FINAL REPORT/RAPPORT FINAL

INTERNATIONAL CONFERENCE ON MALARIA IN AFRICA: CHALLENGES AND OPPORTUNITIES FOR COOPERATION

January 6-9, 1997
Dakar, Senegal

CONFERENCE INTERNATIONALE SUR LE PALUDISME EN AFRIQUE: DEFIS ET PERSPECTIVES DE COOPERATION

TABLE OF CONTENTS

Introduction

The International Conference on Malaria in Africa: Challenges and Opportunities for Cooperation/Conference Internationale sur Le Paludisme en Afrique: Defis et Perspectives de Cooperation was held January 6-9, 1997 in Dakar, Senegal. One hundred twenty malaria experts from 35 countries participated; 50 were from 22 African countries. In addition, representatives from the major funding agencies for malaria research worldwide participated. A list of participants is included as an attachment to this document.

The overarching goal of this conference, as agreed at an international planning meeting held in April 1996, was to strengthen and sustain, through collaborative research and training, the capability of malaria endemic countries in Africa to carry out research required to develop or improve tools for malaria control. The conference was organized to assist in meeting that goal. Instead of presentations of papers by individual scientists, groups of scientists were challenged to identify the most important research questions and the rationale for their choices, to identify the research strategies for answering these questions, and to propose how collaboration would further the research.

About this report

This document is a compilation of reports from focus groups on: pathogenesis, epidemiology, entomology, immunology, antimalarial drugs, health systems and operational research, interventions and mechanisms of cooperation and support for malaria research. In addition, during the conference, it was recognized that several of these groups were considering some of the same cross-cutting issues: case management, vector control methods, training, multiple interventions, and vaccines. Additional focus groups were formed on these topics and reports from these groups are also included.

Only minor editorial changes have been made to the original reports, which were submitted to the Secretariat on the final day of the conference.

Scientific Advisory Committee:

Samba Diallo, M.D., Senegal
Ogobara Doumbo, M.D., Mali
Brian M. Greenwood, M.D., United Kingdom
Wenceslaus Kilama, Ph.D., Tanzania
Louis H. Miller, M.D., USA
Luiz Pereira da Silva, M.D., France

Major Sponsors and Organizers:

National Institutes of Health, USA
Institut Pasteur, France
Commission of the European Communities
The Wellcome Trust, United Kingdom
Medical Research Council, United Kingdom
Ministry of Cooperation, France
World Health Organization

Conference Secretariat:

National Institute of Allergy and Infectious Diseases, National Institutes of Health, USA
Fogarty International Center, National Institutes of Health, USA

The sponsors, organizers and participants wish to express sincere appreciation to the President of the Republic of Senegal, His Excellency Abdou Diouf, and to the Minister of Health of Senegal, His Excellency Ousmane NGom, for their support during the preparation and conduct of this conference. We gratefully acknowledge the assistance of Dr. Fode Diouf, Ministry of Health, and the members of the local organizing committee. Dr. Jean-Paul Moreau and the staff of the Institut Pasteur de Dakar provided invaluable assistance during the conference. We recognize the outstanding effort of Dr. Sharon Hrynkow, Fogarty International Center, NIH, in ensuring the success of this conference.

This report is available on the Internet at: www.niaid.nih.gov/dmid/malafr/

For more information, contact John R. La Montagne, Ph.D.

Director, Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Room 3A18, Solar Building
6003 Executive Blvd.
Rockville, Maryland
USA
20852
Phone: 301-496-1884
Fax: 301-480-4528
Internet: malaria@nih.gov

Part I. Scientific Priorities

Pathogenesis Focus Group Report

Introduction

- Malaria is important because it causes disease and death.
- Available preventive methods are not sufficient to abolish these.
- Understanding the mechanism of malaria morbidity and mortality will provide opportunities for new methods of disease prevention and treatment.

Current situation

- At least one million African children die each year of severe malaria, mainly cerebral malaria and severe anemia.
- Malaria in pregnancy is a major cause of low birth weight and infant mortality.
- Only a small proportion of those with symptomatic infections progress to severe and complicated disease; an unknown proportion of those with severe malaria seek hospital care.
- The progression from mild symptoms to death can be extremely rapid. Even with the best available treatment, case fatality rates are high.
- Disease mechanisms are poorly understood at both the molecular and clinical level.
- Different sites have different patterns of disease - the underlying pathogenetic mechanisms may also differ. Thus, findings from one site may not be generalized to another.
- At the present time there are no surrogate markers for the important endpoints of the disease process, e.g. mortality, severe disease and low birth weight. In vivo and in vitro models are useful for hypothesis generation but proof of causation in clinical pathogenesis must be conducted on human patients.
- There are only a few centers in Africa with the capacity to conduct sufficiently detailed studies on patients with severe and complicated malaria infections.

Expediting pathogenesis research

Scientific process

Pathogenesis research is mostly hypothesis-driven. There are three major phases in taking an theory about pathogenesis from the point of discovery to the point of practical implementation.

Hypothesis generation. This typically arises from observations made by investigators working at a single site. The discovery may be laboratory-based or may arise initially from clinical observations. Ultimately, however, the discovery phase of hypothesis generation involves both clinical phenomena and laboratory-based correlates.

- ***Hypothesis testing.*** Often this is by disease association in case-control studies. Multiple sites are needed to determine (a) technical reproducibility and (b) whether the same pathological processes can be generalized to different sites.

- ***Experimental intervention studies.*** Causal relationships in human malaria infections can only be established via intervention studies with critical endpoints (e.g., mortality, sequelae, low birth weight). As large numbers of patients are required for such studies, the most expeditious approach is to coordinate the efforts of multiple sites simultaneously.

Roadblocks

- Lack of information about variation in the patterns of clinical disease in different geographical settings,
- Requirement for hypotheses to be tested in more than one location, and:
- Requirement for large sample size, both for testing of disease associations and of experimental interventions.

Recommendation

Develop a continent-wide capacity to assess hypotheses. Each center would contribute to:

- Standardized data collection
- Hypothesis validation (e.g. case control studies)
- Investigations of causality by experimental interventions
- Improved scientific dialogue between different centers.

Specific hypotheses

Certain hypotheses are already at the stage where functional correlations have been observed with disease severity, and multicenter collaborations (± expedited molecular characterization) are needed to take the work forward.

This report provides some examples of this process.

However it must be emphasized that there are other hypotheses of major interest where preliminary clinical data are now being developed at individual sites.

Parasite cytoadherence

A recent study demonstrated that parasitized erythrocytes attach to chondroitin sulfate A in the human placenta. Protection is achieved in multigravid women, perhaps after the acquisition of antibodies which inhibit this binding process. The parasite CS-A binding protein may thus be a target of protective immunity and its characterization is an urgent objective. This phenomenon is potentially of public health significance and needs to be tested in other settings.

- It has been found in several sites that cerebral malaria is associated with increased parasite rosette formation, and there is evidence that anti-rosetting antibodies are defective in cerebral malaria patients. The latter result requires replication at other sites as it has therapeutic implications.

- For many years there has been debate about precise contribution of cerebral sequestration to the pathology of cerebral malaria and specifically the role of interactions between PfEMP-1 variants and different endothelial adhesion molecules. The cloning of PfEMP-1 allows for variant-specific typing in brain sections from autopsy samples currently being collected. This project is at the stage of integrating clinical findings (at post mortem) with laboratory findings (specific PfEMP-1 variants).

Malaria toxins

High TNF levels are associated with cerebral malaria, and there is emerging evidence that antibodies which inhibit parasite-induced TNF cerebral production are associated with protection from malaria. This association should be tested at other sites. It emphasizes the importance of molecular the characterization of the parasite factors that induce TNF, and of generating inhibitory monoclonal antibodies as tools for the investigation of the anti-toxic immunity hypothesis.

- A Stage 3 experimental intervention, in the form of a large study of anti-TNF therapy in cerebral malaria, failed to show any benefit. A number of practical limitations could have explained this failure and it is worth pursuing alternative approaches of suppressing excessive production of inflammatory mediators in cerebral malaria, e.g. using pentoxifylline.

Other mechanisms

- A number of pathophysiological processes are potentially of considerable importance, including hypoglycemia, lactic acidosis, raised intracranial pressure, fluid and electrolyte abnormalities, continued convulsions, respiratory abnormalities.
- Also potentially important are the roles of nitric oxide and free oxygen radicals
- These topics merit detailed evaluation at individual sites.

Neglected questions

Anemia
The pathogenesis of malarial anemia is recognized to be multifactorial, and to have a variable clinical presentation ranging from its common association with chronic low-grade infection in young children, through to more fulminant hemolytic anemia. The topic has been surprisingly neglected, considering its huge impact on the well-being of African children. A renewed effort begins with more detailed clinical descriptions of the presentation of anemia in different sites followed by hypothesis generation. There are preliminary data suggesting that several different mechanisms may be involved, e.g. antibody-binding to erythrocytes, cytokines, and dyserythropoiesis.

Relationships between transmission intensity and disease severity
There is emerging evidence that attack rates of severe malaria may be lower in areas of higher transmission intensity. Validation of this hypothesis involves a multidisciplinary effort in multiple sites, after which the generation of new hypotheses regarding possible mechanisms (immunologic adaptation, parasite genotype/diversity, or host genetics and development) would be warranted. This topic is fundamental for the understanding of pathogenetic mechanisms in general and its pursuit would be significantly accelerated by coordinated data collection in a number of sites.

Other important issues
- The biology of asymptomatic parasitemia.
- The significance of co-infections between different plasmodial species, and between malaria and other infections including HIV; and also interactions with nutritional status.

Recommendations

- Expedite research in those areas where functional correlations have been established with disease severity
    - Chondroitin sulfate A-binding in pregnancy
    - Rosetting
    - Antibodies against TNF-inducing factors

- Expedite research in neglected topics, notably malaria anemia

- Develop a continent-wide capacity for pathogenesis research
    - Database of clinical presentations in different geographical settings
    - Multicenter studies of disease associations
    - Prove causality by experimental interventions

Pathogenesis Focus Group:

Chairperson: Terrie Taylor (USA/Malawi)
Rapporteur: Dominic Kwiatkowski (UK)

Thomas Egwang (Uganda)
Francine Ntoumi (Gabon)
Akintunde Sowunmi (Nigeria)
Peter Kazembe (Malawi)
Kalifa Bojang (Gambia)
Ibrahim ELhassan (Sudan)
Christian Roussilhon (France/Senegal)
Christopher Newbold (UK)
Malcolm Molyneux (UK/Malawi)
Patrick Duffy (USA/Kenya)
Mats Wahlgren (Sweden)
Peter Kremsner (Germany/Gabon)
Ronan Jambou (France/Madagascar)
Jean-Louis Sarthou (France/Guyana)

Entomology Focus Group Report

Introduction

The epidemiology of malaria is driven by the dynamics of the mosquito vectors. Thus, 90% of the world□s malaria is in Africa because it is home to the three most effective vectors. Vector control has been the means of eradication of malaria from numerous regions of the world, and has dramatically reduced its incidence in some regions of Africa. The vector remains the key link in the transmission of malaria, and hence, warrants a new and serious research effort.

New research tools are available, such as genomics, genetic manipulation, GIS, and satellite-based remote sensing that represent quantitative leaps in research opportunities. These opportunities span the whole spectrum from basic to operational research, and link laboratory and field research.

Two main areas of research were identified for specific consideration:

Transmission: research ranging from operational to strategic that leads to a better understanding of transmission as a sound basis for effective control

Strategic vector research: priority strategic research areas that are likely to lead to new or improved methods of malaria control

1. TRANSMISSION

Scientific Question: How can a better understanding of malaria transmission promote effective malaria control?

Rationale*:* There is increasing realization that malaria transmission is more heterogeneous than previously understood. This includes the complex interactions of the host, parasite, vector species and environment. A greater understanding of these interactions is essential to the development of new, improved and focused control measures.

How to answer the question*:*

A. By conducting field studies of vector populations to quantify transmission intensity
    1. Relations between transmission intensity and disease (and immunity)
    2. Role of vectors in the transmission of specific genotypes of malaria parasites
    3. Population genetics and gene flow of vectors relative to transmission
    4. Preparation of field sites for evaluating new control methods (eg, genetically altered mosquitoes)

B. By using GIS and remote sensing techniques to evaluate vector populations and transmission

1. Spatial and temporal heterogeneity in vector populations and transmission
2. Identification of environmental determinants regulating vector distributions
3. Malaria risk maps relative to vectors and transmission intensity
4. Predictive models of transmission and malaria infection/disease
5. GIS as a tool for malaria vector control programs

C. By determining factors limiting transmission
    1. Infectivity of gametocytes and the efficiency of malaria sporogonic development in mosquitoes.
    2. Parasite development and survival in mosquitoes relative to climate/microhabitat selection by vectors.
    3. New approaches and models for better understanding the transmissibility of malaria parasites.
    4. Identification of natural transmission blocking mechanisms and impact on transmission

D. Provide entomologic support for field trials
    1. Vector control programs
    2. Malaria vaccines

E. By developing new tools
    1. For identifying species complexes
    2. For sampling mosquitoes and measuring transmission
    3. For monitoring insecticide resistance in vector populations
    4. For evaluating the transmissibility of malaria parasites
    5. For assessing the infectivity of sporozoites in mosquito salivary glands
    6. For sampling mosquitoes for determining house-specific sporozoite inoculation rates
    7. For assessing larval ecology
    8. For evaluating vector behavior

F. Consider the impact of human activities on vector populations and transmission
    1. Irrigation/agriculture, urbanization, and deforestation
    2. Natural disasters, war, and movement of refugees
    3. Climate change

How collaboration might help answer the question:

A high level of integration is needed between vector research and studies to assess infection/disease in human populations, to test the efficacy of malaria vaccines, and to address issues of vector control. Entomologists pursuing questions relating to transmission will benefit by strong linkages with scientists from other disciplines (e.g., epidemiologists, statisticians, ecologists, population geneticists, molecular biologists, etc.).

***Needs**:*

- Strengthen African research centers in entomology
- Train African scientists in entomology (complementary lab and field experience)
- Promote research partnerships between African scientists and experts elsewhere
- Use the latest information technology to facilitate access to knowledge by all partners (e.g., *Anopheles gambiae* database)
- Standardize molecular tools for identification of vectors and parasites
- Create DNA reference collections for vector and parasites

2. STRATEGIC VECTOR RESEARCH

We have prioritized two areas of research likely to lead to new or improved methods for malaria control.

2A. Genetic manipulation of vector populations:

Scientific Question: How can genetic manipulations of vectors be used to control malaria?

***Rationale**:* Existing methods of control are inadequate in areas of high transmission. However, genetic transformation is a powerful new tool for manipulating the biology of organisms. In combination with an efficient genetic driving mechanisms, it could be used to disrupt the disease carrying capabilities of natural mosquito populations.

