



Malaria and pregnancy

EDCTP Stakeholder meeting

Place: Vienna, Austria

Date: 15 June 2007

Author(s) :

Michael Makanga

Version Number:

01

Date of approval:

02/08/2007

By:

Charles S Mgone

Table of contents

| | |
|--|----|
| 1. Introduction..... | 3 |
| 2. Science and products..... | 4 |
| Overview of presented products | 4 |
| Summary discussion on products and science | 5 |
| Meeting deliberations: | 5 |
| 3. Sites in Africa | 7 |
| Overview of presented sites: | 7 |
| Summary discussion on Sites in Africa | 7 |
| 4. EDCTP procedures | 10 |
| Overview EDCTP procedures | 10 |
| 5. Recommendations to EDCTP | 11 |
| Annexes | 12 |
| Annex 1: Hosting country contribution to the stakeholder meeting | 12 |
| Annex 2: EDCTP Guidelines for Stakeholder meetings | 13 |
| Annex 3: Instructions for presentations | 18 |
| Annex 4: Agenda..... | 19 |
| Annex 5: List of participants | 20 |
| Annex 6: Discussion paper | 22 |

1. Introduction

The EDCTP stakeholders' meeting on malaria and pregnancy hosted by Austria was the ninth among the ten thematic stakeholders' and consultative meetings organised by EDCTP in the planning and implementation of the new strategy for funding projects. The aims of the meeting were to identify treatment products available for clinical trials involving malaria in pregnancy; identify capacity gaps and requirements for conducting clinical trials and to agree upon the mode of formulating grant proposals, either through open calls or brokering. This meeting was chaired by Dr Philippe Deloron of the Institut de Recherche pour le Développement (IRD), Faculté de Pharmacie, Paris, France.

2. Science and products

Overview of participating organisations

Public organisations:

- Institut de Recherche pour le Développement (IRD), Faculté de Pharmacie, Paris, France: (<http://www.ird.fr/>)
- Vienna School of Clinical Research (VSCR), Austria: (<http://www.vscr.at>)
- Institute of Tropical Medicine Antwerp, Belgium: (<http://www.itg.be/itg>)
- Medical Research Council, UK: (<http://www.mrc.ac.uk/index.htm>)
- Statens Serum Institut, Denmark: (<http://www.ssi.dk>)
- Bundesministerium für Bildung und Forschung, Germany: (<http://www.bmbf.de>)
- Subdirección General de Evaluación y Fomento de la Investigación (SGEFI), Spain
- Liverpool School of Tropical Medicine: (<http://www.liv.ac.uk/lstm>)
- European Commission: (http://ec.europa.eu/index_en.htm)
- EDCTP: (<http://www.edctp.org>)

Public Private Partnerships:

- The Medicines for Malaria Venture (MMV): (<http://www.mmv.org>)
- Malaria Clinical Trials Alliance (MCTA): (<http://www.indepth-network.org/mcta>)

Private Sector: None

Other:

- East African Network for Monitoring Antimalarial Treatment: (<http://www.eanmat.org>)

Overview of presented products

A presentation on antimalarial products in development was given by Dr Carl Craft of MMV. This addressed products currently in MMV portfolio that applied to both malaria treatment in general and malaria in pregnancy.

MMV has 24 projects in its product development portfolio. Of these five, all of which are artemisinin based, are in phase III testing. These include chlorproguanil-dapsone (LapdapTM) artesunate (CDA), coartem[®] dispersable, artesunate - pyronaridine (Pyramax[®]) and dihydroartemisinin - piperaquine for uncomplicated malaria and intravenous Artesunate for severe malaria. MMV expressed willingness to have synergy with EDCTP on phase IIIb studies involving any of these products in their product development portfolio. It was also reported that MMV already has embryo-

toxicological studies data on both the artemisinin and the companion drugs for the products in their portfolio. Synthetic endoperoxides have shown reduced toxicity in pregnancy based on animal study data (MMV personal communication).

Other products that are in the pipeline include tafenoquine for the treatment of *Plasmodium vivax*, currently in phase II and not funded, isoquine (an improved aminoquinoline) on hold, MK-4815 awaiting toxicology results and funding, and 4(1H)-pyridone GSK-932121 a backup product for previous pyridines. The last three are in preclinical phase and the remaining 15 projects are still in discovery and exploratory phases. Tafenoquine is however not a good candidate for use in pregnancy because it is likely to be harmful to glucose 6 phosphate deficient (G6PD) newborns.

Summary discussion on products and science

The chair gave a scientific overview on the field of pregnancy-associated malaria (PAM) covering effects of PAM in both unstable and stable transmission areas; PAM consequences for both for newborn and mother; placental cytoadherence; current prevention strategies; case management; current issues about Intermittent Preventive Treatment (IPT); requirement for a better IPT; ongoing prevention trials in Africa and future prevention involving VAR2CSA-based vaccine in development and additional putative targets currently being identified.

Meeting deliberations:

It was recognised that there is shortage of drugs that could safely be used both in intermittent preventive treatment in pregnancy (IPTp) and in case management of malaria in pregnancy especially during the first trimester. Currently quinine is the only antimalarial available that can safely be used for case management during the first trimester. Sulfadoxine – pyrimethamine (SP) safety has never been studied. Although it is of interest and relevant, first trimester studies are practically not feasible.

Two themes were drawn from the recommendations of the research strategy multi-planning meeting that was held in London in June 2006 to which EDCTP was represented. The themes included:

- (i) Case management in Africa, Asia and Latin America. Africa to be covered by EDCTP support. To identify at least two drug combinations that are safe, practical to use (three day regimen or shorter) and highly effective for treatment of uncomplicated *falciparum* and *vivax* malaria in pregnancy.
- (ii) Prevention in Africa.
 - a. To optimise the existing regimen IPTp with SP in context of ITNs (integrated approaches)
 - b. New drugs for IPTp: To identify at least one safe and effective alternative to SP

It was generally agreed that establishment of safety and efficacy of the available antimalarials, both registered and in development was crucial in order to identify alternatives to SP. The choice of new drugs, however, should be based on use of GMP products and availability of sufficient phase I data. The outcome variables of prevention studies should include birthweight, maternal anaemia and death. Parasitological parameters though important may not necessarily match clinical outcome in pregnancy. It was also highlighted that studies of malaria in pregnancy

should have longer periods of follow up to cover period of delivery and the first month of the post-partum period.

HIV/AIDS co-infection in pregnancy associated malaria was proposed to be an important area. Trials involving investigations on antiretroviral interaction with antimalarials could be explored. Also IPTp with alternatives to S-P in HIV infected women where S-P is not recommended could be supported. It was, however, encouraged that trial designs should take into account the national policies of different countries on HIV testing. Pharmacokinetics components in these in both phase II and IIIb studies should be encouraged.

Congenital malaria was mentioned but not considered to be a priority area.

