EDCTP

European & Developing Countries Clinical Trials Partnership

STAKEHOLDER MEETING

REPORT ON MALARIA

VIENNA, AUSTRIA

19-20 SEPTEMBER 2013

Towards the second EDCTP programme

The EDCTP Stakeholder Meeting on Malaria is part of a series of thematic stakeholder meetings planned to contribute to the shaping of the strategy and funding approach of the second EDCTP programme. EDCTP held other stakeholder meetings on HIV/AIDS, tuberculosis and other mycobacterial infections, neglected infectious diseases, as well as on research ethics review and regulatory affairs. In 2014, a stakeholder meeting will be held on capacity building.

The stakeholder meetings are supported by the European Union through a Seventh Framework Programme (FP7) grant to the Coordination and Support Action project EDCTP-Plus (FP7-304786) as part of the preparations for the second phase of the EDCTP programme. This report reflects the views of the authors. The European Union is not liable for any use that may be made of the information contained herein.

EDCTP was created in 2003 as a European response to the global health crisis causedby the three main poverty-related diseases (PRDs) of HIV/AIDS, tuberculosis and malaria. Currently EDCTP is a partnership between 16 European countries, the European Union and sub-Saharan African countries. The aim of the programme is to accelerate the development of new or improved drugs, vaccines, microbicides and diagnostics for HIV/AIDS, tuberculosis and malaria through a balanced partnership of European national research programmes on PRDs with their African counterparts in collaboration with the pharmaceutical industry and like-minded organisations.

The second EDCTP programme is expected to start in 2014 as part of the European research framework programme Horizon 2020. Its scope is based on the current objectives and achievements and will be expanded to include: all clinical trial phases I-IV including health services optimisation research; other neglected infectious diseases; closer collaboration with industry, like-minded product development partners and development agencies; and collaborative research with other developing countries outside sub-Saharan Africa.

Contents

Acronyms and abbreviations

CHMI	Controlled Human Malaria infections
EDCTP	European & Developing Countries Clinical Trials Partnership
EDCTP2	Second EDCTP programme, expected to start in 2014
Horizon 2020	Framework Programme of the European Union for the funding of research and innovation in Europe running from 2014 to 2020
IPT(p)	Intermittent preventive therapies (in pregnancy)
NoE(s)	Network(s) of Excellence
PDP	Product development partnership
SMC	Seasonal Malaria Chemoprevention

1. Executive summary

The meeting was part of the preparations for the second programme of the European & Developing Countries Clinical Trials Partnership (EDCTP2). The two-day event was attended by 63 invited participants, including researchers from academia, representatives of product development partnerships and pharmaceutical industry, policy makers, funding agencies and other like-minded organisations.

Discussions were structured around the following main presentations, each followed by lively discussions.

- Prof. Abdoulaye Djimdé: keynote address
- Dr Michael Makanga: plans and progress towards EDCTP2
- Dr Tim Wells: the global antimalarial drugs portfolio
- Four short presentations on treatment of severe malaria; malaria co-infections; antimalarials for use in pregnancy; and diagnostics
- Prof. Robert Sauerwein: the global malaria vaccine portfolio
- Prof. Umberto D'Alessandro: malaria control in context of elimination strategies
- Panel discussion on partnerships with eight discussants.

The opinions and recommendations shared are summarised below within five main themes: Antimalarials I: Global Drugs Portfolio, Antimalarials II and Diagnostics, Global Vaccine Portfolio, Malaria control, Partnerships.

Antimalarials I: Global Drugs Portfolio

Recommended actions

- Support clinical trials for assessment of novel antimalarials where there are product development gaps in the global portfolio for treatment of uncomplicated (symptomatic and asymptomatic) and severe *Plasmodium falciparum* malaria, as well as prevention of *P. vivax* relapses
- Explore proactively products in the translation stage to identify promising products that address key therapeutic gaps in order to facilitate that they reach the clinical development pipeline
- Support exploration of new and existing antimalarial drugs in pregnancy; determine safety in all trimesters of pregnancy, particularly the first trimester
- Support optimisation of new antimalarials for key target populations, including paediatric populations, pregnancy, co-infections (like HIV, TB) and co-morbidities (like malnutrition)
- Support development of paediatric formulations for new antimalarial drugs
- Explore new delivery approaches for administration of novel antimalarials.

Antimalarials II and Diagnostics

Recommended actions

- Reconsider the age of the population included in clinical trials, as epidemiology suggests that the malaria burden is now shifting to include older children and adults, in whom progression to severe malaria occurs in areas where this was previously only seen in young children
- Strengthen health services by exploring the barriers to the deployment of key antimalarials
- Support harmonisation and standardisation of data collection, recording and secure long term storage in centralised data management systems, as there is a lack of capacity to pool and safely store data, due to limited

skilled personnel and differences in data management systems
- Improve the effectiveness of diagnostic tools in the field for:
  - Rapid diagnostic testing, including in areas working towards malaria elimination
  - Community level diagnosis for reducing malaria transmission, and monitoring community-level interventions aimed at malaria elimination
  - Prompt, accurate evaluation of antimalarial drug resistance
  - Diagnostic platforms that detect each stage of the life cycle of malaria parasites and each Plasmodium species.
- Pool safety data across studies, as the majority of studies are underpowered for assessing safety, in order to identify safety concerns that are dose-dependent or specific to the target population.