***How to answer the question**:*

A. By developing tools for genetic manipulation of the mosquito
    1. Germ line transformation
    2. High density genome mapping
    3. Large fragment genomic libraries
B. By identifying genes that will confer parasite controlling phenotypes
    1. Parasite refractory mechanisms
    2. Mosquito immune mechanisms
    3. Parasite/mosquito interactions during sporogonic development
    4. Behavior modification (e.g.. host preference)
C. By developing ways to drive genes into populations
    1. Transposons
    2. Symbionts
    3. Meiotic drive
    4. Chromosomal aberrations
D. By defining the genetic structure of vector populations
    1. Populations dynamics
    2. Population structure

3. Effective population size
4. Between species (within species complexes) gene flow

E. Develop the logistics, personnel, methods and public awareness for undertaking and assessing field trials

How collaboration might help answer the question:

With support of WHO/TDR and others, a number of the required tools are already in different stages of development in advanced laboratories of Europe and North America, but several of the key aspects of this goal, such as the identification of new parasite refractory mechanisms, determination of vector population structure, and the ultimate testing and implementation of this control strategy will require major participation of African scientists and institutions.

Needs*:*

- Strengthen Centers of Research Excellence in vector biology in Africa
- Train African scientists in the cognate disciplines
- Identify sites for vector population analysis and future field trials
- Promote collaboration between African scientists and experts elsewhere
- Use the latest information technology to facilitate access to knowledge by all partners (e.g., *Anopheles gambiae* database)
- Strengthen and coordinate centers that maintain reference strains of vectors and DNA of field collections

2B. Vector Ecology and Behavior

Scientific question: How will an improved knowledge of vector ecology and behavior lead to improved malaria control?

Rationale*:* Most of what is known about African vectors has been developed in response to efforts to define their role in malaria transmission. Furthermore, most of the ecological and behavioral information known about *Anopheles gambiae* was obtained from studies that did not identify the specific species within the *An. gambiae* complex that was being studied. Thus, many of the key aspects of vector ecology and behavior are not being studied.

How to answer the question*:*

A. By obtaining better knowledge of vector ecology
    1. Larval and adult ecology
    2. Niche partitioning between sibling species
    3. Intraspecies geographic variation in ecology
    4. Population modeling

B. By obtaining better knowledge of vector behavior
    1. Olfaction and host seeking

2. Mating and oviposition behavior
3. Do vectors memorize a home range?
4. Intraspecies geographic variation in behavior

How collaboration might help answer the question:

Expertise in modern techniques of insect ecology, chemical ecology, and behavior needs strengthening in Africa.

Needs*:*

- Recruit scientists from other disciplines (e.g. mathematicians, ecologists, population geneticists)
- Stimulate interdisciplinary approaches to vector research
- Train research leaders from African countries in such disciplines
- Promote research partnerships within Africa and between Africa and other regions
- Identify and strengthen centers of research in vector ecology and behavior
- Strengthen and coordinate centers that maintain reference strains of vectors and DNA of field collections
- Use the latest information technology to facilitate access to knowledge by all partners (e.g., *Anopheles gambiae* database)

Entomology Focus Group:

Chairperson: Yeya Tour (Mali)
Rapporteur: John Beier (USA)
Ousmane Faye (Senegal)
Andrew Githeko (Kenya)
Patrick Rabarison (Madagascar)
Brian Sharp (South Africa)
K.J. Njunwa (Tanzania)
Christopher Curtis (UK)
Didier Fontenille (France/Senegal)
Julian Crampton (UK)
Frank Collins (USA)
Hans Herren (Switzerland/Kenya)
Harold Townson (UK)

Immunology Focus Group Report

The purpose of studying the immunology of malaria is to aid the rational design of interventions to reduce the mortality and morbidity of the disease. Immunology can contribute to malaria control in Africa by leading to the development of vaccines and by providing immunological tools to follow up other interventions. Rational vaccine design is dependent upon an understanding of the mechanisms of protective immunity and identification of the target antigens.

Two areas were considered:

1. What are the mechanisms and antigenic targets of naturally acquired and vaccine induced immunity?

***Scientific question**:* How do humans acquire immunity to malaria?

***Rationale**:* We do not fully understand the immune effector mechanisms which confer protective immunity to the various manifestations of malaria infection and disease in different populations, under different epidemiological conditions, and at different stages of acquisition of immunity. Identification of the components of these effector mechanisms, and their fine specificity, dynamics and regulation is crucial for the identification of target antigens to be considered for vaccine development. A large number of antigenic molecules have been described but their physiological function and immunological importance have not been fully characterized. There is a need to identify/characterize molecules involved in pathogenic processes. In addition such studies can provide the tools that are required for monitoring the immunological consequences of a wide range of different types of interventions.

***How to answer the question**:* The dynamic nature of immune responses necessitates repeated sampling in longitudinal studies. Priority should be given to prospective longitudinal and case-controlled studies, although there is a need for additional descriptive studies in infants (< 1yr) in different epidemiological settings, especially in areas of marginal malaria transmission. Cross sectional studies are less informative; however, to provide background data for vaccine testing, potential vaccine trial centers should begin to collect serum and parasite material, on a regular cross-sectional basis, and store samples for future evaluation of antigen-specific serology and parasite diversity.

Specific priorities for investigation in populations where malaria is endemic include:

- investigating the role of maternal immunity in protection of neonates
- determining mechanisms of pregnancy-specific immunity
- determining the effect of infection during pregnancy on the subsequent immune response of the child (tolerance, premuniti
- determining the importance of anti-toxin(s) immun
- determining whether or not induction of anti-to exacerbate parasitemia
- investigating interactions with other infectious disea parasitic nematodes
- investigating the role of the immune system preventing malaria-related anemia
- performing immunological follow up of all interventi

***Gaps identified and action required**:*

There is a need to coordinate more effective immunology of malaria in Africa. Inventories have immunological field sites and laboratories in Africa. Th to carry out studies under a variety of epidemiological to be done most effectively:

- networks should be established of existing progra erythrocytic, erythrocytic and transmission blocking to standardize protocols.
- an agreed set of data should be collected in a compatibility and comparison amongst different fie endemicities.
- existing serological and clinical databases should the capacity to evaluate new antigens

Productive scientists should be supported to c driven research and this will require the developm and staffed regional centers, with the facilities ne complex biological assays.

- such centers will require stable independent in funding as the expense of equipping and maintaini likely to be beyond the scope of national governm be closely associated with national programs.
- long term secure funding (10 years or more) is vita of facilities needed to conduct longitudinal studie time periods necessary to follow the slow acquisitio follow up of interventions.
- such regional centers of excellence would be linked study sites in different epidemiological settings, capacity to prepare rapidly and to stabilize samples
- the strengthening of good regional laboratories collaboration between African scientists, redu American/European technical expertise and wo training and technology transfer. There already laboratories in Africa that are well-equipped and laboratories would form the basis for initiat sophisticated collaborative studies in the region.

Links with pediatric immunologists need to be established to study the importance of immune competence in neonates.

2. Is it possible to develop reproducible assays that correlate with protective immunity?

***Scientific question**:* do immunological assays correlate with protective immunity?

Rationale: There are two aspects to this question. The first is the measurement of protective responses induced by vaccination with parasite antigens; the second is elucidation of protective responses that occur in naturally exposed populations. Naturally acquired protection may be the result of multiple effector mechanisms acting against different antigens and different stages of the parasite and requiring a variety of different assays.

Although we define protective immunity as the absence of clinical disease, most in vitro functional assays measure reduction in parasite numbers or growth. The relationship between parasite density and clinical disease is unclear, but it is difficult to develop in vitro assays for clinical protection. The validation of in vitro assays requires correlation with protection in human studies of protected and non-protected individuals in vaccine trials, or in longitudinal or case-control studies. The results of these assays will inform decision making at pivotal points during the vaccine development process.

***Existing assays**:* We surveyed all the assays available for the different stages of parasite development. Existing simple rapid assays (for example ELISA, IFA and agglutination to measure antibody) may indicate the prevalence, level and specificity of an immune response but do not provide an indication of functional activity. Functional assays measure a biological activity, such as inhibition of sporozoite or merozoite invasion or transmission blocking activity. These methods are more complex technically demanding and may require very expensive equipment; many of these assays require very labile samples and viable short-lived cells. At the present time none of these assays have been validated in a clinical setting.

Specific priorities:

- Optimization of existing assays,
- Standardization of assays using well-characterized and renewable reagents,
- Validation of proposed mechanisms of immunity, identification of limitations in the effective use of these assays in a field setting, and;
- Development of assays to correlate with pathological processes.

***Gaps identified and action required**:*

Immunological assays need validation, to show correlation with protection.

- The successful vaccination of humans with defined antigens and the conduct of well-designed longitudinal studies will allow the evaluation of existing assays to identify those that are most relevant to protection.

Assays need to be standardized between labo comparison of data obtained by different investiga

- Standardization requires the identification, produc reference reagents and protocols. To achieve consensus achieved through regular exchanges workshops involving researchers worldwide.
- The development and standardization of assays c certain regional reference laboratories in Afric enabling the tests to be used routinely and di laboratories.
- The training of competent and experienced Africa and technicians, as well as access to the most up essential.
- Specific funding is required for the imple recommendations.

There is need to modify some existing assays t in Africa.

- Miniaturization to allow the use of small amounts of
- Wherever possible, complex functional assays sh simpler surrogate assays. The complicated nature has restricted their widespread use.
- Replacement of methods reliant upon the use of ra

There is the need to develop additional immunolog

- Currently, assays on human material only reflect the peripheral circulation. Alternatives to peripher material for studies need to be considered. For e hypersensitivity may be used to provide a measure
- Convenient assays are required that measure para severe disease, for example rosetting or cytoad difficult to develop.

Procedures are required to facilitate the exchan between laboratories; to avoid delay during imp exemption from customs regulations.

Immunology Focus Group:

Chairperson: Odile Puijalon (France)
Rapporteur: Rose Leke (Cameroon)

Laurence Ralamboranto (Madagascar)
Alioune Dieye (Senegal)
Robert Mshana (Ethiopia)
Moussa Kone (Cote d'Ivoire)
Susan Mutambu (Zimbabwe)

Geoffrey Targett (UK)
Anthony Holder (UK)
Pierre Druilhe (France)
Philippe Deloron (France)
Adrian Hill (UK)
Carole Long (USA)
David Kaslow (USA)
Eleanor Riley (UK)
Ruth Nussenzweig (USA)
Dominique Mazier (France)
Olivier Garraud (France/Senegal)
Howard Engers (WHO/TDR)
Mats Wahlgren (Sweden)
Christopher Newbold (UK)

Antimalarial Drugs Focus Group Report

I. STATE OF THE ART: ANTIMALARIAL DRUGS CURRENTLY IN USE OR UNDER DEVELOPMENT

Consideration of antimalarial drugs began with a general review of drugs currently available, drugs in clinical studies, drugs in transition from pre-clinical to clinical studies, drugs in pre-clinical studies, and potential antimalarial drug targets. The consensus of the working group based on this review was that an inadequate number of potential new antimalarials are now moving actively in the pipeline from basic science to clinical studies.

A. ANTIMALARIALS CURRENTLY USED FOR TREATMENT

	Drug	Indication	Comment
1	Chloroquine	Severe and Uncomplicated Malaria	Limited by the prevalence of resistance
2	Fansidar (Pyrimethamine, Sulfadoxine)	Uncomplicated	Limited by the prevalence of resistance
3	Amodiaquine	Uncomplicated	Potential chloroquine alternative
4	Quinine/Quinidine	Severe and Uncomplicated	Limited by toxicity
5	Halofantrine	Uncomplicated	Potential cardiac toxicity, and resistance, esp in Southeast Asia
6	Mefloquine	Uncomplicated	Limited by resistance in Southeast Asia
7	Artemether/Artesunate	Severe and Uncomplicated	Potential neurotoxicity
8	Malarone	Uncomplicated	Recently introduced combination of atovaquone and proguanil

B. ANTIMALARIALS CURRENTLY USED FOR PROPHYLAXIS

	Drug	Comments
1	Chloroquine	Limited by the presence of resistance
2	Mefloquine	Limited more by side effects than resistance
3	Proguanil	Limited by the occurrence of resistance
4	Pyrimethamine (Daraprim)	Limited by the occurrence of resistance
5	Doxycycline	Limited by side effects - photosensitivity, vaginitis

C. ANTIMALARIALS UNDER CLINICAL STUDY FOR TREATMENT

	Drug	Indication	Comment
1	Arteether	Severe and Complicated	Injectable preparation in oil, acts rapidly
2	Pyronaridine	Uncomplicated	Oral formulation/potential low cost alternative with chloroquine resistance
3	Chlorproguanil /Dapsone	Uncomplicated	Alternative to Fansidar which may have greater activity
4	Artesunate Suppositories	Uncomplicated Malaria (*npo*)	For treatment of vomiting patients at sites without injectable antimalarials
5	Co-Artemether		Artemether + benflumitol

D. ANTIMALARIALS UNDER STUDY FOR CHEMOPROPHYLAXIS

	Drug	Comment
1	Azithromycin	Doxycycline replacement for young children and pregnant women
2	Malarone	

E. DRUGS IN TRANSITION FROM PRE-CLINICAL TO CLINICAL TESTING

	Drug	Comment
1	Desbutyl Halofantrine	Halofantrine metabolite, which may be less cardiotoxic
2	Aminoquinoline Analogs	Modifications of chloroquine active against resistant *P. falciparum*
3	WR 238605	8-Aminoquinoline intended as single dose replacement of primaquine, with potential schizonticidal and transmission-blocking activity against *P. falciparum*

F. POTENTIAL ANTIMALARIAL DRUGS IN PRE-CLINICAL TESTING

	Drug	Comment
1	Phospholipid Inhibitors	Active in vitro and in *Aotus* monkeys against chloroquine-resistant *P. falciparum*

G. LEAD COMPOUNDS UNDER INVESTIGATION

	Compound	Comments
1	Malperox Compounds	
2	Protease Inhibitors	
3	Biguanides	
4	Acridine Compounds	Analogs of floxacrine with no obvious cross-resistance to other antimalarials
5	Bisquinolines	
6	Ferrocene Chloroquine	

H. POTENTIAL ANTIMALARIAL DRUG TARGETS

One of the major concerns of the working group was that the available drugs focus on a limited number of biological targets. Therefore, there was a consensus that substantial scientific effort should be devoted to the development of additional novel targets, in the hope that those drugs would not demonstrate cross-resistance with presently known antimalarials.

