Malaria treatment policy and drug resistance monitoring in countries of South-East Asia Region

Report of a Workshop
Bali, Indonesia, 15-17 September 2010

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Abbreviations

ACPR	adequate clinical parasitological response
ACT	artemisinin-based combination therapy
AUSAID	Australian Agency for International Development
DOT	directly observed therapy
ELISA	Enzyme-linked immunosorbant assay
HRP2/pLDH	Histidine-rich protein 2/parasite lactase dehydrogenase
GFATM	The Global Fund to Fight AIDS, Tuberculosis and Malaria
GMP	Global Malaria Programme
GMS	Greater Mekong Sub-region
PCR	polymerase-chain reaction
PK	pharmacokinetic study
PQ	primaquine
RDT	rapid diagnostic test
SEARO	WHO Regional Office for South-East Asia
TES	therapeutic efficacy study
UNICEF	United Nations Children's fund
USAID	United States Agency for International Development
WWARN	World-Wide Antimalaria Resistance Network
WHO	World Health Organization

Executive Summary

Antimalarial drug resistance is a major problem which hinders the effective control of malaria in the South-East Asia Region. The rapid spread of resistance to several antimalarial drugs has led to revision of the national treatment guidelines and intensification of monitoring of therapeutic efficacies of the currently used antimalarial drugs. The recent emergence of artemisinin resistance in the Greater Mekong Sub-region necessitated the strengthening of drug resistance monitoring and networking for effective information exchange that is essential for tracing the spread of the resistance. Several new tools have been being developed and are deployed for drug resistance monitoring.

The workshop was organized with the primary aims of updating and revitalizing the therapeutic efficacy studies and drug resistance monitoring for strengthening the treatment of malaria in Member States. Seven Member States along with related research institutes and partners participated in the workshop.

The current national treatment guidelines and results of the recent therapeutic efficacy studies were reviewed. Lessons learnt from the Mekong Malaria Programme, with particular emphasis on the efforts to maintain quality drug resistance monitoring and networking, were shared. New WHO guidelines for malaria treatment and new tools for drug resistance monitoring were reviewed and discussed. The WHO–WWARN (WorldWide Antimalarial Resistance Network) collaborative project was presented and discussed.

Member States developed the broad country workplans for drug resistance monitoring for *P. falciparum* and *P. vivax* in the next 1-2 years and identified the technical assistance required. All participating countries committed to conduct therapeutic efficacy studies applying the upgraded study protocol. The country focal points were identified for drug resistance monitoring and networking. A follow-up workshop is planned in early 2012 in order to review the spread of artemisinin resistance in the SEA Region.

1. Background

Antimalarial drug resistance is a major problem which hinders the effective control of malaria. The rapid spread of resistance to antimalarial drugs over the past few decades has led to intensification of the monitoring of their therapeutic efficacy to ensure proper clinical management of cases and early detection of changing patterns of resistance. This will facilitate the revision of national malaria treatment policies. Monitoring of therapeutic efficacy over time is an essential component of malaria control. The results of therapeutic efficacy (*in vivo* tests) provide the most important information for determining whether first- and second-line drugs are still effective and also provide evidence for ministries of health to update their national malaria treatment policies.

The role of WHO in the global management of drug resistance has increased enormously. Its normative and standard-setting role results in a harmonized approach to this global concern. In order to interpret and compare results within and between regions and to follow trends over time, tests must be conducted with similar standardized procedures. WHO has standardized the available methods. Since 1996, WHO has updated the protocol for assessing antimalarial drug efficacy (2003) on the basis of expert consensus and feedback from the field. WHO has also prepared a field manual on *in vitro* assays for the sensitivity of malaria parasites to antimalarial drugs (2007) and a guideline on genotyping malaria parasites to distinguish between re-infection and recrudescence during therapeutic efficacy tests (2008). Genotyping is now becoming mandatory with the longer follow-up of patients.

Routine drug surveillance systems put in place by countries and coordinated by WHO have demonstrated that the failure rate of currently used artemisinin-based combination therapies is increasing in areas on both sides of the Thai-Cambodian border, due mainly to local emergence of resistance to artemisinin derivatives. WHO is investigating this problem and implementing strategies to contain and prevent further dissemination of resistance.

All countries in the SEA Region have adopted ACT for the treatment of uncomplicated *P. falciparum* malaria, except for DPR Korea that reports only *P. vivax* and Maldives which is a non-malaria endemic country. These countries have implemented ACT for treatment of uncomplicated falciparum malaria nationwide. India is an exception and has initiated ACT only in falciparum-prevalent areas. But it has recently expanded the strategy for countrywide implementation under its National Drug Policy on Malaria (2010).

All countries in the Region monitor drug resistance using two main methods, i.e., therapeutic efficacy of drugs (*in vivo* study) and drug susceptibility of malaria parasites (*in vitro* study). Member States conduct therapeutic efficacy studies according to the WHO standard protocol for assessment and monitoring of antimalarial drug efficacy for treatment of uncomplicated falciparum malaria (2003). Some countries also monitor efficacy of chloroquine against vivax malaria. The efforts on monitoring therapeutic efficacy are not sustained due to shortage of trained staff and lack of funds in many countries. Only a few countries (Thailand, Myanmar and Bhutan) conduct studies on a regular basis. *In vitro* tests are generally not routinely conducted, except in Thailand and Myanmar.

During the 1980s, the WHO Regional Office for South-East Asia (SEARO) supported Member States through a special project, "the Regional Collaborative Programme on Antimalarial Drug Resistance", which included both *in vivo* and *in vitro* studies. However, following the termination of the project the work was meant to be carried out as a routine activity by Member States.