Global Malaria Vaccine Portfolio

Recommended actions

- Prioritise the evaluation of the safety and efficacy of vaccines in vulnerable populations, such as pregnant women and children
- Focus on products where proof of concept has been established

Malaria Control

Recommended actions

- Evaluate the added value of innovative combinations of intervention packages for the control and elimination of malaria, while maintaining a broad selection of interventions
- Address the challenge of asymptomatic and sub-microscopic malaria infections, i.e. the hidden reservoir of malarial infections which tends to increase as malaria transmission decreases
- Investigate drug safety and effectiveness, focusing on understanding the dose-response relationship in special populations
- Improve the effectiveness of diagnostics for emerging problems in malarial control (e.g. drug resistance, hidden reservoir), including field-based PCR sensitivity tests
- Strengthen monitoring and evaluation tools, e.g. spatial statistics.

Partnerships

The breadth of the recommendations made by participants in all five areas was considered remarkable and will inform EDCTP in the planning of the second phase of its programme.

Key issues identified included:

- Coordination with other funding organisations to fill gaps, while keeping in mind the importance of diversification in project funding within the remit of the EDCTP programme
- Advocacy role of Networks of Excellence (NoEs), e.g. towards national stakeholders
- Raising funds locally and internationally for sustainability of NoEs
- Synergy between NoEs and integrated projects
- Need for clinical trial related training for all cadres in NoEs
- Need for harmonisation of safety data capturing and storage procedures.

Cross-cutting issues

Recommended actions

- Use the NoEs as potential platforms for the development and dissemination of quality assured, standardised assays and protocols, e.g. for real time PCR, microscopy and other diagnostics
- Promote capacity building in Africa, particularly with regards to translational studies (phases I and IIa) and clinical trial sponsorship.

2. First Day

The meeting was the third of five thematic stakeholder meetings held as part of the European & Developing Countries Clinical Trials Partnership's preparations for its second programme (EDCTP2). The two-day event took place in Vienna, 19-20 September 2013 and was co-hosted by the Austrian Ministry of Science and Research and the Medical University of Vienna. It was attended by 63 invited participants, including researchers from academia, representatives of product development partnerships and the pharmaceutical industry, policy makers, funding agencies and other like-minded organisations.

Introductory remarks

In the meeting's brief opening session Mag. Barbara Weitgruber welcomed the group on behalf of the Austrian Ministry of Science and Research and stressed the importance of addressing malaria in Africa and the world. She commented that EDCTP is an example of a successful collaboration, not only for research, but also for practice. Next Dr Christiane Druml also welcomed the group on behalf of the Medical University of Vienna, stating Austria's commitment to malaria prevention and control, and therefore its readiness to support this EDCTP Stakeholder Meeting.

Prof. Charles Mgone, Executive Director of EDCTP, expressed his thanks to the Ministry and the University of Vienna for hosting EDCTP. He also thanked the participants for attending the meeting, including representatives of EU Member States and industry. He spoke of his wish for the gathering to produce recommendations at the end of the two-day meeting which will support EDCTP in its next phase.

Introduction by Dr Salim Abdulla

Dr Abdulla, Director of the Ifakara Health Institute, Tanzania explained he will act as chairperson to facilitate the discussion for the day, while Prof. Karen Barnes, University of Cape Town, South Africa will act as co-chair and summarise the day's meeting. He presented the agenda and stated the presentations were to stimulate discussion. The participants briefly introduced themselves.

Plans and progress towards EDCTP2: Dr Michael Makanga

Dr Michael Makanga, EDCTP Director of South-South Cooperation and Head of the Africa Office, spoke of the mission, objectives and scope of EDCTP and gave a summary of the grant schemes and trials supported thus far. He also outlined the importance of the regional NoEs for clinical trials with integrated capacity development and networking. He stated that partnership is the basis of the programme.

Next he reviewed the current EDCTP projects and provided a brief overview of the three previous Malaria Stakeholder meetings to date: malaria vaccines (1 January 2007); malaria treatment (2 June 2007); and pregnancy associated malaria (3 June 2007). He summarised the malaria projects that EDCTP supported in line with recommendations from these stakeholder meetings. He continued with a summary of the transition to an expanded scope of EDCTP2 in 2014 under Horizon 2020. The objective of the stakeholder meetings is to provide input for the EDCTP strategic and operational business plans, as well as work plans for clinical studies, epidemiological studies and capacity development. Lastly, Dr Makanga stated the expected outcomes of this meeting were to:

- Review the current state of the malaria research field
- Identify key research areas, current opportunities and barriers to progress
- Provide recommendations regarding the EDCTP strategy for support of malaria research, such as priority research topics for calls for proposals, cooperative projects, products in the pipeline for evaluation by EDCTP, capacity building initiatives, and funding partnerships.

Keynote address: Prof. Abdoulaye Djimdé - Recent research advances in malaria prevention and control

Professor Djimdé from the University of Bamako, Faculty of Science and Technology, Mali noted the research advances in malaria prevention and control and then focused on updates regarding product development and combined interventions. He reviewed the failure of vaccines tested thus far (limited protective efficacy) and attributed this to the diversity of the parasite population. He stated that the delivery of whole-organism vaccines has improved, which shows promise for protection against malaria. He highlighted barriers to malaria vaccine development and stressed that vaccines which interrupt malaria transmission will be key for elimination.

