks for clinical trials in HTM**
- **How to effectively involve disease control programmes in clinical trials**

**Issues:**

- First step should be networking like-minded partners at country level, then at regional level and then at broader level.
- Need to involve preferably countries with functional disease control programmes.
- Need to create awareness on the advantages of networking among scientists and programmes.
- Need for conducting trials including those supported or recognised by disease control programmes so that research responds to their needs.
- Need for financial support to networks.
- Need for building networks around a project or a disease control portfolio.
- Need for getting the networking beyond a project or trial (sustainability).

- Need for strengthening existing institutions to lead in networking with less emphasis on creating new such institutions.
- Need for regional meetings to encourage networking.

### Recommendations:

EDCTP should:
- Support costs that come with networking.
- Support meetings among partners in networks (including DCCC meetings to stimulate formation of such networks).
- Support setting up communication channels between network partners e.g. dedicated website, listserv, etc.
- Assist sustaining networks beyond a trial or a project on which their formation was based.
- Provide a data base of potential collaborative institutions, spelling out capabilities of each.

### Summary of networking recommendations

- Support costs that come with networking
- Support meetings among partners in networks (including DCCC meetings to stimulate formation of such networks)
- Support setting up communication channels between network partners, e.g. dedicated website, listserv etc
- Assist sustaining networks beyond a trial or a project on which their formation was based
- Provide a data base of potential collaborative institutions, spelling out capabilities of each

## Training

Facilitator/Rapporteur **Dicky Akanmori** (Ghana), **Michael Makanga** (Uganda)

### Theme: Developing skills in the context of clinical trials

**Main topics for discussion:**
- **Mentorship**
- **Centres/nodes of excellence for clinical trials**
- **Harmonisation of training initiatives**

### Mentorship

**Issues:**
- Use Senior Fellowships to build teams.
- Consortiums should be formed to address this.
- N-S expertise sharing after pre-proposal stage.
- There should be sufficient time and budget allocation to enable short-listed groups to meet together to develop full proposals.
- Will give ownership to Africans, improve number of African-led investigators and generally improve research culture in Africa.

**Recommendations:**
- Create EDCTP mentorship programme
- Provide budget for full proposal development of teams/consortia
- Establish a network of research scientists including statisticians (and epidemiologists) willing to mentor junior staff in African sites
- EDCTP should modify calls to accommodate contributions by pharmaceutical industry
- Donor Trust required

### Centres/nodes of excellence for clinical trials

**Discussion:**
- Research excellence vs clinical trial capacity
- Criteria needed
- Add publication record, ability to attract grants, training of postgraduates and affiliation with academic institution to existing criteria of infrastructure
- Formal accreditation not essential?
- Need to deal with resistance of northern countries to use of funds to assist weaker unrelated site/centre.
- Responsibilities of nodes to be spelt out in calls
- Clear plan for assisting weaker sites as a proposal review criterion/networks to help assess sites.
- NEPAD to assist with peer review for assessment

**Recommendations:**
- All stakeholders to be involved in developing nodes of excellence
- Assessment should be compulsory for all sites
- Add new criteria of publications, grants and training to existing EDCTP criteria for site assessment.

### Harmonisation of training initiatives

**Issues:**
- Is there a need? Who provides it? Which programmes?
- EDCTP to access and utilise available guidelines (clinical research and regulatory)
- Need for all the PPPs to harmonise their CT implementation guidelines
- Important for quality control/quality assurance
- Laboratory training SOPs reference ranges in different countries a major challenge
- Various levels of training (clinicians, research nurses, laboratory staff, monitors, data managers = research team)
- Who? – AMANET, FOGARTY, NIH
- Mutual recognition – harmonisation
- University certification
- Anglophone/Francophone – language divide

**Recommendations:**
- EDCTP to provide platform for harmonisation of guidelines
- All PPPs to table their CT implementation guidelines
- EDCTP to actively collaborate with other agencies on training

**Summary of training/capacity development recommendations**

- **Mentorship**
  - Create EDCTP mentorship programme
  - Provide budget for full proposal development of teams/ consortia
  - Establish a network of research scientists including statisticians (and epidemiologists) willing to mentor junior staff in African sites
  - EDCTP should modify calls to accommodate contributions by pharmaceutical industry
  - Donor Trust required
- **Centres/nodes of excellence for clinical trials**
  - All stakeholders to be involved in developing nodes of excellence
  - Assessment should be compulsory for all sites
  - Add new criteria of publications, grants and training to existing EDCTP criteria for site assessment
- **Harmonisation of training initiatives**
  - EDCTP to provide platform for harmonisation of guidelines: all PPPs to table their CT implementation guidelines
  - EDCTP to actively collaborate with other agencies on training

# General discussion and concluding recommendations

Following general discussion of all of the recommendations that stemmed from the round table discussions, a condensed list of primary recommendations from the Forum was compiled. EDCTP Partnership Board was charged with the responsibility to consider these points in the next revision of the Joint Programme of the Action, which is the EDCTP's formal mechanism for translating Forum recommendations into action and into funding via calls for proposals.

## Overall recommendations – HIV/TB/ Malaria

### HIV

- Microbicides studies
- Drugs for children and MTCT
- Simplification of ART
- Centres of excellence for monitoring of resistance
- Vaccine trials, with focus on mucosal vaccines

### TB

- New diagnostics in context of definition of trial end-points
- Studies of adjunctive therapy (e.g. steroids) in extrapulmonary and other TB
- Expand activities to more adequately cover the available drug product portfolio

### Malaria

- IPT in pregnancy
- Preparation of sites for vaccine trials
- Synergise with partners on standardisation of end-points and assays
- Alternative to quinine for severe malaria
- Work on uncomplicated malaria
- Diagnostics?

### Cross cutting

- Studies of co-infection and implications for drug treatment (e.g. HIV-malaria, HIV-TB)
- Strengthen regulatory capacity
- Traditional medicine?

## Overall recommendations – Capacity and Training

### Laboratory capacity

- Build laboratory capacity to identify resistance to drugs (HTM)
- Fund work on immunological correlates of protection (HTM)
- Link the development of capacity to clinical trials
- Develop proficiency training
- Build regional reference laboratories and repositories

### Networks

- Support meetings/networks across diseases (through DCCC?)

### Training

- Establish centres of excellence on data management and developing skills
- Develop research culture (focusing on undergraduates)
- Encourage PIs to link their teams to networks
- Link with industry for training in quality assurance and monitoring

### Cross cutting

Advertise more widely EDCTP calls and activities

# Concluding remarks

**Pascoal Mocumbi**, Haut Représentant, EDCTP

Speaking on behalf of EDCTP I would like to thank all of the participants who have taken part in this Second Forum of EDCTP, which has taken place in Africa. The first Forum was held in Europe – so we are now equal! We have had the opportunity to learn from and understand what the various participants are doing, and to assess ourselves - where we are, where we are going, and what needs to happen to continue our march towards the implementation of the Joint Programme findings.

It was said from the beginning that this Forum would be a working Forum, and indeed we have worked hard, often over-running the times for our meetings, but we seemed always willing to continue to talk, which for me means that there is a commitment to implementation.

Now we have to consider - what are we going to do from now until the next Forum? We have a commitment to deliver on what we have discussed. We will have a list of what needs to be done. We are learning that EDCTP has a lot of followers, including the Minister of Health of South Africa, who as guest of honour made a statement at our dinner. This political commitment is essential.