It was observed that drug resistance monitoring could not be sustained due to several operational reasons. The availability of funds from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) generally enabled most countries that received such resource to revitalize the drug resistance monitoring. However, this was not systematic and there was a general lack of networking and information sharing. The work on drug resistance is more active in Thailand and Myanmar, which are participating countries of the Mekong Malaria Programme that primarily focuses on drug resistance and drug quality monitoring.

Recently WHO developed a new set of standard protocols as follows:

- Field application of *in vitro* assays for the sensitivity of human malaria parasites to antimalarial drugs, 2007.
- Methods and techniques for clinical trials on antimalarial drug efficacy: genotyping to identify parasite populations, 2008.
- Methods for surveillance of antimalarial drug efficacy, 2009.

Since there have not been any regional meetings to orient or train responsible officers in charge of drug resistance monitoring since 2003, and in view of the potential spread of artemisinin resistance from the original foci in the Thai-Cambodia border region, there is an urgent need to reactivate the networking of drug resistance monitoring particularly in non-Mekong countries. A regional workshop on this was held during 15-17 September 2010.

2. Objectives of the workshop

General objectives

To update and revitalize the therapeutic efficacy studies and drug resistance monitoring for strengthening treatment of malaria in the Member countries.

Specific objectives

The specific objectives of the workshop were to:

(1) review country anti-malarial treatment policy and its implementation.

(2) review implementation status of monitoring therapeutic efficacy of antimalarial drugs, *in vitro* tests and molecular studies.

(3) identify key problems to be addressed.

(4) review and develop country plans for monitoring therapeutic efficacy and antimalarial drug resistance studies.

(5) develop a plan for networking of drug resistance monitoring and its linkage with that in the Mekong Region.

Seven Member States participated in this workshop, namely, Bangladesh, Bhutan, India, Indonesia, Nepal, Sri Lanka and Timor-Leste. Thailand and Myanmar were not invited as the two countries had attended a similar workshop organized by the Mekong Malaria Programme. DPR Korea did not attend as the country reports only vivax malaria which was not primary focus of this workshop. Maldives, which is malaria-free, was not involved.

Dr Rita Kusriastuti (Indonesia) and Dr G.S. Sonal (India) were nominated as Chairperson and Co-chairperson, respectively. Dr Neelima Mishra (India) was nominated as the Rapporteur.

3. Technical sessions

3.1 Malaria situation in the SEA Region

Overview of malaria situation and drug resistance in SEAR

Malaria is endemic in all countries of the SEA Region except Maldives. Seventy-six per cent of the total population of the Region is at risk of malaria. Malaria is highly prevalent at the borders between the eastern parts of Bangladesh, northern Myanmar and the northeastern states of India, eastern states of India, islands of Indonesia and Timor-Leste. Malaria morbidity was on the decline during 2006-2007 but an increase in malaria was observed in several countries during 2008-2009. However, there has been a steady reduction in malaria mortality since. The increase in malaria morbidity was due to increase in case detection and focal outbreaks in some countries. India reported the highest number of parasitological confirmed cases and deaths in 2009 in the SEA Region (96% and 35% respectively). Bhutan, DPR Korea and Sri Lanka are in the pre-elimination phase while India and Indonesia have initiated a phase-wise malaria elimination programme in some states/provinces.

All countries that reported falciparum malaria have revised the national treatment guidelines and have implemented artemisinin-combination therapy (ACT). The last two countries that revised their drug policy and adopted ACT were India (policy revision in 2007 and

implementation in 2009) and Sri Lanka (switched the first-line treatment of falciparum malaria from chloroquine to artemether-lumefantrine in 2008).

All countries in the Region adopted the standard regimen for vivax malaria. Sri Lanka, India and Nepal were the last countries that increased the duration of primaquine for anti-relapse treatment to 14 days (in 2005, 2007 and 2008, respectively). However, it has been observed that the regimen of primaquine for five days generally continues to remain in practice. Indonesia, where both chloroquine-resistant falciparum and vivax malaria are widespread, adopted ACT for both species (artesunate + amodiaquine or dihydroartemisinin-piperaquine).

Drug-resistant *P. falciparum* is widespread throughout the Region. Multi drug-resistant falciparum was reported in the Greater Mekong Sub-region and emergence of artemisinin resistance at the Thai-Cambodia border was recently reported. The Thai-Myanmar border, Myanmar, Bangladesh and some north-eastern states of India are potentially vulnerable to the spread of the artemisinin-resistant strains of *P. falciparum*. In South-Asia, chloroquine-resistance has been reported from all countries whereas sulfadoxine-pyrimethamine resistance was more focalized. Chloroquine-resistant vivax has been reported in some countries but is widespread in Indonesia.

Lessons learnt from the Mekong Region: Artemisinin resistance and its containment project on the Cambodia-Thailand border

In the Greater Mekong Sub-region (GMS) monitoring the therapeutic efficacy of recommended first-line antimalarial medicines are regularly conducted through support from the WHO Mekong Malaria Programme (MMP) and technical partners with financial support from USAID and the GFATM. The Mekong Malaria *in vivo* therapeutic efficacy network is functioning in all six GMS countries, namely Cambodia, People's Republic of China, Lao PDR, Myanmar, Thailand and Viet Nam. The results of therapeutic efficacy studies (TES) are fundamental to update national drug policy on a timely basis. Studies are conducted in an average of 35 fixed sentinel sites as follows: 8 in Cambodia, 2 in Yunnan province and one in Jiangsu province of PR China, 3 in Lao PDR, 8 in Myanmar, 8 in Thailand and 5 in VietNam.