1] Hemoglobin Degradation
2] Drug Transport and Efflux
3] Folate Metabolism
4] Phospholipid Metabolism
5] Purine and Pyrimidine Synthesis (e.g., HGPRT)
6] Cell Assembly/Cell Cycle
7] Oxidant Defenses
8] Macromolecular Synthesis (DNA, RNA, Protein, Lipid, CHO)

II. SCIENTIFIC ISSUES

The working group examined a number of scientific issues, some of which received high priority for their scientific interest (below), and others of which received high priority as points of potential north-south and south-south collaboration (III, below).

A. MONITORING ANTIMALARIAL RESISTANCE

In an era of epidemic drug resistance, surveillance and the use of molecular assays must be based on a clear understanding of "resistance" in the context of *in vivo* and *in vitro* responses. Rigorous characterization of resistant parasites begins with *bona fide* therapeutic failures in which clinical diagnosis, parasitemias and blood levels of appropriate metabolites have been (or can be) determined. *In vitro* assays should follow isolation of parasites from such cases, providing IC50 or MIC values and characterization of mutations in drug-resistance genes as they are found. There exists a broad gulf between our knowledge of clinical and parasitologic resistance, particularly in relation to immune status, and a systematic correlation with *in vitro* assays based on growth parameters or molecular methods. Too often, *in vitro* levels of "resistance" are loosely reported without evidence that the parasites were in fact resistant to therapy *in vivo*. Without vigorous definition of resistance and clear understanding of this relationship to therapeutic failure, our effective use of important drugs and recognition of regions in which they fail will continue to be suboptimal.

Although most agreed that resistance should be monitored, there was not a consensus on how that monitoring should be performed or on how extensive it should be. Most favored *in vivo* testing of commonly used antimalarials. Important issues discussed included: the **test population** (non-immunes, including tourists, provide a better opportunity to detect resistance), and **re-infection** (which is difficult to exclude in endemic areas). Although *in vivo* testing is most realistic, there are two situations in which *in vitro* testing may be particularly helpful: 1] assessment of rapid emergence of resistance against new drugs, and 2] early warning mechanism for drugs already in use. One way to ensure that the results of surveillance are applied to policy is to have the monitoring conducted in part by the Ministry of Health.

However, there are no generally accepted thresholds which are thought to require changing from one antimalarial to another. Such decision making should also recognize that the distribution of resistance may be quite heterogeneous even within one country. One should also recognize that these decisions are driven largely by financial considerations in countries with limited budgets. National policy must recognize the impact of drug resistance levels in neighboring countries.

It is not yet clear whether multiple resistance (as established in Southeast Asia) will also become prevalent in Africa, which should be performed, and monitoring for multi-drug resistance should be performed in a systematic way. In addition to surveillance to determine the prevalence of resistance, it is important to convert that information to health policy (National Formularies), to test strategies such as multiple drug treatment and drug rotation, and to determine whether removal of a drug to which resistance is common (e.g., chloroquine) will result in restoration of susceptibility to that drug. Of note is a proposal from Glaxo-Wellcome to make Malarone available in Africa, Southeast Asia, and Latin America via a controlled donation program administered by the Task Force for Child Survival and Development in Atlanta. This program, which will be directed by an advisory committee of senior scientists and international public health specialists, will ensure that the drug is used appropriately.

***CONCLUSIONS**:* Monitoring antimalarial resistance is essential, and is also an important potential point of north-south and south-south collaboration. Standardization

of the definition of resistance and methods to detect it should receive a high priority. It may be possible to use the Glaxo-Wellcome donation of Malarone as the basis of additional studies in priority areas.

B. MECHANISMS OF ANTIMALARIAL ACTION

This topic provoked a vigorous discussion. When mechanisms of action are identifiable (molecular drug targets), they may lead to the development of more potent analogs (e.g., HIV protease inhibitors). Although such studies may be more definitive in the future, they have been difficult to perform in the past.

***CONCLUSION/RECOMMENDATIONS**:* These studies are essential to identify new molecular targets and should therefore receive continuing and long-term emphasis.

C. MECHANISMS OF ANTIMALARIAL RESISTANCE

Factors such as drug use, endemicity and community practices may enhance selection for resistance. There was a consensus that it was important to determine resistance mechanisms. Subsequent discussion focused on the development of central repositories for well-characterized parasites with information about the drug regimen, parasitologic response, and drug blood levels.

***CONCLUSION/RECOMMENDATIONS**:* The committee recommends the development of repositories containing well-characterized parasites from treatment failures and successes. Continuing studies on mechanisms of drug resistance should be pursued in a broad global context.

D. DEVELOPMENT OF NEW DRUGS

While there are several drugs in the pipeline, there is a continuing need for new drug discovery and development. This is another potentially fertile area of interaction between developing and developed countries. Indeed, it may be a necessity because of the recent loss of support for antimalarial development from pharmaceutical companies. There was a consensus that this would require major outside funding.

***CONCLUSION/RECOMMENDATIONS**:* Discovery, design and development of new antimalarials would benefit greatly from the resources which are routinely brought to bear on the development of anticancer drugs in northern countries. In the absence of that effort, it may be essential to propose alternative strategies.

E. TOXICOLOGY, TOXICITY AND PHARMACOKINETICS

Standard toxicology studies can now be performed by contractors, and should not pose a problem. Study of toxicities not detected during Phase I and II studies (post-marketing surveillance) may be a problem with smaller companies or with development in the absence of commercial involvement. Pharmacokinetics and metabolism may be substantially different among different racial and ethnic groups, and in pregnancy.

A major problem that remains is the treatment and prophylaxis of malaria in pregnant women. Although chloroquine and mefloquine have been found safe in pregnant humans, and proguanil and pyrimethamine are thought to be safe, there is a need for additional study of antimalarials in pregnancy. These studies also pose ethical

issues, which must be addressed.
If a drug development consortium (or other non-industrial base) is formed for drug development, the issue of post-marketing surveillance for side effects will also need to be addressed. Likewise, there should be a consortium of African centers for antimalarial testing, using similar protocols, and examining drugs in parallel at different centers in areas with different types of malaria transmission and endemicity.

***RECOMMENDATIONS/CONCLUSIONS**:* Major unresolved problems which could become foci of collaboration include the use of antimalarials in pregnancy. Although toxicology studies can be performed by contractors, training of individuals and support of institutions will require long-term investment (capacity building - part IV, below).

F. HERBAL MEDICINES

Two of the most important antimalarials now in use were originally identified from herbal medicines. This is a potentially important area of interaction between developing and developed country scientists. In sub-Saharan Africa, most countries have at least one laboratory devoted to such compounds. The isolation of active compounds from such preparations may yield antipyretics, analgesics and other useful compounds, as well as antimalarials. This is an area where collaboration could transform work that is often primarily descriptive to a solid common, biochemical basis for research and simultaneously offer the opportunity for discovery of new compounds.

There is already one International Collaborative Biodiversity Group project supported by the Fogarty International Center, NIH, in Nigeria, Cameroon and the US. Other groups are also active and an inventory of these activities should be obtained.

***RECOMMENDATION/CONCLUSIONS**:* Drug discovery and development should include the study of herbal medicines. These studies should include the identification of lead compounds active against drug-resistant *P. falciparum* and the study of structure-activity relationships.

G. FACTORS THAT INFLUENCE THE DEVELOPMENT, SELECTION AND SPREAD OF RESISTANCE

The effects of transmission intensity, recombination rates and transmission-blocking vaccines on the development, selection and spread of resistance are unknown and should be studied. There was no clear consensus on the effects of transmission intensity, recombination rates, and transmission blocking vaccines on the rate of developing resistance. Recent work suggests that individual parasites may vary substantially in the rate at which they mutate. Factors thought to affect the emergence of antimicrobial resistance in general include:

1. **Antimicrobial Combinations** are of proven efficacy in the treatment of diseases such as TB, leprosy and HIV/AIDS because they limit the emergence of drug resistance. This approach should be evaluated as soon as possible for the treatment of malaria.
2. **Useful therapeutic Life (UTL).** Pharmacokinetic parameters, especially the elimination half-life, $t_{1/2}$, may be important in the selection of drug-resistant parasites.

3. **Sub-Therapeutic Doses (Concentrations).** Although thought to increase the risk of resistance, there are few well-documented examples of this phenomenon.

***RECOMMENDATIONS/CONCLUSIONS**:* The consensus of the group was that the use of multi-drug therapy in malaria to limit the emergence of resistant parasites should be evaluated in the near future.

H. EFFECTS OF HOME TREATMENT

The efficacy of antimalarials in the field is often limited by health care providers who have little understanding of those antimalarials. This is potentially a very vulnerable point in the use and useful life of new drugs. If sub-therapeutic doses (levels) enhance the development of resistance, they will also enhance the spread of resistance. This may be particularly important when drugs for days 2 and 3 of treatment are given to the mother, who then may divide those drugs among all her children. Thus, home treatment often occurs in the context of a drugs prescribed at a clinic or hospital.

***RECOMMENDATIONS/CONCLUSIONS**:* Although most drug studies are performed in hospitals or clinics, most antimalarial use actually occurs in the home (even when the drugs are prescribed in the hospital or clinic). Improvements in education at the provider and consumer level should be incorporated into policy initiatives.

III. POTENTIAL POINTS OF COLLABORATION

A. DEVELOPMENT OF A CONSORTIUM FOR ANTIMALARIAL DRUG DISCOVERY, DESIGN AND DEVELOPMENT

Pharmaceutical companies, which have previously supported antimalarial drug development have recently become less active. In the absence of this support, new and innovative strategies will be necessary to address this problem. Specific strategies to respond to this challenge include the creation of an African Consortium for Antimalarial Drug Discovery, Design and Development. African resources already available to support this strategy include departments of pharmacology, pharmacy and pharmacognosy; departments of traditional and herbal medicine; and primate centers], and centers capable of performing clinical studies). Thus one strength of this proposal is that it draws upon pre-existing African expertise to address a problem of overwhelming importance in Africa which no longer receives sufficient attention or support in non-endemic countries. Initial funding will be required for this initiative from sources such as the World Bank, UNDP, the bilateral donor community and the pharmaceutical industry.

B. MONITORING OF RESISTANCE

Monitoring of resistance is a potential point of north-south collaboration which has the advantages that *in vivo* monitoring is performed in most African countries, and that the results of monitoring are potentially applicable directly to national drug policy. Likewise, it is a potential focus of north-south collaboration because clinically well-characterized isolates are essential for studies of antimalarial resistance.

C. REPOSITORIES OF WELL-CHARACTERIZED PARASITE ISOLATES

One of the major problems in understanding antimalarial resistance is the lack of well-characterized isolates, for which the parasitologic and clinical response, drug regimen and, if possible, drug levels are known. The lack of such material is a major stumbling block in our understanding which should be remedied by establishing repositories of such isolates with the accompanying clinical, parasitologic and pharmacologic data in sub-Saharan Africa.

D. DEVELOPMENT OF A CLINICAL TRIALS NETWORK

Candidate antimalarials must be studied in different areas with different patterns of transmission and endemicity, and at more than 1 center. In most cases, those studies should use similar protocols so the results are potentially comparable. A clinical trials network would accomplish this objective, does not exist, and could draw upon existing expertise at many centers, although it would also require additional investment for the training of personnel and institutional support for physical facilities and data handling (capacity building).

E. STUDIES OF ANTIMALARIALS IN PREGNANCY

The safety of antimalarials in pregnancy can be determined only by studies in humans, with careful longitudinal follow-up. Although these studies have rarely been performed in Africa, recent experience in a number of African countries demonstrates that they are feasible and can be performed well. As with the performance of clinical trials, substantial investment will be necessary, in this instance, primarily for the costs of longitudinal follow-up. In the final analysis, the safety of antimalarials in pregnancy for Africans can be determined only by studies in Africa.

F. STUDIES OF DRUG USE IN THE COMMUNITY

Only community-based studies can examine the potentially selective effects of antimalarials (for resistant parasites) or the effects of antimalarials on transmission. Studies of multidrug treatment to minimize the emergence of resistance and of drug rotation likewise must be performed within the community.

IV. PRIVATE INITIATIVES FOR COLLABORATION

The fact that Glaxo-Wellcome plans to donate Malarone opens opportunities for initiatives related to: effective use of antimalarials for treatment failures (use of Malarone for subjects who failed chloroquine or Fansidar treatment), monitoring for early resistance (to Malarone, as well as its components), and antimalarial use in pregnancy.

V. INFRASTRUCTURAL ISSUES

A. DEVELOPMENT OF A CONSORTIUM FOR ANTIMALARIAL DRUG DISCOVERY, DESIGN AND DEVELOPMENT (see IIIA, above).
B. RESEARCH CAPACITY STRENGTHENING

To accomplish any or all of the 6 priorities for collaborative research outlined above

will require the training of additional African scientists, and continuing support (e.g., re-entry grants) for those who have been trained. Likewise, each of the priority initiatives will require some investment for equipment (institutional support). This should include support for primate facilities for the *in vivo* testing of candidate antimalarials.

C. COMMUNICATION NECESSARY FOR COLLABORATIVE CLINICAL TRIALS

For those who have spent their lives working in the northern countries, it is difficult to imagine making scientific progress in the absence of rapid electronic communication and readily accessible journals. Yet this is precisely the situation in most of sub-Saharan Africa. Even where satellite stations exist and function (at a minority of sites), they do not function in real time and therefore cannot not provide access to the Internet which is comparable to that obtainable elsewhere. In addition, the costs of phone calls, FAX messages and air transportation (of parasites or other reagents) are often greater than elsewhere. Without similar access to current scientific information, the progress of science in sub-Saharan Africa will continue to be limited.

VI. SUMMARY

Antimalarial drugs save the lives of seriously ill children, pregnant women and others every day, and are in fact the basis of malaria control in Africa today. However, antimalarials alone cannot eliminate malaria in areas such as sub-Saharan Africa, where transmission is intense and the majority of the population may be infected and at risk for 6 or more months each year. Unfortunately, the increasing frequency of antimalarial resistance (to chloroquine initially, and now to sulfadoxine-pyrimethamine [Fansidar]) has increased the frequency of severe and complicated malaria. This crisis is complicated by the selective effects of drug pressure (including empirical treatment). As a result, antimalarial resistance (especially resistance to chloroquine) is the major factor responsible for the worsening of the malaria situation in sub-Saharan Africa. Thus the principal goals of antimalarial use are to prevent mortality and decrease morbidity, not to prevent infection or eradicate malaria.

However, the response to this crisis has been inadequate. Because of cost, the presently existing alternative antimalarials known to be active against resistant parasites are typically unavailable at the village level. Thus, the only antimalarials readily available to most Africans and their children, chloroquine and sulfadoxine-pyrimethamine, are those to which resistance has already developed. Recent experience underscores the need to encourage and interest the pharmaceutical industry, which has substantially decreased its support for the development of new antimalarials (REF). What then, are the alternatives? In particular, what strategies which could both address these problems, drawing on pre-existing expertise in both developed and developing countries?