There is a commitment to action and a commitment to delivery. Who is supposed to carry this out? Who is supposed to deliver? We are. I have noticed during the presentations here at this forum what I will call the spirit of Durban, that has been very constructive. I am sure that we have learned to look better at each other – and to look better at EDCTP, and to link better as scientists and as individuals. As we close this Forum, it is crucial that we continue with our contact and partnership.

When the Executive Director opened the Forum she emphasised the need for political alliance and for sustained action. It is important that we commit ourselves to feeding this organisation, and to keep feeding information in. The culture of EDCTP is that of working together. I look forward to what will be the agenda of the next Forum.

Having listened to the quality of the presentations and of the content of the discussions, and thanks to the continued leadership and guidance to ensure that we are going to meet the objectives of the Forum, we are ending this session at least seeing in front of us what is now expected. This did not happen in Rome.

If we take each of us as individuals, as scientists, as institutions, we can't build a partnership if we work apart – we need to consolidate our relations and link to build capacity. In my experience, there is no capacity building if we do not work together constantly and constantly share information about what is going on. We need information from your side, we need information from your teams and we need it from the research support beneficiaries, it is important that they show what they are doing with the funding that they get. Again I stress that it is important that we commit ourselves to feed the organisation.

I encourage you to work to make EDCTP a better partnership. I thank you.

# APPENDIX I
# PARALLEL SESSIONS

On the morning of day 3 of the Forum, extensive parallel sessions were held, which are represented here by means of their submitted Abstracts.

## I: Basic science, clinical trials, networking

**Chairs: Roxana Rustomjee** (South Africa) and **Thomas Egwang** (Uganda)

### Development of vaccines against HIV/AIDS in European networks

**Hans Wolf**, University of Regensburg, Institute for Medical Microbiology and Hygiene, Germany

In response to the growing problems related to HIV infections, industrialised countries responded with strategies to intensify the development of HIV vaccines. INCO projects and the formation of sizeable research clusters allowed strategies starting from molecular epidemiology to evaluation of vaccine candidates in primates and humans. Together with the Chinese Centre for Disease Control, early at onset of the HIV epidemic in China relevant HIV strains could be selected (B clade RL42 and C clade 97CN54; 97CN54 is a B-C recombinant and the most prevalent strain in the Western and North-Western provinces of China).

Using sequence modified genes from 97CN54 a set of immunogens comprising gag pol nef and env was developed, which was found to be highly immunogenic but inactive in their original enzymatic functions. In the context of the EUROVAC cluster and the INCO programme, different presentation systems based among others in DNA-plasmids (COBRA) and vaccinia viruses (NYVAC, MVA, TienTan) have been developed into GMP-manufactured products. These have been evaluated in parallel to the human trials in Rhesus monkeys. The combination of DNA prime vaccinia boost gave a strong immune response in almost all animals in multiple HIV reading frames and on the basis of IFNα, IL-2 and IL-4 Elispots. Parallel experiments using the SHIV 89.6p-model showed protection from disease and rapid clearance of viraemia to set point in challenge experiments.

Data from human trials with NYVAC-C alone look encouraging, with 60% responders. A trial with the combination of DNA-C prime and NYVAC-C boost is ongoing. Data will be presented as well as the needs for a receptive framework for further evaluation of the candidate vaccine and better involvement of DCs.

### Development and potential use of a colorimetric in-house viral load assay for measuring HIV RNA in patients' plasma

**SA Alabi**, S. Kaye, S. McConkey and S. Rowland-Jones, MRC Laboratories, Banjul, The Gambia

**Objectives of the study**: Virus load measurements provide the most direct method of assessing virological response in HIV treatment regimens, and would be useful in monitoring the efficacy of therapeutic HIV vaccines, when available. However, commercially available virus load assays (mostly for HIV-1) are expensive and very often beyond the reach of laboratories in resource-poor settings. We report on a simple in-house virus load assay with colorimetric read-out in use in our laboratory.
**Methods**: Our assay involves three main stages of HIV RNA extraction from patients' plasma using guanidinium thiocyanate; RT-PCR; and detection of target HIV DNA by enzyme-linked oligonucleotide assay (ELONA) using pNPP substrate. The dynamic range of our assay is 400 to 1 000 000 RNA copies/ml, and known positive and negative controls are included in each run to test for assay reproducibility and specificity. The HIV-1 arm of the assay was evaluated with Roche Amplicor HIV-1 RNA kit version 1.5, while the HIV-2 arm was evaluated by limiting dilution analysis.
**Results**: Results obtained using our assay were comparable with those obtained using the Roche Amplicor kit, and our assay was about fives times cheaper. We have received funding from EDCTP for a multicentre evaluation of an improved version of this assay to assess its versatility and possible use in laboratories in developing countries.
**Conclusions**: Our results have shown that we have a virus load assay comparable to but much cheaper than commercial ones, and with potential for wider use, particularly in resource-poor settings.

### The effect of 'strength of evidence' requirements and HIV incidence on the size of Phase III trials for microbicides or HIV vaccines

**Paul Coplan**, International Partnership for Microbicides, USA

**Background**: The US FDA has stated that a single pivotal efficacy trial may suffice for licensure of microbicides under certain conditions if the "strength of evidence" of efficacy is $P<0.005$ (two-sided). The EMEA has not publicised a formal position on this. Alternatively, two trials need to be done with the strength of evidence of efficacy for each trial of $P<0.05$. Sponsors may therefore conduct one large pivotal trial or two smaller efficacy trials. We assess the impact of the strength of evidence requirements and HIV incidence on the size of Phase III trials.

**Methods**: Sample size was calculated for a randomised placebo-controlled trial with 1:1 randomisation and 90% power for a 1-year long study, assuming 15% dropout rate and 50% efficacy using Stata Version 8.
**Results**: Required sample size for the whole trial is shown below:

| | Trial sample size by HIV incidence (% per year) | | | | | |
|---|---|---|---|---|---|---|
| *P* value | 1% | 2% | 3% | 4% | 5% | 6% |
| 2 trials with $P<0.05$ | 30 590 | 15 180 | 10 046 | 7480 | 5939 | 4913 |
| 1 trial with $P<0.005$ | 23 803 | 11 813 | 7815 | 5817 | 4618 | 3818 |

The ratio of sample size for two trials at $P<0.05$ versus one trial at $P<0.005$ is 1.29 for all incidences. As HIV incidence decreased from 1% to 2%, the sample size decreased by 100%, from 2% to 3% by ½, from 3% to 4% by 1/3, from 4% to 5% by ¼, and from 5% to 6% by 1/5.
**Conclusions**: The sample size required for one pivotal efficacy trial is 29% smaller than two Phase III trials. Changes in HIV incidence have a large effect on sample size between 1% to 3% and relatively smaller effects above 4%. At an estimated cost of $6200 per subject in Phase III trials, $13.8 million could be saved by conducting one pivotal efficacy trial instead of two trials if the FDA or EMEA agrees to a strength of evidence requirement of $P<0.005$.
**Key words**: Phase III trials, regulatory requirements, strength of evidence, sample size, HIV incidence

## The newborn immune response to BCG vaccination

Andreia Soares,[1] Joanne Riley,[1] Alana Keyser,[1] Sebastian Gelderbloem,[1] Jane Hughes,[1] Helen Fletcher,[2] Roseann Murray,[3] Greg Hussey,[1] Adrian Hill,[2] Gilla Kaplan,[3] **Willem Hanekom[1]**
1 South African Tuberculosis Vaccine Initiative, Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, South Africa;
2 University of Oxford, UK;
3 Public Health Research Institute, Newark, NJ, USA