Then he discussed in more detail the current issues in antimalarial drugs, specifically the main problem of efficacy. Although progress was slow, there was hope. He suggested that one way to speed-up malaria elimination would be the use of Seasonal Malaria Chemoprevention (SMC, formerly IPTc) and he reviewed the research issues related to SMC. Next, he summarised the issues on drugs for elimination and eradication and reviewed the challenges in vector control. He stressed the need for strengthening malaria diagnosis through proper microscopy training, rapid diagnostic tools, serology tools, molecular tools (PCR) and multitasking diagnostic tools.

Prof. Djimdé concluded with the importance of supporting capacity development and strengthening health systems in order to reduce the burden of malaria. He stated that the large regional EDCTP (and other) partnerships offer opportunities for collaboration with maximum scientific output and impact on public health problems. Finally he stated that as we move to EDCTP2 we need to build on the successes of EDCTP, expand to include all phases of clinical development, include health systems research and strengthening, and better engage African governments.

Antimalarials I: Dr Tim Wells - Global Portfolio of Antimalarial Medicines

Dr Tim Wells, Chief Scientific Officer responsible for the Research and Development Portfolio of Medicines for Malaria Venture (MMV), reviewed the work streams of the global portfolio of antimalarial medicines:

Work stream 1 is focused on making medicines available and safe for all populations, including the paediatric population, pregnant women, and persons with co-infection. Dr Wells stated that obtaining a single dose cure is a priority to ensure high compliance and lower costs and he stressed the importance of the availability of research capacity to conduct these studies in Africa.

The target product profiles for the antimalarial drugs needed are:

1. Fast killers against the blood stage
2. Long persisters against the blood stage
3. Relapse prevention and transmission blocking
4. Chemoprotection.

Work stream 2 is focused on the clinical development of combination drugs for uncomplicated *P. falciparum* malaria. He stressed that safety and drug interaction studies need to be done in the right populations in order to assess efficacy.

Work stream 3 is focused on transmission blocking which needs to be on a parallel track with vaccines. Dr Wells stated that platforms and harmonised protocols are needed to test transmission blocking.

Work stream 4 is focused on pregnant women, as there are not many drugs for this special population. He explained that the safety of artemisinin combination therapy needs to be established for the first trimester of pregnancy and that there is a general need to identify which candidate drugs in the pipeline can be used for malaria treatment in pregnancy.

Work stream 5 is focused on severe malaria and the need for a fast-acting drug. He stated that platforms are needed for assessing the speed of action of different formulations against severe malaria.

Dr Wells stressed that research capacity is needed in three areas:

- Preclinical studies of safety and pharmacokinetics
- Pharmacology platforms
- Formulation development.

Dr Wells went on to describe a number of new molecules under development which are examples of a transformation in drug discovery, as the screening for use in human trials took place extremely quickly. He outlined a partnering strategy for EDCTP2 for phase IIb studies and stated that for all of these molecules there is the need to manage the risk of attrition.

Dr Wells concluded on the basis of the priority work streams for malaria medicines with the following calls to action:

- Make medicines for all
- Make use of the current unparalleled opportunities for developing drugs against uncomplicated malaria
- Make sure that transmission blocking drugs are on a parallel track with vaccines
- Quickly pick the winners for malaria treatment in pregnancy
- For severe malaria parasite reduction platform are needed.

Discussion and recommendations

Speaking as Co-chair Dr Abdulla reminded the participants to focus on key issues and on providing recommendations for EDCTP2. The issues raised are summarised in Box 1.

Box 1: Recommended Actions on Antimalarials I: Global Drugs Portfolio

- Safety of antimalarial drugs in pregnancy, particularly in the first trimester, is a potential priority research area for EDCTP2. Support is needed for exploration of antimalarial drugs in the pipeline for their potential in pregnancy. A potential study design for evaluating safety in the first trimester would be to recruit cohorts of women of child-bearing age before they become pregnant
- Prioritisation and grouping of studies supported by EDCTP2 is needed in order to maximise the number of molecules evaluated. Side by side testing in randomised controlled trials is a possibility for increasing the efficiency of the development of priority molecules in the pipeline
- A proactive exploration of products in the pipeline is needed to identify promising upstream products that address key therapeutic gaps in order to facilitate that these products reach the clinical pipeline
- An important role for EDCTP2 is to support the development of paediatric formulations for antimalarial drugs
- A critical need is to rapidly and accurately identify antimalarial resistance
- Support is needed to explore new delivery approaches for drugs under development
- EDCTP needs to communicate with the regulatory agencies which have a crucial role in the antimalarial drug approval process, as well as with manufacturers to bring them on board early. Harmonisation is needed to provide guidance in the complex process from clinical drug development to approval
- For malaria elimination it will be important to address *P. vivax* malaria, particularly anti-relapse; this is an important topic in certain countries in Africa, e.g. Ethiopia
- The issues in the roll-out of SMC need to be addressed for this intervention to achieve its full potential in malaria control and elimination
- Some suggested that adjunctive therapy is a critical area that should be pursued for treatment of severe malaria; others favoured studies to better understand the pathophysiology of severe malaria
- Highly sensitive PCR testing needs to be implemented in the field in real time for testing drugs acting against asymptomatic parasitaemias, and for transmission blocking
- Focus is needed on platforms and evaluations that cover the full life cycle of the parasite, not just the asexual blood stages
- Support is needed to train technical staff at clinical sites in maintenance and repair of equipment used
- Support is needed for harmonisation and standardisation of trial data collection, recording and in order to secure long-term storage.

