Artesunate-Mefloquine (ASMQ) Fixed-Dose Combination (FDC), an additional tool in the armamentarium to control malaria in Latin-America

1st of December 2011- Rio de Janeiro
Meeting chaired by Dr. Jean René Kiechel
Summary notes

Background

Thirty percent of the total population in territories of the WHO Region of the Americas lives under some degree of malaria risk.[1] Between 2000 and 2009, due to extension of the availability of diagnosis, treatment and vector control measures, reported cases have been reduced between 25% and 50%.[2]

The contribution of Latin America (LA) to the global malaria burden is small, with an estimated <1% (from 560,221 cases[3] or 673,000 cases[4] to ~ 3 million[5] cases) of the total world malaria cases occurring in LA in 2007. These advances represent a window of opportunity to achieve increased malaria control. About 50-60 % of the malaria cases occur in Brazil and the other ~40% are distributed in 20 other countries of Central and South America. [6-7-8]

Despite the fact that overall *P. vivax* accounted for ~70% of all cases reported in 2009[9], *P vivax* populations overlap frequently with *P falciparum* and mixed infections with the two species are common. There is huge uncertainty over the true epidemiology of relapse patterns in most of the *P vivax* endemic world [10] and limited operational information assessing the disease burden for this species.

Key components of an effective malaria control strategy are early diagnosis and prompt treatment, and treatment efficacy is threatened by the emerging resistance to the artemisinin class of drugs. According to the WMR 2010, only 6 out of 23 countries or territories in the Americas currently undertake regular therapeutic efficacy monitoring, so detection of imported resistant strains of *P. falciparum* or emerging new foci of resistance is not likely.

The ACT supply problems, as reported from the Amazon Sub region, are associated with the complexity of implementing procurement processes and with the progressively smaller volume required of these medications.[11] The malaria epidemiological trend towards reducing progressively the number of cases in countries makes it a less attractive market for vendors and requires strengthening support for joint purchases through already existing international mechanisms.[12]

The long production cycle of ACT coupled with its relatively short shelf life (2 to 3 years) and the complexity of the supply systems in countries, make accurate demand forecasts essential.

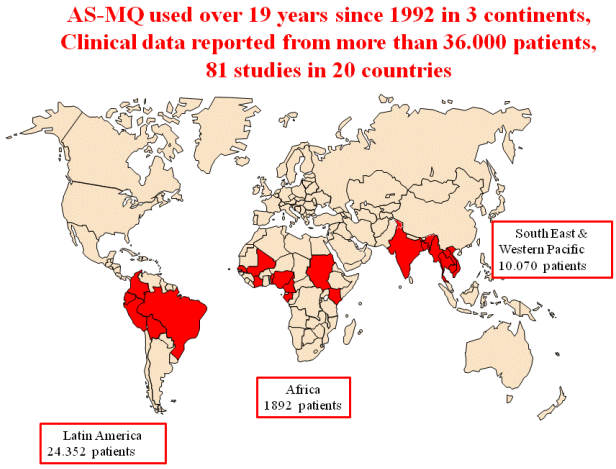
Towards ensuring that new medicines reach those who need them most, the product registration in countries and the international and national supply systems require additional special attention.

To address main challenges for improving access of ACT in general, and specifically of ASMQ FDC, DNDi organized a brainstorming session on December 1st, 2011, with key malaria stakeholders across the private and public sectors in Latin America. The goal was to analyze specific obstacles to the deployment and effective surveillance of ACTs and provide recommendations which also apply to the rest of the tools needed for malaria control.

See the agenda and the list of participants in Annex I.

ASMQ current status & product presentation

Artesunate (AS) and mefloquine (MQ), is an ACT with proven efficacy after 19 years of clinical use, aligned with the WHO recommendations and malaria policies. Both antimalarials are well-established drugs for the treatment of *P falciparum* malaria.



See ref. papers in Annex II

2002-2008: to address the treatment requirements of people most threatened by malaria and underscoring the need for public leadership, the FACT Consortium created by DNDi and TDR developed artesunate–mefloquine (ASMQ) as a fixed-dose combination (FDC). Within the multi-partner FACT Consortium, Farmanguinhos was the first manufacturing partner of ASMQ FDC.