**Objective**: BCG is the only current vaccine against tuberculosis (TB), but affords poor protection against lung disease. Developing novel, better vaccines is urgent, but efforts are hampered by our incomplete understanding of protective immunity against TB. Our objective is to understand this immunity better.
**Methods**: (1) To characterise the BCG-induced immune response, blood was collected from 10-week old infants ($N=200$), vaccinated with BCG at birth. We have developed and validated novel whole blood assays which require small blood volumes to allow sensitive, specific and reproducible measurement of specific immunity.
(2) To determine BCG-induced immune correlates of protection against childhood TB, we have collected, processed and stored blood from another 5675 10-week-old infants vaccinated with BCG at birth. We have subsequently identified >500 of these infants who have developed TB disease ("not protected by BCG"), or who have remained healthy despite exposure to adults with TB ("protected").
**Results**: (1) BCG does indeed induce a potent CD4 T cell response, characterised by diverse cytokine production (IL-2, TNF, IFN-gamma, MIP-1beta, IL-4 and IL-10 are all detected) and diverse memory phenotypes (intracellular cytokine assay, multiparameter flow cytometry). BCG-induced CD8 T cells make cytokines at lower frequencies, or these cells have specific cytotoxic potential (CD107 degranulation assay), but not both. Additionally, specific regulatory CD4 T cells, which control these CD4 and CD8 responses, are induced (Foxp3 mRNA detection by real-time PCR).
(2) We will use these results to guide our immune analysis to identify immune correlates of protection. We will retrieve stored blood of "protected" and "unprotected" infants, and compare immunity induced by BCG.
**Conclusions**: We have developed practical whole blood assays, which may be implemented anywhere in Africa, to reliably measure specific immunity. We show that BCG induces a diverse immune response, and that measurement of multiple immune parameters may be necessary to determine vaccination-induced immune correlates of protection against childhood TB.

## A simple method of collection and processing of sputum sample for molecular diagnosis of pulmonary tuberculosis

Fatma A. Khalid,[1] Sahar M. Bakhiet,[1] E.M. El Amin,[1] Patrick Van der Stuyft,[2] Greet Dieltiens,[2] **Maowia M. Mukhtar[1]**
1 Institute of Endemic Diseases, University of Khartoum, Sudan;
2 Prince Leopold Institute of Tropical Medicine, Belgium

In the World Health Organisation (WHO)-sponsored TB Diagnostics Workshop held in 1997, new diagnostic test priorities for TB were set, including a test to replace acid-fast microscopy for the diagnosis of smear-positive TB, and tests to improve the differential diagnosis of smear-negative TB. This study aimed to adopt and evaluate a simple, fast, sensitive and affordable diagnosis based on detection of *Mycobacterium* DNA in the sputum.

Sputum samples were blotted onto filter papers, air-dried and stored at room temperature then transported to the central laboratory in Khartoum. *Mycobacterium* (DNA) was eluted from the filter paper by distilled water. The bacteria were chemically lysed and the extracted DNA was amplified using a PCR kit with species-specific primers. The sensitivity of detection of *Mycobacterium* DNA in the tested samples was higher than with microscopy. The processing of the filter paper and performance of the PCR required less than 4 hours to determine the positivity of the sample. The method is affordable and the cost is comparable with the routine method.

This study was supported by a Senior Fellowship award from EDCTP.

# Moving HTM vaccines from candidates to products: Preclinical and clinical development in a virtual company

**Bernd Eisele**, MD, CSO, Vakzine Projekt Management GmbH, Hanover, Germany

Vakzine Projekt Management GmbH (VPM) has in-licensed two vaccine candidates for poverty-related infectious diseases:
*A vaccine preventing malaria attacks in endemic areas* based on the full-length (190 kD) merozoite surface protein MSP-1D. MSP-1 is essential for merozoites to enter erythrocytes, a step expected to be blocked by MSP-1-specific antibodies. In addition, there is evidence that MSP-1 induces a cell-mediated, cytotoxic immune response that attacks merozoites in liver cells.

*An improved tuberculosis vaccine* (rBCGΔureC:Hly) based on *M. bovis* BCG. The currently used BCG vaccine has a poor efficacy profile. It induces an insufficient CD8 immune response. VPM's rBCGΔureC:Hly offers the potential for substantially improved protection due to two genetic modifications in the genome of the classic BCG vaccine: knock-in of a listeriolysin gene and knock-out of urease activity resulting in a strong CD4 and CD8 immune response.

VPM manages and finances potential vaccine candidate projects from university laboratories until clinical proof of concept. All activities, such as manufacturing of study medication, preclinical and clinical studies, are contracted-out to competent partners applying GxP to all relevant steps. Thereafter the vaccine candidate will be out-licensed to industry partners. The privately run company was established as part of an initiative of Germany's Federal Ministry for Education and Research (BMBF).

**Critical success factors:**
- Creating a vaccine consortium acting like a virtual company.
- Keeping local conditions in mind (e.g. EPI scheme) when designing the clinical development programme.
- Taking the position of a legal 'sponsor' to guarantee GxP adherence.
- Having experienced project managers on board.
- Keeping a lean and flexible organisation.
- Getting advice from registration authorities right from the start.

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# Comparative efficacy and safety of artemether relative to quinine in the treatment of severe falciparum malaria in an area with high level of chloroquine resistance

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**Introduction**: Severe malaria is a medical emergency with devastating multisystemic effects. It requires prompt treatment with sensitive and safe drugs otherwise death is imminent. Quinine is the favoured drug for the treatment of severe malaria. There are reports of decreased sensitivity and resistance to quinine. Artemether is known to be a sensitive antimalarial and its use is gaining popularity in the treatment of severe malaria.
**Objective**: To evaluate the relative safety and efficacy of artemether compared with quinine in the treatment of severe malaria.
**Method**: Thirty-two patients with severe malaria were randomly assigned to receive either artemether or quinine under medical supervision; 16 patients were allocated into each treatment group. Patients in the quinine treatment group were given 10 mg/kg body weight quinine in 5% dexrose/saline intravenously 8 hourly till recovery from coma or able to take oral dose, while the artemether group were given 1.6 mg/kg body weight intramuscularly for 5 days. The patients were then followed up for 14 days for clinical and parasitological response.
**Results**: Mean fever clearance time for quinine was significantly lower when compared with artemether, (46.50 ± 20.49 vs 72.00 ± 27.71 hours) ($P = 0.006$). The malaria parasite clearance time was, however, significantly lower with artemether than with quinine (31.50 ± 14.45 vs 46.50 ± 6.00 hours) ($P = 0.001$). Parasites subsequently confirmed to be recrudescence by PCR reappeared in one patient by day 7 in the artemether group. However, the parasites cleared after another 5 days' extension of artemether treatment. Adverse events such as tinnitus and insomnia encountered in the quinine group were generally mild. No adverse event of note was observed with artemether.
**Conclusion**: Quinine and artemether were both effective and safe in the treatment of severe malaria in children. However, while quinine resolved fever faster, artemether was better tolerated, showed more rapid malaria parasite clearance, faster and sustained recovery from anaemia, as well as shorter jaundice resolution time.