Antimalarials II and Diagnostics: Prof. Peter Kremsner, Prof. Jürgen May, Prof. Clara Menéndez, and Dr Mark Perkins

Severe malaria by Professor Peter G. Kremsner, University of Tübingen, Germany

Prof. Kremsner began his presentation highlighting the definition of severe malaria, as there are differences between the WHO definition and the simpler one used by the Severe Malaria in African Children Consortium (SMAC). He reviewed the results of several studies on antimalarial drugs for treatment of severe malaria and stated that future studies may explore the use of antibiotics in combination with antimalarial treatment. He highlighted the need to develop rapid tests for detecting malaria parasites and their resistance patterns in combination with other microbes (bacteria) at the same time. He also stated that future studies on malaria prevention may investigate the incidence of severe malaria as an endpoint in intervention trials (e.g. vaccine or transmission blocking trials). For malaria the cause of complications is multifactorial, and many published studies with different adjunct therapy interventions have shown no benefit or harm in the past 30 years. Prof. Kremsner summarised that the key problems

in malaria chemotherapy for severe malaria are resistance and the major issue of delayed haemolytic anaemia. He concluded by stating that future studies should focus first on haemolytic anaemia and in the long term on the development of artemisinin alternatives.

Malaria Co-infections by Professor Jürgen May, Bernard-Nocht Institute, Germany

Prof. May noted that malaria co-infections are a neglected but frequent and relevant issue in clinical trials, and important for child survival outcomes. He stated that acute fever is frequent (>50%) in children reporting to a hospital and children often have other infectious diseases indistinguishable from malaria. He stressed that co-infections need treatment with antimalarial drugs and drugs against bacterial causes of the acute illness, but children often receive insufficient treatment as evidence-based guidelines for clinical management are not available. Thus, malaria co-infections need to be specifically considered in the clinical routine.

Prof. May then reviewed the necessary steps to reduce mortality of coinfections and stressed the need to: perform trials on the effect of available co-treatment schemes; develop drug combinations applicable for co-treatment; conduct trials on supportive therapies of severe febrile diseases; and improve diagnostic tests. He closed by stressing the need for evidence-based guidelines in clinical management of malaria coinfections.

Pregnancy-associated malaria by Professor Clara Menéndez, CRESIB, Spain

Prof. Menéndez highlighted the main features, key issues and challenges in the prevention of pregnancy-associated malaria. She reviewed the WHO recommendation for malaria control in pregnancy in stable transmission areas, namely case management, vector control, and intermittent preventive treatment (IPTp).

For IPTp she stated that studies in pregnancy are needed to evaluate the safety and efficacy of malaria vaccines, and of alternative drugs to artemisinin combination therapy and quinine. There is a need for more sensitive point-of-care rapid tests. She noted that SMC is focused on older children (6 months to 5 years) and that this requires new and unplanned contacts between the target population of children and the health care delivery system.

She concluded that the main issues in IPTp are: to evaluate the barriers for its low implementation and uptake; evaluate cost-effectiveness of IPTp and SMC in different contexts and transmission settings; define transmission thresholds when the interventions are no longer effective; and address the need for paediatric formulations of currently recommended and new alternative drugs for IPTp and SMC for the infant target population. Prof. Menéndez closed stating that EDCTP2 has a key role to play in contributing to the agenda of malaria elimination by targeting the most vulnerable groups of the population.

Diagnostics by Dr Mark Perkins, FIND, Switzerland

Dr Perkins briefly noted historical examples of the importance of establishing a funding plan and policy framework for diagnostic assays. He described the impact of the malaria quality assurance programme to assist manufacturers with current product testing, and of the availability of diagnostic applications on the market. Investments are needed in the technological advances in molecular testing platforms, in order to improve diagnostics. He stated malaria diagnostic trials would be useful for specific clinical syndromes/settings: for the evaluation of novel case management diagnostics; for the evaluation of molecular surveillance tools for detection and/or resistance surrogates; for the assessment of recombinants and markers of disease severity for acute febrile syndrome; and

identification of antigens for tracking infection rates. Dr Perkins closed by stating that we need real time information to measure the effect of antimalarial treatments and other malaria control interventions.

Discussion and recommendations

Speaking as Co-chair Dr Abdulla reminded the participants to focus on key issues and on providing recommendations for EDCTP2. The issues raised are summarised in Box 2.

Box 2: General and specific recommendations

- Reconsider the age of the population to be included in clinical trials, as epidemiology suggests that the malaria burden is now shifting to include older children and adults in whom progression to severe malaria occurs in areas where this was previously only seen in young children
- Strengthen health services by identifying the barriers regarding the deployment of key antimalarials
- Support harmonisation and standardisation of data collection, recording and secure long term storage in centralised data management systems, as there is a lack of capacity to pool and safely store data due to limited skilled personnel and differences in data management systems
- Pool safety data across studies, as almost all studies are underpowered for assessing safety, to identify safety concerns which are dose-dependent or specific to target populations.

Severe malaria

- Focus on adjunctive therapy for treatment of severe malaria
- Focus on artemisinin resistance.

Co-infections

- EDCTP2 should address malaria co-infection and the development of improved rapid testing, whereby NoEs could be a platform for testing
- Move forward clinical management guidelines for paediatric formulations to treat co-infections in children.

Pregnancy associated malaria and intermittent preventive therapies

- Very few African countries follow the WHO guidelines to provide artemisinin combination therapy to pregnant women; the obstacles faced by countries to implement this policy, mostly safety concerns, need to be identified and addressed
- EDCTP2 needs to move forward on the safety of malaria treatment during pregnancy
- There is a need to invest in screening methodologies for better diagnosis during pregnancy
- Support is needed to explore ways to increase coverage of IPTp
- Support is needed to identify winners from the new drugs in the pipeline for use in vulnerable populations.