2008: ASMQ FDC was granted Brazilian registration approval on March 3, 2008 which assures the supply for malaria endemic countries in Latin America.

2008-2010: The transfer of technology for ASMQ between the Brazilian government-owned pharmaceutical company, Farmanguinhos/Fiocruz, and India's generic pharmaceutical company, Cipla, was completed in 2010, with the support and facilitation of DNDi. Designation of Cipla as the manufacturer of ASMQ will make the product available in Southeast Asia and in other parts of the world at affordable pre-agreed prices.

2010: The WHO pre-qualification dossier for the product developed by DNDi & partners was submitted in March 2010, including stability studies of three years of shelf-life for ASMQ FDC tablets.

2011: ASMQ FDC was granted Indian registration approval on November 30, 2011 which assures the supply for malaria endemic countries in Asia.

2011: The ASMQ FDC registration process is underway in countries where AS+MQ is part of the national policy for uncomplicated malaria.[13] Target countries are Cambodia and Malaysia in the Western Pacific region and Thailand and Myanmar in South East Asia as well as Peru, Venezuela, Bolivia and Colombia in the Americas region.

ASMQ product profile:

ASMQ FDC tablets are indicated for the treatment of acute uncomplicated *P falciparum* malaria mono-infection and mixed infections with *P vivax*. Current WHO guidelines on malaria recommend that *P vivax* malaria should be treated with an appropriate ACT particularly where ACTs have been adopted as the first-line treatment for *P falciparum.*

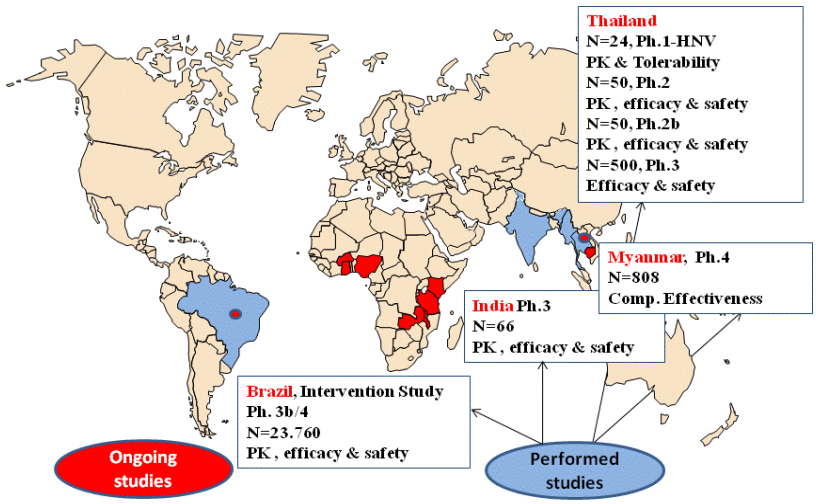
Dosing of ASMQ FDC tablets is based on four age-weight categories. The recommended daily dose for each category is a best approximation of the target dose for each drug: 4 mg/kg for artesunate and 8 mg/kg for mefloquine, corresponding to total doses of 12 mg/kg and 24 mg/kg, respectively.

In patients at the extremes of weight for the corresponding age (such as in cases of malnutrition and obesity), the dose should be adjusted according to the weight of the patient.

For children who are unable to swallow tablets, the tablet(s), which are small (6.0 mm diameter for children <6 years, and 9.6 mm for children 6 years) should be placed on a spoon with water and allowed to disintegrate before oral administration.

The ASMQ FDC has demonstrated efficacy in clinical studies in Thailand, India, Myanmar and Brazil as follows:

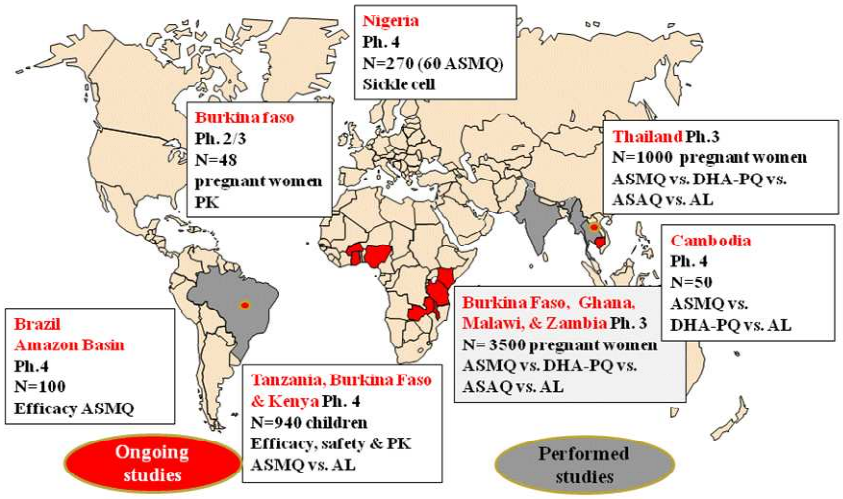
See details of performed studies related to ASMQ FDC development in Annex III



Additional Ongoing Clinical Studies with ASMQ FDC:

A set of studies is ongoing that will provide additional data from more than 4.500 pregnant women from Thailand and Africa and about the tolerability, efficacy and pharmacokinetics of more than 900 children under 5 years old from Tanzania, Burkina Faso and Kenya.

ASMQ FDC, ongoing studies

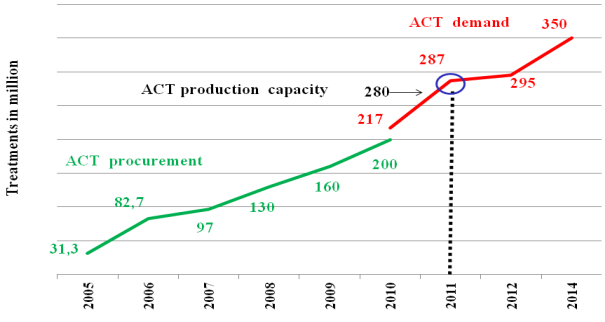


Collaboration between MMV and DNDi

DNDi and MMV share expertise and collaborate in many different ways for the benefit of patients. These collaborations range from reciprocal access to the results of high throughput screening in drug discovery to joint support for clinical studies of approved drugs to determine their optimum usage. As part of its work on developing a single isomer of mefloquine, MMV discovered a route and process for manufacturing mefloquine, which cost much less than conventional methods. This resulted in a reduction in the cost of mefloquine bulk drug from about $1,100/kg to about $400/kg, a reduction of about $1 in the daily cost of mefloquine for an adult. The process is presently being scaled up and licenses are being negotiated with AS/MQ providers in India and Africa. MMV and DNDi are working together to make the same low cost mefloquine available as AS/MQ in Latin America.

Challenges and opportunities with ACT including ASMQ FDC

There are several issues that affect all ACTs, including ASMQ FDC. These include the increasing ACT demand forecast[14-15-16-17] which is summarized below. Moreover, early signals of artemisinin resistance have already been detected in Southeast Asia, and there is a global responsibility to protect the artemisinin class of drugs.



Global ACT demand from several sources: CHAI and RBM

ASMQ FDC production for Brazil and Latin American countries

Farmanguinhos,[18] a public Brazilian pharmaceutical laboratory and one of the Institutions under the Foundation Oswaldo Cruz,[19] has been involved in the development of ASMQ FDC with DNDi and partners since the very beginning in 2002. This partnership and its mission have been of high strategic relevance for both Farmanguinhos and for Fiocruz.

The manufacturing of ASMQ is now taking place in a new production plant in Jacarapaguá (previously in Manguinhos) and April 2012 is the deadline for ANVISA inspection. Once the GMP status is granted, Farmanguinhos will be eligible to join the PAHO Strategic Fund[20] for the supply of ASMQ in the public sector of member state's countries. In the near future, Farmanguinhos also expects to submit the ASMQ FDC dossier for WHO pre-qualification.

For the active pharmaceutical ingredients (API) production (artesunate and mefloquine), Farmanguinhos depends on external supply, which has been mentioned as a constraint to the regular manufacturing process. This is why the development of domestic capacities for the API production is part of further plans at Farmanguinhos/Fiocruz. In the meantime, Farmanguinhos is closely following up the likely availability for end 2012, of biosynthetic artemisinin[21] and low cost mefloquine under development by MMV-DNDi and partners. Depending on the success of these two projects, a price reduction for the final product ASMQ FDC could be achieved in the near future.