# A clinical trial to compare the efficacy of intrarectal versus intravenous quinine in the treatment of childhood cerebral malaria in Mulago Hospital, Uganda

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**Background**: Cerebral malaria is the most lethal complication of *Plasmodium falciparum* infection. Intravenous quinine remains the most effective treatment for severe malaria. Intrarectal quinine can be used as early treatment and could decrease morbidity and mortality associated with severe malaria.
**Objectives**: To compare the efficacy and safety of intrarectal quinine with intravenous quinine in the treatment of childhood cerebral malaria.
**Design**: Randomised double-blind placebo-controlled clinical trial.
**Setting**: Acute care unit of Mulago Hospital, Uganda's national referral hospital.
**Participants**: 110 children aged 6 months to 5 years with cerebral malaria.
**Intervention**: Patients were randomised to treatment with either intrarectal or intravenous quinine.
**Main outcome measures**: Parasite clearance time, fever clearance time, coma recovery time, time to sit unsupported, time to begin oral intake, duration of intervention and death. Adverse drug events were also documented.
**Results**: Overall there was no statistically significant difference in the clinical and parasitological outcomes between intrarectal and intravenous quinine. The coma recovery time 19.4 (SD 18.1) hours v 17.0 (12.1) hours, $P$= 0.47, fever clearance time 26.7 (SD16.1) hours v 29.9 (SD 18.1) hours, $P$= 0.32, parasite clearance time 43.2 (SD 14.2) hours v 41.9 (SD 15.2) hours, $P$ = 0.67, time to begin oral intake 27.5 (SD 21.0) hours v 24.1 (SD 19.8) hours, $P$ = 0.41, time to sit unsupported 43.9 (SD 27.5) hours v 49.3 (SD 79.6) hours, $P$ = 0.64 and duration of intervention 37.7 (SD 21.5) hours v 39.7 (SD 22.3) hours, $P$ = 0.64. Mortality was similar in both groups 4/56 v 5/54, odds ratio 1.32, 95% confidence interval 0.33 to 5.22. Intrarectal quinine was well tolerated and no major immediate adverse events occurred.
**Conclusions**: Intrarectal quinine is as effective and as safe as intravenous quinine in the treatment of childhood cerebral malaria.
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# Malaria infection diagnosed by PCR as a means of evaluating pre-erythrocytic candidate malaria vaccines

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**Background**: The ability to test candidate pre-erythrocytic malaria vaccines in a field setting using a group of tens rather than hundreds of volunteers would greatly facilitate identification of the most promising vaccine candidates. The polymerase chain reaction (PCR) is considerably more sensitive than conventional microscopy for detecting malaria infection. Therefore, we have assessed whether use of this technique on blood samples collected daily might provide a more sensitive way of detecting malaria infection in the context of a malaria vaccine trial than microscopy, and thus allow smaller group sizes to be employed.
**Methods**: Prior to the malaria transmission season, three groups of adult Gambian volunteers (total 102) were studied. Those in group 1 received the pre-erythrocytic candidate malaria vaccines FP9 ME-TRAP and MVA ME-TRAP, those in groups 2 and 3 received rabies vaccine. All volunteers received the antimalarial drugs primaquine and Lapdap (chlorproguanil/dapsone) plus artesunate to eliminate all malaria parasites before the observation period, which commenced 7 days after final vaccination. In addition, volunteers in group 2 received a single treatment with sulphadoxine pyrimethmine (SP) to prevent new infections. During the 28-day surveillance period daily finger-prick blood samples were obtained to provide 0.5 ml of blood for PCR analysis and for preparation of two blood films. DNA extracted from blood samples was analysed by quantitative real-time PCR for the presence of parasite 18S RNA.
**Results**: Eighty-eight per cent of volunteers (90/102) received 3 doses of vaccines and were followed up. Vaccines were well tolerated and no serious adverse events were observed. During the 28-day follow-up period, 70% of volunteers gave daily blood samples. Kaplan-Meier curves obtained using varying PCR-estimated parasite densities (20, 100 and 1000 ppml) showed a high level of positivity in all groups when the most sensitive cut-off was used, but discriminated between volunteers in the SP group and the others when a more stringent cut-off was employed. There was no evidence for protection against infection in the group which received the malaria vaccines.
**Conclusion**: The very intensive blood sampling required for this method of testing vaccine efficacy was acceptable. This is the first demonstration of the use of malaria parasitaemia as detected by PCR as the primary endpoint in a field trial.
**Funding**: Gates Malaria Partnership, Wellcome Trust.

## Multi-site trial of combination antimalarial therapy: Evaluation of efficacy, safety and tolerability in Uganda

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**Objectives**: To compare the efficacy and safety of artemisinin-based and other combination therapies in four districts in Uganda with varying transmission intensity.
**Methods**: The studies were randomised single blind trials with 28-day follow-up. Study sites, selected for geographic diversity, were: Jinja (medium-high endemicity, entomological inoculation rate (EIR) = 7), Arua (very high endemicity, EIR = 393), Tororo (very high endemicity, EIR = 591), and Apac (very high endemicity, EIR = 1564). We enrolled 2160 patients aged 6 months or greater with uncomplicated falciparum malaria. Patients were randomised to receive chloroquine (CQ) plus sulfadoxine pyrimethamine (SP); amodiaquine (AQ) plus SP; or AQ plus artesunate (AS). Primary endpoints were the 28-day risks of parasitological failure either unadjusted or adjusted by genotyping.
**Results**: Of the patients 2081 completed follow-up, of whom 1749 (84%) were under the age of 5 years. The risk of recrudescence after treatment with CQ+SP was high, ranging from 22-46% at the four sites. This risk was significantly lower ($P<0.01$) after AQ+SP or AQ+AS (7-18% and 4-12%, respectively). Compared to AQ+SP, AQ+AS was associated with a lower risk of recrudescence but a higher risk of new infection. The overall risk of recurrent infections was similar at two sites and significantly higher for AQ+AS at the two highest transmission sites (risk differences = 15% and 16%, $P<0.003$). Median duration to failure was shorter with recrudescences compared to new infections (26 days vs 27 days, $P=0.03$), and over 75% of both recrudescences and new infections occurred after 20 days of follow-up. Gametocytes during follow-up were more common with recrudescences (51% vs 43%, $P=0.02$). Serious adverse events were uncommon with all regimens.
**Conclusion**: AQ + AS was the most efficacious regimen for preventing recrudescence, while AQ+SP was the best regimen for preventing retreatment. Both regimens were markedly superior to CQ + SP. The high endemicity of malaria in Africa may impact on the efficacy of artemisinin-based combination therapy.