Diagnostics

Improve the effectiveness of diagnostic tools in the field for:

- Rapid diagnostic testing, including in areas working towards malaria elimination
- Community level diagnosis for reducing malaria transmission, and monitoring community-level interventions aimed at malaria elimination
- Prompt accurate evaluation of antimalarial drug resistance
- Diagnostic platforms that detect each stage of the life cycle of malaria parasites and each Plasmodium species.

Recommendations

Discussion took place to identify the key research areas, possible cooperative projects and capacity building initiatives to contribute towards the EDCTP2 strategy for supporting malaria research.

Key research areas

- Explore the effect of malnutrition on malaria outcomes in children, specifically iron deficiencies
- Investigate the relative contribution of malaria in hospitalised children in different parts of Africa to define a baseline against which malaria control interventions can be assessed
- Invest in site preparation; especially support periodic evaluation of normal ranges as part of site preparation
- Support trials in school-aged children as there is an underestimated prevalence in this target group. Studies might benefit from the existing infrastructure of schools
- Support clinical trials exploring the interaction between co-morbidities and malaria, including drug-interactions with commonly used drugs
- Support research on health systems to understand why available tools are low in uptake.

Development of cooperative projects

- Link NoEs with researchers in the field
- Use bottom-up input for broad calls and projects
- Utilise the EDCTP website to promote networking
- Support Member State initiatives for multi-country cooperation.

Capacity building initiatives

- Support innovative ways to engage with the national programmes in-country to have African governments co-fund science and technology projects
- Address the under-representation of certain countries in the NoEs
- Extend even more support to senior African researchers to develop their own research groups, for example by supporting five-year professorships at African institutions
- In addition to regional NoEs, consider establishing global skill-based NoEs as an enabling platform for disciplines with scarce skills, such as phase I clinical trials, pharmacokinetic studies, and transmission blocking studies
- Support external quality assurance for labs
- Engage with other European funding schemes and networks that offer valuable resources, e.g. the Innovative Medicines Initiative (IMI) and the Global Health Trials which provide standards for continuing education.

Summary of the first day: Prof. Karen Barnes

Prof. Barnes, University of Cape Town, South Africa thanked the participants for the inspiring and thought-provoking presentations and contributions. She then provided a concise summary of the first day.

She commented on the remarkable contribution made by EDCTP to date, with the clear alignment of funding policy with the recommendations made in earlier stakeholder meetings, and the substantial investments made to advance clinical trials on malaria in Africa.

She noted the challenge posed by artemisinin resistance and the need for new drugs. The

evaluation of novel compounds in the next five years could be transformative and should include the identification and optimisation of drugs best suited for various indications and populations.

With elimination now firmly on the agenda, Prof. Barnes stressed it will require the accelerated development of drugs needed for transmission blocking, as well as a shift in malaria surveillance and interventions at the population level. She stated that elimination requires better use of new drugs in order to protect vulnerable populations, and the use of improved delivery strategies. She recommended that we not only focus on novel drugs, but also identify the optimal use of available drugs to prolong their useful therapeutic life, thus also paving the way for the optimal deployment of novel compounds. She stated that diagnostics play a key role in quality control and that we need field-based real-time PCR testing with improved sensitivity.

Prof. Barnes commented that taking these goals forward requires further strengthening of drug development platforms in Africa. She stated this capacity building has to include capacity for phase I and IIa studies in Africa, support of research infrastructure, and engaging African countries for co-funding.

Prof. Barnes closed saying that it is essential to use partnerships in order to improve the efficiency of clinical trials and that innovative funding models for vaccine development and malaria control should be explored.

3. Second day

Short introduction by Prof. Karen Barnes

Prof. Karen Barnes, University of Cape Town, South Africa, thanked as Chair the hosts and welcomed the participants for another productive day of discussion.

Global Vaccine Portfolio: Prof. Robert Sauerwein

Prof. Robert Sauerwein, Radboud University Medical Centre, The Netherlands reviewed the long term goals for a malaria vaccine. He stated that to achieve the long term goals there is a need for:

- Surrogate immunological and/or (specific) efficacy endpoints in order to accelerate development
- Faster ways to test new antigens for proof-of-concept in experimental medicine and translational research
- Development of standardised methods of measurement of transmission in relationship to vaccines interrupting malaria transmission.

He highlighted the interim results of efficacy trials in the Clinical Malaria Vaccine Trials 2013 and explained the reasons for the limited success of the subunit vaccines. The presentation continued with a discussion of the Rainbow Table from the Global Portfolio Clinical Malaria Subunit for Vaccine Development which contains 45 projects in advanced pre-clinical and clinical phases. Prof. Sauerwein stressed the need to approach the goal of 75% protection. He stated that as currently vaccines provide no more than 30-50% protection there is a clear need for new candidates and new vaccines from the vaccine pipeline to strengthen the global vaccine development portfolio.

Prof. Sauerwein explained that there is now a focus on the next generation of vaccines and on transmission blocking. He reviewed the strategies for vaccines with attenuated *P. falciparum* sporozoites and their clinical development, as well as the availability of the Controlled Human Malaria Infection (CHMI) model as a major advantage for validation in malaria vaccine development.