ASMQ FDC produced by Farmanguinhos was granted Brazilian registration approval in 2008 and is currently used for the treatment of uncomplicated malaria in Brazil, particularly in the Amazon area. To ensure the supply for malaria endemic countries in Latin America, Farmanguinhos needs a more clear estimation of the demand. The logistics for its distribution outside Brazil require additional procedures. If the product were to be registered in other countries in the Americas, and specifically for the public sector procurement, ASMQ FDC could benefit from the PAHO revolving Fund system.

ASMQ FDC procurement & distribution in Latin American countries

The PAHO Strategic Fund has been developed by the Secretariat of the Pan American Health Organization at the request of PAHO Member States, and for the benefit of Member States. It provides support to overcome obstacles that countries tend to face in the acquisition of essential public health supplies:

- In the area of demand forecasting for pharmaceutical products, it offers technical support in planning, programming, and forecasting of supplies to ensure continuous availability.
- Also, it offers the possibility to acquire products that meet international quality standards.
- For expensive products and supplies of limited availability, the Fund aims to negotiate competitive prices by consolidating demand and achieving economies of scale.
- In price referencing, it provides information to the Member States.
- In relation to pharmaceutical products available through other global initiatives, this system will serve as a link with suppliers prequalified at international level.

The Fund links the acquisition of medicines and essential public health supplies with technical processes in planning and programming.

It is also known as the Regional Revolving Fund for Strategic Public Health Supplies.[22] This system has already been used for malaria, specifically for the procurement of Coartem®.[23]

Additional priorities highlighted by PAHO to improve access:

- ✓ Clinical support to deploy pediatric formulations
- ✓ Alignment to regulatory requirements
- ✓ Knowledge, management and information availability

ACT estimation of needs and demand forecast

The ACT demand forecasts currently available at international level are probably a reliable estimate of needs, but these forecasts are not systematically considered by ACT manufacturers as the base for investing in scaling up production capacity accordingly. This makes it extremely difficult for donors to plan adapted disbursement of funds.[24]-[25]

ACTs are more expensive than chloroquine, so efforts have been made to estimate the demand, mainly for Africa where malaria is a major public health burden. Several attempts to define a reliable methodology have been made[26]-[27]; however malaria programs that hold the responsibility for the ACT demand forecast often struggle with stock outs, attributed to deficiencies in quantification and lack of precise and timely information on supplies and inventories.[28]

Many diverse indicators influence the estimation of ACT needs including the malaria transmission profile and its burden, the *Plasmodium* diversity in each specific setting, the composition of the market, the performance of the public sector on the malaria coverage actions, the genetic profile of the human and parasite populations, the epidemiological surveillance systems and the demographic structure of the community.

Current availability of several quality assured ACTs and the imminent arrival of several new products should be taken into consideration, aligned to the degree of local parasite resistance to the companion drugs of artemisinins. The national strategies adopted towards reducing drug pressure will also influence the demand forecast. For example, strategies like multi first line treatment could use several ACTs for the treatment of uncomplicated malaria, reducing the pressure on the different partner drugs. In addition, selected products will be chosen for specific use at community level, for special population groups like pregnant women or children < 5 y.o., and a country could also choose a unified therapy in settings where *P vivax & falciparum* coexist.

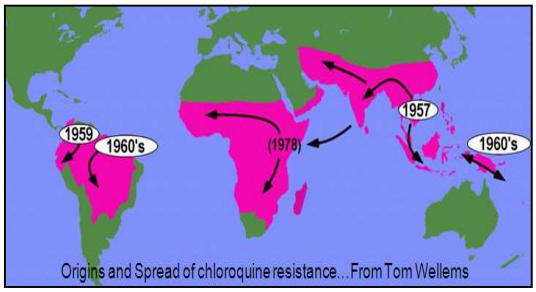
Due to the complexity of the demand forecast and acknowledging the responsibility of National Malaria Control Programs, there was consensus that many malaria stakeholders should contribute to discussions of this issue.