# II Operational research, capacity building and training

**Chairs**: **Wen Kilam**a (Tanzania) and **Alioune Dieye** (Belgium/Senegal)

## Mapping African HIV/AIDS randomised controlled trials – the route to prospective trial registration

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**Objectives**: To identify and describe randomised controlled trials on HIV and AIDS conducted in Africa and to map their spatial distribution using exact geographical coordinates.
**Design**: Construction and analysis of a data base of trials conducted wholly or partly in Africa and reported before 2004.
**Data sources**: CENTRAL, Medline, Embase and LILACS.
**Results**: Our comprehensive search yielded 284 distinct records that were potentially eligible for inclusion in the data base. Of these, 150 articles reported on 77 eligible trials published or reported from 1987 to 2003. Seven trials were identified exclusively from the CENTRAL data base. Trials were conducted in 18 of 48 countries in sub-Saharan Africa. None were conducted in north Africa. Only 19 had a principal investigator located in an African country. Forty two trials assessed prevention and 35 assessed treatment. Most studies were funded by government agencies outside Africa ($N = 43$), with the pharmaceutical industry providing partial support to 16 of these. The pharmaceutical industry provided full or partial support to a further 18 trials. Only 43 trials reported conducting a power calculation for determining sample size. There was no mention of ethical approval or informed consent in 19 and 17 trials respectively.
**Conclusion**: The relatively small number of HIV/AIDS trials conducted in Africa is not commensurate with the burden of disease. Geographical mapping as an adjunct to prospective trial registration is a useful tool for researchers and decision makers to track exiting and future trials.
**Read full paper in *BMJ* 2005; 331: 742-746.**

## The PROMISE PEP study: Peri-exposure prophylaxis to prevent postnatal HIV transmission and promote HIV-free survival – a realistic alternative for low resource settings?

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According to the WHO consultation in April 2005, there are two possible ways of improving HIV-free survival post-natally that need to be studied in low-resource settings where replacement feeding is difficult: maternal highly active antiretroviral therapy (HAART) and peri-exposure prophylaxis (PEP) to the infant during breastfeeding. The PROMISE PEP study investigates the second option: it is a randomised controlled four-centre trial that will measure the efficacy of prolonged PEP with a single antiretroviral (ARV) regimen to prevent postnatal transmission of HIV-1 and death in children born to HIV-1-infected mothers that have already benefited from a WHO-recommended enhanced perinatal ARV regimen or, if mother needs it, highly active antiretroviral therapy (HAART).

Mother-infant pairs will be enrolled from communities participating in an already funded community randomised trial on exclusive breastfeeding (EBF) promotion in order to simultaneously measure the effect of PEP. It will thereby be possible to measure any substantial interaction between EBF promotion and PEP, which would be programmatically very important to identify. The four sites are localised in Burkina Faso, Uganda, Zambia and South Africa, thus cutting through Africa and aiming at high generalisability.

**Primary objectives**: To measure the efficacy of PEP with single ARV regimen regularly from birth until one month after cessation of BF (maximum 8 months of age) on the risk of postnatal HIV-1 transmission and on HIV-1-free survival until 2 years of age.

**Secondary objectives**: To measure any interaction between EBF promotion and PEP in reducing postnatal HIV-1 transmission; to measure to what extent PEP influences the incidence of hospitalisation for severe childhood illnesses in children born to HIV-1-infected mothers; to measure to what extent PEP influences infant growth in children born to HIV-1-infected mothers; at the four study sites, to build clinical trials capacity, specifically in trials-based measurement of programmatically relevant interventions for prevention of mother-to-child transmission of HIV-1 (PMTCT).

The study is currently seeking additional funding.

## Population-based HIV surveillance in a large open-cohort at the Africa Centre Demographic Information System (ACDIS) in rural KwaZulu-Natal, South Africa

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**Objectives**: We present results of a large population-based HIV survey in northern KwaZulu-Natal. Prevalence trends by age and sex from the currently ongoing second survey round (2005) are compared with data from the first survey round. Additionally, we highlight first trends concerning attitudes towards participation in this longitudinal HIV survey. Attention is given to this setting as an open cohort under surveillance and future possibilities to conduct intervention and clinical trials in the ACDIS area.

**Methods**: The HIV survey started in June 2003, including women aged 15-49 and men aged 15-54 years ($N$ = 33 520). Eligible were all residents and a randomly selected sample of 'non-residents' (migrants). 'Dried blood spots' were taken by fieldworkers during home visits and analysed using ELISA. Those participants who want to know their results can access them confidentially in community-based counselling centres. Completing the first round in December 2004, the second survey round has been ongoing since January 2005 (total eligible $N$ = 31 477), with 23 495 (74.6%) actually under repeated observation.

**Results**: During the first round the overall contact rate for eligible residents was 66.9%. Of the residents 12 251 were tested for HIV (overall consent rate 59.5%; however, men older than 39 years were significantly less likely to consent than women). HIV prevalence was 27.2% for women and 13.7% for men, the female age group 25-29 years showing a very high prevalence of HIV of 52.2%. We will compare these data with first trends from the currently ongoing second round, and analyse attitudes towards participation in the survey.

**Conclusions**: This population-based longitudinal HIV survey will provide new findings regarding the dynamics of the HIV epidemic in a high-prevalence area in rural South Africa. This survey will allow new opportunities to establish intervention and clinical trials in a closely monitored and circumscribed population seriously affected by HIV/AIDS.

# Experience with ART adherence counselling at Muhimbili National Hospital, Dar es Salaam, Tanzania

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**Background**: In July 2004 the Tanzanian Ministry of Health initiated a pilot care and treatment programme at Muhimbili National Hospital (MNH). The pilot programme was designed to inform the national scale-up of antiretroviral therapy (ART). The goal was to initiate 1300 patients on ART over a period of 3 months. We report our initial experience in offering adherence counselling to these clients
**Methods**: Clients were seen at the MNH HIV/AIDS clinic from July to October 2004. All eligible patients were offered ART adherence counselling prior to therapy initiation, and thereafter at every refill appointment. ART was initiated only after both counsellor and client were satisfied with the readiness of the client to start therapy. Assessment of degree of adherence was by self-report as well as pharmacy refill performed quantitatively, while patients' attitudes to the exercise and problems associated with offering adherence counselling were ascertained using qualitative methods.
**Results**: By 30 September 2004 1286 patients were enrolled in care and 881 patients were put on ART having undergone adherence counselling. More than 65% of the enrollment occurred in the first 8 weeks of the pilot programme, indicating strong demand for HIV care and treatment services among people living with HIV/AIDS in Dar es Salaam. By the end of October 2004 a total of 1655 patients were in care and 1172 (70.82%) on ART. Patients on ART included 59% women, 31% men, and 10% children. The loss to follow-up rate was 11%. Overall, clients reported good satisfaction with the quality of care offered at the clinic, and 85% demonstrated good understanding on issues pertaining adherence to ART. At follow-up, it was noted that clients achieved 95% adherence with ART. However, long client waiting times emerged as a significant problem when the clinic caseload exceeded 100 visits per day.
**Conclusions**: The achievements and experiences of the MNH ART clinic showed that good adherence is possible in a resource-poor setting with extreme staff shortages, and should be initiated early, before initiation of ARV therapy. However, as such progammes scale-up, they should be prepared to face up to huge practical challenges.