MMV expressed interest of collaboration on studies involving intravenous (IV) artesunate and phases IIIb and IV studies involving products which are in their pipeline. It was, however, emphasised that applicants should obtain prior authorisation from MMV or other product developers for use of unregistered products.

Mefloquine which is not part of MMV portfolio was also mentioned as a product with potential for use in pregnancy that could be investigated.

The MiP consortium is looking into having a group academic and research institutions serving as potential sponsors for studies of malaria in pregnancy.

The table below summarises the products in the MMV product development portfolio that were discussed in this meeting.

| Name of Product | Presented by | Where in pipeline |
|--|---------------------|--------------------------|
| Chlorproguanil-dapsone (Lapdap [®]) - artesunate (CDA) | MMV | Phase III |
| Coartem [®] Dispersable Tablet | MMV | Phase III |
| Dihydroartemisinin - piperaquine | MMV | Phase III |
| Artesunate – pyronaridine (PYRAMAX [®]) | MMV | Phase III |
| Intravenous Artesunate | MMV | Phase III |
| Tafenoquine | MMV | Phase II |
| Isoquine (an improved aminoquinoline) | MMV | Preclinical testing |
| 4 (1H)-pyridones Back ups | MMV | Preclinical testing |
| MK-4815 | MMV | Preclinical testing |

3. Sites in Africa

Overview of presented sites:

Dr Feiko ter Kuile gave a presentation on behalf of the Malaria in Pregnancy (MiP) consortium. Currently MiP membership includes 12 research institutions in Africa (listed in table below) with an additional 8 to be determined; eight academic and research institutions in UK, Belgium and Spain with potential expansion to institutions in France, Germany, Netherlands, Sweden and Finland in 2008; other member institutions are in Asia, Americas, USA and Australia. The MiP consortium secretariat is at the Liverpool School of Tropical Medicine, UK and has established an online MiP library (<http://www.update-software.com/publications/malaria>).

A presentation from EANMAT was given which showed some of the upcoming research sites with potential for development. The Developing Countries Coordinating Committee (DCCC) representative from Congo Brazzaville and researchers from the MRC Gambia and University of Buea gave input from the West and Central African point of view.

Summary discussion on Sites in Africa

It was generally acknowledged that there were still a limited number of sites to conduct clinical trials on malaria in pregnancy in Africa. MiP consortium was encouraged to consider including more institutions from the Central part of Africa linking sites that are more established with those that are upcoming. It was encouraged to have a good balance between ability to conduct clinical trials and geographical representation. A strategy to encourage African investigators early enough in proposal development process was also highlighted.

Willingness of African national programmes to facilitate studies involving treatment of malaria in pregnancy was pointed out crucial to the success of this initiative. It was therefore advised to increase interaction with policy makers and also to use WHO country offices as focal points.

The table below summarises the southern partner institutions that were either represented or featured in discussion of sites in Africa through their association with Malaria in Pregnancy (MiP) Consortium and EANMAT.

| Name of site | Country | Trial experience | Represented in person |
|---|----------------|--------------------------|------------------------------|
| Centre de Recherche Entomologique de Cotonou (CREC) | Benin | Yes (drugs/ ITNs) | No (part of MiP Consortium) |
| University of Cotonou | Benin | Yes (drugs) | No (part of MiP Consortium) |
| Centre Muraz, Bobo-Dioulasso | Burkina Faso | Yes (drugs and vaccines) | No (part of MiP Consortium) |
| Centre National de Recherche et de Formation sur le paludisme (CNRF), | Burkina Faso | Yes (vaccines) | No (part of MiP Consortium) |

| | | | |
|--|--|--|---|
| Ouagadougou | | | |
| Ministère de la Santé Nanoro | Burkina Faso | No (drugs) | No (part of MiP Consortium) |
| University of Yaoundé | Burkina Faso | Yes (drugs) | No (Antwerp Institute of Tropical Medicine) |
| University of Buea | Cameroon | Yes (drugs) | No (part of MiP Consortium) |
| Centre d'Etudes sur les Ressources Végétales (CERVE), Brazzaville | Cameroon | Yes (drugs) | Yes |
| Albert Schweitzer Hospital (HAS), Lambaréné | Congo - Brazzaville | Yes (drugs) | Yes |
| Medical Research Centre (MRC), Laboratories, Fajara | Gabon | Yes (drugs and vaccines) | No (part of MiP Consortium) |
| Centre for Innovation Against Malaria (CIAM) | Gambia | Yes (drugs and vaccines) | Yes |
| Navrongo Health Research Centre | Gambia | Yes (drugs) | No (part of MiP Consortium) |
| Kwame Nkrumah University of Science and Technology (KNUST), Kumasi | Ghana | Yes (drugs/vaccines) | No (part of MiP Consortium) |
| Presbyterian Health Service, Agogo | Ghana | Yes (drugs/vaccines) | No (part of MiP Consortium) |
| KEMRI-Wellcome Trust Collaborative Centre, Kilifi | Ghana | Yes (vaccines) | No (part of MiP Consortium) |
| KEMRI-CDC/Walter Reed, Kisumu | Kenya | Yes (drugs and vaccines) | No (part of MiP Consortium) |
| KEMRI-CDC/Walter Reed, Kisumu | Kenya | Yes (drugs and vaccines) | No (part of MiP Consortium) |
| EANMAT Sentinel Sites | Kenya – 8 Uganda - 8 Tanzania mainland – 8 Rwanda – 6 | Majority of these have potential for upgrading and are health centres involved in routine drug efficacy testing not clinical trials. (Tororo & | No (Antwerp Institute of Tropical Medicine) |

EDCTP Stakeholder meeting: Malaria and pregnancy

Vienna 14 June 2006

| | | | |
|--|-----------------------------|---|------------------------------|
| | Burundi – 6 Zanzibar – 2 | Jinja in Uganda and Rukara in Rwanda currently involved in EDCTP supported drug clinical trial) | |
| University of Malawi, Blantyre | Malawi | Yes (drugs) | No (part of MiP Consortium) |
| UNICEF Malawi, Lilongwe | Malawi | Yes (vaccines) | No (part of MiP Consortium) |
| The Malawi-Liverpool-Wellcome Trust (MLW) Research Programme, Blantyre | Malawi | Yes (drugs) | No (part of MiP Consortium) |
| Malaria Research Training Centre, Bamako | Mali | Yes (drugs and vaccines) | No (part of MiP Consortium) |
| Manhica Health Research Centre | Mozambique | Yes (drugs and vaccines) | Yes /part of MiP Consortium) |
| University of Maputo | Mozambique | Yes (drugs) | No (part of MiP Consortium) |
| University College Hospital, Ibadan | Nigeria | Yes (drugs) | No (part of MiP Consortium) |
| Zankli Hospital, Abuja | Nigeria | Yes (drugs) | No (part of MiP Consortium) |
| Central University Hospital (CUH), Kigali | Rwanda | Yes (drugs) | No (part of MiP Consortium) |
| Ministry of Health, Kigali | Rwanda | Yes (drugs) | No (part of MiP Consortium) |
| University of Dakar | Senegal | Yes (drugs) | No (part of MiP Consortium) |
| National Institute for Medical Research (NIMR) | Tanzania | Yes (drugs) | No (MiP consortium member) |
| Ifakara Health Research and Development Centre (IHRDC), Ifakara | Tanzania | Yes (drugs/vaccines) | No (part of MiP Consortium) |
| Makerere University, Kampala | Uganda | Yes (drugs/vaccines) | No (part of MiP Consortium) |