Prof. Sauerwein offered the following suggestions for EDCTP2:

- To bridge the gap between preclinical development and clinical trial (link up with Horizon 2020) in view of the need for more antigens/products
- To invest in a portfolio of clinical trial capacities, i.e. in settings of different endemicities and transmission intensities
- Further exploitation in North and South of the CHMI model, the availability of which has been shown to be a great asset.

Comments

Participants offered various comments and suggestions:

- SMC may be an appropriate intervention in specific situations; it is necessary to demonstrate its added value
- Design studies on the use of vaccines in the context of SMC
- Address transmission blocking as it is essential for elimination strategies
- There is a possible synergy between transmission blocking vaccines and transmission blocking antimalarials
- Priorities for vaccines: study safety of RTS,S vaccine in vulnerable populations such as pregnant women and children; focus in the clinical phase on products with proof of concept; focus on phase I trials; fund proposals by academia

- There is an urgent need to improve upon the current benchmark (RTS,S vaccine) in view of elimination strategies
- Involve investigators upstream in the process, i.e. in the preclinical phase to improve phase I clinical trials
- Explore the safety, efficacy and potential applications of the CHMI model combining drugs and vaccines as possibly a powerful tool
- Support capacity building so that translational studies can be increasingly carried out in Africa (strong agreement). This includes building capacity for organisations to act as sponsor of clinical trials in the South, manage clinical trials and take responsibility for vaccine portfolio's (ownership in the South)
- Organise expert groups on particular topics which can advise the EDCTP Strategic Advisory Committee
- Coordinate with other funding organisations such as the European Commission (Seventh Framework Programme and upcoming Horizon 2020) and US National Institutes of Health for filling of funding gaps (general agreement); maintain balance between aiming for impact in the field and diversification in project funding
- Create a network of institutions that could form a sponsor pool or support institutions to assume the responsibility of sponsoring or managing trials; Ministries of Health should be involved to find solutions regarding insurance
- NoEs could be a starting point for establishing a standard protocol for real-time PCR, for platform building and in order to ensure dissemination of the standard protocol
- Develop tools to determine pre-existing levels of immunity and exposure in the population.

Summing up, Prof. Barnes identified key points on the Global Vaccine Portfolio from the discussion – see Box 3.

Box 3: Global Vaccine Portfolio – key points

- Regarding vaccines priority should be given to studies on the safety of vaccines in vulnerable populations, such as pregnant women and children
- Focus on products for which proof of concept is already established
- Use of the NoEs as a starting point for establishing a standard protocol for real time PCR, for platform building, and in order to ensure dissemination of the standard protocol
- Promote capacity building in Africa with regards to translational studies, as well as sponsorship and ownership of clinical research
- Coordination with other funding organisations to fill funding gaps, while keeping in mind the need for diversification in project funding.

Malaria control: Prof. Umberto D'Alessandro

Prof. Umberto D'Alessandro, Theme Leader for Disease Control & Elimination of the Medical Research Council Unit, The Gambia, commented on the paradigm shift in surveillance and approach when the aim is elimination. He reviewed the differences between malaria control and malaria elimination and stated that with the current methods, elimination is only achievable in areas with extremely low transmission. He stressed that the hidden reservoir of malaria infection is the main problem for malaria elimination today. Based on new literature he reviewed the asymptomatic malaria infections and presented research from

The Gambia and Senegal showing regional differences in prevalence rates and issues with long-lasting insecticidal nets. He presented two broad approaches to address malaria: active case detection (reactive and proactive), and presumptive treatment (mass drug administration).

Prof. D'Alessandro stated that EDCTP can play an important role in Seasonal Malaria Chemoprevention as an intervention. He highlighted that the side effects of primaquine are dose-dependent and he presented his study exploring the lowest dose of primaquine still being effective in asymptomatic carriers. He closed stating that artemisinin combination therapy strategies have been adopted by a number of malaria control programmes worldwide, and that the factors affecting effectiveness are not well understood. In his view, the best way forward is to support community-based, cluster randomised trials to determine the effectiveness of an intervention package.

Comments

Further contributions from the floor were then invited and the following issues received attention:

- Uniform application of control interventions is no longer possible due to high migration, especially during seasons of peak transmission
- For vector control, vector outcomes need to be defined more precisely. There is a need for alternative approaches to insecticides
- Promote investigation at cluster level for evidence of changes in transmission and resistance at community level. Case-control methodology would also be useful at the individual or community level. The use of spatial statistics for detection of hotspots would be useful as component of trials
- A partner drug to primaquine is needed to protect primaquine from resistance
- Ethical considerations need to be addressed when using control groups for randomised control trials
- Cost-effectiveness models are needed to ensure sustainability of malaria treatment
- Support is needed for phase IV testing of the safety and effectiveness of interventions, such as investigating the frequency of adverse events after discharge
- Address the *P. vivax* challenge to elimination
- RTS,S efficacy in older children should be studied
- Focus on asymptomatic carriers.

Summing up, Prof. Barnes identified several recommendations for malaria control based on the discussion – see Box 4.

Box 4: Malaria Control – recommendations

- Evaluate the added value of innovative intervention packages for control and elimination of malaria and be broad in the selection of interventions
- Focus on the hidden reservoir of malarial infections, asymptomatic parasitaemias
- Investigate drug safety (e.g. primaquine) in vulnerable populations (paediatric population, pregnant or lactating women) using – and pooling - trials which aim to understand the dose-response relationship in order to inform international guidelines
- Improve the effectiveness of diagnostics for identifying emerging problems in malarial control (e.g. drug resistance, hidden reservoir), including field-based PCR for greater sensitivity
- Strengthen monitoring and evaluation tools, e.g. spatial statistics for targeting.