# Patterns and seasonality of malaria transmission in a rural endemic zone in middle Ghana (Kintampo district)

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**Introduction**: Malaria is by far the most threatening public health disease in sub-Saharan Africa. Approximately 80% of malaria cases and 90-95% of malaria-related deaths in the world are estimated to be in Africa. As widely reported, some areas in sub-Saharan Africa receive over 300 to 800 infective bites per person per year (ib/p/y). The pattern and seasonality of malaria transmission are very important indicators for control measures and drug or vaccine evaluation. The middle belt of Ghana showing a very distinct ecological setting (forest savannah) presents an interesting malaria transmission picture.
**Methods**: Sixteen communities were chosen as study sites depicting the micro-ecological setting of the middle zone of Ghana. The CDC Light Trap Catch (LTC) was used to collect mosquitoes in rooms of randomly generated compounds from the Kintampo Demographic Surveillance System (KDSS) data base. Traps were set weekly and occupants of rooms receiving traps were given an untreated bednet to sleep under for that night. Anopheline vectors were morphologically identified into species using keys of Gilles and De Meillion (1968). Heads and thoraces of the two major vectors of malaria, *Anopheles gambiae* and *An. funestus*, were checked for the presence of circumsporozoite (CS) antigens of Plasmodium *falciparum* using the sandwiched ELISA method. Roughly 200 corresponding legs of *An. gambiae* species were checked by PCR to identify the sibling species within the complex.
**Results**: A total of 664 LTCs captured 19 835 mosquitoes. Anopheline vectors comprised 35.2% *funestus*, 10.6% *gambiae*, 1.8% *rufipes* and 0.1% *pharoensis*. Non-Anophelines captured comprised 51.3 % Culex and 1.0% Aedes species which were subsequently discarded. *An. Funestus* (Af) and *An. Gambiae* (Ag) had 1.5% and 4.7% proportions respectively infective. A total of 8418 samples were assayed by CS-ELISA. An entomological inoculation rate (EIR) of 269 ib/p/y was calculated in this area for the 1-year period of the study (Nov. 2003 to Nov. 2004). EIR peaked during the wet months (April-November) with an average of 214 ib/p/y. During the dry months (December-March) an average EIR of 54 ib/p/y was sustained. Inoculation rates by species by season revealed the following: Ag 81 ib/p/y and Af 65 ib/p/y during the minor wet season (July-November) and Ag 45 ib/p/y and Af 9 ib/p/y during the major wet season (March-June). The dry periods (Dec-Mar) sustained an EIR of 13 ib/p/y and 41 ib/p/y for Af and Ag respectively. An overall EIR by species clearly shows *An. gambiae* at 166 ib/p/y to have a higher inoculation rate than *An. funestus* at 102 ib/p/y. A proportion of legs taken through PCR indicated *An. gambiae* to be the dominant species within the complex.

**Interpretation**: An all year round transmission was clearly observed from these results. The two major malaria vectors are seen contributing to malaria transmission in phase and out of phase at different times of the year. However, *An. gambiae* remains the main vector, contributing immensely to transmission despite its low numbers.

## Malaria microscopy and clinical trials

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Microscopy, the accepted 'gold standard' for malaria diagnosis and monitoring of antimalarial drug and vaccine efficacy, is a subjective technique. This makes the method dependent on the microscopist's proficiency. There are no accepted international standards on the performance of microscopy from sample collection to result interpretation. More often in publications the details of how microscopy was performed are lacking, despite the fact that it is the most critical step in the study. In most study sites there is no comprehensive evaluation and training of microscopists.

Microscopy, unlike other tests, has not been subjected to rigors of quality control and quality assurance. We know that false-positive slides can ruin promising products in developmental stages. To avert the problems of microscopy in clinical trials, we have developed a series of training and proficiency testing of microscopists, and quality control and quality assurance of microscopy processes. This is a preamble to the development of microscopy centres of excellence.

## Epidemiological study on the prevalence and incidence of pulmonary tuberculosis in Kumasi (Ghana) in preparation of TB vaccine studies

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Promising tuberculosis (TB) vaccine candidates have been developed and a variety of antigen preparations will soon be available. In preparing and strengthening appropriate sites to conduct Phase II/III trials it is proposed to (i) conduct a study on epidemiological parameters of TB in addition to those assessed in a current study on host-related genetic factors relevant to TB in Ghana, West Africa, a country with a high TB incidence; (ii) strengthen local capacities for conducting clinical trials, in particular of Phase II/III studies, in Kumasi, Ghana.

The study will take advantage of results and the infrastructure of studies on the genetic susceptibility to TB that are currently performed in Kumasi, Ghana. Four thousand participants in the Ashanti Region, Ghana, shall be included to:

- collect additional information on the prevalence/incidence of TB and LTBI in adults in the Ashanti Region of Ghana;
- obtain information on relevant demographic variables of the study site;
- supplement information on HIV infections concomitant to TB and on the presentation of TB;
- strengthen established data processing systems;
- implement ICH-GCP guidelines and provide appropriate training under the surmises of stringent ethical considerations; and
- provide the long-term feasibility of conducting proof of concept/Phase III studies.

The participating African institution, Kumasi Centre of Collaborative Research in Tropical Medicine (KCCR), provides excellent facilities, in particular the infrastructure, four-wheel drive vehicles, and well-trained African personnel; 400 $m^2$ of laboratory space, including immunology, mycobacterial, virology and molecular biology units are run by Ghanaian and European scientists. Curative services are provided by the Komfo Anokye Teaching Hospital and surrounding urban hospitals. New buildings include a conference room, cafeteria, and a guesthouse. KCCR enables scientists from Ghana and abroad to conduct timely biomedical bench research and to use an outstanding infrastructure in Africa.

KCCR considers training a key investment for development. KCCR contributes to postgraduate programmes of University of Science and Technology, Kumasi, by supporting students in their postgraduate training and upgrading laboratory technicians.

## Problems and solutions in implementing a study of the immunogenicity of BCG in HIV-infected infants

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**Objective**: To describe challenges encountered in implementing study procedures of a project comparing the immunogenicity of BCG in HIV-exposed and non-exposed infants, and how these were addressed successfully.

**Methods**: As part of a risk-benefit assessment of the practice of BCG vaccination of HIV-infected infants, we are comparing BCG-induced immunity between infants perinatally infected with HIV, and infants born to HIV-negative mothers, over the first year of life.

**Results**: We described a newly developed practical system for enrolling mothers recently diagnosed as HIV-infected, to

guarantee confidentiality. We explained procedures optimised to address prevalent community stigmatisation of HIV-positive persons, since study nurses have been recognised as working with these patients during home visits.

We delineated study procedure adjustments during the study period demanded by:

(a) the introduction of a new regimen to prevent perinatal HIV transmission;
(b) the morbidity and mortality profile of our study population; and
(c) the introduction of antiretroviral therapy during the study period.

Finally, we addressed critical issues surrounding separation of research procedures and clinical care. For example, clinician resistance in providing antiretrovirals when required had to be addressed through meetings with these providers and by introducing a clinical CD4 T-cell count at the time of HIV infection diagnosis in the study infants.

**Conclusions**: The challenges of completing a clinical immunological study in a population affected by HIV infection demands an adaptable, imaginative and sympathetic approach. We have overcome hurdles to put our study on track to complete enrollment of all 411 required participants by the end of 2005, and to complete all study procedures by the end of 2006.

## Tubercolosis case finding through a village outreach programme in rural Southern Ethiopia: A community randomised trial

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**Background**: A successful TB control programme should be able to address two key questions: what proportion of cases has been identified, and how soon?; and what proportion of patients has successfully completed treatment? Case detection is one of the key elements of DOTS, and could be influenced by individual, social and biomedical factors. A remarkable delay in case detection has been noted in many resource-poor settings. Early detection of infectious cases is key to reducing transmission of the bacilli. Improved diagnostic settings and procedures may yield better results if complemented by mechanisms to improve access to these services.

Ethiopia ranks seventh among 22 TB high-burden countries. Half of the population have to travel >2 hours to get care in a public health facility, and private clinics are nearly non-existent in rural areas. Patients usually present late for diagnosis and treatment. A new community-centred health service initiative has been launched.

**Objective**: To ascertain whether case-finding through a community outreach programme has an effect on case notification rate, pretreatment symptom duration and treatment outcome of smear-positive pulmonary TB in rural Ethiopia.

