Towards an African-Driven Malaria Vaccine Development Program: History and Activities of the African Malaria Network Trust (AMANET)

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Abstract. The African Malaria Network Trust (AMANET), whose mission is to promote capacity strengthening of African malaria research institutions, was founded in 2002 and is currently focusing on malaria vaccine development. AMANET has trained over 900 African malaria researchers at workshops relevant to clinical trials of candidate malaria vaccines that will meet scientific, ethical, and international Good Clinical Practice standards. African centers selected for developing malaria vaccines initially undergo a needs assessment, followed by filling gaps in short- and long-term training, provision of essential equipment, and infrastructure improvement. Four centers from different malaria eco-epidemiologic settings are being strengthened; two of these have been approved for carrying out malaria vaccine trials. Researchers from prospective trial sites are mentored at northern institutions undertaking Phase 1a and/or 2a trials; five researchers are undergoing doctoral training. AMANET has sponsored one successful Phase 1b trial; three more are underway. Expert site audits will precede launch of phase 2b trials. Several lessons have been learned: the building of comprehensive capacity, essential for undertaking internationally acceptable trials including their sponsorship, is complex and costly. AMANET has spent over US$ 1 million on capacity strengthening of its leading trial center. Despite the high costs, development of three other sites is underway and there are plans to develop two more sites. To succeed, genuine north–south collaboration based on mutual trust and sharing of available information and responsibilities has been essential. AMANET as a sponsor has assumed roles usually reserved for the pharmaceutical industry, yet is operating where regulatory authorities are generally weak or wanting.

INTRODUCTION

For centuries, malaria has adversely affected the history of sub-Saharan Africa; its control during the past century however concentrated on urban areas where colonial authorities and traders lived and in agricultural estates and mines whose products sustained industries in the colonizing countries. When the global malaria eradication program was showing signs of success, which coincided with the wave of national independence, the eradication program was abandoned in Africa on the pretext of mainly administrative and financial constraints. However, the strategies were continued elsewhere. As a consequence, the malaria situation in Africa worsened; now Africa bears the brunt of the world malaria burden estimated at 500 million malaria cases and up to 3 million malaria deaths per annum, and costing an estimated US$ 12 billion annually. The African Summit on Roll Back Malaria (RB M) therefore endorsed the RB M initiative whose cornerstone strategies are prompt diagnosis, early correct treatment, and the use of insecticide treated nets (ITNs). But these strategies are threatened by increasing drug and insecticide resistance.

Despite recent intensification of malaria control investments aiming at reducing the malaria burden by half by the year 2010, this RB M goal may not be attained. There will undoubtedly be a need to scale up and fine tune the application of ITNs and artemisinin-combination therapy (ACT) and the fast development and deployment of new medicines. These approaches may contain and hopefully halt the deteriorating malaria situation, although its reversal by 2015 as envisaged in the Millennium Development Goals (MDGs) is doubtful.1 There is therefore a need to develop entirely new tools that would contribute to the fight of a resilient enemy and reverse its devastation. Therefore, “the development of an effective malaria vaccine represents one of the most important strategies for providing a cost-effective addition to currently available malaria control interventions.”2 The RB M summit therefore “called upon development partners to invest in malaria vaccine development in Africa and strengthen research.”3

Malaria vaccine development has witnessed considerable research for almost 4 decades. The development of pre-erythrocytic malaria vaccines (e.g., RTS.S) with their considerable market potential for short-term travelers recently attracted much interest from public health, after showing promising benefit in malaria endemic settings.4 On the other hand, asexual stage candidates have experienced limited testing, as have transmission blocking vaccines, despite their potential public health importance.