| | | | |
|--|--------|----------------------|-----------------------------|
| Ministry of Health, Kampala | Uganda | Yes (drugs) | No (part of MiP Consortium) |
| University of Zambia, Lusaka | Zambia | Yes (drugs) | No (part of MiP Consortium) |
| University Teaching Hospital (UTH), Lusaka | Zambia | Yes (drugs) | No (part of MiP Consortium) |
| Tropical Disease Research Centre, Ndola | Zambia | Yes (drugs/vaccines) | No (part of MiP Consortium) |
| Ministry of Health, Lusaka | Zambia | Yes (drugs) | No (part of MiP Consortium) |

4. EDCTP procedures

Overview EDCTP procedures

EDCTP can fund proposals through an open call or a brokering procedure. Both were explained to the audience. More information is available in the Guidelines for Stakeholders' meetings (see Annex 2)

Summary discussion EDCTP funding procedure and timelines for initiating funding procedure

It was generally agreed that an open call would be the appropriate funding procedure for malaria in pregnancy. However, it was also agreed that consortia rather than individuals should be encouraged to apply.

Recommended procedure:

Open call for proposals with all funds in one envelope but addressing the two high priority areas stated in the meeting recommendations. These clinical trials were recommended to cost approximately 5 million Euros on average for both case management and IPTp studies.

Recommended time to initiate funding procedure (s):

Call for proposals to be published as soon as possible in 2007.

Possible funding partners:

| Pledged and potential contributions to topic | | | |
|--|-------------|------------------------------------|---------------------------------------|
| Organisation | Country | Amount | Certainty |
| MMV | Switzerland | To be determined (tbd) | |
| DNDi | Switzerland | Tbd | |
| | UK | Cash contribution of 800,000 Euros | Yes: for African and UK investigators |

| | | | |
|--|-------------|------------------------|---|
| | Spain | Cash contribution tbd | Spanish participation required |
| | Germany | Cash contribution tbd | Germany participation required |
| | Austria | Cash contribution tbd | Towards capacity development: training aspects |
| | France | No firm commitment | French participation required |
| | Denmark | No firm commitment | No |
| | Belgium | No firm commitment | No |
| | Netherlands | Not present in meeting | NACCAP already supporting group in MiP consortium |

5. Recommendations to EDCTP

1. Open call for proposals was recommended. However. Applications must come from consortia instead of individual researchers.
2. To support conduct phase IIIb clinical trials on case management of malaria in pregnancy using alternatives to chloroquine, sulphadoxine –pyrimethamine (S-P), and quinine antimalarial drugs in management of uncomplicated malaria. These studies should focus on efficacy and safety of antimalarials tested and may include pharmacokinetics.
3. To support conduct studies on intermittent preventive treatment of malaria in pregnancy using alternatives to the standard S-P regimen. Alternatives may include alternative drugs or alternative to the 2 or 3 doses S-P regimen. These studies may involve HIV–infected individuals.
4. To put all the available funds in one basket and support calls for proposals on the following:
 - Phase III b studies in pregnancy including systematic pharmacokinetic studies in recommendation 2
 - IPTp studies using alternatives to the standard S-P regimen in recommendation 3
5. To encourage applicants to collaborate with basic researchers involved studies linked to clinical trials that require samples that may answer critical research questions.

Annexes

Annex 1: Hosting country contribution to the stakeholder meeting

| Estimate of all costs covered by hosting country | |
|--|----------------|
| Item | Amount |
| Travel | |
| Hotel | |
| Catering | 2,064.03 Euros |
| Administration support | |
| Venue | |
| Other | |
| Sum | 2,064.03 Euros |

Signed by organising Member State:

Name

Date

Annex 2: EDCTP Guidelines for Stakeholder meetings

Introduction

This document aims to describe all aspects related to the aim, organisation and outcome of the EDCTP stakeholder meetings.

EDCTP aims to organise to 2 types of stakeholder meetings: 7 meetings will focus on disease specific topics and one meeting will concentrate on Nodes of Excellence. The disease-specific topics will have a focus on products in the pipeline. These topics are listed below:

- Malaria treatment and malaria in pregnancy (combined meeting)
- Malaria vaccines
- TB treatment
- TB vaccines
- HIV treatment
- HIV vaccines
- HIV microbicides

The Nodes of excellence meeting will focus on the integrated approach of EDCTP towards the establishment of regional nodes of excellence in sub-Saharan Africa with particular focus on reference laboratories and centres specialised in data management encompassing clinical trials design, conduct, and analysis skills, building on sites with existing capacities and competences in these areas.

These guidelines aim to describe the generic approach towards organising both types of meetings. All stakeholder meetings on disease related topics will be hosted by one of the participating European Member States whereas the stakeholder meeting about Nodes of Excellence will be hosted by one of the African partners participating in EDCTP. The expected outcome, communication aspects, timelines and financial issues concerning stakeholder meetings will be clarified. In addition the role of the hosting member state, the organising committee including the independent chair as well as the expected list of participants are described.

To ensure transparency these guidelines are made public and the EDCTP Secretariat will ensure that the implementation will be carried out and documented correctly.

Aim and objectives of a stakeholder meeting

A stakeholder meeting is a one day meeting. It is the start of a process that leads towards EDCTP funding one or more projects through a call or brokering procedure.

The expected outcome of these meetings is:

1. To make recommendations to EDCTP for:
 1. The development of cooperative projects and coordination of efforts
 2. Priorities for EDCTP:
 1. for disease specific topics EDCTP requires priorities in terms of product and sites whereas
 2. for nodes of excellence EDCTP needs priorities in terms of sites, location as well as required skills and capacity
2. Expression of a willingness of the various stakeholders to contribute to the topic both in financial as well as practical terms. These will be followed up by the EDCTP secretariat.
3. Establishment of trust in the EDCTP approach with our stakeholders.

The meetings with a disease-specific topic will have the following objectives:

- Identify products in the pipeline
- Identify potential suitable sites to do the trial
- Recommend priority in terms of product and sites
- Recommend if the funding procedure is a call or brokering or no-go
- Recommend EDCTP timelines concerning the initiation of funding for each topic area

EDCTP Stakeholder meeting: Malaria and pregnancy

Vienna 14 June 2006

The stakeholder meeting on Nodes of Excellence has similar priorities:

- Identify potential sites
- Identify needs in terms of skills and capacity
- Recommend priorities in terms of needs and sites
- Recommend if the funding procedure is a call or brokering or no- go
- Recommend EDCTP timelines concerning the initiation of funding

Organisational aspects

All stakeholder meetings on disease-related topics will be hosted by one of the participating European Member States whereas the stakeholder meeting about Nodes of Excellence will be hosted by one of the African partners participating in EDCTP.