Monitoring Antimalarial Resistance

ACTs combine a short acting artemisinin with a longer lived partner drug; this strategy has been extremely effective, and is one element in a decline in malaria morbidity and mortality in many regions of the world. Unfortunately, malaria is an extremely common infection in many locations, and this strategy requires very heavy use of the antimalarials. In response, the parasites eventually evolve resistance to the drugs in use, necessitating a change in drug

policy. Resistance to both chloroquine and sulfadoxine-pyrimethamine (SP) arose and spread widely in the malaria endemic world beginning in the 1970's, and the change to ACTs was the response to this development. Recently, it has become clear that resistance to the artemisinin component of ACTs has also appeared in Southeast Asia, raising the fear that these parasites will also spread and compromise the efficacy of the ACTs that are now the mainstay of malaria treatment.

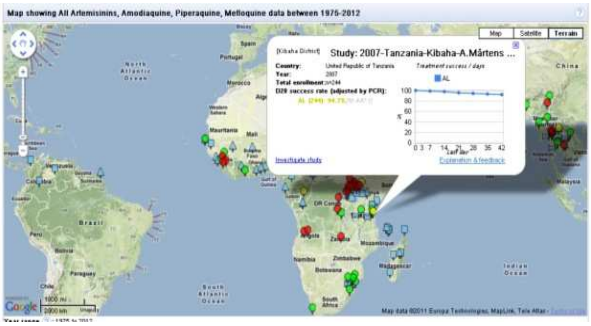
The resistance to both chloroquine and SP arose in the same region of Western Cambodia, and spread relatively quickly throughout Asia and even to Africa. It is remarkable that the changes in artemisinin susceptibility have appeared in the same area, and the possibility that these parasites could follow the same path has triggered a major public health alarm.



However, it is often overlooked that resistance to both chloroquine and SP arose independently in South America, and the genetic changes in those resistant parasites are unique to the continent. We currently do not know the mechanism or genetic basis of artemisinin, but we do know that it is based on genetic changes in the parasites themselves. Thus, Latin America needs to pay close attention to the patterns of drug efficacy within the region, cognizant of the threat of decreased efficacy of both the artemisinins and the partner drugs with which they are paired.

The importance of surveillance within Latin America is underscored by another parallel with the conditions of malaria in Western Cambodia. This region at the Thai-Cambodian border has rather low malaria transmission, a mixture of falciparum and vivax malaria, many migrants coming to the area for legal and illegal logging and mining, and profligate use of monotherapies, especially artemisinins. These conditions are rather similar to some Amazon border regions, and could again function as the cradle of new resistance in Latin America- this time to artemisinins and partner drugs like mefloquine.

The WorldWide Antimalarial Resistance Network (WWARN http://www.wwarn.org) serves the global malaria community through the provision of high quality data resources, a collection of research tools and a global forum for exchange of scientific and public health information on matters relating to antimalarial drug resistance. An internet-based platform that can receive data in any file format on the clinical, molecular, in vitro or pharmacological aspects of drug efficacy has been designed. The system receives data sets with individual patient or parasite information and transforms uploaded data into a common format. The contributor receives a detailed analytical report, and with permission, a very brief summary of the outcomes is added to the WWARN Explorer, a map showing the trends and information currently in the repository.



Answering key questions in public health requires integration of large, diverse data sets over time and space. The common format of the WWARN repository provides a platform so that groups who have uploaded data can pool and analyze them appropriately. The group can then work collaboratively with this much larger data set to address these important questions. For example, groups are currently engaged in the analysis of:

- early parasitological response following ACT treatment in African clinical trials;
- the effect of mg/kg dosing strategies on the risk of treatment failure in patients treated with currently recommended ACTs;
- the role of candidate molecular markers of lumefantrine and amodiaquine resistance in clinical outcomes of ACTs;
- the contribution of inadequate lumefantrine exposure to the risk of treatment failure.

WWARN is eager to collaborate with the many scientists and public health professionals in Latin America so that comprehensive, timely information can be generated to track the emergence and spread of drug resistance, inform drug policy and containment efforts in this region.

Ongoing actions in Latin America

In the Americas region, Brazil, Peru, Venezuela, Bolivia and Colombia, AS+MQ is part of the national policy for the treatment of uncomplicated malaria.