BIRTH OF THE AFRICAN MALARIA VACCINE TESTING NETWORK (AMVTN)

The SP66 malaria vaccine trial in Tanzania constituted a major water-shed event for malaria vaccine development in Africa; it bypassed traditional trial sites, and revealed the potential of public funding for the development of interventions intended for poor malarious communities.5,6 To guide future malaria vaccine trials in Africa, a conference attended by 81 scientists from across Africa, Europe, and the U.S. was convened in Arusha, Tanzania during February 1995; it founded the African Malaria Vaccine Testing Network (AMVTN), whose major objectives were to prepare Africa for planning, undertaking, and coordinating future malaria vaccine trials. The conference underscored the need for capacity strengthening in aspects relevant to malaria vaccine trials.

AMVTN GIVES BIRTH TO AMANET

Although AMVTN addressed many of the issues identified by its founders, particularly in strengthening human capacity

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essential for Africa’s greater participation in malaria vaccine development, African malaria research institutions remained unprepared for testing malaria vaccines. During the turn of the millennium it became abundantly clear that trials of malaria vaccines in the future could still favor the few stronger malaria research institutions in Africa, which generally had strong historical links with northern institutions. AMVTN was therefore transformed into the African Malaria Network Trust (AMANET) in 2002, with the goal of further strengthening the network enabling it to create a level playing field, whereby previously weak African-led and African-owned malaria research institutions would also undertake malaria vaccine trials meeting international scientific, ethical, Good Clinical Practice (GCP), and regulatory standards. Furthermore the anticipated increase in new test products, particularly from genomics will call for more test sites.

The capacity strengthening activities undertaken by AMVTN and later by AMANET include international conferences, training workshops, professional training, and characterization and strengthening of future trial sites, which culminated in malaria vaccine trials by AMANET strengthened trial sites. The rest of this article outlines the governance of AMANET and activities undertaken in each of the mentioned areas. The activities of the Multilateral Initiative on Malaria (MIM) whose Secretariat is now housed at AMANET are not covered in this article.

GOVERNANCE OF AMANET

The AMANET organ gram is shown in Figure 1. The General Assembly comprising representatives of malaria R&D institutions in Africa and allied non-African institutions outside Africa is the topmost organ; it is mainly responsible for electing members of the Board of Trustees (BOT) and of the Scientific Coordinating Committee (SCC). The AMANET constitution is available at the AMANET website.

The BOT, which constitutes 10 members, is the ultimate authority that oversees the general governance, regulation, and control of AMANET. The SCC is composed of 12 members and receives and reviews reports from the Secretariat and the Expert Committees; it advises the BOT on scientific matters; it reviews research proposals, trial protocols, and letters of expression of interest; it also monitors and evaluates ongoing and completed research projects. The members of all AMANET organs are outstanding scientists drawn from across Africa, Europe, and the U.S.

AMANET operates through a Secretariat, which is mainly charged with mobilizing and managing grant funds, publicizing AMANET activities, capacity strengthening, and networking of African malaria research institutions.

INTERNATIONAL CONFERENCES

AMANET holds “biennial” Scientific Conferences during which various themes and sub-themes relevant to the AMANET mission are addressed. Over the years, subsequent Conferences have looked deeper into Africa’s role in malaria vaccine development (Table 1).

MALARIA RESEARCH INSTITUTIONS IN AFRICA

To promote networking, sponsorship, and collaboration of malaria researchers and their institutions in Africa, baseline

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**Figure 1.** AMANET structure.
information was necessary. Therefore, a survey was conducted and this led to development of a directory of malaria research institutions in Africa (National Institute for Medical Research 1997, unpublished document), which was summarized by Pagnoni and Lamizana (1997, unpublished data).

**TRAINING WORKSHOPS**

The 1995 conference identified weaknesses in African researchers that would hinder their optimal participation in the development of malaria vaccines. Many of these observed gaps related to training that is not routinely provided in university coursework. It was therefore decided to address these weaknesses through short-term training workshops (Table 2) as summarized in various issues of the AMANET Newsletters.8