There are at least 6 collaborative strategies which have this potential:

1. **Development of a consortium for antimalarial drug discovery, design and development** with strong support from industry and with commitment to the study and development of herbal medicines;
2. **Monitoring of resistance** based on isolates from patients treated under controlled conditions

3. **Repositories of such, well-characterized parasite isolates** in Africa available to interested investigators;
4. **Development of a clinical trials network** to study new antimalarials, especially those with activity against resistant parasites;
5. **Studies of antimalarials in pregnancy,** and;
6. **Studies of the rational use of antimalarial drugs in the community,** including multidrug therapy, educational improvements at the consumer and provider level and expeditious clinical study of antimalarials active against otherwise resistant parasites.

Each of these strategies is a potential platform for interaction among investigators from developing and developed countries.

Accomplishment of these goals will require a mixture of strategies such as those outlined above, basic research, and infrastructural development. In basic research, the malaria genome initiative and other innovative approaches are likely to identify important new drug targets. Because identification and validation of these leads will require a thorough understanding of parasite biology, cell biology, biochemistry and genetics, training of African scientists in these disciplines should be a priority. Additional infrastructural steps that will be necessary include inventories of investigators and institutions working on malaria, support for training and institutional development (capacity building), access to current scientific information and other investigators via E-Mail and Internet.

The present state of antimalarial drug development does not meet either the needs or the expectations of sub-Saharan Africa. For this reason, new and innovative strategies will be necessary. Models which should be examined for leads include the successes of the software industry in Southeast Asia and the drug industry in Malaysia. This strategy should encourage entrepreneurial activity, sustainability and full participation of African institutions. With judicious investment based on talented African investigators, venture capital strategies and capacity building, it should be possible to turn this overwhelming liability into an asset, which could become a focus for the development of industry in sub-Saharan Africa.

Antimalarial Drugs Focus Group:

Chairperson: Lateef A. Salako (Nigeria)
Rapporteur: Donald J. Krogstad (USA)

Philippe Brasseur (France)
Thomas G. Egwang (Uganda)
Daniel E. Goldberg (USA)
Michael B. Heisler (USA)
Ronan Jambou (Madagascar)
Wilbur Milhous (USA)
Theonest K. Mutabingwa (Tanzania)
Ayoade M.J. Oduola (Nigeria)
Pascal Ringwald (Cameroon)
Gwiria M.H. Satti (Sudan)
Henri Vial, PhD (France)

Marian Warsame (Sweden)
Oladapo Walker (Republic of the Congo)
William Watkins (Kenya)
Thomas E. Wellems (USA)
Jack J. Wirima (Malawi)
Dyann F. Wirth (USA

Epidemiology Focus Group Report

Introduction

African malaria has not one but many epidemiologies, with differing patterns of disease in different endemic areas. An implicit understanding of epidemiology underlies all control programmes. In the past, as control and eradication were attempted largely through attacks on the vectors, epidemiology was concerned solely with transmission; illness and death due to malaria were largely ignored as research topics. Now that control is concerned with the reduction of morbidity and mortality by varied means, a fuller understanding is needed.

Malaria transmission in Africa encompasses a wider range of basic case reproduction rates than anywhere else, and the relation between transmission and disease has been re-opened as a research issue by recent direct field studies in both East and West Africa and by the results of intervention trials with insecticide-treated bed nets. In the light of recent detailed longitudinal studies of malaria in Senegal, on disease differences between highly areas of East Africa, host genetic variability in The Gambia and parasite genetic variability in Senegal, Tanzania and Sudan, there is a need to rethink basic malaria epidemiology and the relations between transmission, infection and disease, based on longitudinal field studies, hospital studies and the use of new parasite-genetic techniques. This improved understanding will influence control strategy and affect the ways in which we assess the efficiency of currently used control methods and strategies, evaluate new control tools such as vaccines and impregnated bednets and identify the best targets for antimalarial control measures.

Epidemiology lies at the intersection between the laboratory sciences and control, in that tools developed by them have to be assessed in the field. The effectiveness of health systems is also determined by epidemiological methods, whilst the relation to entomology is so close that often in the past people behaved as though the two were identical. The focus group, aware of specific focus groups on various interventions and on vectors, has therefore not addressed these areas.

The epidemiology focus group identified the following four main fields of activity that were considered as priorities for collaborative epidemiological research:

1.) Relationships between transmission, infection, disease and death

Studies of these relationships involve multidisciplinary longitudinal observations of defined communities and of sick populations related to such communities. They can be used to answer multiple scientific questions, of which some key ones are specified below. But it is important to recognize that a defined population study is analogous to a whole laboratory and not to a single experiment: it costs a large amount to set up, but can then tackle many questions. For example, it is possible to investigate the consequences of impregnated bed net use for the immune status of endemic populations using them. In addition, such research will provide new information on the human host/parasite/vector relationships, information which will open new ways to study pathogenesis and mechanisms of protective immunity.

The main questions identified within this broad category as of highest priority were:

Scientific Question**:** What are the determinants of severe, life-threatening malaria?

Rationale: We presently lack a detailed appreciation of the clinical and demographic consequences of *P. falciparum* exposure among African populations. Failure to understand the relationship between the frequency of parasite exposure and the development of immune mechanisms which prevent illness and death is a barrier to the rational introduction of insecticide treated bed nets across the continent. Research on this subject is necessary to guide other disease control approaches currently being developed.

Extending current epidemiological studies of severe and complicated malaria across a wider range of endemicities, ecologies and populations will allow the examination of a) the transmission determinants of age-specific and syndrome-specific (e.g. cerebral and severe anemia complications) disease risk; b) host and parasite genetic mechanisms implicated in severe disease, necessary to support vaccine development; c) the present burden and pathologies associated with mortality across the continent necessary to plan new and innovative clinical interventions.

Approach: Such studies necessitate continuous, detailed and well standardized clinical surveillance protocols at hospital settings with appropriate diagnostic facilities. The selection, enumeration and epidemiological characterization of at-risk populations immediately surrounding these clinical settings allows the examination of risk within the population and between populations. To-date there are less than five settings in Africa able to undertake such studies, so restricting the generalization of either the effects of transmission intensity upon the risks of severe manifestations of falciparum malaria as well as a continental perspective of host, parasite and environmental risks for severe malaria.

Scientific question: What are the host, parasite and environmental processes which modulate the balance between transmission, infection and disease in African endemic malaria.

Rationale*:* Populations living in Africa are generally exposed to high levels of malaria transmission. In many individuals, there is a highly regulated state of permanent infection through most of the life. Immunity plays a large role, yet children are intermittently ill and often die. We need to understand the processes involved in order to predict the effects of and decide on specific control measures.

Approach*:* The proposed approach is the long-term longitudinal follow-up of populations which have been clearly defined clinically, biologically, sociologically, entomologically, ecologically and demographically. The size of such populations, the parameters to be followed and the modes for this follow-up will vary according to primary specific objectives of a given study, in particular according to whether the study of morbidity or mortality linked to malaria constitutes one of these objectives. In all cases, the essential factors to increase the chances of obtaining major unexpected results are probably the number of parameters simultaneously studied, as well as the frequency and the length of their follow-up.

Scientific Question: How does genetic diversity of host, parasite and vector influence the epidemiology of malaria?

Rationale: The recent availability of DNA sequence information from the rapidly expanding databases of the human, malaria and anopheline genome projects makes it timely to describe and ask how polymorphisms in genes of hosts and parasites can influence the epidemiology of malaria in Africa. Availability of sensitive PCR technology make studies of a large number of DNA sequences possible from a limited amount of field material feasible. Variation in human host genes has been associated with both susceptibility and resistance to the clinical outcome of malaria infection. The recent description of genes involved in expression of variable adhesion phenotype of P. falciparum also makes it timely to begin to dissect the relative importance of host and parasite polymorphisms in the etiology of severe malarial disease.

Approach: Both longitudinal and cross-sectional collection of polymorphism data from host, parasite and vector must be achieved as an integral part of epidemiological studies to define:

- The role of host genetic factors and parasite virulence in the clinical outcome of malaria infection
- Dynamics of malaria infection within and between mosquito and human hosts
- The population genetics of vector and parasite in Africa in relation to patterns of infection and disease
- Drug resistance

Scientific Question: What are the determinants of infectiousness of gametocytes to the mosquito vector?

Rationale: During the era of vector control the biology and epidemiology of transmission of malaria from the human host to the mosquito vector was largely unstudied. The process of infectiousness involves the production of transmission stages, gametocytes. Direct feeding of mosquitoes on human gametocyte carriers has demonstrated that it is not always possible to associate the presence of gametocytes with successful transmission to the mosquito vector due to modulation of infectiousness by host factors and antimalarial drugs. Description of age-specific patterns of infectiousness in relation to gametocyte carriage as well as an understanding of the role of host factors and antimalarial drugs in induction of infectiousness are urgently required. This information can be used to develop a better theoretical framework for transmission as well as to assess the potential success of transmission-blocking vaccines and other interventions.

Approach: Longitudinal, age-specific studies of community patterns of infectiousness to local anopheline vectors must be completed in areas of different transmission intensity to monitor the potential for transmission before and after interventions. The effect of host factors and antimalarial drugs on infectiousness should be considered in the context of appropriate clinical trials.

Scientific Need. To achieve progress on these practical problems, there is a strong need for more standardized methodology and quality-controlled techniques so that valid

inter-area comparisons can be made. This applies to all epidemiological variables from clinical conditions to PCR technology.

Rationale: Several research groups are producing data on e.g., parasite diversity and vector identification using different methods of collection of samples, storage conditions and reagents.

Approach: In order to facilitate comparative studies and reduce the number of variable conditions and methods, a workshop on standardization of these methods, applied to field material, is strongly recommended.

Scientific Question. New information referred to above on disease, molecular epidemiology and drug resistance can be used to achieve a new synthesis of malaria epidemiology**.**

Approach*:* The case has already been made for a new synthesis, which is likely to take the form of a series of epidemiological models incorporating the new information and giving as much guidance to controllers as did the Garki and Macdonald models of transmission earlier. The data will be provided by studies of the types outlined in the preceding and following sections of the report.

2.) Epidemiology of Resistance to Antimalarial drugs, and Development of appropriate drug policies.

There is a major challenge presented by resistance to anti-malarials. In particular, the severe impact on malaria mortality of the spread of resistance to chloroquine, the limited number of antimalarials available and the fact that resistance to almost all of these occurs and is spreading gives cause for grave concern. In spite of the recognized urgency of this problem, very little research is currently underway in Africa toward the discovery of solutions. This is all the more serious as there is little current research undertaken by drug companies toward developing new antimalarials.

As far as epidemiology is concerned, two main lines of research seem to constitute priorities: first, a better understanding of the mechanisms which favor the emergence and spread of resistance to each drug; second to identify criteria which would allow better choice of first and second line modes of treatment. However, an appropriate beginning will be to gather research workers from the countries involved on a regular basis to initially bring together available data and move forward from there. The overall aim is to determine the epidemiology of antimalarial drug resistance in Africa and to use this information to assist in the development of appropriate drug policies.

Scientific Question: What is the current situation in Africa concerning drug susceptibility, based upon in vivo and in vitro data?

Rationale: A large amount of information exists, at present, based upon varying sources (e.g. clinical records, surveys, research projects etc.) though methodology used is not always comparable. Some data on non-response to treatment precludes quality control on drug(s) used, assessment of drug uptake and presence of metabolites.

Approach: It is important to evaluate the present situation and, for such an objective, a collaborative effort or network of interested workers is proposed. The initial task of this group would be to map such good data as are in existence on the distribution of resistance to each antimalarial drug and then to gather more data by standardized and quality-controlled methods on drug resistance as assessed by in vitro and in vivo methods, by PCR methods as applicable and in terms of operational treatment failure; distinguishing the different types of data. Specific subsequent activities should include that:

1. Tests for chloroquine and amodiaquine be carried out, in parallel, in vivo and in vitro, under identical methodology and in well defined epidemiological settings.
2. WHO/OMS assays for S/P susceptibility be improved and implemented for field studies.
3. Quinine resistance in Africa be studied, especially in relation to treatment of severe malaria.
4. Standardized asays for chloroquine, amodiaquine, mefloquine, S/P, quinine and halofantrine should be carried out on a regular basis, in the same areas, in order to map regions in Africa.

Assays for new drugs should be used, prior to local utilization of these drugs.

***Scientific Question*:** How to associate genes involved with drug resistance with development of molecular probes aimed at field studies?

Rationale: Laboratory studies have revealed that alleles of some genes are associated with drug resistance. This has been best exemplified by studies on DHFR and resistance to pyrimethamine. PCR methodology has further allowed confirmation that recrudescent parasites following clinical treatments are genuinely resistant, and not due to new infections. It will be possible to make studies on the spread of parasites resistant to drugs by such PCR methods, once the genes determining resistance are identified. The genes involved in resistance to chloroquine, mefloquine and new drugs remain to be fully identified, and are under investigation at present. Such studies will need standardized methodologies to be developed, including collection and storage of samples, etc.

A continuous effort should be made to utilize the data to provide advice on drug policies.

3.) Impact of Environmental Change on Malaria

Both human interventions and environmental changes mean that the epidemiology of malaria in Africa is being altered in complex ways. The changes are unevenly distributed through Africa, but include:

(i) Climatic determinants of malaria transmission, including regular annual cycles, irregular climatic variation between years, and systematic change of the global warming type. Predicting such malaria epidemics is of practical importance, the more so as they appear to have become more prevalent recently.

(ii) Environmental changes due to socioeconomic development projects. Many forms of

development give rise to environmental changes that affect malaria transmission. They include water resource developments for power or irrigation, deforestation and urbanization. Certain forms of irrigation have shown different effects on malaria in different parts of Africa and specific studies are proposed of this topic.

(iv) Human behaviour change, including migration as refugees, or occupational or urban migrants.
Whilst behavioral research will need to accompany any proposed control interventions, the group wished to emphasize the need for adequate attention to be given to urban malaria. This is likely to be an increasing problem as the proportion of people living in cities tends towards 40% by the year 2000 and almost all epidemiological studies have been of rural populations so far.

(iv) Environmental methods of malaria control, such as insecticide-treated bed nets, may possibly affect human immunity as well as transmission.

There is also a need to document the baseline malaria epidemiological picture throughout Africa.

Scientific Task: Establishment of a Pan-African malaria database which integrates heterogeneous data towards a better understanding of the spatial epidemiology of malaria in Africa.

Rationale. Extensive information exists on the occurrence of malaria as an infection in Africa, but it is of variable quality and uncollated, although this would provide a baseline for both epidemiological understanding and control efforts. A beginning has been made by the MARA/ARMA Collaborative Project, and this can be augmented. Malaria across Africa is heterogeneous in its distribution, disease patterns and basic transmission biology. Central to the collaboration is the belief that these factors should guide malaria control. However, there are no adequate databases or maps which provide these epidemiological tools.