Partnerships: panel presentations

Co-chair Prof. Barnes presented the partnership panel. Its objectives were to stimulate discussion and encourage recommendations on potential partnerships that EDCTP may engage in. Representatives from eight key organisations gave brief accounts of their present position regarding research partnerships in malaria.

Prof. Francine Ntoumi, Congolese Foundation for Medical Research, Republic of Congo spoke of the importance of the EDCTP-supported regional Networks of Excellence (NoE) to strengthen the participation of African countries in clinical research. She stated this has resulted in multiple partnerships: between North and South for transfer of techniques, fundraising, and training; between collaborators in Africa; and between networks and their local communities. She stated support is needed for training of professionals.

Dr Philippe Guerin, Worldwide Antimalarial Resistance Network (WWARN), spoke of the focus on malaria elimination and the specific need for standardised and automated tools and services for data collection, curation, sharing, and long term secure storage. He stated there is a need to provide quality assurance schemes and for data sharing to enable pooled analyses. He stressed the need to agree on minimum standards in order to facilitate data sharing and that we have an ethical responsibility to store and pool data for the long term to ensure optimal use of available data.

Prof. Christian Burri, Swiss Tropical and Public Health Institute, welcomed the transformative need for institutions to develop a portfolio of their projects, invest in human resource management and planning, perform quality assurance, and assume sponsorship/responsibility for clinical trials. He provided two examples of successful partnerships between institutions to transform field sites into highly regarded research centres.

Dr Val Snewin, Wellcome Trust, congratulated EDCTP on its success in providing for training fellowships and undertaking clinical trials. She stated funders are increasingly interested in working in partnership and provided four recommendations to EDCTP from the perspective of the Wellcome Trust: 1) EDCTP to be more involved with the ESSENCE group of funders; 2) EDCTP to find a mechanism to work on filling gaps that are complimentary to Calls for Proposals and based on a strategic overview; 3) EDCTP to address the sustainability of clinical trial sites/personnel and promote networking between sites; 4) EDCTP to exchange expertise with other funders regarding clinical trial management and evaluation as part of capacity building for EDCTP staff.

Dr Inmaculada Penas-Jimenez, Directorate General of Research and Innovation of the European Commission, highlighted the activities of the Commission that has supported numerous malaria research projects through the Seventh Framework Programme. Her recommendation was for EDCTP to collaborate with organisations which seek funding from the European Commission via Horizon 2020 basic science research grants. She stated there is a need to have a good platform of partnership to discuss priorities and ensure financing, and stressed the importance of the public-private partnership.

Dr Janice Culpeper, Bill & Melinda Gates Foundation, explained that the Foundation's strategy on malaria is to focus on elimination of malaria by supporting: product development; better vector control tools; elimination of the reservoir of infection in asymptomatic and symptomatic patients; more sensitive diagnostics; and malaria control for special populations. She stated joint funding with EDCTP

may be possible on small grants once areas of interest are agreed upon, while recognising the benefit of funders choosing to support different areas (e.g. the Foundation particularly supports product development and EDCTP capacity building).

Dr Odile Leroy, European Vaccine Initiative, stated the key challenge of collaborative research in the field of malaria is the issue of multiple funders funding one project which results in complex funding schemes (e.g. financial rules are different for each funder). She stressed harmonisation efforts are needed across different diseases and different products.

Dr Esthel van Brackel, GlaxoSmithKline Biologicals, welcomed collaboration between EDCTP and the pharmaceutical industry and provided the following recommendations for EDCTP: 1) EDCTP to provide epidemiological data and modelling to guide industry initiatives; 2) EDCTP to develop research sites according to strategic planning; 3) EDCTP to create a repository of African trial sites to facilitate linking with industry; 4) EDCTP to consider providing accreditation of research sites; 5) EDCTP to liaise between different partners playing roles in conducting malaria clinical trials; 6) EDCTP to play a leadership role in private-public collaborations and to build a pharmacovigilance system/platform.

Comments on panel contributions: partnerships in malaria

The discussion largely concerned how the NoEs might collaborate in partnership with EDCTP. Most frequently mentioned was the need to reinforce the role of the networks in Africa and address the challenges of sustaining the networks, e.g. through professorships. NoEs also need to communicate with national stakeholders in an advocacy role. Also mentioned was the need to find synergies between NoEs and integrated projects, as well as with private and public funders.

Key issues regarding partnerships were identified by Co-chair Prof. Karen Barnes and are presented in Box 5.

Box 5: Partnerships – key suggestions

- Advocacy role for NoEs, i.e. towards national stakeholders
- Raise funding locally as well as internationally for sustainability of NoEs
- Create synergy between NoEs and integrated projects
- Need for training as part of the activities of the NoEs
- Need for harmonisation and pooling of safety data
- Need to identify a mechanism and process for minimum standards to facilitate data sharing.

Conclusion of the meeting: Dr Salim Abdulla

The meeting ended with a comprehensive summary by Co-chair Dr Abdulla of the main challenges identified and the recommendations for the second phase of EDCTP.

Dr Abdulla highlighted the progress that has been made in the development of malaria vaccines and the current focus on vaccines that will provide higher protection and reduce transmission. He noted the change of perspective and strategies now that we have transitioned from malaria control to malaria elimination, such that CHMI is a useful tool to predict performance of products in the field.