**NEEDS ASSESSMENT AND SELECTION OF PROSPECTIVE TRIAL SITES**

The directory of malaria research institutions in Africa was followed by a detailed needs assessment exercise, which identified their strengths and weaknesses. Thereafter, selection of potential sites for evaluation of malaria vaccines was undertaken. This process also considered malaria transmission intensities across tropical Africa, as shown in Figure 2. So far AMANET has provided capacity strengthening grants to Center National de Recherché et de Formation sur le Paludisme (CNRFP) of Burkina Faso, the Muhimbili University College of Health Sciences of Tanzania, the Tropical Diseases Research Center (TDRC), Ndola, Zambia, and Tanzania’s National Institute for Medical Research (NIMR), Tanga Center. Makerere University Medical School in Uganda was recently approved for AMANET sponsorship. It is planned to add two more sites. Besides receiving AMANET capacity strengthening grants, these institutions are prioritized in other AMANET activities. The following sections discuss the main activities included in the AMANET capacity strengthening grants.

**Professional training.** To fill critical gaps in professional research personnel, this program targets meeting the institutional needs for specific professional training in critical areas such as Epidemiology, Immunology, Molecular Biology, and

**TABLE 1**

AMVTN/AMANET “Biennial” scientific conferences

<table>
<thead>
<tr>
<th>Conference number</th>
<th>Date/year</th>
<th>Venue</th>
<th>Number of participants</th>
<th>Theme</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>February 1995</td>
<td>Arusha, Tanzania</td>
<td>81</td>
<td>Assessment of the criteria for malaria vaccine trials in Africa, their role in a global context, and identification of the possibilities and modalities for the establishment of an African malaria vaccine testing network.</td>
</tr>
<tr>
<td>2nd</td>
<td>November 1997</td>
<td>Accra, Ghana</td>
<td>80</td>
<td>Integration of recent research on African malaria epidemiology with developments in immunology, molecular biology, and malaria vaccine research.</td>
</tr>
<tr>
<td>4th</td>
<td>February 2004</td>
<td>Arusha, Tanzania</td>
<td>74</td>
<td>Results from Clinical Development and Trials of Malaria Interventions.</td>
</tr>
<tr>
<td>5th</td>
<td>February 2007</td>
<td>Zanzibar</td>
<td>120</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2**

AMANET Training workshops

<table>
<thead>
<tr>
<th>Title</th>
<th>Year and venue</th>
<th>Number of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design and methodology in malaria vaccines trials (2)</td>
<td>1997 (Ifakara, Tanzania), 1999 (Manhica, Mozambique)</td>
<td>34</td>
</tr>
<tr>
<td>Data management in intervention trials (3)</td>
<td>1997 (Ouagadougou, Burkina Faso), 2005 (Bamako, Mali), 2006 (Bamako, Mali)</td>
<td>54</td>
</tr>
<tr>
<td>Good clinical practice (GCP)</td>
<td>1998 (Accra, Ghana), 2000 (Bagamoyo, Tanzania), 2004 (Ouagadougou, Burkina Faso), 2003 (Bagamoyo, Tanzania), 2005 (Zanzibar, Tanzania), 2006 (Bagamoyo, Tanzania)</td>
<td>162</td>
</tr>
<tr>
<td>Trial sites needs assessment</td>
<td>2002 (Nairobi, Kenya)</td>
<td>9</td>
</tr>
<tr>
<td>Molecular biology &amp; immunology in malaria vaccine development</td>
<td>2000 (Franceville, Gabon), 2001 (Bagamoyo, Tanzania), 2002 (Maputo, Mozambique), 2004 (Johannesburg, South Africa), 2005 (Yaoundé, Cameroon), 2006 (Kampala Uganda)</td>
<td>158</td>
</tr>
<tr>
<td>Malaria vaccinology in developing countries</td>
<td>2005 (Bagamoyo, Tanzania)</td>
<td>34</td>
</tr>
<tr>
<td>AMANET/MIM African health research leaders</td>
<td>2002 (Usa River, Arusha, Tanzania) and 2006 (Dar es salaam, Tanzania)</td>
<td>38</td>
</tr>
<tr>
<td>SOPs for ethical review of health research</td>
<td>2003 (Entebbe, Uganda), 2005 (Dar es salaam, Tanzania)</td>
<td>50</td>
</tr>
<tr>
<td>Strengthening PIs</td>
<td>2003 (Harare, Zimbabwe)</td>
<td>26</td>
</tr>
<tr>
<td>Proposing and reporting on intervention trials</td>
<td>2004 (Arusha, Tanzania)</td>
<td>25</td>
</tr>
<tr>
<td>Advanced training in bioethics</td>
<td>2004 (Zanzibar, Tanzania)</td>
<td>60</td>
</tr>
<tr>
<td>Afro-immunoassay network</td>
<td>Several (Accra, Ghana)</td>
<td>Various</td>
</tr>
<tr>
<td>Financial accounting and procurement procedures</td>
<td>2005 (Arusha, Tanzania)</td>
<td>13</td>
</tr>
<tr>
<td>Grand total</td>
<td></td>
<td>913</td>
</tr>
</tbody>
</table>
Figure 2. AMANET site selection flow chart.
Parasitology. Presently, AMANET is sponsoring 5 Ph.D. candidates at CNRFP; 4 of these received Masters degrees under AMANET sponsorship. TDRC-Ndola and NIMR-Tanga, which came under AMANET sponsorship later, have 2 Masters degree trainees each.