Approach. MARA/ARMA uses a GIS approach to integrate, basic malaria data, with, administrative boundaries, population, climate, topography etc. The malaria data are presently collated using a standardised proforma to capture parasitological, clinical and entomologic survey data. This is conducted via five regional centers, each responsible for approximately seven neighboring countries, and is coordinated from South Africa. This collaboration was initiated by epidemiology groups within Africa and represents a model of South-South collaboration.

It is envisaged as an integral part of national and international control activities and to date has had a dynamic interaction with national malaria control programmes in pilot countries. Products will be conveyed to malaria control personnel and researchers in each country to continue the interaction and development of the product.

The current structure of the collaboration is limited by a logistic barrier which could be overcome by further decentralisation to encompass individual country representatives. Funds would be required to extend the collaboration to achieve an interactive Pan African database.

Scientific Question: What determines and how can we predict malaria epidemics and other climatically induced changes in malaria transmission?

Rationale: Short-term and long-term changes in climate affect the distribution and severity of malaria and its transmission, especially in areas of "fringe" malaria, usually constrained by either altitude or latitude. These epidemics are often regional in nature in areas where the primary causes are climatological. The forecasting of such annual epidemics in terms of severity to forewarn control authorities is of importance.

Approach: To assess the impact and predict the place and time of malaria epidemics by means of the combination of integrated and robust geographical information systems and remote sensing.

Scientific Question: What are the consequences of socioeconomic developments for malaria; in particular, the effects of irrigated rice cultivation upon malaria and its transmission.

Rationale: Most work on health in socioeconomic development projects is case by case. But for widely replicated developments there should be more general conclusions, perhaps for different ecological regions. A good example with which to develop this concerns irrigated rice cultivation in Africa, which is currently increasing rapidly and is of great practical importance. Empirical studies in West Africa have shown the counter-intuitive result of no malaria increase, while in Madagascar the adverse effect has been great.

Approach: A series of comparative studies may lead to generalizable conclusions. Current work in Cote d□Ivoire, Senegal and Mali has led to the development of methods that could be used in other areas to define the boundaries between adverse and neutral effects of rice irrigation on malaria.

Scientific Question: What are the consequences of urbanization for the type and pattern of malaria in populations?

Rationale: Urbanization will be the dominant sociological change in Africa during the coming century and has already gone from about 16% to 40% in the last 50 years. It seems likely that the fall in transmission leads to a decline in incidence but an increase in severe and fatal disease.

Approach: Longitudinal epidemiological studies need to allow description of the evolution of malaria in urbanizing populations (changes in anopheline populations, morbidity and mortality, population migration and the transmission of parasite strains).

4.) Malaria surveillance for guiding health services

There are few reliable malaria surveillance systems in Africa and even fewer that are used to guide control programmes. This results from the lack of motivation or low-quality of the health services as well as use of microscopic diagnosis and the poor recording and use of data. Moreover, the most relevant indicators and the follow-up methods adapted to each epidemiological situations remain poorly identified.

Scientific Question: How can effective and appropriate surveillance systems be developed and operationally implemented for malaria and its resulting morbidity and mortality in Africa.

Approach: Much of what needs to be done is operational. Highly applied or operational research may be needed to design a functional low-cost system capable of recording mortality from malaria by involving medical workers in surveillance and with the design of standardized log books and other recording systems. It will in some areas be necessary to establish rapid assessment techniques at various levels of the health system to collect reliable data on malaria. There will be a particular need to develop an affordable and reliable method of measuring malaria mortality on a large scale.

PRACTICAL ASPECTS OF EPIDEMIOLOGICAL RESEARCH

Development of epidemiological studies of a large enough scale to allow a contribution to the rapid reduction of the weight of malaria in Africa encounters many impediments that need to be overcome. In particular:

- The small number of African epidemiologists and the small number of non-African epidemiologists that have a good knowledge of malaria.
- The difficulty to mobilize in one given place, under the same programand for sufficiently long periods, specialists in the numerous disciplines needed for an integrated approach.
- The rarity of organizational structures functioning sufficiently well to cope with the numerous logistical problems associated with field studies.
- Obtaining the substantial and long term funding, minimum 10 years, that are necessary for integrated epidemiological studies.
- It was felt strongly by the group that project budgets for socioeconomic development projects should include a small percentage for relevant health studies and that health matters, including malaria, should be addressed from the first stages of planning.
- Epidemiological studies require close involvement with the malaria-affected communities. In this context it is essential for those Northern epidemiologists who work in Africa to remain for periods of 4 or more years if they are to contribute well to the work and to capacity building. They should also not be under so much pressure to produce results quickly that they neglect to foster the work of indigenous trainees.

In order to carry out this work it will be necessary to identify the structures which constitute centers of excellence (or can become such) in different African countries and to provide them with strong support by funding organizations. They would have the mission to develop collaborative programs, to provide on-site training of African scientists and to receive scientists from the Northern countries. The proposals for epidemiology depend heavily on development of South-South and South-North thematic networks and increasing standardization of methodology.

Epidemiology Focus Group:

Chairperson: David Bradley (UK)
Rapporteur: Jean-Francois Trape (France/Senegal)

Kwadwo A. Koram (Ghana)
David le Sueur (South Africa)
Thomas Sukwa (Zambia)
Oumar Gaye (Senegal)
Achille Massougbodji (Benin)
David Walliker (UK)
Karen Day (UK)
Pascal Millet (France/Gabon)
Bernard Nahlen (USA/Kenya)
Jean Roux (France/Madagascar)
Robert Snow (UK/Kenya)
Virgilio E. Do Rosario (Portugal)

Health Systems and Operational Research Focus Group Report

Introduction

Effective malaria control is dependent on the functioning of the health system. It is also dependent on policy-makers being willing to give priority to malaria control, which itself is dependent at least in part on being able to persuade them that effective measures against malaria are feasible and affordable.

Health systems and operational research must:

- Be context specific
- Help decision makers find locally appropriate solutions
- Lead to actions that are sustainable
- Strengthen the capacity of health managers and health workers to do operational research to solve their problems
- Involve those who must implement research results, especially the district health team and national malaria control programme staff
- Enable districts and countries to learn from one another.

Research is needed both to gain new knowledge, and to bring together and share existing knowledge. Making the results of research widely available is vital, as is drawing on existing research capacities within countries.

The focus group identified 5 general areas for consideration. These are:

1. Understanding health seeking behavior in relation to malaria in order to improve home and self-treatment of fever;
2. How to improve peripheral level services, especially with regard to treatment and access;
3. How to identify, introduce and strengthen non -drug control measures;
4. The use of routine monitoring and evaluation to ensure adequate performance;
5. Regulation and quality control of drugs and insecticides.

1. The household level and health seeking behavior

***Scientific question**:* How can home and self-treatment of fever be improved?

***Rationale**:* For the present and the near future case management both at the household and the health facility level remains the best strategy to control malaria. While promotion of the use of insecticide -treated bed nets and curtains and other control strategies must continue, self-treatment continues to be widely practiced in most of Africa, both in rural and urban areas. The socio-economic realities (poverty, hunger, civil conflicts etc) and the nature of health services in most countries will also not change in the near future. Although there are disadvantages associated with home and self-treatment (e.g. misdiagnoses-diagnosis, lack of compliance with drug regimens, use of inappropriate drugs and dosages, non-recognition of severity of

symptoms, contribution to development of drug resistance) if improved it will not only contribute to the reduction of severe malaria but will also have socio-economic benefits. These include reduction of time spent on seeking care and traveling to health facilities, reduction of household expenditure on malaria, and reduction of time spent caring for sick children.

How to answer the question: Social science methods are best placed to address questions related to health seeking behavior such as:

- Peoples perceptions of malaria
- Pathways that are used for treatment i.e. self-treatment with over the counter drugs, home therapies, health facilities, traditional healers and others
- Decision making dynamics for health care at the household level
- Means to improve public awareness of the need to seek appropriate treatment and comply with drug regimens, of the dangers of fake drugs on the market and the seriousness of malaria as a disease
- Use of research results to inform Information-Education-Communication activities that can be used to increase populations and policy makers awareness of the above issues.

In addition, social scientists need to contribute to studies of*:*

- The integration of traditional practitioners, drug sellers and other retailers, and civil and religious leaders into malaria control activities, and;
- The packaging of drugs to improve compliance.

How collaboration might help answer the question: Small scale studies have been conducted in several countries in Africa to address these questions. There is however a great need to enhance South-South collaboration in order to understand better the health seeking process and the potential to influence it.

Identified gaps: There is need to conduct multi-country studies with standardized methodologies. Although training of social scientists has been a priority, there is still a lack of manpower to address these and related issues in most countries of Africa.

2. The district health system

Scientific question: How can the peripheral level of the health service that provides treatment for malaria be improved?

By the peripheral level we refer to services provided at the district, sub-district and community level by service providers in the public as well as the private biomedical sector. Improvement includes access-related issues such as geographical distribution of services, payment systems etc.

Rationale: Prompt, effective and appropriate management of acute clinical episodes of malaria is one of the strategies for effective control of malaria. This requires a basic health system which works and is universally accessible.

How to answer the question: Research is needed to provide answers to the following issues:

- How can managerial capacity to provide services effectively be improved?
e.g. capacity to do accurate estimation of drug and other supplies requirements at all levels and planning to ensure regular availability; to maintain revolving drug funds

- How can the quality of technical care be improved?
e.g. improving training and supervision approaches which will actually result in behavioral change of providers in the public and private sectors endemic and which will ensure diagnostic and treatment competence

- What are the behavioral and interpersonal factors affecting quality of care provided and how can they be improved/changed:
e.g. provider and client perceptions of the health service and their roles; quality of provider/client interactions and the factors which influence it

- How can access to services be improved:
This can be broken down into sub-questions such as:
  - How can geographical access be improved given the limited resources available from government?
  - How can affordability of the health service be improved: i.e., how can exemptions for those unable to pay be made workable and effectively applied; what alternatives are there to fees e.g. pre-payment schemes, community based insurance, etc.?

How might collaboration help answer the questions: Within country bring together all the multidisciplinary actors to define problems, share experiences and seek solutions. This will include academic researchers, policy makers, malaria control program staff, district and peripheral level workers. Between African countries compare and share experiences, methodological issues, etc. With the North, share experiences, discuss methodological issues, etc.

Identified gaps: lack of knowledge of how to improve services given already known problems of peripheral health services; solutions need to be based on encouraging local problem-solving.

3. Identify/introduce and strengthen local (non-drug) control measures

Scientific question: What current and potential local malaria control (non-drug) measures exist, who are the actors involved (communities, government, NGO, private sector), and how can malaria control efforts be strengthened and improved?

Rationale: Given decentralization reforms in many countries, increased responsibility is being given to the district level to manage malaria control activities and to work with communities. District staff need to be able to identify what non-drug malaria control measures are feasible and effective. In addition, in most African countries the non-governmental sector (the NGOs and the private sector) has been increasingly recognized as an important component of the health sector. For malaria control little

experience is available so far on the role and integration of this sector and more investigation and experimentation is urgently required.

How to answer the questions: The following detailed questions need to be explored:

- What non-drug control measures (such as bednets, local environmental control) are feasible and effective in what circumstances, and how are they best organised?
- How can the activities of the various government departments including the national malaria control programme and other actors be coordinated and integrated at the local level?
- What is the willingness and ability of the community to pay for malaria control services?
- What traditional savings mechanisms exist and can they be built on to improve financial access to preventive malaria control services such as bednets?
- Is it feasible to introduce general or targeted subsidies for malaria control measures when they are not implemented through government services (e.g. vouchers for mothers to purchase nets from the private sector)? Who should provide the subsidy?
- Can large-scale employers be encouraged to promote and provide malaria control measures such as bednets?

Pragmatic medium- and large-scale projects, working with different implementation and financing models and different combinations of public and private sectors, need to be started in different settings and evaluated properly.

How might collaboration help answer the questions: Local, non-governmental malaria control services need to be discussed widely both within and between malaria endemic countries. Existing experience needs to be made available widely. South-South networking and a central service collecting and disseminating the relevant information are urgently required.

Identified gaps: Few national research or control personnel are competent in operational research. Collaboration between researchers and implementers is often weak. Little practical experience exists.

4. Monitoring and evaluation

Scientific question: How can monitoring and evaluation be used to improve the performance of malaria control programs?

Rationale: Adequate tools are available for malaria control but are often not optimally used by malaria control programs because of a variety of factors (organizational, social, economic). One approach to this problem consists of the effective use of prograe monitoring and evaluation (M&E), defined as the systematic collection of data to improve health programs and guide the allocation of program resources. It could assist programs in: a) detecting problems in program performance and impact; b) correcting the problem(s) identified; and c) assessing the extent to which the corrections have improved the program. Data derived from M&E would also prove useful in decision making for policy development, and to obtain support from national health policy makers and international agencies.

How to answer the question: A standard protocol should be developed that includes well designed and realistic M&E activities and indicators (of epidemiological impact, program outcomes, and program activities), and applied by programs at national and/or district levels. The activities would be conducted by personnel at national or district level at regular intervals (e.g, every 3-6 months). The usefulness of the M&E would be measured in terms of its feasibility, the problems identified and corrected, and the resulting improvements in program performance and impact.

How collaboration might help answer the question: Collaboration at the national level (between districts and central levels, with feedback of evaluation data; between researchers and implementers) and between different endemic countries, through use of a standard protocol (with local variations as needed) would pool experience in a synergistic manner. A relatively limited input would be needed from non-endemic countries, in specific areas.

Identified gaps: Initial M&E protocols have already been developed by African program managers (> 20 countries), and field tested. These protocols need more extensive field testing to assess their usefulness (see above) and long-term sustainability in a limited number of settings. If encouraging results are obtained, such protocols could be proposed as an integral component of malaria control activities.

5. Regulation and quality control

Scientific questions: What legislation should countries have in place to control the importation, advertising, distribution, quality and use of products such as drugs and insecticides? What are the best means for enforcement of legislation?

Rationale: The pharmaceutical market is in most countries largely unregulated, whether because legislation is non-existent or out-dated, or is not enforced. This leads to problems of sale of inappropriate drugs, counterfeit drugs, and diluted insecticides. Further problems arise from lack of quality control facilities, and non-standardization of drug content. An additional issue is the imposition of taxes on public health products such as nets, which raises their price and hence reduces demand.

How to answer the questions: Comparative studies investigating how countries regulate pharmaceuticals and related products and enforce regulations. Both Francophone and Anglophone countries should be included since their approaches may be quite different. The aim would be for countries to learn from each other, and to identify what approaches are likely to be most successful to the design of legislation, enforcement, quality control and taxation.