All meetings will be organised by an Organising Committee that consists of:

- An independent expert to chair
- A representative of the hosting country. For the European Member States this is the European Networking Officer (ENO) representing the country while for the Nodes of Excellence meeting this role should be fulfilled by the relevant member of the Developing Country Coordinating Committee (DCCC),
- The Partnership Board (PB) and DCCC disease experts
- The Executive Director and Operations Manager from the EDCTP Secretariat

The independent chair will be identified by EDCTP Secretariat, PB and DCCC representatives of the organising committee before the date of the stakeholder meeting is set. The candidate will be approved by the GA in a written procedure. If the hosting country is identified before a chair is selected the representative of the hosting country will also be involved in selecting the chair. The Terms of reference for the Independent chair are the following:

To work with the EDCTP stakeholders' meeting planning group to ensure that the meeting is planned and implemented transparently avoiding or declaring any conflict of interest to give an optimal, independent and objective advice to the EDCTP. This, via the EDCTP Secretariat should take into account the following:

1. The presence of appropriate representation of all significant bodies including industry, private-public partnerships and other stakeholders that are relevant to the topic; ensuring that the representation at the meeting is sufficiently senior to contribute with authority
2. There are appropriate and effective arrangements for conducting the meeting including drafting and approving of the agenda; noting of the attendance; ensuring of adequate participation and deliberation of all the relevant issues
3. Provision in an agreed timescale of a good quality report of the meeting.

Travel and hotels are arranged in close collaboration between the hosting country and the EDCTP Secretariat and the hosting country is expected to play an active role in this. The hosting country should organise location, catering and administrative support as well as assist delegates with their visa requirements. In addition the hosting country is responsible for sending out the invitations to participants. The final list of participants to be invited will be provided by the EDCTP Secretariat in collaboration with the Organising Committee.

Participants

It is a requirement that the following parties are represented at the stakeholder meeting:

- Funders both from the European Member States and if applicable third parties. Each European Member State will be asked to send one representative. It is up to the individual country to accept this invitation or not
- Product developers, Public Private Partnerships and/or industry (disease specific topics only)
- Representatives of African sites that have the capacity to carry out phase II or III trials

EDCTP Stakeholder meeting: Malaria and pregnancy

Vienna 14 June 2006

- Experts in the field. Each European Member State may bring one expert of their own choosing
- Independent experts if applicable.

Most participants will be identified by the Organising Committee with the exception of the representatives of the European Member States. Each European Member State is free to send one expert in the field and one representative of their funding body of their own choosing.

It is normally expected that a stakeholder meeting will have no more than around 40 participants.

Invitations to the participants need to go out at least 6 weeks in advance.

Agenda

The agenda for the stakeholder meeting is set by the Organising Committee using the format developed by the EDCTP Secretariat. The generic format for the meetings on disease specific topics is shown below.

EDCTP Stakeholder Meeting

Topic
location, date 2007
Address
Contact

| Agenda items | By | Timelines |
|---|------------|-----------|
| <i>Coffee/Tea</i> | <i>All</i> | |
| 1.0 Welcome by host | host | |
| 2.0 Approval of the Agenda | All | |
| 3.0 Science and products 3.1 Scientific overview of the field 3.2 Products in the pipeline: relevant stakeholder (more added if required) More added if required | | |
| Coffee break | All | |
| 4.0 Discussion on products and science | All | |
| 5.0 Sites in Africa 5.1 Relevant stakeholder (more added if required) 5.3 DCCC | | |
| Lunch | All | |
| 6.0 Discussion on sites | all | |
| 7.0 EDCTP procedures | SEC | |
| 8.0 Recommendations on how to proceed in terms of products, sites and funding procedure | all | |
| 9.0 Summary of recommendation | Chair | |

Communication

Because EDCTP stakeholder meetings should demonstrate transparency and independence it is important that the meetings are widely advertised and that the hosting country does not have a perceived conflict of interest with the topic. EDCTP will however, not publish a call for participants. The advertisements for the stakeholder meetings will focus on announcement of topics, locations, aims and dates. They should list a contact address and encourage those that would like more information to make contact. If someone contacts EDCTP with a wish to participate, this request will be passed on to the Organising Committee who will make a decision.

Advertising of the stakeholder meetings will be through the following means:

- Internet:
 - EDCTP website
 - Requesting constituency members to publish at their websites
 - Other relevant websites
- Paper advertisement:
 - Publishing of adverts in Lancet as soon as all the dates are set
- Ask EDCTP constituencies to communicate to appropriate parties

EDCTP Stakeholder meeting: Malaria and pregnancy

Vienna 14 June 2006

- If the opportunity arises mention of EDCTP stakeholder meetings in presentations or meetings

Timelines

The dates for the various stakeholder meetings will be set as soon as the independent chair and hosting country have been identified and once the chair agrees to the Terms of Reference. It is expected that the stakeholder meetings for TB vaccines, malaria vaccines, HIV vaccines and HIV treatment will take place during the first quarter of 2007. The stakeholder meetings for Nodes of Excellence, malaria treatment/pregnancy, TB treatment and HIV microbicides are scheduled for the second quarter of 2007.

Financial issues

If the stakeholder meeting is hosted by a European country, it is expected that this country will at least as a minimum cover the costs for use of the location, catering during the meeting, administrative support and any other local expenses. If the hosting country is African these costs need to be discussed with the EDCTP Finance Manager. EDCTP will normally pay for travel and hotel for external participants as well as for PB and DCCC members. EDCTP expects that the European Member states will at least pay for travel and hotel of the participants they delegate. EDCTP will pay for travel and hotel of European MS participants and experts only if the European Member State is unable to do so.