Brazil

An open label, intervention and implementation study in Brazil[29] has been carried out to evaluate the impact of programmatic use of ASMQ FDC in the reduction of *P. falciparum* malaria incidence in comparison with the standard antimalarial regimen used in Brazil. This effectiveness study has been conducted in seven municipalities in the Acre and Pará regions. Patients were administered one or two tablets of ASMQ FDC (25/55 mg or 100/220 mg) daily for 3 days, or the standard regimen of quinine plus doxycycline and primaquine. Patients were followed-up on D7 and D40, and a thick blood smear analysis performed. The total population who received ASMQ between June 2006 and December 2008 numbered 23,845. A significant effect of the ASMQ intervention was observed in all evaluated outcomes [Incidence Rate 0.34 (0.20–0.58); Ratio Falciparum/Vivax 0.67 (0.50–0.89); Admissions 0.53 (0.41–0.69)], with a decrease in the mean level of the time series, adjusted for the trend and seasonality. Interaction effects between months and intervention were also evaluated. An elimination of the end of the year seasonal malaria peak was seen post-intervention, and no serious adverse events relating to the use of fixed-dose ASMQ were reported. Authors concluded that in the remote region of the Juruá valley, the early detection of malaria by healthcare workers and treatment with fixed-dose ASMQ was feasible and efficacious, significantly reducing the incidence and morbidity of multidrug-resistant Pf. Following the assessment of its programmatic impact, the FDC of ASMQ is part of the national policy as alternative first line for the treatment of uncomplicated malaria.[30]

Additional actions contributed to the reduction of *P falciparum* in the Brazilian Amazon area, already implemented previously to the mentioned Intervention study. Concerning *P vivax*, which made up to 80% of the cases in the region, the National Program of malaria and the related Committee is considering the possibility of adding the gametocide primaquine to the ACT on the last day of treatment. A study in that direction will be performed in 2012 in line with the burden represented by *vivax*, considering primaquine for a 7 days administration instead of over 14 days as it is currently recommended. A grant from the Brazilian national budget has been recently approved for that purpose. Furthermore, Tafenoquine, a drug under development by MMV is also being considered for future studies.

A strategy of using multiple ACTs is under consideration by the Brazilian national malaria program with the goal of reducing drug pressure and decreasing the risk of development of resistance against artemisinins. A new national guideline for the treatment of malaria will be published before the end of 2011; ASMQ will be reserved for low malaria transmission areas to handle the need to ensure an adequate interval in between two treatments with ASMQ FDC, linked to the long half-life of mefloquine.

Brazil, a member of RAVREDA, is planning to perform a series of in vivo and in vitro, as well as molecular studies to monitor ACT efficacy in endemic areas.

Venezuela

Despite efforts towards controlling malaria and the introduction of ACTs, the number of *P. falciparum* cases in Venezuela has increased; this may be related to aspects of early access to and the appropriate use of the drugs. There are currently 45.000 malaria cases per year, of which 20% are related to *P falciparum*.

The use of AS+MQ is currently the national policy for the treatment of uncomplicated *P falciparum* in Venezuela. Discussions are underway for DNDi-Farmanguinhos to make a donation of ASMQ FDC, while the process for product registration by Farmanguinhos is being completed and the integration of ASMQ FDC in the PAHO Revolving Fund system is operational.

Venezuela is no longer part of RAVREDA; however, the national malaria program is looking for ways to improve the antimalarial monitoring of resistance and to set up a national pharmacovigilance system.

MMV involvement in Latin America

MMV is collaborating with GSK in the development of tafenoquine for vivax malaria. One clinical site is currently actively recruiting patients in Peru and another site in Brazil is expected to start recruitment in the next few months. The discovery and development of drugs for the radical cure of vivax malaria is becoming increasingly important to MMV. Latin America will be an important region to undertake clinical trials of such drugs should they pass successfully through preclinical safety and efficacy studies.