The principal investigators in the GMS countries are regularly updated through emails, training workshops and wrap-up meetings organized by WHO-Mekong Malaria Programme on new elements of study protocols with intensive exchange of relevant technical information and publications. Through intensified Therapeutic Efficacy Study (TES) that covered both parasite species (*P. falciparum* and *P. vivax*), regular regional (training) workshops and cross-checks of data quality, unusual therapeutic failure rates can be early detected. Polymerase chain reaction (PCR) technique is applied in the GMS to differentiate recrudescence and new infections. The national and field capacity to implement and report on TES have been built up with increasing attention by WHO and partners to improve the quality of field work (protocol adherence by field workers) and quality of all generated data and overall reporting. Temporal and spatial data analysis is applied.

The lessons learnt include:

(1) The key observation of early signs of artemisinin tolerance/resistance is the persistence of falciparum parasites on Day 3 from the onset of treatment (preferably 72 hours post-initial treatment). It was observed that on the Cambodia-Thailand border parasite clearance time (PCT) of ACT is significantly delayed in an increased proportion (>10%) of investigated patients matching entry criteria (e.g. parasite counting from 500 to 100 000/microlitre of blood).

(2) Sentinel sites can be maintained for several years and this is one of the best practices to look at trends over time and space. The protocol has to be modified in locations where malaria is almost disappearing (e.g. northern provinces of Lao and eastern provinces of Thailand).

(3) The national malaria control programmes have to maintain the capacity of national and peripheral staff to monitor drug resistance with particular attention to the production of quality data to inform policy-makers.

(4) Increasing therapeutic failure rates of existing first-line antimalarial medicines trigger research on new co-formulated antimalarial drugs.

(5) The emergence of *P. falciparum* resistance to artemisinins on the Cambodia-Thailand border is a regional and global threat. Local, regional and global efforts are ongoing in an attempt to identify and contain the spread of resistant strains. A two-year bi-country project was initiated in January 2009 with the financial support of the Bill and Melinda Gates Foundation. The containment project aims to eliminate artemisinin-resistant falciparum parasites primarily in the hot spot (hard core) zone 1 and aims to actively identify and eliminate resistant parasites in zone 2 (surrounding areas of the hard core zone). The containment operations are currently being implemented in 17 border provinces (10 in Cambodia and seven in Thailand).

(6) Monitoring drug resistance has been intensified in all GMS countries. From the last two-year results, there is evidence that resistant parasite strains have emerged in southern Viet Nam, southern Myanmar and on the border between Myanmar and the Yunnan province of PR China. Preliminary results are being cross-checked through additional studies with results shared among and beyond GMS countries in the SEA Region.

(7) Chloroquine and sulfadoxine-pyrimethamine resistance has originated at the Cambodia-Thailand border before spreading to other areas/countries through population migration. The border area is exactly the same place where artemisinin resistance had been detected now as during 2005-2006 (at Trat province of Thailand and Pailin province of Cambodia). Malaria control programmes should carefully monitor drug resistance, e.g. in the potential routes of the resistant strains to take more pro-active actions.

3.2 Technical update on treatment and drug resistance monitoring

WHO guidelines for the treatment of malaria (2nd edition)

The WHO Guidelines for the Treatment of Malaria (*2nd edition*) was disseminated by WHO in March 2010. It provides a framework for the development of specific diagnosis and treatment protocol in countries. The key recommendations in the 2nd edition that were updated from the 1st

edition published in 2005 include: (a) emphasis on the necessity of prompt parasitological confirmation by microscopy or rapid diagnostic tests (RDT); (b) the 5th recommended ACT option (i.e., dihydroartemisinin-piperaquine); (c) single dose of primaquine (0.75mg/kg) for its antigametocytocidal action in the treatment of falciparum malaria, especially in the pre-elimination and elimination programmes (d) ACTs (except for artesunate and sufadoxine-pyrimethamine) for treatment of chloroquine-resistant vivax malaria; and (e) dihydroartemisinin-piperaquine for the treatment of malaria among travelers returning to non-endemic countries.

Update on drug-resistance monitoring

Therapeutic efficacy study (in vivo study)

The concept and definition of drug resistance was reviewed. A standardized *in vivo* test system for assessing response of *P. falciparum* to chloroquine was developed in 1965 and revised in 1972. In 1996 WHO developed the study protocol for the therapeutic efficacy study. In 2009, a new standard protocol for assessment of the therapeutic efficacy study of falciparum and vivax malaria was developed and disseminated. Other methods {i.e., *in vitro* tests, polymerase chain reaction (PCR) test, molecular studies and pharmacokinetic study} and their pros and cons were presented. The genotyping is compulsory for TES. Blood samples for PCR analysis should be collected on Day-0 (day of initial treatment) and on any day of treatment failure.

WHO has been supporting Member States in monitoring drug efficacy. The global database on therapeutic efficacy of antimalarials was developed and shared (www.who.int/malaria/resistance.htm). This information is very useful for revising the national malaria treatment policy. WHO has lowered the threshold level of treatment failure from 25% in 1998 to 10% in 2005. Over the past three years WHO GMP has produced several guidelines and templates related to drug resistance monitoring. Though most countries conduct TES and update their national drug policy, TES is rarely conducted on a routine basis. Most countries change their sentinel sites and could not sustain TES due to shortage of funds, trained personnel or decentralization of the programmes.

The standard protocol for assessment of TES of falciparum and vivax malaria was presented in detail followed by questions and answers. Application of the templates for data entry and analysis was demonstrated. Some technical issues such as ethical clearance of the TES, importance of pharmacokinetic study and guiding principles for country workpslans on drug resistance monitoring were discussed.