**Methods**: The study was conducted in two rural districts in southern Ethiopia, with 32 rural communities randomly allocated to intervention or control groups. Health workers from 7 health centres held monthly diagnostic outreach at 12 intervention communities and obtained sputum samples from symptomatic TB suspects for sputum microscopy. Trained community promoters mobilised house-to-house and at popular gatherings, and symptomatic individuals were encouraged to visit the outreach team or a nearby health facility. Smear-positive TB patients from the intervention and control communities diagnosed during the study period were prospectively enrolled. Primary outcome measures were case notification rate, pretreatment symptom duration and treatment outcome.

**Results**: The 2003 mid-year population of the 32 study communities was 352 891. Case-notification rates among all age groups were intervention group 124.6/105 person-years; control group 98.1/105 person-years ($P$=0.12). Corresponding rates among adults aged >14 years were intervention group 207/105 person-years; control group 158/105 person-years ($P$=0.09). The proportion of patients with >3 month symptom duration: intervention communities 41%; control communities 63% ($P$<0.001). Pre-treatment symptom duration in the intervention group showed a 55-60% reduction over time compared with a 3-20% reduction in the control group. Treatment success: intervention 81%, control 75% ($P$=0.12). Default: intervention 16%; control 22% ($P$= 0.11).

**Conclusion**: The intervention was effective in improving the speed but not the extent of case-detection for smear-positive TB in this setting. TB patients from the intervention communities had comparable treatment outcome (slightly higher treatment success and slightly lower defaulter rate) to controls. Through an outreach once a month and continuous mobilisation by community promoters it was possible to reduce delay in TB diagnosis by at least a half. Symptom duration in the control group showed little variation over the year. Despite a notable difference that may be potentially important, increase in case notification was not statistically significant. Larger studies in multiple settings may be helpful in determining whether such interventions have a significant effect on case notification.

## The Trial Protocol Tool: A software tool designed to assist health-care researchers with the production of a trial protocol

Kirsty McCormack, Shaun Treweek, Edgardo Abalos, Marion Campbell, Craig Ramsay, **Carl Lombard**, Merrick Zwarenstein on behalf of the PRACTiHC Collaboration

The first step in running a high-quality pragmatic randomised controlled trial (RCT) is to produce a high-quality protocol. Despite the existence of many research tools and resources available to help with this, they are spread across hundreds of books, journals and websites, and there is little available to assist with the actual writing of a protocol.

The Trial Protocol Tool (TPT) is a software tool designed to assist health care researchers with the production of a trial protocol. It was developed by the PRACTiHC (Pragmatic Randomised Trials in Health Care) collaboration, funded by the European Commission's 5th Framework Programme, to support research for developing countries.

The TPT has been developed as a Microsoft Windows HTML help system, is available in English and Spanish, and packages relevant research tools and resources in a single, easily accessible and practical tool. The tool's knowledge base was developed by extensive review of the scientific and regulatory literature and through consultation with leading trialists from 11 countries. The TPT includes:

- **What should be in a good protocol?** – a template to assist in the production of a protocol and designed to reflect the requirements of research governance and good clinical practice. Each section includes an introduction; a checklist of things to consider when writing a protocol; illustrative examples; additional resources (e.g. checklists, software, example documents, guidelines and links to websites and relevant training material); and further reading.
- **Useful documents** – guidelines, handbooks, and key papers.
- **Protocol library** – a library of funded trial protocols.
- **Teaching resources** – a collection of teaching materials that support both course organisers and participants.
- **Web resources** – links to organisations, gateways, databases, and free access journals.
- **Glossary** – based on the glossary in the Cochrane Collaboration Handbook.

The TPT was evaluated by PRACTiHC through using it as the core teaching tool and material in four RCT training workshops run in Southern Africa. The TPT enabled the trainees to develop their research question into a draft protocol during the workshop (3 days). The feedback from these workshops was used to improve the composition of the TPT.

**The TPT is downloadable for free from www.practihc.org, and should help health care researchers to design robust trials and to write high-quality protocols.**

## The fight against TB/HIV/AIDS and malaria in Africa: The role of data management

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Field trials of interventions against TB/HIV/AIDS and malaria are complex and expensive, especially in developing countries, and particularly Africa. Fostering closer collaboration and networking between European and sub-Saharan Africa partners involved in health research and capacity building is very important in these disease areas. However, careful planning is needed while conducting such trials in order to avoid a premature or unsuccessful end. The objective is to highlight aspects of data management that are vital to the successful completion of health-related trials or clinical trials, especially dealing with unforeseen problems that are usually overlooked.

To meet acceptable standards and enhance the reproducibility of studies, careful monitoring of the quality of data collected and entered and the process of keeping study populations under surveillance is of great importance. Data management plays the central role as the link between all disciplines in any trial, including fieldwork, laboratory, the clinic, collaborators, sponsors and statistics. In the fight against these dreadful diseases, do not start any study without first consulting a data manager.

**Key words**: Data management; TB/HIV/AIDS, Malaria, Health-related trials, Developing countries; Africa; Planning
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## Research and technology development in the African context: Bridging the impasse between the African and Western worldviews

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**Preamble**: As we evaluate the progress made towards achieving the Millennium Development Goals, the tailspin plunge in Africa's development benchmarks after 40 years of independence comes into sharp contrast with remarkable achievements in Asia and much of the rest of the world. This begs the questions: What are we doing wrong? What role if any does research and development play?

Technology transfer is widely acknowledged as the key to progress, with many success stories abounding of developing countries making the great leap into industrialised and developed economies. In Africa the story is different. Africa has refused to pay the price for development. Is she (Africa) justified in doing so? The goal of technology transfer, a product of research and development, is to meet a specified need. However, one's needs are intricately linked to one's perceptions. Africa's perceptions, thoughts, ethos and value systems have been traditionally denied by the mainstream, and attempts made to systematically supplant Africa's indigenous worldview with the West's enlightened worldview. The West is deemed enlightened through science and research, whereas Africa is deemed not to have any inherent value due to a lack of indigenous scientific culture. Consequently, Africa is relegated in the mainstream to the role of eternal recipient of the West's nobleness, which endows her with knowledge, wisdom and integrity. For her part, Africa responds to this high-handedness by the shunning of the Western worldview and reassertion of her indigenous knowledge and values.

The two remain locked in an unsolvable impasse: the one denying the value and contribution of the other, and the other responding to the affront in similar fashion. As scientists from the North or the South, our baby (development) has been thrown out with the bathwater (research and development

as a type of the Western worldview). This is a philosophical treatise that seeks to shed new light on the role of research and development in Africa. It calls for a paradigm shift on the part of researchers and policy makers across the North-South divide.

The views and opinions expressed in this presentation do not necessarily reflect those of the Kenya Medical Research Institute.