He summarised the following challenges identified at the Stakeholder meeting that may be addressed by EDCTP2:

- Identify mechanisms to pool safety data from different trials
- Develop harmonised methods for assessments of products
- Develop diagnostic tools and interventions for areas of low transmission intensity
- Work on the hotspots for malarial transmission
- Collaborate early on in vaccine development to bridge the gap between pre-clinical and clinical evaluation in Africa
- Establish testing models of effectiveness in the field
- Improve models of use and delivery of vaccines with other interventions
- Improve diagnostics at point of care
- Invest in products which demonstrate proof of concept
- Look for new opportunities for partnerships with other organisations for innovative pooling of international funding
- Create a dialogue to define a strategy for the development of infrastructure and capacity
- Explore ways to sustain the NoEs and consider skill-based networks
- Support the regulatory infrastructure in Africa
- Support cost-effectiveness modelling
- Explore environmental management and integrated management of vector control
- Move funding towards research programs, institutions and teams to diminish dependence on individuals
- Support long term capacity building by offering: professorships, substantial department funding to attract researchers outside Africa to work in Africa, excellence in laboratory, career tracks for scientific as well as support staff
- Support methods for computing and modelling of big data
- Continue investment in harmonisation
- Promote coordination between different stakeholders.

Closing: Prof. Charles Mgone and Dr Pascoal Mocumbi

Prof. Charles Mgone, Executive Director of EDCTP, thanked the participants, hosts and chairs for the successful meeting. Dr Pascoal Mocumbi, EDCTP High Representative, provided closing remarks on the importance of African partnership and ownership, and ensuring the continued involvement of the EDCTP Networks of Excellence in the second programme of EDCTP.

Annex 1. List of participants

Name	Institution	Country
Abdulla, Salim	Ifakara Health Institute	Tanzania
Alano, Pietro	Istituto Superiore di Sanità - Consortium CIRM-ISS (Italian Malaria Network)	Italy
Ashorn, Per	University of Tampere	Finland
Barnes, Karen	University of Cape Town/ Worldwide Antimalarial Resistance Network (WWARN)	South Africa
Bassyouni, Hager	EDCTP	Netherlands
Bauer, Hemma	Austrian Federal Ministry of Science and Research	Austria
Beattie, Pauline	EDCTP	Netherlands
Beretta, Isabella	State Secretariat for Education, Research and Innovation (SERI)	Switzerland
Berkis, Uldis	Ministry of Education and Science of Latvia	Latvia
Berzosa, Pedro	Instituto de Salud Carlos III (ISCIII) National Center of Tropical Medicine	Spain
Blázquez Domingo, Montserrat	EDCTP	Netherlands
Böcking, Detlef	Deutschen Zentrum für Luft- und Raumfahrt e.V. (PT DLR)	Germany
Bompart, François	European Federation of Pharmaceutical Industries and Associations (EFPIA) / Sanofi	France
Borrmann, Steffen	Magdeburg University School of Medicine	Germany
Breugelmans, Gabrielle	EDCTP	Netherlands
Burri, Christian	Swiss Tropical and Public Health Institute (Swiss TPH)	Switzerland
Cisse, Badara	Malaria Capacity Development Consortium	Senegal
Cot, Michel	L'Institut de recherche pour le développement (IRD)	France
Culpepper, Janice	Bill & Melinda Gates Foundation	USA
D'Alessandro, Umberto	The Institute of Tropical Medicine in Antwerp (ITM)/ Medical Reseach Council The Gambia	The Gambia/Belgium
Debré, Patrice	Hôpital Pitié Salpêtrière	France
Deloron, Philippe	IRD	France
Dieye, Alioune	Institut Pasteur Dakar	Senegal
Djimdé, Abdoulaye	University of Bamako	Mali
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Duparc, Stephan	Medicines for Malaria Venture (MMV)	Switzerland
Ethelston, Sally	PATH Malaria Vaccine Initiative (MVI)	USA
Guerin, Philippe	WWARN	UK

Habarugira, Jean-Marie	EDCTP	Netherlands
Hill, Adrian	The Jenner Institute - University of Oxford	UK
Hoffman, Steve	Sanaria	USA
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Krumina, Angelika	Riga Stradins University	Latvia
Leboulleux, Didier	MVI	Switzerland
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Makanga, Michael	EDCTP	Netherlands
Marinucci, Francesco	PARTEC Essential Healthcare	Germany
May, Jürgen	Bernard-Nocht Institute	Germany
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Mocumbi, Pascoal	EDCTP	Mozambique
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Mwapasa, Victor	College of Medicine University of Malawi	Malawi
Noedl, Harald	Medical University of Vienna	Austria
Ntoumi, Francine	Congolese Foundation for Medical Research	Congo
Ogutu, Bernhards	Kenya Medical Research Institute (KEMRI) / Strathmore University	Kenya
Olesen, Ole	EDCTP	Netherlands
Pandya, Lara	EDCTP	Netherlands
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Perkins, Mark	Foundation for Innovative New Diagnostics	Switzerland
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Ramharter, Michael	Medical University of Vienna	Austria
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Sengoelge, Mathilde	Meeting Rapporteur	Austria
Sirima, Sodiomon	Centre National de Recherche et de Formation sur le Paludisme (CNRFP)	Burkina Faso
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Theisen, Michael	Statens Serum Institute (SSI)	Denmark
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Colophon

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