**Detailed characterization of trial sites.** All institutions selected for AMANET strengthening must undertake detailed field site characterization activities, which involve intensive epidemiologic and demographic investigations, including detailed data on malaria parasites and vectors, molecular biology, and immunology relevant to malaria vaccine development.

Moreover, AMANET founded and supports the Afro-Immunoassay Network whose main objective is to establish specific immuno-epidemiologic assessments to develop a uniform “gold standard” for the evaluation of promising asexual stage malaria vaccines. Agreed standard operating procedures have been developed and are used to compare results from different laboratories situated in varying malaria epidemiologic settings. The network with a hub at the Noguchi Memorial Institute for Medical Research in Accra, Ghana includes other centers in Senegal, Burkina Faso, Gabon, Zimbabwe, and Tanzania.

**Malaria vaccine field trials.** The testing of malaria vaccines in Africa like elsewhere must follow standard procedures as outlined by the International Conference on Harmonization of Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. In this regard, AMANET must maintain quality assurance and quality control systems to ensure compliance with GCP and the trial protocol. To achieve this, the AMANET BOT and the SCC established a Scientific Advisory Panel (SAP) from which Clinical Development Teams (CDTs) are selected. The CDTs oversee the development of each malaria vaccine candidate. The CDT together with the clinical trial monitor ensure that the trial investigator team is not only adequately qualified, but that it has adequate staff, facilities, equipment, and time. Moreover for every trial there is a Data Safety Monitoring Board (DSMB).

Because the private sector is not likely to fund malaria vaccine development, AMANET had to elicit public-sector support for linking malaria vaccine efforts in the north, with those in Africa. This support was eventually gained through the European Malaria Vaccine Initiative (EMVI) and the Network (AMVTN) of Stage I and II malaria vaccine candidates. The network with a hub at the Noguchi Memorial Institute for Medical Research in Accra, Ghana includes other centers in Senegal, Burkina Faso, Gabon, Zimbabwe, and Tanzania.

The relationship between EMVI and AMANET is illustrated in Figure 3: EMVI provides a mechanism that sees candidate molecules through current Good Manufacturing Practice (c-GMP) and clinical testing in Europe, followed by AMANET sponsored testing by African institutions in Africa starting from Phase Ib. Recently AMANET has devised an alternative mechanism of attracting potential vaccines through open advertisements.

For a product to enter the AMANET testing pipeline, the AMANET Secretariat receives an application from the developer, which is processed according to Figure 4. The application, which must include an investigator’s brochure (IB), draft clinical development plan, GMP certificate, batch release protocol, and all pertinent literature is submitted by the Secretariat to 4 expert reviewers after signing confidentiality and conflict of interest agreements. The reviewers’ findings are presented to the SCC, which deliberates the recommendations, and if suitable for sponsorship, the BOT is requested to make the necessary financial allocation. The protocol is prepared by the identified testing center in collaboration with the AMANET Secretariat. The targeted trial center and its field site must undergo an external detailed expert audit before undertaking an AMANET funded trial.