# APPENDIX II. INTRODUCTORY PRESENTATIONS – ROUND TABLES

**Please note: Unless an abstract appears, all of the listed presentations appear on www.edctp.org**

## Round Table I Parallel groups HIV/AIDS, TB and Malaria

- **Conducting clinical trials in Africa towards evidence-based interventions for HTM control**
- **Drug and vaccine clinical trials: lessons on partnerships and research collaborations based on field experience**

### HIV/AIDS

Facilitator/Rapporteur: **Britta Wahren** (Sweden), **Simon Agwale** (Nigeria)

### Microbicides

Gita Ramjee (South Africa)

### CHAPAS

Kifube Chintu (Zambia)

### Mother-to-Child-Transmission

Jerry Coovadia (South Africa)

### The Kesho-Bora study: Challenges for implementation

Stanley Luchters, International Centre for Reproductive Health, Mombasa, Kenya, for the Kesho-Bora study team

# Tuberculosis

Facilitator/Rapporteur: **Alwyn Mwinga** (Zambia), **Voahangy Rasolofo** (Madagascar)

## Toward testing novel tuberculosis vaccines in Africa: the South African Tuberculosis Vaccine Initiative

**Tony Hawkridge,**[1] Willem Hanekom,[1] Hassan Mahomed,[1] Deon Minnies,[1] Lawrence Geiter,[2] Gregory Hussey[1]

1 South African Tuberculosis Vaccine Initiative, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, South Africa;

2 Aeras Global Tuberculosis Vaccine Foundation, Maryland, USA

**Objective**: To develop the infrastructure for testing novel tuberculosis (TB) vaccines in Phase I, II and III clinical trials.

**Methods**: Over the last 5 years we have established a rural field site outside Cape Town for clinical trials. The 4000 square km area has a population of 350 000 and a very high incidence of TB (>2,000/100 000/year in <5 year olds). A dedicated laboratory was established in Cape Town, as well as dedicated administrative, ethical, regulatory, and data management support structures.

At the clinical site we have focused on setting up clinical and epidemiological structures for reliably identifying and diagnosing TB. We are also conducting various epidemiological, clinical and immunological studies in preparation for testing novel TB vaccines. For example, an ongoing Phase IV study aims to determine whether route of BCG vaccination (intradermal vs percutaneous) is associated with differential protection against clinical TB; 11 766 infants have been enrolled in this randomised controlled trial. Two newly started cohort studies will focus on the epidemiology of tuberculosis infection and disease, on diagnostic modalities, and on methods of follow-up; the first involves 4800 neonates and the second 8000 adolescents, both target populations of future vaccines.

**Results**: We described critical experiences in vaccine preparedness, such as obtaining accurate epidemiological data, including data on morbidity and mortality, ensuring cohort retention, and choosing TB case definitions, identifying TB cases, and verifying these. We described how we have monitored research quality, addressed ethical and regulatory issues, and have ensured community participation. Recruitment, training and supporting an effective personnel complement were also described.

**Conclusions**: Our vaccine evaluation site, with its supportive infrastructure, is now ready for novel TB vaccine trials; the first Phase I trial will commence in August 2005.

## Oflotub TB drug trials consortium

Christian Lienhardt (France)

Please see text from presentation under Plenary session II.

## TB/HIV co-treatment drug studies

Neil Martinson (USA)

## Multicentre evaluation of MDR tuberculosis treatment regimens

Karin Weyer (South Africa)

# Malaria

Facilitator/Rapporteur: **Ricardo Thompson** (Mozambique), **Thomas Egwang** (Uganda)

## Lessons learnt from vaccine trials

Mahamadou Thera (Mali)

## Drug trials and drug resistance network

Theonest Mutabingwa (Tanzania)

## Setting up malaria vaccine testing facilities

Aissatou Toure Balde

## Testing new strategies for malaria control: seasonal IPT

Badara Cisse (Senegal)

# Round Table II

**Capacity building, training and networking: Practical approaches to strengthening capability and developing research partnerships**

- Investing in sustainable human resource capacity building and career development for clinical research in Africa
- Institutional capability for clinical research and laboratory support in Africa – invest in existing structures or develop new ones? Is this an opportunity for interdisciplinary (HTM) cooperation?
- Practical approaches to developing research networks for clinical trials in HTM – which are the successful examples we can follow?
- How to effectively involve disease control programmes in clinical trials

# Laboratory capacity development for drug and vaccine studies

Facilitator/Rapporteur: **Karin Weyer** (South Africa) and **Francine Ntoumi** (Congo)

## Requirements for support laboratories for malaria trials

Thomas Egwang (Uganda)

## Requirements for support laboratories for TB trials

Jenny Allen (South Africa)

## Requirements for support laboratories for HIV trials

Alwyn Mwinga (Zambia)

# Networking and Health Service Capacity Development

Facilitator/Rapporteur: **Getachew Aderaye** (Ethiopia) and **Thomas Nyirenda** (Malawi)

**Theme: Developing research networks – how to do it and to sustain them**

## Clinical trials on malaria and capacity building at Kumasi Centre forCollaborative Research in Tropical Medicine

**J. May**, O. Adjei, J. Evans, R. D. Horstmann, T. Kruppa
Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR), Ghana, and Bernhard-Nocht-Institute for Tropical Medicine (BNI), Germany

The philosophy behind Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR) is to facilitate collaborative research projects between Ghanaian and Northern and Southern partners. The KCCR was created jointly by the Ministry of Health of the Republic of Ghana, the Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, and the Bernhard-Nocht Institute for Tropical Medicine Hamburg, Germany.

Major ongoing malaria studies are currently performed on human genetics of mild and severe malaria and Intermittent Preventive Treatment of malaria in infants (Agona). Further substantial work continues on other topics at the districts and villages Agogo (Buruli ulcer), Dunkwa (Onchocerciasis, Buruli ulcer) and Essiama (Elephantiasis).

KCCR is situated on the university campus in Kumasi, the capital of Ashanti Region. It lies within the rain forest zone and has a population of more than one million. Institutes facilities were opened in October 2003. In addition to the laboratory and administration block, the new buildings include a lecture and conference room, cafeteria, guesthouse, vehicle workshop, and animal house. These facilities will enable scientists from Ghana and abroad to conduct timely biomedical bench research, working alongside each other in fully equipped laboratories, and to make use of an outstanding infrastructure for epidemiological field studies. In addition KCCR has established three research field stations field in Dunkwa, Agogo and Essiama with purpose-built laboratory facilities. The Centre has 31 permanent employees and 70 field workers including nurses, medical officers and scientists has staff strength of 30 and comprises up to 130 temporarily employed hospital and field personnel to support the projects.

KCCR is currently contributing to the postgraduate programme of KNUST by supporting 12 students in their postgraduate training. Two students defended their M.Phil. theses in the Department of Microbiology at the School of Medical Sciences, Faculty of Science, in 2003. Two of three Ph.D. students are currently working at BNI, and 8 Master's students are integrated in KCCR research programmes. Furthermore, 6 European doctoral students participated in field and laboratory work at KCCR. It also supports the continuous education of clinicians, laboratory technicians and counsellors.

## Amplifying the African agenda for microbicides advocacy

Sean Mellors on behalf of Manju Chatani (Ghana)

## Developing multicentre clinical trial partnerships at country level

Amina Jindani (UK)

# Training

Facilitator/Rapporteur: **Dicky Akanmori** (Ghana) and **Michael Makanga** (Uganda)
Theme: Developing skills in the context of clinical trials

## INDEPTH: Higher-degree training courses in Africa

Kobus Herbst (South Africa)

## Expertise in designing clinical trials– where is it coming from?

Andrew Nunn (UK)

## Infectious disease clinical trials monitoring programme activities in Africa: A collaborative model

Jemimah Oduma (USA)

## Capacity building in Africa in clinical trial conduct and ethics review

Dicky Akanmori (Ghana)

# APPENDIX III

# List of Participants, Second EDCTP Forum

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