AMI-RAVREDA:

The Amazon Network for the Surveillance of Antimalarial Drug Resistance (RAVREDA) refers to the network organized in 2001 by several countries of the Amazon sub region, with PAHO, to respond to the challenge of antimalarial drug resistance in the Amazon. The Amazon Malaria Initiative (AMI) was launched in 2001 by the United States Agency for International Development, Office for Infectious Diseases in Latin America and the Caribbean (USAID/LAC) as its mechanism for focusing its financial and technical resources in support of the Roll Back Malaria Partnership (RBM) in Latin America.[31]

Both RAVREDA/AMI have developed a successful partnership during ten years so far, and at present country members are: Bolivia, Brazil, Colombia, Ecuador, Guyana, Peru and Surinam in the Amazon Basin and since 2008, five Central America countries: Belize, Guatemala, Honduras, Nicaragua and Panamá. AMI-RAVREDA works with the important collaboration of Centers for Disease Control and Prevention (CDC) of the United States, Management Sciences for Health's Rational Pharmaceutical Management Plus (MSH/RPM Plus) program, the United States Pharmacopoeia's Promoting the Quality of Medicines in Developing Countries USP/PQM) program and Research Triangle International, RTI.

Main lines of the AMI/RAVREDA Plan of Action:

- ✓ Surveillance of antimalarials resistance and efficacy
- ✓ Antimalarials access and use
- ✓ Quality control of antimalarials
- ✓ Malaria Diagnosis quality and access
- ✓ Malaria Entomology and Vector Control
- ✓ Malaria Epidemiology and Information Systems

Thanks to the joint regional efforts, malaria is declining in most countries of the Americas. Between 2000 and 2009, the total number of confirmed cases dropped by 43%, with reductions of more than 50 % in 15 countries.

All the countries integrating the network have adopted ACTs as 1st line treatment for uncomplicated *P falciparum* malaria and more than 17 studies related to chloroquine resistant *P vivax* have been performed among other relevant actions.[32] However, there are still challenges, especially ensuring the continuous supply of ACT and the implementation of systematic processes to monitor the appropriate application of standards and protocols.[33]
The support provided by AMI/RAVREDA towards improving regional coordination with one voice while filling the gaps on new arising issues is crucial for the control of malaria.

The proposal prepared by Dr. Chang in “One Regional ACT scheme for the Amazon Basin” was beyond the scope of this meeting and will require a separate expert discussion.

AMI/RAVREDA ongoing challenges:

- ✓ Sustainable use of diagnostic test previous ACT treatment
- ✓ Decrease of malaria interest by key decision makers
- ✓ Coexistence of various epidemiological profiles of malaria
- ✓ Logistic management with small volumes of ACTs
- ✓ Low turnover of antimalarials (shelf life)
- ✓ Lack of antimalarials and weakness of knowledge on malaria in settings with very low malaria incidence

For the ASMQ implementation, DNDi, WWARN and AMI/RAVREDA will explore ways to strengthen collaboration.

Main conclusions of the meeting

- ❖ Excellent opportunity to meet with key regional malaria stakeholders;
- ❖ Need for further discussion on extremely relevant issues such as the monitoring of antimalarial resistance and the elaboration of a demand forecasting for ACT;
- ❖ A special attention to solve barriers to overcome ASMQ regulatory aspects related to drug registration in countries;
- ❖ Management of supplies knowledge and guide on PAHO Strategic Fund require wider diffusion for better understanding;
- ❖ National Malaria Programs could better benefit from the potential support of WWARN for monitoring antimalarial resistance, for data sharing, publishing papers and for designing study protocols;
- ❖ Vivax studies are of high priority in LA; further protocol design could be a good opportunity to gather several stakeholders, all products and experts on vivax.

Considering the relevance of upcoming issues it has been recommended to follow up:

- ✓ ACT demand forecasting: PAHO Strategic Fund and regulatory aspects, Dr. Christophe Rerat and Dr. Mayira Sojo Milano (PAHO) will take the leadership, involving key stakeholders;
- ✓ Exploring ways to share available efficacy data from Brazil (ASMQ and other antimalarials): Carol Sibley (WWARN) and Ana Carolina Santelli (NMCP Brazil) will follow up. Contacts to be established with other country representatives and WWARN;
- ✓ Availability of ASMQ: Daniel Mechali (DNDi) and Dr. Pizzo (NMCP Venezuela) will make a proposal for patients in Venezuela. Discussion will be resumed with Peru and Bolivia, whose representatives could not attend the meeting in Rio.

DNDi will renew an invitation in 6 months time to resume discussions.

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