So far the AMANET Secretariat has received and processed several applications for sponsorship of product development. The first application was from the Institute Pasteur in Paris and concerned MSP3 (Merozoite Surface Protein-3), which recently underwent phase 1b testing by the CNRFP. The trial was entirely run by a Burkinabe research team from CNRFP; the Malaria Research and Training Center in Mali provided the study monitor; quality assurance was performed under an African scientist from the Institute Pasteur, Dakar. The results of this trial have recently been published. Given these results and satisfaction of the GO criteria, a phase 1b age de-escalation trial including toddlers and infants has started in Burkina Faso and Tanga, Tanzania; the latter site is mesoendemic for malaria.

AMANET is currently sponsoring a phase Ib trial of the Apical Membrane Antigen (AMA 1) candidate malaria vaccine in adults Bandiagara, Mali by the Malaria Research and Training Center. The trial of GMZ 2 (combination of the Glutamate Rich Protein (GLURP) and MSP 3) earmarked for Albert Schweitzer Hospital in Lambaréné, Gabon will start soon.

**CONCLUSIONS AND LESSONS LEARNED**

The founding Conference in 1995 was quickly followed by developing a directory of malaria research institutions in Africa, which revealed that the majority of them were weak and not yet prepared to undertake malaria vaccine trials. AMVTN and later AMANET have been in the forefront in
organizing training workshops, which have benefited over 900 African malaria researchers from across the continent, and have gone a long way in creating an enabling environment for testing malaria vaccines, other malaria intervention candidates, and overall research. Indeed they have also built expertise, which is now used by other trial sponsors including the recently established Malaria Clinical Trials Alliance (MCTA). Moreover in recognition of this experience, AMANET has organized several workshops upon the request of several international organizations, including the: WHO Initiative for Vaccine Research (IVR) and TDR; Office for Human Research Protections (OHRP) of the US Department of Health and Human Services; US National Institutes of Health (Bioethics), and the newly founded MCTA.

Professional training is critical for undertaking research. However, most of the existing research personnel in Africa also constitute research leaders for site characterization, and other research endeavors such as trial monitoring. Thus, they are inevitably stretched to a point where they may not be appropriate Principal Investigators for clinical trials. Therefore there is a need to develop a mass of needed trialists on the continent. The investments required to achieve this and ensure the provision of all essential equipment and infrastructure are immense. These areas deserve more attention from research and trial sponsors. In essence, sponsorship of clinical trials is costly because it includes these often hidden costs. For example, AMANET has already invested close to US$ 1 million in its most advanced center. Not infrequently new clinical batches and product reformulations may be needed; one clinical batch to cover phase Ib and IIb trials for a synthetic peptide costs around US$660,000, whereas a phase Ib vaccine trial averages US$330,000.

Because the sponsor role is new to Africa, it has been necessary for AMANET to appoint and train trial monitors, prepare standard operating procedures, and generic trial protocols. Contract Research Organizations (CROs) and Contract Research Associates (CRAs) have a definite role to play. Provision of necessary insurance and indemnity for trials in Africa is another substantial challenge. AMANET statutory bodies as the SCC and SAP have been indispensable as sci-

![Figure 4. Flow of test product from the developer to the testing site. SCC, Scientific Coordinating Committee.](image-url)
cient reviewers and clinical development team members; the diverse expertise and global nature of these bodies has abundantly benefited the product development process.

North–south networking based on trust is absolutely essential, as exemplified by the constitution of AMANET statutory bodies and the relationship between AMANET and EMVI. Moreover, northern research partners play key roles of advocacy. A major lesson learned is that the development of appropriate intervention products demands input from northern and southern research communities, African research participants, African governments, bilateral and multilateral donor agencies, non-governmental organizations, and the private sector, all of which are indispensable.

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