In vitro tests

In vitro tests provide a quantitative measure of intrinsic drug sensitivity/activity and the studies are independent of the patient's immune system and pharmacokinetics. The studies are useful when applied to novel drugs prior to the clinical trials. There are several methods currently available for *in vitro* studies, as follows:

(1) WHO *in vitro* (micro-test) which has been conducted by Member States since the 1980s. The test is based on morphological (microscopical) assessment of parasite growth under the influence of antimalarial drugs in a 24-hour culture. Though the test is highly standardized and easily applicable in field conditions, it is very labour intensive. There are several advantages of this test.

(2) Isotopic *in vitro* test based on measurement of metabolic activity of the parasite by assessment of the uptake of radioactively-labelled precursors (e.g. 3H-labelled hypoxanthine). There are several advantages and disadvantages: it is a highly reproducible test but requires very expensive laboratory equipment.

(3) Fluorometric test (e.g. SYBR-Green I, Picogreen) works on measurement of parasite biomass by the fluorometric measurement of stained parasite DNA.

(4) ELISA-based assays based on the measurement of parasite biomass by measuring proteins in an ELISA assay. This novel approach of *in vitro* drug sensitivity assay is based on antigens of malaria parasites (HRP2 and pLDH).

The principles and laboratory techniques as well as advantages and disadvantages of all five tests were presented and discussed.

Integrated *in vivo* and *in vitro* (HRP2) approach and pharmacokinetic studies were applied in the artemisinin resistance containment project at the Thai-Cambodian border. Potential molecular markers of artemisinin resistance were also validated. Results of *in vitro* tests (HRP2 based) conducted at some sentinel sites in SEA Region countries and the co-relation between *in vitro* and *in vivo* tests were presented.

It was concluded that the new *in vitro* drug sensitivity assays provide a highly sensitive, rapid, and relatively simple method to quantify intrinsic antimalarial drug action in the field as well as laboratory settings. In the presence of resistance the results are closely co-related with those obtained with traditional assays, and when done with fresh samples in parallel with *in vivo* testing the results are closely correlated with the clinical outcome (ELISA-based assays). The *in vitro* tests provide an objective measure of intrinsic drug sensitivity even before the first cases of treatment failure occur and are independent of the patient's immune system. The tests are useful as they are applicable to novel/multiple drugs even before clinical testing. However, though the *in vitro* tests are very useful, there are many limitations and most countries are unable to conduct the tests or sustain them. The challenges are how Member States could integrate the *in vivo and in vitro* approach in assessing drug resistance.

Molecular markers

Molecular markers are available for detection of resistance of drugs of several chemical classes, i.e. 4-aminoquinolines (chloroquine), antifolate (sulfadoxine-pyrimethamine) and amino-alcohols (mefloquine). However, molecular markers of sesquiterpene lactone (i.e. artemisinin derivatives) are not yet available.

Other tools

Genotyping to distinguish between re-infection and recrudescence is compulsory for TES. Pharmacokinetic study (measurement of blood drug levels) is another tool used for drug resistance monitoring. These two methods were discussed in the therapeutic efficacy study section.

3.3 Current national treatment policy

Bangladesh

P. falciparum is the predominant species (approximately 85%). The country has introduced RDT on a large scale since 2007 for diagnosis of *P. falciparum*. Malaria microscopy is available at upazila (sub-district) health complexes and in other hospitals.

ACT (artemether-lumefantrine) is the first line of treatment for uncomplicated falciparum malaria while in special situations quinine, together with tetracycline or doxycycline, for seven days is the second line of treatment to address treatment failure. Intravenous or intramuscular quinine followed by oral quinine for up to seven days is recommended for severe falciparum malaria cases. Artemether or artesunate are used in selected cases. Parenteral quinine may be used as pre-referral treatment. The rectal artesunate is still not registered in the country and has been proposed to be used for pre-referral treatment whenever it is available.

The standard recommended regimen for vivax malaria is chloroquine for three days and primaquine for 14 days, except for pregnant women and infants when primaquine is omitted.

A significant reduction of malaria deaths during 2007-2009 was observed. This was likely to be the impact of improved case management, early diagnosis using RDT at the community level and effective treatment with ACT.

Bhutan

The number of reported cases and deaths are low and the malaria programme aims to eliminate malaria deaths and transmission. Falciparum malaria accounts for about 60% of the total malaria cases.

ACT (artemether-lumefantrine) is the first-line treatment for uncomplicated falciparum malaria. Quinine is prescribed for malaria in pregnancy. Injectable artemether (i.m.) or quinine (i.v. infusion) are used for severe falciparum malaria.

The standard recommended regimen for vivax malaria is chloroquine for two to three days and primaquine for 14 days, except for pregnant women and infants when primaquine is omitted.

India

The incidence of malaria is declining over the past 2-3 decades but the proportion of falciparum malaria cases is steadily increasing. *P. falciparum* accounts for about 50% of the total confirmed malaria cases. All fever cases suspected to be malaria are investigated by microscopy or RDT for *P. falciparum*. *P. falciparum* cases are treated with ACT (artesunate for three days + sulphadoxine-pyrimethamine for one day). A single dose of primaquine is prescribed on the second day. Pregnant women with uncomplicated *P. falciparum* are treated with quinine during the 1st trimester and ACT (artesunate + sulfadoxine-pyrimethamine) during the 2nd and 3rd trimester. Severe malaria cases are treated with quinine infusion or parenteral artemisinin derivatives (i.v. artesunate or i.m artemether or arteether).