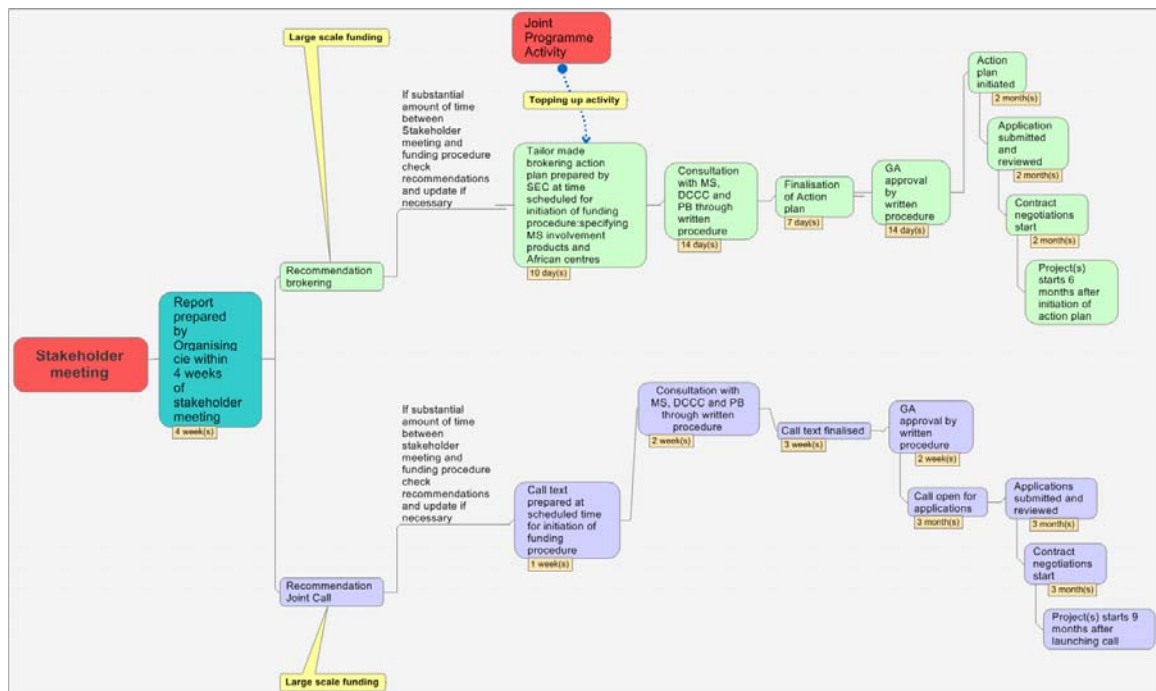
Outcome/follow up

The organising committee will produce a report of the meeting within 4 weeks. The report will be presented to EDCTP. EDCTP will initiate its funding procedures at the appropriate time after considering the report. The timing for launching calls or brokering initiatives can range from 2007-2009 depending on the on the availability of products and sites. A final list of expected dates for initiation of funding procedures will be prepared after all stakeholder meetings have taken place. The diagram below summarises both funding procedures. More information on the EDCTP funding procedures can be found at the website.

A summary of both procedures is described below:

- *Call for proposals*
A call text is drafted based on the recommendations that came out of the stakeholder meeting. After consultation of the various EDCTP constituencies and approval of the General Assembly the call will be published. An EDCTP call is normally open for applications for a period of 3 months. The applications are then checked against the eligibility criteria as defined in the call text and eligible applications will be reviewed by at least 2 external experts as well as the EDCTP Scientific Review Committee (SRC). The SRC ranks the applications and makes a recommendation for funding. This recommendation is examined by the PB which ensures the quality of the review procedure and also assess if the proposal is in line with the EDCTP strategy. The PB makes the final recommendation for funding to the General Assembly who approves the application.
- *Brokering*
A brokering action plan is prepared by the EDCTP Secretariat and requires to be approved by the General Assembly after consultation with the EDCTP constituencies. The action plan will be initiated resulting in an application for funding. This application is checked for eligibility as described in the brokering action plan and reviewed by at least two external experts as well as the relevant EDCTP SRC. The SRC make a recommendation for funding or rejection which is examined by the PB which examines both the procedure as well as the alignment of the project with the EDCTP strategy. Upon recommendation of the PB the GA make the decision to fund the project or not.

EDCTP Stakeholder meeting: Malaria and pregnancy
Vienna 14 June 2006



Annex 3: Instructions for presentations

Expected outcome of the meeting

The expected outcome of the EDCTP stakeholder meetings is to make recommendations to EDCTP for:

3. The development of cooperative projects and coordination of efforts
4. Priorities for EDCTP in terms of product and sites
 - Expression of a willingness of the various stakeholders to contribute to the topic both in financial as well as practical terms.
 - Establishment of trust in the EDCTP approach with our stakeholders

The stakeholder meeting is considered the start of a process that leads towards EDCTP funding of one or more projects through an open call or brokering.

Audience

The audience will be a mixture of experts in the field and people who represent funding agencies and may not have a scientific/medical background. Therefore we would like to suggest that your presentation should be aimed at a general audience.

Expected contents of your presentation

Given the expected outcome of the meeting and the composition of the audience EDCTP would like to provide you some points regarding the expected contents of your presentation.

If you talk about science and products

- A short introduction on the organisation you are representing
- Without going into too much scientific details basic information about the products in the pipeline:
 - Basic principles of the product
 - Status with respect to clinical testing: what has been done/what is ongoing and what is planned/needed
 - Availability of the product
 - Restrictions with respect to the use of the product: is it only available for persons associated with your organisation/is it for sale?

In addition to the presentation could you provide a short summary document on each product that should enable the participants to the meeting to assess its scientific validity and potential.

If you talk about sites in Africa

- A short introduction on the organisation you are representing
- Basic information about the sites you are representing:
 - Capacity and trial experience
 - Commitment to other trials/availability to do the trial
 - Local malaria situation

Duration of your presentation

The time available per presentation is limited to 15 minutes. The presentations will be followed by an initial discussion of 1 hour.

Annex 4: Agenda**EDCTP Stakeholder Meeting
Malaria and pregnancy**

Vienna June 15 2007

Palais Porcia, Herrengasse 23

0900-1530

Aim of the meeting:

- Identify and prioritise potential products in the pipeline
- Identify potential suitable sites to do the trial
- Recommend if the funding procedure of EDCTP will be an open call, brokering or whether EDCTP should fund this topic at all
- Recommend EDCTP 's timeline concerning the initiation of funding for this topic

| Agenda items | By | Timelines |
|---|---|---------------------|
| <i>Coffee/Tea</i> | <i>All</i> | <i>09:00 – 9:15</i> |
| 1.0 Welcome | Charles Mgone, Christiane Druml and Chair Philippe Deloron | 9:15 – 9:30 |
| 2.0 Approval of the Agenda | All | 9:30-9:40 |
| 3.0 EDCTP procedures | Charles Mgone | 9:40-9:50 |
| 4.0 Science and products | Philippe Deloron Carl Craft | 9:50-10:05 |
| 4.1 Scientific overview of the field | | 10:05-10:20 |
| 4.2 Products in the pipeline: MMV | | |
| <i>Coffee break</i> | <i>All</i> | <i>10:20-10:35</i> |
| 5.0 Discussion on products and science | All | 10:35-11:00 |
| 6.0 Sites and existing networks in Africa | Feiko ter Kuile Umberto D'Allesandro | 11:00-11:15 |
| 6.1 Malaria in Pregnancy Consortium | | 11:15-11:30 |
| 6.2 Overview sites in Africa | | |
| 7.0 Discussion on sites | all | 11:30-12:30 |
| 8.0 Concluding remarks on sites | Chair | 12:30-12:24 |
| <i>Lunch</i> | <i>All</i> | <i>12:45-13:30</i> |

EDCTP Stakeholder meeting: Malaria and pregnancy

Vienna 14 June 2006

| | | |
|--|------------------------------|--------------------|
| 9.0 Member States commitment | Member State representatives | 13:30-14:15 |
| 10.0 Recommendations on how to proceed in terms of products, sites and funding procedure | all | 14:15-15:00 |
| 11.0 Summary of recommendation | Chair | 15:00-15:15 |
| <i>Tea</i> | <i>all</i> | <i>15:15-15:30</i> |

Annex 5: List of participants

Bernhards Ogutu Ragama, Kenya
Walter Reed Project
P.O. Box 54
00200 Kisumu
Kenya.