How collaboration might help answer the questions: Collaboration between African countries is required. Some specific Northern expertise on regulation may be useful.

Identified gaps: The studies would fill a major information gap, and help policy makers take action.

Ethical issues in health systems and operational research

Health systems and operational research is by definition population- and client-oriented, problem based and participatory. Therefore it is implicitly and/or explicitly an intervention. Thus ethical aspects have to be respected as much as in clinical intervention studies.

Three main aspects have to be considered, which relate to the dilemma between legitimate research curiosity and protection of the personal rights of the researched communities and its members.

***Ethical aspects pertaining to the research question**:*

- Is the research question relevant?
- Is the research question acceptable to the people, does it bear on religious or cultural norms?

***Ethical aspects pertaining to the research methods**:*

- Are the research methods relevant to the research question?
- Is there justification to deal with informants vs. the rest of the population, with the study population vs. a control group?
- Are the research methods likely to cause harm by intruding into privacy or cultural or religious values?
- Is informed consent obtained, and what problems relate to the procedure of obtaining informed consent?

Ethical aspects of data analysis, dissemination and follow-up

- Are the data made available to all partners of the research, i.e. also to the researched target population?
- Is provision made to protect the informants and the communities from any negative impact of the information they have given to the researcher?
- Is there assurance that the research results are useful also for the researched community?

Training needs

Health system and operational research capacity is very weak in all countries, and awareness is poor of its potential contribution to improving service planning, management and delivery. Health system and operational research is a multidisciplinary activity, that needs both training in specific health system research approaches and methods, and training in the disciplines that must be involved. Thus training at the masters and doctoral levels is required in disciplines such as anthropology, sociology, economics, and epidemiology. Training in health systems and operational research needs to be provided through workshops for researchers from universities, control programs, and districts. Workshop topics should include research protocol development, qualitative and quantitative research methods, and data management. In addition, training is needed to raise awareness among national malaria control programs and health service staff of how research can help them tackle problems in their daily work.

Collaboration

Since capacity and experience in health system and operational research is scarce, collaboration between countries is vital so that researchers can learn from each other and malaria control program staff and health staff more generally can learn how research can improve their work. Some specific disciplinary support in specialised fields such as economics and other social sciences may need to be provided from the North

in the short-term, until sufficient local capacity is available. In addition, collaboration between countries is extremely important to enable them to compare experiences and learn what approaches to strengthening policy, management and service delivery are feasible and effective in what circumstances.

Highpoints from the health systems and operational research group - Perspectives from the Chairperson

The group struggled with the realities of peripheral health services in many countries, namely poorly paid and motivated staff, shortages of supplies and weak supervision. Efforts have been made to strengthen services over a number of years, with limited success given the overwhelming problems of lack of resources and capacity. However, the group was encouraged to hear of a number of successes in districts which have made strides to improve services themselves, within existing resource constraints. These experiences need to be documented and shared.

The Africans in the group particularly emphasized the importance of research at the household level: most malaria in Africa is dealt with at that level, by home and self treatment using drugs purchased from private sources. Much more emphasis needs to be placed on understanding this behavior and how to improve treatment practices at the household level.

Despite a number of years of effort to train researchers, capacity is still extremely weak in vital disciplines such as the social sciences including economics. Moreover, while such training is still badly needed, it is not sufficient on its own to produce researchers who can undertake health system and operational research. Further sensitization and skill development is required, through for example short workshops on research protocol development and specific research methodologies such as qualitative methods.

The group identified a key need to train health service staff at all levels, including the national malaria control program, in operational research approaches. There is some experience of doing this in the general field of health services in Africa, which could be drawn on and applied to malaria control. Decentralizaion reforms in a number of African countries are providing district teams with greater ability to manage their resources and improve services: this provides an opportunity which should be taken advantage of.

The operational research agenda for bednets is relatively well developed because of the recent emphasis it has received (though the research has largely yet to be carried out). Other approaches to malaria control need similar attention.

Finally the discussions of the group made abundantly clear that unless health systems and operational research were taken seriously, the products of more basic research would not be exploited effectively.

Health Systems and Operational Research Focus Group:

Chairperson: Anne Mills, United Kingdom -- Rapporteur: Halima Mwenesi (Kenya)

Moses Aikins (Ghana) Irene Agygpong (Ghana)
Akpa R. Gbary (Burkina Faso) Elisabeth Feller-Dansokho (Senegal)

Phuc Nguyen-Dinh (USA) H.J. Diesfeld (Germany)
Christian Lengeler (Switzerland)
Marc de Bruycker (Commission of the European Communities)
Pater David (France)

Case Management Focus Group Report

BACKGROUND: Malaria case management strategies should be considered as an integral and, at present, most important part of malaria control programs.

Case management strategies must be based on sound knowledge of the epidemiology of malaria in the area in question taking into consideration the population most at risk, for example young children, pregnant women, those resident in certain geographical areas, and occupational risk groups, as well as seasonality of malaria, etc. Knowledge of the local pattern of resistance of parasites to antimalarial drugs is also essential to planning case management strategies.

Case definitions are required for each level of treatment. Mothers have their own case definition which is generally accurate, but there may be symptoms or signs which are not recognized as signs of malaria, such as convulsions. Case definition for mild malaria is required for peripheral health care workers which may be dependent solely on signs and symptoms or which may include blood film examination, dependent on the availability of facilities. Peripheral health care workers must have criteria for recognizing cases of severe disease which require special treatment or referral. At major health centers simple working definitions are needed for routine clinical care, more complex definitions are needed for research projects during which cases are studied in more than one center.

An effective case management strategy requires that appropriate treatment be given at each level including home, peripheral health clinic, and major health center or hospital. This strategy is facilitated by provision of standard treatment protocols, requiring health education to ensure adequate home treatment and training and monitoring of clinical staff to ensure that treatment protocols are followed in the health facilities. Effective drugs must be available at all levels of the delivery system.

CONSTRAINTS: Some of the factors that prevent case management strategies operating effectively at present include:

- Failure to recognize malaria as a fatal illness
- Failure of mothers to recognize signs of severe malaria
- Use of inappropriate or inadequate courses of treatment by health care providers, especially when drugs are bought for home usage
- Poor adherence to treatment guidelines both at the health center and hospital, resulting from inadequate supervision, in-service training, and monitoring
- Lack of availability of appropriate drugs at the right place, resulting from poor planning or cost
- Use of ineffective drugs either because of parasite resistance or because the drugs are inactive.

RESEARCH PRIORITIES

Most of the major research issues relating to case management are very practical ones that can be handled most appropriately within malaria control programs. The design of many research projects on case management must be dependent on local circumstances. There are, however, some research questions that are more generally applicable. The following research issues were considered high priority.

Can the introduction of effective case management strategies reduce severe morbidity and mortality from malaria in African children? One possible approach suggested by the interventions group is the monitoring of the effect of introducing an effective drug in the context of an effective case management program into an area where the parasite has become resistant to the drugs used previously.

Can improved home management, achieved through better education of mothers and improved access to appropriate drugs, reduce severe disease? Planning such a study depends on acquiring detailed knowledge of how mothers perceive malaria, its treatment, and prevention.

Investigation of the comparative efficacy of immediate treatment at health centers of cases of severe malaria with an injection of quinine or rectal artemesinin before referral to a hospital.

Investigation of the most effective ways of monitoring how well-managed cases of malaria are at the community level and at health centers.

Determining the most effective ways of detecting treatment failures within the context of routine clinical care.

Finally, the group wished to draw attention to the major problems for case management that will arise when it is no longer possible to use cheap and safe drugs for the treatment of malaria in Africa. Now is the time when consideration should be given to ways in which research (for example on cost recovery, insurance, etc.) could help in lessening the impact of this change when it occurs.

Case Management Focus Group:

Chairperson: Brian Greenwood (United Kingdom)
Rapporteur: Kalifa Bojang (The Gambia)

Peter Kremsner (Germany)
Pater Kazembe (Malawi)
Elisabeth Feller-Dansokho (Senegal)

Vector Control Methods Focus Group

The main questions identified by the group on vector control methods were:

1. What organizational structures and methods are needed for the widespread implementation of the use of impregnated bednets in Africa?

2. What is the role for insecticide spraying of houses and how can it be improved?

3. What are the relative merits of house spraying and impregnated bednets?

4 What is the role of larval control of anophelines in Africa?

5. How immediate is the threat of physiological and behavioral resistance to pyrethroids and
what can be done about it ?

6. Will vector control be beneficial to human health in the long term, especially in areas where transmission is initially intense?

Question 1: What organizational structures and methods are needed for the widespread implementation of the use of impregnated bednets in Africa?

Rationale:

Insecticide impregnated bednets place a relatively small quantity of insecticide directly in the path of the host seeking mosquito. Recent operational use of impregnated bednets in China and large scale trials in Africa have been successful in controlling malaria morbidity and/or mortality. Data from the Gambian National Impregnated Bednet Programme indicate that impregnated bednets are as cost effective as childhood vaccination in reducing child mortality, but there are as yet no large scale programs of operational use of impregnated bednets in Africa. About 15 small projects have been funded by WHO/TDR on how to implement and finance impregnated bednet programs. In addition further work remains to be done on different insecticide-fabric combinations and it is not yet known what percentage of the beds in a community need to be equipped with nets to achieve effective malaria control.

Approaches:

(i) Larger scale studies to investigate promotional and distribution methods and to compare (a) free distribution of bednets, and/or the insecticide with which to treat them, as a preventive health programme comparable with the donor funded Expanded Programme of Immunization, (b) subsidized distribution, (c) encouraging private sector involvement by social marketing and tax exemption.

(ii) Comparison of different insecticide-netting fabric combinations (including those with an insecticide incorporated into polyethylene fiber) with respect to

effectiveness in repelling and killing vectors and nuisance insects, controlling transmission, cost and sustainability by communities.

(iii) Comparison, using a standardized protocol, of entomological and malariological results in different operational trials where coverage is likely to be lower than in efficacy trials.

Barriers:

Lack of sufficient information provided to Ministries of Health about recent data on impregnated bednets; financial constraints; inadequate methodologies for measuring effectiveness; lack of consensus about methods of payment.

Role of collaboration:

Bringing together of social scientists and applied entomologists; because any one locality can only use one financing method, rapid exchange and comparison of experiences in bednet trials and operations in Africa and elsewhere is particularly important; electronic media should have a role here.

Question 2: What is the role for insecticide spraying of houses and how can it be improved?

Rationale:

House spraying attacks adult vectors which rest in houses, which is the usual post-feeding behavior of *An. funestus* and of many populations of the *An. gambiae* complex. This method aims to prevent mosquitoes from living long enough for sporozoite production to be completed. House spraying can eradicate An. funestus, and in southern Africa, has been successful for several decades. It has been used to bring highland epidemics under control and some earlier trials in malaria endemic, tropical, lowland areas were also successful. Biodegradable pyrethroids are now being substituted for DDT and there are moves to decentralize the organization of house spraying.

Approaches:

- Investigation of whether house spraying should, and can successfully be, decentralized to district level where managers and teams of spraymen are not specialists at this job.

- Comparisons of the persistence of different pyrethroid compounds on different types of building material , of the effectiveness of mist blowers as a substitute for conventional compression sprayers and of the need to spray buildings other than human dwellings.

- Investigation of means of maintaining teams able to carry out spraying and stores of insecticide as measures of epidemic preparedness.

Barrier:

Lack of sufficient trained manpower.

Role of collaboration:

Training and sharing of experience, especially from those in southern Africa with decades of experience of this method.

Question 3: What are the relative merits of house spraying and impregnated bednets?

Rationale:

Historical evidence suggests that house spraying can be as efficacious as impregnated bednets in reducing child mortality. It is important that any decision to replace house spraying by impregnated bednets is not made merely because the latter method is currently fashionable. An objection by many householders to house spraying with older insecticides was that a visible deposit was left on walls, but this is not true of modern pyrethroids which are used at about 1% of the dosage of DDT. There has so far only been one trial comparing the same pyrethroid compound for bednet impregnation and for house spraying.

Approach:

More extensive comparison of use of pyrethroids for house spraying or for impregnation of bednets, with respect to effectiveness against vector species (including ability to eradicate *An.funestus*), control of disease transmission, cost and acceptability to human communities.

Question 4: What is the appropriate role of larval control of anophelines in Africa?

Rationale:

In the 1930s and 1940s larval control was used to eradicate invading populations of a species of the *Anopheles gambiae* complex from Brazil and Egypt. However, on a smaller scale, larval control depends on finding a high proportion of the breeding sites within mosquito flight range of the community which it is desired to protect. This is difficult to do in humid, tropical, rural areas.

Approach:

Investigation of the role of larval control (a) in towns where the Anopheles breeding sites are limited in extent, (b) in irrigation projects where the breeding sites created are large but well defined and should be the responsibility of the project management to control, (c) in southern Africa where winter conditions present opportunities for effective larval control.

Barrier:

Where community based larval control is attempted by environmental management, it is often incorrectly targeted at sites which do not contain larvae of vector anophelines but of other types of mosquito.

Question 5: How immediate is the threat of physiological and behavioral resistance to pyrethroids and what can be done about it ?

Rationale:

DDT resistance has evolved in many, but not all, sprayed vector and bedbug populations. Pyrethroid resistance is a problem in several agricultural pests and can be selected artificially in *Anopheles* species. It has been reported in *An.gambiae* in Cote d'Ivoire and Kenya but has not been found after 7 years use of impregnated bednets in China and in a small Tanzanian village.

Approaches:

(i) Comparison of pyrethroid susceptibility testing by (a) conventional measurement of % mortality after one hour□s exposure, with (b) observation of the time for knockdown when mosquitoes are made to walk on impregnated netting.

(ii) Routine testing with a standardized protocol for resistance in bednet trials and operations, especially in situations where there is little opportunity for immigration of mosquitoes which have not been exposed to pyrethroids. Where posible, tests should compare exposed populations with nearby unexposed ones, rather than with absolute standards. Where resistance is suspected, the F1 bred without selection from wild mosquitoes should be tested so as to guard against the possibility of misleading results arising from the decline of pyrethroid tolerance with mosquito age or the rise of tolerance as a result of prior sub-lethal exposure to pyrethroids. If resistance is encountered the strain should be made available for further research by appropriate laboratories.

(iii) Establishment, where possible, whether the source of selection of pyrethroid resistance is house spraying, impregnated bednets, agricultural or domestic insecticides.

(iv) Testing examples of pyrethroid resistance for positive or negative cross resistance to organophosphates and other classes of insecticide which might be used as alternatives to, or mixed with, pyrethroids for resistance management.

(v) Testing for possible genetic or phenotypic effects of use of pyrethroids in causing a shift to early evening or outdoor biting, i.e. behavioral resistance.