In cases where parasitological diagnosis is not possible due to non-availability of either timely microscopy or RDT, suspected malaria cases are treated with a full course of chloroquine, till the results of microscopy are received. Once the parasitological diagnosis is available, appropriate treatment as per the species, is to be administered.

The standard recommended regimen for vivax malaria is chloroquine for three days and primaquine for 14 days, except for pregnant women and infants when primaquine is omitted.

Chemoprophylaxis is recommended only in selected groups in high *P. falciparum* areas. Daily doxycycline is recommended for short-term travellers (less than six weeks) while weekly mefloquine is recommended for long-term travellers.

Indonesia

P. falciparum accounts for about 54% of the total malaria cases. Phase-wise malaria elimination programme has been launched in several parts of the country. The policy on malaria diagnosis and treatment includes:

(a) promotion of parasitological diagnosis (microscopy or RDT) and discontinuation of clinical diagnosis; (b) implementation of ACT for treatment of falciparum and vivax malaria and a ban on artemisinin monotherapy.

Chlorquine-resistant falciparum was first reported in 1973. Beside *P. falciparum* resistance to chloroquine, *P. vivax* resistance to chlorquine is widespread throughout the country. The drug policy was revised in 2004 and ACT (artesunate + amodiaquine) was introduced for the first-line treatment of falciparum and vivax malaria. In 2008, a new combination (dihydroartemisinin-piperaquine) was introduced in Papua and West Papua for the treatment of both falciparum and vivax malaria. A single dose of primaquine is given to all falciparum cases (except pregnant women and infants) while 14 days primaquine is given for anti-relapse treatment in vivax cases. Quinine and doxycycline for seven days is prescribed for falciparum treatment failure cases and quinine for seven days is prescribed for vivax treatment failure cases.

For severe malaria, artemether i.m. followed by oral ACT (artesunate + amodiaquine) or artesunate i.v. followed by oral ACT (artesunate + amodiaquine) or quinine infusion followed by oral quinine + doxycycline is given. Primaquine is always prescribed in all cases without contraindications. The country is preparing to revise the national treatment guidelines.

Information on the burden of malaria in pregnancy is limited. A small scale study in Timika province reported a prevalence of about 17% of malaria among 2 570 deliveries. The programme is integrating malaria prevention among pregnant women with immunization and ANC programme. Regarding treatment of malaria during pregnancy, quinine is recommended in the 1st trimester while artesunate + amodiaquine or dihydroartemisinin-piperaquine are prescribed in the 2nd and 3rd trimesters.

Nepal

Malaria is highly endemic in the southern parts of the country (the Terai region). The incidence of malaria is declining but the proportion of *P. falciparum* is steadily increasing (7% in 1999 to 24%-27% during 2006-2009). The country is strengthening definitive diagnosis through microscopy

or RDT. However, a full dose of chloroquine over three days is prescribed for clinically suspected malaria cases (i.e. probable malaria).

ACT (artemether-lumefantrine) is recommended for all parasitologically confirmed falciparum cases. Alternative options include quinine in combination with tetracycline or doxycycline or clindamycin for seven days. For severe falciparum malaria, intravenous artesunate is recommended in preference to parenteral quinine (i.v. infusion).

The standard recommended regimen for vivax malaria is chloroquine for three days and primaquine for 14 days, except for pregnant women and infants when primaquine is omitted.

Sri Lanka

Chloroquine-resistant *P. falciparum* malaria has been observed in Sri Lanka since 1984. No multidrug resistant case was detected in locally infected patients, except an extremely low number of locally infected *P. falciparum* cases who were resistant to sulfadoxine-pyrimethamine. ACT (artemether-lumefantrine) was introduced for the treatment of falciparum malaria in 2008. Efficacy of this combination remains high and no resistance to it has so far been documented.

All *falciparum* malaria patients are required to be hospitalized for three days. The artemether-lumefantrine is to be given under direct observation therapy (DOT). Primaquine is also given in a single dose, after completion of the ACT therapy for antigametocyte effect and transmission reduction.

For pregnant women with uncomplicated falciparum malaria, quinine is recommended in the 1st trimester and ACT is recommended in the 2nd and 3rd trimester. In severe falciparum cases, the recommended regimens include i.v. quinine followed by oral quinine for a total of 7 days in the 1st trimester, whereas i.v. quinine followed by oral ACT is recommended in the 2nd and 3rd trimester.

The standard recommended regimen for vivax malaria is chloroquine for three days and primaquine for 14 days, except for pregnant women and infants when primaquine is omitted.

Timor-Leste

The National Treatment Guidelines were revised in 2002 and implemented up to 2006. The National Drug Policy was revised in 2007 based on evidence of sulfadoxine-pyrimethamine resistant *P. falciparum*. ACT (artemether-lumefantrine) was introduced as the first-line treatment of uncomplicated falciparum malaria. The second-line treatment when treatment failure is reported includes quinine in combination with doxycycline or tetracycline. For treatment failure of falciparum malaria and for pregnant women, quinine and clindamycin is recommended.

Three options are recommended for severe falciparum malaria; quinine i.v. infusion or artesunate (i.m. or i.v,) or artemether (i.m.). Rectal artesunate is recommended for pre-referral treatment.

The standard recommended regimen for vivax malaria is chloroquine for three days and primaquine for 14 days, except for pregnant women and infants when primaquine is omitted.