Tel: +254 20 722541
Fax: +254 20 720030
bogutu@wrp-ksm.org

Carl J Craft, MMV Switzerland
Medicines for Malaria Venture (MMV)
International Center Cointrin
Entrance G, 3rd floor
Route de Pré-Bois 20
P.O. Box 1826
CH-1215 Geneva 15
Switzerland.

Tel: +41 22 799 4067
Fax: +41 22 799 4061
craftjc@mmv.org

Christa Janko, Austria
Vienna School for Clinical Research
Barichgasse 40-42
A-1031 Vienna
Austria.

Tel: +43 (1) 713 40 5111
christa.janko@vschr.at

Clara Menendez, Spain
Center for International Health,
Hospital Clinic
Gran Via de les Corts Catalanes, 585
08007 Barcelona
Spain.

Tel: +258 21 810002
Fax: +258 21 810002
MENENDEZ@clinic.ub.es

Charles S. Mgone, Netherlands
EDCTP Secretariat
P.O. Box 93015
2509 AA, The Hague
The Netherlands.

Tel: +31 70 3440890
Fax: +31 70 3440899
mgone@edctp.org

Christiane Druml, Austria
Ethics Committee of the Medical
University of Vienna
Borschkegasse 8b,
Vienna 1090
Austria.

Tel: +43 (140400) 2147
Fax: +43 (140400) 1690
christiane.druml@meduniwien.ac.at

Dario Zanon, Belgium
European Commission
rue de Cheup de Mors 21 03/53
BE1044 Brussels,
Belgium.

Tel: +32 (2) 2080250
Fax: +32 (2) 2084561
dario.zanon@cec.eu.int

Claudia Herok, Germany
BMBF
Hannoversche Str. 28-30
10115 Berlin
Germany.

Tel: +49 1888-57 5296
Fax: + 49 1888-57 8 5296
Claudia.Herok@BMBF.BUND.DE

EDCTP Stakeholder meeting: Malaria and pregnancy

Vienna 14 June 2006

Francine Ntoumi, Netherlands
EDCTP Secretariat
P.O. Box 93015
2509 AA, The Hague
The Netherlands.

Tel: +31 70 344 0891
Fax: +31 70 344 0899
ntoumi@edctp.org

David Coles, Netherlands
EDCTP Secretariat
P.O. Box 93015
2509 AA The Hague
The Netherlands.

Tel: +31 70 3440885
Fax: +31 70 3440899
coles@edctp.org

Harald Noedl, Austria
Head of the Exp. Tropical Med. and
Field Research unit,
Inst. of Specific Prophylaxis and
Tropical Medicine
Medical University of Vienna
Kinderspitalgasse 15
Vienna, Austria.

Tel: +43-1-4277-64882
Fax: +43-1-4277-64899
Email:
harald.noedl@meduniwien.ac.at

Michael Ramharter, Austria
Department of Internal Medicine I,
Division of Infectious Diseases,
Medical University of Vienna,
1090 Vienna
Austria.
Tel: (01) 40400 4440

michael.ramharter@meduniwien.ac.at

Philippe Deleron, France
IRD UR010, Laboratoire de
parasitologie, Faculte de pharmacies,
4 avenue de l'observatoire
75006

Marcus Gmeiner, Austria
Vienna School of Clinical Research
Koelblgasse 10,
1030 Vienna,
Austria.

Tel: +43 1 7134051-16;
Fax: +43 1 7134051-99
markus.gmeiner@vscr.at

Diana Dunstan, UK
Medical Research Council,
20 Park Crescent
London W1N 1AL
United Kingdom.

Tel: +44 (207) 637 6021
Fax: +44 (20) 76366289
diana.dunstan@headoffice.mrc.ac.uk

Michael Makanga, South Africa
EDCTP,
PO Box 19070,
Tygerberg 7505,
Cape Town,
South Africa

Tel: +27 21 938 0819
Fax: +27 21 938 0569
makanga@edctp.org

Peter Kremsner, Germany
University of Tuebingen
Wilhelmstrasse 27
72074 Tuebingen
Germany.

Tel: +49 (7071) 29 87179
Fax: +49 (7071) 295 189
peter.kremsner@uni-tuebingen.de

Rafael de Andrés Medina, Spain
Subdirección General de
Investigación Sanitaria-Fondo de
Investigación
Instituto de Salud Carlos III,

EDCTP Stakeholder meeting: Malaria and pregnancy

Vienna 14 June 2006

PARIS Cedex 10
France.

Tel: (+33) 014 281 94 01
Fax: (+33)015 373 96 17
phillipe.deleron@ird.fr

Sam Dunyo, the Gambia
Medical Research Laboratories
PO Box 273
Banjul
The Gambia

Tel: +220.5735421
Fax: +220 4496513
sdunyo@mrc.gm

Eric Achidi,
University of Buea,
Department of Medical Laboratory
Science, Faculty of Health Sciences,
63, Buea,
Buea
Cameroon

Tel: +237 773 9498
Fax: +237 332 2272
Achidi_e@yahoo.com

Lars Hviid, Denmark
Centre for Medical Parasitology,
Copenhagen University Hospital
Nørregade 10
P.O. Box 2177
DK-1017 Copenhagen K
Denmark

Tel: +45 35 45 79 57
Fax: +45 35 45 76 44
lhcmp@rh.dk

Hemma Baver, Austria

Sinesio Delgado 628029
Madrid
Spain.

Tel: +34 (91) 822 2508
Fax: +34 (91) 387 7766
rdam@isciii.es

Umberto D'Alessandro,
Prince Leopold Institute of Tropical
Medicine
Nationalestraat 155
2000 Antwerp
Belgium

Tel: +32 3 247 6354
Fax: +32 3 247 63 59
Udalessandro@itg.be

Feiko ter Kuile
Liverpool School of Tropical
Medicine,
Pembroke Place
Liverpool L3 5QA
UK

Tel: +44 (0)151 705 3287
Fax: +44 (0)151 705 3329
terkuile@liv.ac.uk

Michael Alifrangis, Denmark
Østre Farimagsgade 5,
Building 22-23,
Postbox 2099,
1014 Copenhagen K,
Denmark

Tel: +45 3532 7680
Alifrangis@cmp.dk

Margarete Endl, Austria

Annex 6: Discussion paper

Pregnancy-associated malaria

Philippe Deloron, IRD, Paris, France

Epidemiology

In areas endemic for malaria, the pregnant woman is at high risk for malaria. Every year, twenty-five millions of pregnant women are exposed to malaria in sub-Saharan Africa, and pregnancy-associated malaria (PAM) is of serious public health concern¹. In areas where malaria transmission is intense, its main consequences are a low birth weight (LBW) for the baby and a severe anemia for the mother².