Barrier:

Lack of personnel trained in the detection of resistance and insufficient information exchange.

Role of collaboration:

Short training courses in methods of resistance detection and sending all valid data from resistance tests (whether positive or negative) to the WHO to be made widely available, e.g. through electronic media.

Question 6: Will vector control be beneficial to human health in the long term, especially in areas where transmission is initially intense?

Rationale:

It is speculated that, in areas of intense transmission, reduction in transmission may increase severe disease. Furthermore, it is possible that the initial successes of bednets may disappear during long-term application because of fading of pre-existing immunity levels.

Approaches:

(i) Continuation of the monitoring of the effectiveness of vector control trials or operations for several years, with avoidance of the ethical objection to keeping a designated population as untreated controls for a long period by (a) case control studies, or (b) regular incorporation of new untreated control communities into the trial with extension of the treatment to previous control communities.

(ii) Comparison of the age specific rates of malaria morbidity (fever with high parasitemia, anemia and cerebral malaria) and mortality in different human communities which show a wide natural range of levels and seasonality of malaria transmission (entomological inoculation rate). The communities with low transmission are indicators of the likely situation after vector control has been applied and sustained for several years in a previously intensely malarious community.

(iii) As soon as a satifactory blood stage vaccine is available, test of integration of it with vector control with the intention that the vaccine replaces the lost natural immunity and the vector control moderates the challenge to the vaccine.

Barrier: Difficulty of identifying methodology which is scientifically valid and ethically acceptable.

Vector Control Focus Group:

Chairperson: Fred Binka (Ghana)
Rapporteur: Christopher Curtis (United Kingdom)
Christian Lengeler (Switzerland)
Marc Coosemans (Belgium)
J.H.Ouma (Kenya)
Jo Lines (United Kingdom)
N.T.Marbiah (Liberia)
Charles Mbogo (Kenya)
Bernard Nahlen (USA/Kenya)
Kato Njunwa (Tanzania)
Moses Aikins (Ghana)
Halima Mwenesi (Kenya)
Patrick Rabarison (Madagascar)
Ousmane Faye (Senegal)
Brian Sharp (South Africa)
Jean Meli (Cameroon)

Vaccines Focus Group Report

THE GROUP CONSIDERED IT IMPORTANT TO STRESS THE FOLLOWING GENERAL POINTS:

1. There has been enormous progress during the past 10-20 years in regard to establishing the feasibility and the capacity to develop malaria vaccines.

2. Preerythrocytic, asexual, transmission blocking, and multi-stage vaccines are all considered to be potentially important tools for control of malaria in Africa, and fulfillment of the long term goal of eradication is unlikely to occur in the absence of such vaccines.

3. Fulfillment of goals regarding testing and deployment of malaria vaccines is being slowed considerably by insufficient funding and capacity for:

    a. R&D scale process development, emphasizing expression and purification of recombinant proteins.

    b. Production and formulation of GMP grade vaccines.

4. To promote increased communication, education, improved clinical trial execution capacity, and quality and comparability of trials, an e-mail network and a central repository should be established so that whenever possible, researchers can provide information regarding their conduct of clinical trials, and copies of clinical protocols.

5. Researchers must be vigilant in keeping appropriate national health authorities and scientists aware of all aspects of the malaria vaccine development process. This could be coordinated through the African Malaria Vaccine Testing Network and the WHO.

6. Improved communication between all participants of vaccine development and evaluation is essential. The African Malaria Vaccine Testing Network is a critical new effort that is poised to make a major contribution to the vaccine development and evaluation process.

SHORT TERM ACTIVITIES AND GOALS

1. Field trials of a limited number of preerythrocytic and asexual stage vaccines are underway in Africa, and during the next five years, it is anticipated that other vaccines will be studied. Trials of these vaccines should be conducted in a variety of epidemiologic settings with the goal of providing clear, consistent and reproducible evidence of decreasing the risk of malaria. These trials should be designed and executed so as to provide maximum information for improving our understanding of protective immunity and for improving subsequent vaccine design.

2. During the next five years, there should be continued efforts in strengthening

the capacity for African institutions and scientists to independently demonstrate that one or more malaria vaccines are capable of reducing infection, morbidity, or mortality at a desired level of efficacy in a range of epidemiologic settings in Africa. This will require increasing the capacity to conduct Phase I and Phase II trials of safety, immunogenicity, and experimental challenge in semi-immune populations.

3. Efficacy trials of malaria vaccines will require the identification and characterization of a number of field sites suitable for evaluating the expected number of vaccine candidates. Such sites should be established with the data base, skills, resources, and infrastructure necessary for conducting high quality Phase III efficacy trials. The African Vaccine Testing Network has made an important start towards achieving this goal. It should be recognized that field sites developed for vaccines may not be able to exist on their own, and therefore should be integrated into larger health and malaria research efforts. The epidemiologic, clinical, and laboratory data collected at each site using current and emergent parameters of malaria epidemiology, biology and immunology will be useable for multiple purposes.

4. The evaluation of asexual stage vaccines presents a special problem. A high priority for further research is the evaluation of efficacy at a point prior to undertaking large scale field trials. New approaches to solving this technical problem are urgently required, and solutions may be found in collaborative studies involving African vaccine testing facilities where access to semi-immune populations may offer unique opportunities for study design.

5. In general, the safety requirements for studies of malaria vaccines in Africa is similar to that used in the North. Since live vectored recombinant vaccines are likely to be available, the special safety concerns associated with administration of live vectored recombinant vaccines to individuals with concurrent infections (especially HIV infection) and the potential environmental impact of these vaccines must be considered as early as possible in the vaccine development process.

6. To promote the vaccine development process and general technology transfer to African institutions, a process development laboratory for recombinant proteins should be established at one or more African research facilities.

7. Understanding of protective immunity may be best understood by studying vaccine antigens individually, but ultimately, combinations of individual antigens are likely to be formulated as multicomponent vaccines. It is recognized that there are many technical and scientific issues in combining antigens that must be addressed to accomplish this goal.

MEDIUM TERM GOALS:

1. Deployment of a cost effective vaccine.

    a. This will require a process by which the vaccine will have undergone

critical evaluation, for example, multiple Phase III trials showing a reduction of malaria morbidity followed by a multicenter study that shows a significant reduction in mortality.

b. This may require capacity building in Africa, including manufacturing, regulatory affairs, and alternative distribution strategies.

2. Careful evaluation and monitoring of the overall health impact of deployed vaccines on a long-term basis. In the presence of continued transmission a system must be developed for long term follow up of vaccine safety, the health and immune status of vaccinated populations, the biology of the parasite (development of vaccine-resistant mutants) and the impact on transmission dynamics.

3. Ongoing research and development of improved vaccines. Recognizing that a multiplicity of vaccine tools are likely to be required, the identification and deployment of new, improved and complementary vaccines will be essential.

Vaccines Focus Group:

Chairperson: Stephen Hoffman (USA)
Rapporteur: Palle Hoy Jakobsen (Denmark)

Pedro Alonso (Spain)
Andrew Kitua (Tanzania)
Laurence Ralamboranto (Madagascar)
Moussa Kone (Cote d□Ivoire)
Adrian Hill (UK)
David Kaslow (USA)
Ruth S. Nussenzweig (USA)
Alioune Dieye (Senegal)
Kwadwe A. Koram (Ghana)
Soren Jepsen (Denmark)
Louis Molineux (Switzerland)
Ripley Ballou (USA)
Howard Engers (WHO/TDR)

Multiple Interventions Focus Group Report

Multiple interventions are likely to be more effective than single interventions in controlling or eradicating malaria in most settings in Africa. There are several existing and hypothesized means of intervening in the transmission of and disease caused by malarial parasites including measures aimed at: 1) the vector; 2) the parasite or the disease it causes; and 3) the interaction of the human host, the parasite and/or the mosquito. These interventions include:

Interventions directed against the mosquito:

- Reducing adult mosquito numbers, e.g., house spraying, anti-mosquito vaccines
- Reducing larval numbers, e.g., larvicidal agents
- Reducing vector susceptibility, e.g., transgenic mosquitoes

Interventions directed at reducing man-vector or parasite transmission:

- Chemicals directed at the parasite, e.g., antigametocytidal agents
- Immune interventions, e.g., transmission-blocking vaccines
- Socioeconomic, e.g., housing construction, human behavior
- Chemical personal protection measures, e.g., DEET
- Mechanical barriers, e.g., bed nets
- Combination measures, e.g., impregnated bed nets

Interventions directed at the parasite or the disease it causes:

Chemotherapy

- Preventing infection, e.g., prophylaxis
- Treating clinical disease, e.g., case management
- Treating parasitic infection, e.g., mass treatment

Vaccines

- Pre-erythrocytic, e.g., anti-sporozoite/liver stage
- Asexual blood stage, e.g., anti-merozoite
- Anti-disease, e.g., anti-toxin

There are at least three concepts to consider:

1. Combination of multiple interventions may be more effective than using single interventions, specifically individual interventions that may not be fully effective alone may be completely effective, either by additive or synergistic effects, when combined with other interventions.

2. Combination of multiple interventions may prevent complications that might arise if one of the interventions were used alone. Examples include: loss of natural immunity after vector control measures are employed could be prevented by vaccines that restore natural immunity; or, spread of drug resistant parasites could be slowed by adding anti-gametocytidal agents.

3. When eradication is considered all three types of intervention will usually have to be employed.

Recommendation:

When testing or deploying any new intervention in most settings in Africa, multi-disciplinary expertise is critical in the design of, measurement of outcomes from, and the implications of the new intervention, particularly when there are pre-existing interventions in use in the target population.

Chairperson/Rapporteur: David Kaslow (USA)

Pedro Alonso (Spain)
Brian Sharp (South Africa)
Brian Greenwood (United Kingdom)
Louis Molineaux (Switzerland)

Part II. Mechanisms of Cooperation and Support

Mechanisms of Cooperation and Support Focus Group Report

Introduction

There was consensus in the group that coordinated activities between the various agencies are needed to offer increased opportunities for scientists from three continents to jointly address scientific topics concerning malaria in Africa, and to support defined research areas in which international partnerships are most likely to pay off, but also to fully exploit the existing mechanisms to facilitate genuine partnership between scientists from the different continents.

First and foremost it should be clear that the organizers of this conference intend to harness existing mechanisms to foster international collaboration in the field of malaria. Therefore, a brief overview of these mechanisms for collaboration is being prepared.

It has been recognized by the supporting organizations that talking about existing collaborations alone is not sufficient. We have to identify the mechanisms to support such collaborative efforts.

First of all, the conceptual framework for scientific collaboration between partners from the North and the South should be clearly defined. To that end, a working document has been prepared ahead of this meeting, which was reviewed by numerous experienced colleagues in this field and will be distributed to all participants after the meeting.

After this initial inventory stage, specific discussions followed the plenary sessions about how the collaboration between the supporting agencies could respond as adequately as possible to the needs defined by the scientific community present as the conference. The existing mechanisms to support collaborative projects are not always effectively exploited and improved information will be provided to the scientific community to improve efficiency.

The Agencies represented further committed to collaborative action to develop a realistic framework for sustainable collaborative programs.

The need for long-term and substantial capacity building, which was recognized as a priority in all working groups, will be featured very prominently in these collaborative actions.

In the short term, a number of specific areas and actions are defined in this report.

For the medium-long term, closer collaboration between research and control programs and synergy with development-based funding will be actively pursued.

Specifics

1. CONSENSUS PRINCIPLES FOR INTERNATIONAL SCIENTIFIC COLLABORATION

Relevance for developing countries of malaria research is obvious.

Research must be of the highest scientific standard and guaranteed by peer review.

Research ranging from fundamental biomedical research to operational research and health systems research is considered relevant to address the problem of malaria in Africa.

Genuine partnerships in setting the agenda of collaborative research and distributing tasks and resources are essential.

Programs of high scientific quality will lead to sustainable research collaboration and resource development in Africa, including human resources development and institutional support.

Ethical review should be organized in the country of action.

2. COORDINATION

Mechanisms must be developed, where needed, to coordinate approaches among agencies supporting malaria research and control activities through exchange of basic data on supported projects and on any new initiatives.

Co-funding of activities and coordinated development of scientific projects should be considered if there is an expressed need by the scientific community.

Electronic means of communication, such as is supported by the European Commission's Scientists for Health and Research for Development (SHARED) initiative and by the Malaria Foundation's Malaria Research Network (MRN), can be exploited for this purpose.

3. TRAINING AS A CORNERSTONE

Training should include all levels, including Ph.D. and post-doctoral training. The principles laid out in the WHO/TDR programme for training, capacity building and re-entry grants provides a useful framework.

Training should be done as much as possible in Africa, and/or linked to

research projects. (The Open University principle should be exploited as a mechanism).

Wherever possible regional coordination of training should be stimulated.

In addition to training of African professionals, providing relevant experience for Northern scientists in endemic areas is also a great concern, in order to maintain a critical mass in the North for collaboration in the field of tropical medicine and international health.

4. CAREER DEVELOPMENT

Defined career paths should be made for African scientists and maximal efforts should be made to sustain them.

Possibilities for amending principal investigators salaries should be exploited.

The public sector character of most research efforts in Africa precludes free salary negotiations, but on the other hand is an important element of political support for research in Africa.

5. SCIENTIFIC EXCHANGE

Scientific information and information on research managerial issues is as important in Africa as it is in the North.

Very serious efforts have to be made to enable efficient access to information for African scientists, including provision of software, hardware and adequate training.

Provisions for keeping on-line and paper information updated and the systems operational should be made.

Practical possibilities for the development of such systems are known and will be provided in the final report.

Actual visits and exchange periods for scientists at all levels from the North and the South are crucial in all phases of the research process, and should also include preparatory visits if necessary.

The existing funding mechanisms for exchange of scientists are not always accessible to researchers from the South. These should be more efficiently exploited.

6. CAPACITY BUILDING AND MULTI CENTER APPROACHES

Capacity building should be tailored to the needs of science: Build labs

around science, not empty labs.

Building on existing capacity is the preferred mechanism.

International collaboration would have a strong justification where the problem can not be efficiently addressed in a single country, or by a single donor.

Multi-center approaches are evident where evaluation of tools and field studies in the broadest sense for malaria are concerned.

Such MULTI CENTER networks should be fully exploited for training.

Purely biomedical research projects are likely to take a smaller form (bilateral and small networks).

Defined short term possibilities

There was some confusion in the plenary session about the generic term Networking.
Therefore a definition of three levels of networking was developed:

All activities supported in the future will be based on the general principles laid out above:

1. Communication

- **Definition**

  Electronic systems, newsletters etc. Useful for scientists and policy makers alike, based on ongoing research and used for conceptual innovation, access to support mechanisms, electronic journals etc.