Discussion

- Compliance of primaquine for anti-relapse treatment is doubtful. All countries with vivax malaria have implemented 14 days primaquine but little is known about its compliance.
- The national treatment policies are very much in line with WHO recommendations and implemented by the malaria control programmes. However, in many countries private providers are not aware of the national treatment guidelines or do not fully comply with them.
- Parenteral quinine is still recommended in most countries for treatment of severe falciparum malaria as the first option. Even though quinine still remains effective, its side effect, especially hypoglycaemia is very common and countries should switch to parenteral artemisinin wherever feasible.

3.4 Country status of monitoring of *P. falciparum* and *P. vivax* resistance

Bangladesh

Therapeutic efficacy studies (TES) were conducted in 2002 on combination of chloroquine and sulfadoxine-pyrimethamine for treatment of *P. falciparum* which indicated very low ACPR (69%-74%). Following revision of the treatment regimen, artemether-lumefantrine was introduced. The 42 days TES (both non-DOT and DOT approaches) in June 2006 and March 2007 revealed 99%-100% cure rates. The same combination was tested again in a 28-day study during May - October 2009 and the results showed 98% - 100% ACPR. The ongoing TES is conducted in three sentinel sites. The National Malaria Control Programme (NMCP) will start TES on vivax malaria in one moderately by vivax endemic area in a border district.

TES on vivax malaria is not done as the number of vivax cases is very low.

Bhutan

Therapeutic efficacy studies were conducted on both *P. falciparum* and *P.vivax*. There are five sentinel sites (two hospitals and three basic health units). The WHO study protocol was followed. All patients were followed up for 28 days and all *P. falciparum* cases hospitalized for three days. Artemether-lumefantrine for treatment of *P. falciparum* malaria cases was tested annually from 2005 to 2009. Chloroquine for treatment of *P. vivax* was also tested annually from 2004 to 2009. Both the treatments provided very high (100%) ACPR but the total number of cases studied was low especially during the last two years due to reduction in malaria incidence. *In vitro* studies were not conducted.

India

Therapeutic efficacy studies were conducted on both *P. falciparum* and *P. vivax*, by the National Vector Borne Disease Control Programme and in collaboration with the National Institute of Malaria Research team. Eleven and two sentinel sites were assigned for falciparum and vivax, respectively.

The most recent study in 2009-2010 revealed that efficacy of ACT (artesunate + sulfadoxine-pyrimethamine) on falciparum malaria was high (94%-100%) and efficacy of chloroquine for treatment of vivax was 100%. Parasite clearance time and gametocytaemia pattern were studied.

It was found that there were some sentinel sites where less than 80% of falciparum cases had parasite cleared after 48 hours of initial treatment. Genotyping (MSP2) was applied to differentiate between recrudescence and new infections. To monitor the drug resistance pattern in the samples for chloroquine resistance, molecular markers (*Pfcrt*) were studied in randomly selected samples from all the study sites obtained on Day 0. To monitor the drug resistance pattern in the samples for SP resistance, molecular markers (*dhfr and dhps*) were analyzed for the samples obtained at Day 0.

The molecular studies indicate high prevalence of chloroquine resistance in areas of low transmission while the mutation ranges between 41.18% to 100 % in high transmission areas. SP mutation is not very high in the study areas and a majority of samples show single mutation. The ongoing efficacy studies are being conducted for the period 2010-2011 in 15 sentinel sites throughout the country.

Indonesia

The country has a long history of drug resistance since 1978. Widespread drug resistance of both *P. falciparum* and *P. vivax* to chloroquine was reported. There were six sentinel sites for drug efficacy studies.

During 2000-2004, ACPR of chloroquine for treatment of vivax malaria was 80%-90% except in S. Lampung district where ACPR was only 33% in 2002. Amodiaquine for treatment of vivax malaria was studied only in Bangka district and ACPR was 97%.

Artesunate + amodiaquine (artemisinin-based combination therapy) was deployed as first-line treatment for uncomplicated falciparum malaria. During 2003-2005, the combination with dosage of amadiaquine at 30mg/kg BW was relatively more efficacious than that of 25 mg/kg BW (ACPR higher than 90% and 80%-90%, respectively)

In 2005, a comparative study between artesunate + amodiaquine and dihydroartemisinin-piperaquine was carried out in Timika, Papua district. The ACPRs were 52 and 84 respectively.

High-degree resistance of both vivax and falciparum malaria in Timika, Papua District was presented. In two studies conducted in 2007 high relapse rates were observed in vivax cases treated with artemether-lumefantrine and artesunate + amodiaquine as compared to dihydroartemisinin-piperaquine. Based on these findings, a change in the national drug policy was made in March 2006 and dihydroartemisinin-piperaquine became the first-line treatment of uncomplicated cases of all four parasite species and for treatment of malaria in the 2nd and 3rd trimesters of pregnancy.

Nepal

Drug-resistance monitoring was started in 1978 and *in vivo* and *in vitro* studies were conducted. Chloroquine-resistant falciparum was first reported in 1984 and subsequently resistance was reported in several districts. In 1996-1997, sulfadoxine-pyrimethamine that replaced chloroquine lost its efficacy. In 2000 late treatment failure rate of falciparum cases treated with sulfadoxine-pyrimethamine was 57%. In 2003 efficacy of sulfadoxine-pyrimethamine was very low in Jhapa district. ACT (artemether-lumefantrine) was studied in Jhapa district in 2007 and in Dhanasha district in 2008 and high efficacy (ACPR 100%) was reported. This combination was studied in a Bhutanese refugee camp in Jhapa district and ACPR was 100%.

Chloroquine for treatment of vivax malaria was studied intermittently, i.e. in Kanchanpur district in 2003, Dhanasha and Dadeldhura districts in 2008 and Kanchanpur district in 2009 and the results showed high ACPR (100%).