In low endemicity areas, the impact of unstable malaria on pregnant women may vary with the intensity of transmission, and thus the level of immunity acquired by the mothers. The most severe complications of *Plasmodium falciparum* infection, such as cerebral malaria or pulmonary oedema which may lead to maternal death, affect women with the lowest levels of immunity. Clinical malaria attacks with high fever and maternal anaemia are also frequent, they affect indifferently primigravidae and multigravidae. On the foetus, abortion, stillbirth or LBW are frequent.

In high endemicity areas, the picture is very different. Parasitaemias are more frequent and parasitic densities are more important during the first and, to a lesser extent, the second pregnancy, than in multigravidae or in non-pregnant women. Clinical signs of malaria, such as fever, are unfrequent³. Anaemia is also more frequent in pregnant women, and more pronounced in primigravidae than in multigravidae. The aetiology of anaemia in pregnancy is multifactorial but most studies showed a strong association between malarial infection of the placenta or peripheral blood and haemoglobin levels, confirming it is a major cause of anaemia, even in the presence of other factors⁴. The effect of maternal anaemia on the course and outcome of pregnancy is difficult to establish. Mild anaemia (haemoglobin < 11 g/dl) is very common in pregnant women living in malaria-endemic areas (e.g. 72 % in Zaire or 94 % in Papua-New Guinea), but does not seem to originate serious problems. Severe malaria (haemoglobin < 7 g/dl) is associated with adverse perinatal outcomes, such as maternal mortality or LBW of the baby. The prevalence of severe anaemia varies greatly (less than 3 % in Zaire, 9 to 10 % in Tanzania or coastal Kenya). A comprehensive review of all studies published between 1985 and 2000³ estimated that maternal anaemia contributed to 7-18 % of LBW and to 25 % of total infant mortality. Maternal mortality is difficult to estimate but it was estimated to 0.5 – 23 % in hospital studies and 2.9 – 17.6 % in community studies⁵.

Placental infection occurs more frequently than parasitaemia in the maternal peripheral blood, affecting 10 % to 34 % of all pregnant women, and primigravidae are more heavily and more often infected than multigravidae. All investigations show a constant association between placental infection and LBW, which has a strong bearing on neonate and infant morbidity, particularly in first births. The mean decrease in birth weight associated with placental infection ranges from 55 g to 348 g (all parities), which corresponds to an approximate twofold increase in the proportion of LBW, which usually affects 10 % - 15 % of births in malaria-endemic areas. The overall contribution of maternal malaria to LBW is estimated to 8-14 % of all deliveries in malaria-endemic areas³. As for maternal mortality, the impact of maternal malaria infection on perinatal and infant mortality is not easy to assess, but was estimated to 3 – 8 % of infant mortality, which corresponds to an approximate 75,000 to 200,000 infant deaths each year³.

Since the onset and the rapid spread of AIDS epidemics in malaria transmission areas, questions have been generated on potential interactions between the two infections. HIV-positive women show an increase in the prevalence and density of parasitaemia compared to HIV-seronegative women⁶. Moreover, the usual pattern of increased prevalence and parasite density in primigravidae is altered, HIV-seropositive primigravidae having a similar risk of malaria as HIV-seropositive multigravidae⁷.

Pathophysiology

During pregnancy, massive sequestration of *P. falciparum* parasites in the placenta is likely to reduce materno-fetal exchanges, explaining the frequency of LBW babies born from infected mothers. However, two recent studies have shown that pregnant women infected with *P. vivax* were also likely to give birth to LBW babies, suggesting that local or systemic production of selected inflammatory cytokines may also play a role in the pathological process⁸.

P. falciparum parasites infecting pregnant women express an antigenic profile different from parasites encountered in non-pregnant hosts. This characteristic of PAM parasites is related to placenta-expressed receptors that participate in the selection of parasite phenotypes with a given specificity for these receptors. Chondroitin-sulfate A (CSA) is the major receptor for placenta sequestration⁹, and the number of parasite ligands involved in placenta sequestration is consequently highly

restricted as compared to those implicated in cerebral malaria where several endothelial receptors may be involved. Although PAM parasites do preferentially bind to CSA, variable abilities were described among different placental isolates¹⁰. Demonstration of different binding abilities among placental isolates showed particular interest as high binders were associated with high risk of LBW, and transcribed higher level of *var2csa* compared to low binders¹¹, emphasizing the role of *var2csa* in PAM. The expression of a particular variable surface antigen (VSA) by parasites binding to CSA in the placenta elicits variant-specific antibodies that are able to inhibit the cytoadherence of placental parasites to the human syncytiotrophoblast. The decreasing susceptibility to pregnancy associated malaria with increasing parity is reflected by the acquisition of VSA_{CSA}-specific antibodies¹². Recombinant CSA is efficient in inhibiting and reversing the placental cytoadherence of infected erythrocytes. VSA_{CSA}-specific antibodies do react with placental parasites from all malaria endemic areas¹³, and antibodies raised against of PfEMP-1 (the major antigen constituting VSA) also inhibit the binding of placental parasites to CSA¹⁴. This constitutes a tremendous opportunity for the likelihood of making happen a vaccine against pregnancy associated malaria in the near future. To identify cross-reactive epitopes driving protective immunity within multiple sub-variants of the VAR2CSA is needed to defining critical constructs as vaccine candidates.

Current prevention and control strategies

1- Intermittent preventive treatment

Current main prevention strategy consists in intermittent preventive treatment (IPT) with SP. With this regimen, a single curative dose of three tablets is given two or three times (depending on the date of first visit) at ANC visits. This regimen appears to be better accepted by pregnant women than regular drug prophylaxis, and to be effective to reduce the prevalence of placental infection, severe maternal anaemia, and LBW^{7, 15}. It has been described that placental malaria and LBW for HIV-positive women were improved by monthly SP treatment but not by two doses only. If confirmed, this may have important consequences on prevention strategies, indicating that HIV-positive women should receive three SP doses at least¹⁶. SP is the only drug recommended for IPT during pregnancy, but given the rapid spread of SP-resistance in Africa there is an urgent need for assessing the protective effect of

alternative drugs or drug combinations that are safe for the pregnant woman and effective.

In areas of Africa where resistance to SP is high, alternatives to SP require urgent evaluation for use in pregnancy.

Some safety and efficacy clinical trials with other drugs than SP

- Chloroquine (Mali)
- SP+Azithromycin (Malawi, Tanzania)
- Mefloquine (Benin, Tanzania)
- Artesunate+SP (South Africa)
- Artemether-lumefantrine (Uganda)
- Chlorproguanil-dapsone (Tanzania)

2- Insecticide-treated nets

Vector control can act as a complement to prophylaxis to prevent adverse effects of malaria in pregnant women. Only the effect of insecticide-treated bed-nets (ITN) has been evaluated so far. The results are contradictory, as some studies indicated improvement in maternal anaemia, parasitaemia and LBW¹⁷, while others did not evidence any noticeable effect of ITN use on either mother or fetus¹⁸.