- **Funding**

  Relatively minor, additional to research activities
  Specific activities needed to enable full participation and benefit for African partners.

- **Duration**

  As long as the field is active.

2. The Concerted Action

- **Definition**

A mechanism to enable supportive activities to the scientific activity: exchange of scientists, information, reagents and data, repositories, training, standardization regular meetings.

- **Support**

  Specific, relatively limited funds, linking research Centers with compatible interests in which the research itself is already funded.
  In our particular field also used to (bottom up) generation of partnerships

- **Duration**

  As long as co-ordination of research activities has added value, both at the research and at the research management level.

3. The Multicenter Research Network:

- **Definition**

  Any research collaboration around a scientific topic in which more than two Centers are involved.

- **Support**

  Through regular funding mechanisms.

- **Duration**

  as long as the science binds it together

All levels of networking are recognized as valuable in specific circumstances, and mechanisms will be sought for support to each of them where science defines a need.

-Specific examples to be supported within the existing mechanisms:

CONCLUSIONS

The conference recognizes the importance and success of international support for malaria research activities.

The existing mechanisms for supporting malaria research should be continued and better exploited through improved information exchange among malaria research funders.

Joint funding of malaria research activities by multiple agencies should be encouraged and can be facilitated through information exchange.

Malaria research activities in Africa will be enhanced if science-driven, shared research supporting activities such as drug and vaccine-trials networks, training programs and parasite strain depositories are provided as an adjunct to existing research activities.

An innovative and highly flexible approach to offering structured support for such facilities based on commonly established criteria such as scientific excellence, strengthening existing capacity in and outside Africa and acceptance of rules governing and respecting mutually beneficial balanced partnerships is desirable. Providing this through the coordinated investment of several agencies from Africa, Europe and the US to support activities and institutions would represent a significant advance in international cooperation on malaria research and control activities.

Mechanisms of Cooperation and Support Focus Group:

Chairpersons: Barend Mons (Netherlands Organization for Scientific Research)
and Thomas Nchinda (WHO/TDR)
Rapporteur: Christian Marchal (Ministry of Cooperation, France)
Jean-Marie Bruno (Ministry of Cooperation, France)
Daniel Colley (Centers for Disease Control and Prevention, USA)
Catherine Davies (The Wellcome Trust, United Kingdom)
Robert Howells (The Wellcome Trust, United Kingdom)
Marc de Bruycker (Commission of the European Communities)
Paul Hagan (Commission of the European Communities)
Richard Feachem (World Bank)
Malayah Harper (World Bank)
Robert Mshana (Organization for African Unity)
Mamadou Traore (Institut National de Recherche en Sante Publique, Mali)
Harold Varmus (National Institutes of Health, USA)
John La Montagne (National Institutes of Health, USA)
Maxime Schwartz (Institut Pasteur)
Keith McAdam (Medical Research Council, United Kingdom)
Michael Gottlieb (National Institutes of Health, USA)
Ebrahim Samba (WHO/AFRO)

John Paul Clark (USAID)
Wenceslaus Kilama (Tanzania)

Training Focus Group Report

Given that the focus of this meeting concerns perspectives for collaboration in research, discussion was limited to doctoral and post-doctoral training, the level that prepares trainees for an independent research and leadership role.

Rationale: African nations suffer from a shortage of health scientists of doctoral level, and thus often must resort to having public health priorities driven by international organizations and foreign consultants. Socio-sanitary development needs are important research components. Only the training of a sufficient number of African scientists will enable their countries to define and execute their own research priorities.

Type of training required:

Long-term training, of doctoral (Ph.D.) or post-doctoral level:

Long-term training in Northern countries has fostered the development of the leaders of science in Africa today. This training has proven itself to be valuable although it is expensive (over $100,000 USD for a complete Ph.D. training). However, because of decreased funds for training, training in African institutions (regional training centers) is to be encouraged. As all different training resources and expertise are generally not available in a single institution, priority is to be given to the creation in Africa of "consortiums of training institutions". Training can also be provided by research institutions in Asia. PhD projects should address health questions related to relevant home country priorities.

The indications and modes of post-doctoral training must be examined with care. Post-doctoral projects should preferentially be linked to ongoing research projects in Africa, thus favoring the establishment of African research networks.The trainee would thus ensure regular and close interactions between mentors in different institutions.

It may is preferable for the trainees to delay their post doctoral period and return to their home institution as soon as the PhD has been obtained. In all cases, financial support must be provided to trainees upon their return, in the form of re-entry grants, to enable them to initiate research in their home institutions.

Short -term training:

The indications of short-term training should be tailored to specific needs, for example the necessity to acquire expertise in a given technique. Such training can be provided through a short period in a specialized laboratory, or through participation in a workshop, a training course, or in the context of a focused research project. It is also important that managerial training be provided.

Objectives of training:

Acquisition of scientific autonomy: Upon successful training, investigators should be capable of independently carrying out high quality research righr from its conception and protocol development to its execution and reporting.

Institutional capacity building*:* Investigators should be trained to ensure institutional capacity building through the creation of expanding research groups and through the establishment of balanced and productive collaborations.

Technology transfer*:* Training should lead to the establishment of new technical approaches in the home laboratory.

Means to ensure sustainability:

Financial, social and political sustainability are to be ensured. Interaction between control programs and academic institutions must be encouraged. Long-term commitment must be obtained both from governments and external funding institutions. A defined professional position must be available to the trainee upon return, allowing carreer-building. Resources offered by a re-entry grant are of utmost importance, bolstered/continued by national funding, and when possible, by research development and maintenance grants. Legitimate financial needs can be met through various mechanisms, such as income supplementation, field allowances, financing of travel to present data at scientific meetings.

Given the crucial need to increase the number of African scientists, it is essential to encourage funding organizations to dedicate a fixed proportion of their budget to training.

Training Focus Group:

Chairperson: Samba Diallo (Senegal)
Rapporteur: Peter H. David (France)

Wen Kilama (Tanzania)
Rober T. Guiguemde (Burkina Faso)
Luiz Pereira da Silva (France)
John H. Ouma (Kenya)
Howard Engers (WHO/TDR)
Thomas C. Nchinda (WHO/TDR)
Ogobara Doumbo (Mali)

Part III. Final Comments

FINAL COMMENTS

Question: What mechanisms are needed in the short term to advance research on malaria in Africa?

Background: The worsening situation with respect to the control of malaria, especially in Africa, demands the development and implementation of new and improved methods to limit the impact of this disease on public health and socioeconomic development. This demand can only be met by research at all levels from fundamental biomedical research through to clinical and field testing of new intervention strategies as well as by health systems and operational research to assess the effectiveness of control programs. Although the existing tools for malaria control have been compromised, e.g. by the evolution and spread of drug resistant parasites, there is reason to believe that recent advances in biomedical research will improve the situation. Moreover, there is an increasing number of well-trained investigators and centers studying malaria in and Africa to address important research questions.

Although large investments in research and development on malaria will ultimately be needed to lessen the burden of malaria on populations living in Africa, it is recognized that several more modest but immediate investments would be able to enhance the research effort as it now exists. Such investments would enhance coordination of ongoing research projects and their results and would promote collaborative research efforts.

PROPOSED SPECIFIC OBJECTIVE 1

To develop the mechanisms needed to ensure that systems are available for the timely communication of information to scientists working in Africa.

Rationale: Timely scientific information exchange is essential for promoting and coordinating research activities in Africa. Electronic communication systems widely available to scientists working in industrialized countries are less than optimal for scientists working in Africa. Access to e-mail and the Internet will promote rapid communication between investigators working at different sites as well as access to online literature and data available to scientists outside Africa. Subsequent development of electronic networks would promote the use of common databases which will facilitate research efforts at multiple sites across the continent.

Recommendation: Institutions and agencies supporting malaria research in Africa should install/improve electronic communications systems which would enhance information exchange between scientists in the North and their counterparts in Africa.

Action Needed: Analyze the results of a National Library of Medicine (NIH,USA) study, and others as needed, on electronic communications availability in Africa. Provide the results of that report to funding agencies and identify the systems and resources needed to ensure access to e-mail and Internet to research institutions and centers in Africa.

PROPOSED SPECIFIC OBJECTIVE 2:

To establish mechanisms which will enhance the capacity to conduct collaborative/multicenter research in Africa.

Rationale: It has been articulated that a number of aspects of malaria research in Africa would be greatly enhanced if collaborative/coordinated activities were conducted at multiple sites in Africa. Such coordination would provide access to larger numbers of samples (parasites, vectors and people) across the continent in different environmental and epidemiological settings. Combined with standardization of reagents and research and clinical protocols, coordination would lead to greater comparability of results among these different sites in these settings. Researchers working on malaria research in Africa, including pathogenesis, vector biology, immunology, host and parasite genetics, have indicated that comparable information from different sites would greatly increase the power of their individual studies. Moreover, results from multiple sites are absolutely essential to the generalizability of information coming from trials of interventions (drugs, vaccines, vector control etc.)

Recommendation: Institutions/agencies supporting malaria research should establish a coordinated effort to identify resources for use in the support of activities that would facilitate the conduct of coordinated/multicenter studies. This pool of funds would be made available for the peer-reviewed support of such activities as establishing common protocols, acquiring common materials and reagents, database management and construction, as well as developing repositories of materials of parasite, vector human origin. Such resources could be used to support facilities for the analysis of samples originating from multiple sites.

As scientists are increasingly aware of similar activities across the continent, they may seek to establish flexible networks to obtain results from multiple locations. Such networks would not be fixed entities, rather they would be driven by the scientific needs of the research questions. Available funds would be used to support some of the infrastructural needs that would such networks require.

Action Needed: Institutions and agencies supporting malaria research in Africa will meet quickly following this meeting to identify resources and to determine the mechanisms by which the fund would be made available to investigators and centers interested in addressing research questions at multiple sites in Africa.

Annexes

Annex I. Parasite Repositories

There is a need for well-characterised strains for use as standard parasite material in labioratories engaged in malaria research. At present, the World Health Organization (TDR) funds a Registry of Standard Strains of Malaria Parasites at the University of Edinburgh, Scotland. Its functions are :-

(i) Maintenance of a small number of standard clones of *Plasmodium falciparum*, characterized for a variety of genetic markers including alleles of major antigens and variations in sensitivity to the commonly used antimalarial drugs.

(ii) Maintenance of other cloned and uncloned isolates of *P. falciparum* representing the main malaria-endemic regions of the world.

(iii) Maintenance of a comprehensive collection of cloned and uncloned isolates of the rodent malaria species *P. berghei, P. yoelii, P. chabaudi* and *P. vinckei.*

(iv) Supplying research laboratories with samples of this material.

The collection is maintained as deep-frozen stabilates in liquid nitrogen. At any one time, a small number of these parasites are routunely maintained in culture or animals in the laboratory. Dispatch of parasites to other laboratories is normally carried out using deep-frozen material in liquid nitrogen “dry shippers”. A list of the parasites available is available as a worldwide web page on the Internet.

It is envisaged that the functions of the Registry could be expanded to include other types of study on material of clinical interest. For example, filter paper samples containing fingerprick samples of blood can be used as a source of parasite DNA for gene sequencing studies following PCR of genes of interest. Thus, to investigate polymorphisms in genes thought to be involved in drug-resistance, such an approach could be used with samples of parasites obtained from patients who have undergone treatment with the drugs of interest. To study polymorphisms in genes for candidate vaccine antigens, a comprehensive collection of DNA samples can be made from isolates from areas where vaccine trials are planned or have taken place. It is not envisaged that such samples will be sent to other laboratories, but would be a souce of reference material for use in the repository by visiting research workers.

It is proposed that repositories of such material should be established in appropriate African countries. These centers would be developed in close collaboration with the Registry in Edinburgh, which would keep back-up material.

The requirements for developing such centers are as follows :-

1. Two centers should be established, one in west Africa, and one in east or southern Africa. The selection of the sites would be based on logistical considerations, including (a) transport, (b) infrastructure, and (c) communication.

2. Criteria for selection of parasite samples :-

(a) *Samples for intervention studies, vaccine studies, etc.* These would be fingerprick samples on filter paper, taken from a large sample of the residents of the communities under study.

(b) *Chemotherapeutic studies*. For these, ideally one requires blood samples which can be cultured for *in vitro* drug tests, taken before treatment and at recrudescence, if this occurs. Filter paper samples would also be taken for PCR analysis.

3. Equipment needs:-
(a) -70^{o}C deep-freezer, with CO_2 back-up, and preferably liquid nitrogen storage system.
(b) Regular laboratory freezer (-20^{o}C) for filter paper samples.
(c) Computer data-base system with access to Internet.

4. Utilization of material. Ideally, research workers should carry out their studies in the laboratories where the repositories are held. Until this is feasible, centers in Europe and the USA would be identified for collaborative studies, to which appropriate samples would be taken. It is anticipated that the centers would be eventually equipped to facilitate these activities in Africa.

5. Transport of material. It is envisaged that samples will be made available to other research laboratories in Africa, and these would be sent by airfreight.

Annex II. Resources for Host Genetic Studies of Malaria

The investigation of host genetic susceptibility factors has provided insights into pathophysiological and immune protective mechanisms in malaria. The potential of this approach is increasing with new powerful methods of human genome analysis. Towards this goal there is a requirement for DNA studies of two types: case-control studies and family studies.

Large case-control studies of genetic factors in severe and mild malaria have been undertaken in two populations in East and West Africa (Kilifi, Kenya and The Gambia). Some DNA from these studies remains available and is being used for ongoing collaborative genetic susceptibility studies with African scientists. There is a need for further large data sets from other African populations. A repository of cell lines to provide a renewable source of DNA for such studies would be valuable.

Family studies of severe malaria are required to utilize the power of developing genetic linkage approaches to identifying new malaria resistance and susceptibility genes. This new undertaking would likely require multi-center studies in Africa to generate a repository of cell lines or DNA from a large numbers of families with more than one affected child.

Annex III. Malaria Vector Reference Collections

CONCEPT

Research on malaria vectors increasingly requires access to colonies of the principal vector species and various chromosomally defined strains and to DNA reference samples. The establishment of a series of linked reference collections for such materials would greatly facilitate collaborative research and should be given a high priority.

An important consideration in such a proposal is the need to prevent accidental introduction of new malaria vector strains and species into regions where they do not currently occur.

PROPOSAL

We propose the establishment of three - four linked reference collections to be based within current centers of excellence in malaria vector research. These reference collections would both stimulate collaboration and promote the exchange of research materials. A possible arrangement might be:

AFRICA: 1-2 centers

EUROPE: 1-2 centers

NORTH AMERICA: 1-2 centers

NEEDS

1. Commitment of research groups to lodge materials with center
2. Ready access of research community to collections
3. Close coordination between centers
4. Common, networked database for collections
5. Research on cryopreservation
6. Equipment and support staff