The patients enrolled in all the studies mentioned above were followed up for 28 days as per the WHO study protocol. The fixed sentinel sites are not fully established. The country is considering increasing the number of sentinel sites and engaging more partners and setting up a region-wise drug resistance monitoring network.

Sri Lanka

The country monitored the efficacy of *P. falciparum* and *P. vivax*. Chloroquine-resistant falciparum was reported in 1984 following two focal falciparum outbreaks and application of mass chloroquine administration which was possibly the cause that led to chloroquine resistance. There were several reports of chloroquine resistance in 1996, 2003 and 2004. The first case of sulfadoxine-pyrimethamine resistant falciparum was reported in 1992. There is no chloroquine resistant vivax so far.

There are difficulties in enrolling eligible cases for therapeutic efficacy studies due to low malaria incidence. All enrolled falciparum cases are hospitalized for three days and followed up for 28 days. All enrolled vivax cases are followed up for 14 days. Due to low malaria incidence all malaria cases are followed up post-treatment by regional medical officers.

Large-scale epidemiological studies of drug resistance and molecular studies are not possible.

Timor-leste

Being a newly established country with lack of national capacity, drug resistance monitoring is not conducted. Recommendations were made on sharing of information from Indonesia on drug resistance monitoring and border collaboration for joint drug resistance monitoring.

Mekong countries

The Mekong network of drug resistance monitoring was formally established in 2000. All the six Mekong countries actively participated in the set up and maintenance of sentinel sites expected to perform therapeutic efficacy studies according to a standardized study protocol. Several workshops have been organized during the last decade to improve the quality of all protocol procedures (microscopy, clinical and laboratory records, PCR and data management), consolidate and publish results, upgrade the study protocol and increase the capacity of national experts and field staff to perform studies, analyze data and inform national policy makers through solid reports.

The keys to success include regular funding, maintenance of fixed sentinel sites, good data management, technical support including training sessions with all principal investigators (PIs) and information sharing with partners.

In addition to regular funding and day-to-day coordination, one of the critical issues is for countries to be in a position to maintain sentinel sites over the years. This is important to assess trends and overall understanding of epidemiological pattern including through specific markers of drug resistance. There are 34 fixed sentinel sites in Mekong Region as follows:

Cambodia: Eight sites (four alternating every two years).

PR China: Three sites: two in Yunnan Province (Mekong area) and one in Jiangsu province (Eastern China).

Lao PDR: Three sites

Myanmar: Eight sites (four alternating every two years)

Thailand: Eight sites (four-six alternating every two years)

VietNam: Four-five sites.

Since parasite counting and parasite clearance time are key elements to effectively monitor the efficacy of medicines, qualified or "level-one" WHO accredited microscopists should be part of the TES team and quality microscopy assurance procedures be in place for slide validation. All data have to be internally and externally cross-checked, including the overall database.

Efforts have recently been made to introduce PCR techniques in all GMS countries in order to distinguish recrudescences and re-infections. Moreover, when needed to validate unacceptable therapeutic efficacy failure rates, more complex pharmacokinetic studies are conducted

Using PIs and microscopists from the Mekong Region to cross-check data across countries is recognized as one of the best practices within the Network.

The issue of full adherence to study protocol was discussed. As therapeutic efficacy studies are not research studies but expected to be routinely conducted mostly by national malaria control programmes, the

major concern is the quality of data generated. The Mekong Network is addressing that situation by working more closely with PIs and partners such as the WWARN Molecular Network looking at increasing the quality of PCR techniques and improving the quality of field operations and good clinical practices (GCP).

Discussion

- Conducting therapeutic efficacy studies requires national ethical clearance and when funded by WHO requires Ethics Review Committee (ERC) clearance following approval from WHO.
- The PIs of the GMS countries are required to register the therapeutic efficacy studies with the Australia/New Zealand Clinical Trial (ANZCTR) at this website www.anzctr.org.au. This is a new WHO requirement for publication of any study.
- Several countries expressed the need for strengthening of microscopy quality control for malaria treatment and for reliable data of drug-efficacy studies. Countries should have a core of "qualified microscopists" (WHO accreditation and certification) assigned to the sentinel sites that periodically undergo proficiency assessment, and refresher courses for field-based microscopists prior to the start of a TES, to ensure quality assurance in malaria diagnosis and counting.
- PCR technique is mandatory for any therapeutic efficacy study. Countries should plan to collect paired blood samples for differentiation of recrudescence and reinfections. WHO-SEARO should support countries that do not have PCR capacity and facilitate sending PCR samples to reliable laboratories.
- In view of emerging artemisinin resistance in the Mekong Region, lessons learnt indicated that prolonged parasite clearance time at Day 3 (beyond 72 hours) was an indicative early sign. It was strongly suggested that all investigators of TES should carefully monitor this parameter. Since the time when enrolled patients receive the first dosage of treatment varies greatly, it was suggested that the investigators record the time of drug intake, in order to precisely monitor parasite clearance time at 48 and 72 hours from start of treatment.

3.5 WWARN and collaboration with WHO

The WorldWide Antimalarial Resistance Network (WWARN) was presented by Dr Philippe Guerin. WWARN is a collaborative project with WHO with the primary focus on tracking the emergence and spread of antimalarial drug resistance. The WWARN is supported financially by the Bill and Melinda Gates Foundation. WWARN's aim is to improve the quality of collected data, strengthen existing facilities, bridge regional gaps and compile clinical and laboratory data in a standardized way to support evidence-based decision making. The work of the network is spread over six modules as follows: Clinical, pharmacological, *in vitro*, molecular, informatics and drug quality.