3- Case management of malaria during pregnancy

The case management of malaria during pregnancy is an essential component of malaria control. The WHO recommended a standard of intervention packages for the prevention and cure of severe anaemia in pregnant women (presumptive treatment for malaria and helminthes plus daily iron + folic acid supplements) and Enhanced Care (Standard of care plus multivitamins and a 2nd dose of anthelmintic). The recommended antimalarial drug for treatment of uncomplicated malaria during pregnancy is quinine.

As reported by Nosten *et al.*²⁰ the kinetics, safety and efficacy of available antimalarial drugs including combination therapies are poorly documented because pregnant women are systematically excluded from clinical trials.

Gaps in pregnancy-associated malaria

In Africa, few pregnant women suffer from clinical malaria and require treatment that is recommended to involve quinine. Finding new drugs to treat and/or prevent

malaria infection in pregnancy is an urgent need. Currently control of malaria in pregnancy is mainly based on administering IPT with SP to pregnant women. The efficiency of this strategy is threatened by the spread of SP-resistant parasites in Africa. However, recent data suggest that its efficiency in semi-immune pregnant women might be underestimated, when basing estimates of SP efficacy on drug trials performed in immunologically naïve children. Although the administration of IPT during the second half of pregnancy (after week 20) is effective to reduce the prevalence of placental infection, anaemia, and LBW, it has been shown that malaria infections occurring in the early pregnancy may have a negative impact on the occurrence of LBW¹⁹. As SP is contra-indicated during the first trimester, this may constitute an additional reason for the search of an alternative to SP. Indeed, safe and effective new drugs or new combinations are required as alternative to SP for IPT. Such identification of new compounds will certainly be slowed by both the almost complete lack of pharmacokinetics data in the pregnant woman and the lack of efficient methods for evaluating treatment efficacy in PAM. Pharmacokinetics information need to be defined for many of the new drug combinations.

References

1. WHO. A strategic framework for malaria prevention and control during pregnancy in African region. Report ARF/MAL/04/01. 2004; Brazzaville 2004.
2. Nosten F, ter Kuile F, Maelankiri L, Decludt B, White NJ. Malaria during pregnancy in an area of unstable endemicity. *Trans R Soc Trop Med Hyg* 1991; **85**:424-429.
3. Steketee RW, Nahlen BL, Parise ME, Menedendez C. The burden of malaria in pregnancy in malaria-endemic areas. *Am J Trop Med Hyg* 2001; **64S**:28-35.
4. Shulman CE, Graham WJ, Jilo H, *et al*. Malaria is an important cause of anaemia in primigravidae: evidence for a district hospital in coastal Kenya. *Trans R Soc Trop Med Hyg*, 1996; **90**:535-539.
5. Brabin BJ, Verhoeff F. The contribution of malaria. In: McLean AB, Neilson JP (eds). *Maternal morbidity and mortality*. London: RCOG, 2002; 65-78.
6. Steketee RW, Wirima JJ, Bloland PB *et al*. Impairment of a pregnant woman's acquired ability to limit *Plasmodium falciparum* by infection with human immunodeficiency virus type-1. *Am J Trop Med Hyg* 1996; **55**:42-9.
7. Shulman CE, Dorman EK, Cutts F *et al*. Intermittent sulphadoxine-pyrimethamine to prevent severe anaemia secondary to malaria in pregnancy: a randomised placebo-controlled trial. *Lancet*, 1999; **353**:632-636.

EDCTP Stakeholder meeting: Malaria and pregnancy

Vienna 14 June 2006

8. Nosten F, McGready R, Simpson JA, Thwai KL, Balkan S, Cho T, Hkirijaroen L, Looreesuwan S, White NJ. Effects of *Plasmodium vivax* malaria in pregnancy. *Lancet*. 1999; **354**:546-549.
9. Fried M, Duffy PE. Adherence of *Plasmodium falciparum* to chondroitin sulfate A in the human placenta. *Science*. 1996; **272**:1502-1504.
10. Tuikue Ndam NG, Fievet N, Bertin G, Cottrell G, Gaye A, Deloron P. Variable adhesion abilities and overlapping antigenic properties in placental *Plasmodium falciparum* isolates. *J Infect Dis*. 2004; **190**:2001-2009
11. Tuikue Ndam NG, Salanti A, Bertin G, Dahlbäck M, Fievet N, Turner L, Gaye A, Theander T, Deloron P. High level of *var2csa* transcription by *Plasmodium falciparum* isolated from the placenta. *J Infect Dis*. 2005; **192**:331-335
12. Staalsoe T, Shulman CE, Bulmer JN, Kawuondo K, Marsh K, Hviid L. Variant surface antigen-specific IgG and protection against clinical consequences of pregnancy-associated *Plasmodium falciparum* malaria. *Lancet*. 2004; **363**:283-289.
13. Fried M, Duffy PE. Maternal malaria and parasite adhesion. *J Mol Med*. 1998; **76**:162-171.
14. Avril M, Gamain B, Lepolard C, Viaud N, Scherf A, Gysin J. Characterization of anti-*var2CSA*-PfEMP1 cytoadhesion inhibitory mouse monoclonal antibodies. *Microbes Infect*. 2006; **8**:2863-2871.
15. Verhoeff FH, Brabin BJ, Chimsuku L, Kazembe P, Russell wb, Broadhead RL. An evaluation of the effects of intermittent sulfadoxine-pyrimethamine treatment in pregnancy on parasite clearance and risk for low birthweight in rural Malawi. *Ann Trop Med Parasitol* 1998; **92**:141-150.
16. Parise ME, Ayisi JG, Nahlen bl *et al*. Efficacy of sulfadoxine-pyrimethamine for prevention of placental malaria in an area of Kenya with a high prevalence of malaria and human immunodeficiency virus infection. *Am J Trop Med Hyg* 1998; **59**:813-822.
17. D'Alessandro U, Langerock P, Bennett S, Francis N, Cham K, Greenwood BM. The impact of a national impregnated bed net programme on the outcome of pregnancy in primigravidae in The Gambia. *Trans R Soc Trop Med Hyg* 1996; **90**:487-492.
18. Shulman CE, Dorman EK, Talisuna AO *et al*. A community randomised controlled trial of insecticide treated bednets for the prevention of malaria and anaemia among primigravid women on the Kenyan coast. *Trop Med Int Health*, 1998; **3**:197-204.
19. Cottrell G, Deloron P, Fievet N, Sow S, Gaye O, Le Hesran JY. Prediction of *Plasmodium falciparum* placental infection according to the time of infection during pregnancy. *Acta Trop*, 2006; **98**:255-60.

20. Nosten F, McGready R, Mutabingwa T. Case management of malaria in pregnancy. *Lancet Infect Dis.* 2007; 7(2):118-25.