The network aims to support the work of WHO in order to detect early signs of parasite tolerance/resistance. The network encourages scientists and stakeholders from across the globe to collaborate in order to address common goals in malaria treatment and eradication. One of the challenges of this network is collaboration with national malaria control programmes and malaria research groups in malaria-endemic countries to obtain individual patient data for standardized analysis.

Dr Guerin displayed WWARN's website (www.wwarn.org) and its web-based interface, the WWARN explorer, which is a user-friendly tool to view aggregated patient data from antimalarial drug resistance studies. He also encouraged participants to visit the website and experiment with the web-based tools when analysing their data. He emphasized that investigators would always retain control over how their contributed data would be displayed and used.

Dr Pascal Ringwald informed the meeting that WHO's roles related to drug resistance monitoring include supporting Member States in monitoring drug resistance, compiling and analysing data, reviewing research and updating methodologies. It also regularly publishes WHO Global Drug Resistance Database which is useful for formulating evidence-based drug policy.

WHO signed the memorandum of understanding with WWARN on 17 June 2009 in a three-year pilot project involving the transfer of data and exchange of information concerning the development of tools to facilitate the monitoring of antimalarial drug efficacy and drug resistance. Two areas

in which WWARN can play particularly important roles to improve data on drug resistance monitoring are: (a) pharmacokinetic studies, and (b) molecular markers for drug resistance.

Regarding formalities of information sharing, WHO has prepared legal template letters that can be used at national level for agreement in sharing information with WWARN. The decision for sharing information with WWARN lies with the individual national malaria control programme and the Ministry of Health and will depend on country rules and regulations.

Potential areas of collaboration between WHO and WWARN include the following:

(1) Participation of WHO to promote WWARN activities.

(2) Participation of consultants designated within WWARN.

(3) Promotion of country data sharing with WWARN.

(4) Dissemination of samples to WWARN reference laboratories.

(5) Co-sponsored meetings on an ad hoc basis.

(6) WWARN as one central source of information.

He concluded that while WHO is actively working with Member States on monitoring drug resistance, WWARN should promote the above-mentioned activities.

Discussion

- The participants expressed their concerns about difficulties over the release of raw data as this is always kept confidential until the data is published in scientific journals.
- It is still unclear if there is an agreement on intellectual property rights (IPR) over the main WWARN database
- Discussion on possible collaboration between Member States and WWARN were as follows:
  - Support on analysis of *in vitro* data.
  - Training of investigators on pharmacokinetic study, molecular markers, etc.
  - Creation of data repository.

4. Country workplans

A break-out session was organized and participants attended individual country groups to discuss the workplans for drug resistance monitoring in the next two years. The country workplans are given in Table 1.

Table 1: ***Country workplans***

Country	Therapeutic efficacy study				In vitro tests and other studies	Funding sources	Comments
	Sentinel sites	Pf/Pv	Drug regimen	Study period/ frequency			
Bangladesh	3 sites	Pf	artemether-lumefantrine	April–October 2011		WHO and GFATM	
		Pv	No plan as vivax malaria prevalence is low and has a history of good clinical response.				The meeting recommended to initiate vivax study.
Bhutan	1 site at Gelephu (Central Referral Hospital and 4 nearby BHUs)	Pf	artemether-lumefantrine	March-October 2011	PCR for TES		One WHO short term consultant for a 3-day training workshop and support on PCR analysis.
		Pv	chloroquine	March-October 2011			
India	13 sites.	Pf	artesunate + SP	alternate year 2009-2013	In vitro test PCR Pharmacokinetic study of artemisinin. Molecular markers for all drugs (especially SP).	World Bank loan is available for TES.	Technical support from WWARN is required for determination of artesunate blood level and accreditation of microscopists. WWARN is also requested to support genotyping
	2 sites.	Pv	Chloroquine.				

Country	Therapeutic efficacy study				In vitro tests and other studies	Funding sources	Comments
	Sentinel sites	Pf/Pv	Drug regimen	Study period/ frequency			
Indonesia	7 sites Timika (Papua) Sorong (West Papua) South Halmahera (N. Maluku) West Sumba (E. Nusa Tenggara) Flores (E. Nusa Tenggara) Atambua (E. Nusa Tenggara) Lampung (Lampung).	Pf	artesunate-amodiaquine and dihydroartemisinin – piperaquine.		PCR for TES Pharmacokinetic study of artemisinin.	GFATM, WHO UNICEF, AusAID, Wellcome Trust.	National training courses to be organized on microcopy, data management, good laboratory practice (GLP) and pharmokinetic (PK) studies. WWARN is requested to support PK studies.
	Same as above.	Pv	artesunate + amodiaquine				
Nepal	4 sites Jhapa, Kailali.	Pf	artemether-lumefantrine		PCR for TES but required support on PCR sample analysis.	GFATM	One WHO consultant is required for 2 days – training workshop.
	Dhanusha and Nawalparasi.	Pv	Chloroquine				
Sri Lanka	Hospital-based study No fixed sentinel sites due to low malaria incidence.	Pf	artemether-lumefantrine + PQ	Non-specified.	PCR for TES study.	The 8th Rd GFATM.	Plan to upgrade existing PCR lab to support sample analysis. WHO Technical support required for data analysis, microscopy. Molecular studies. Dr Ringwald suggested enrollment of all patients without inclusion criteria. All other cases should be followed up to 28-42 days (for malaria elimination purpose).
		Pv	chloroquine + PQ.				

Country	Therapeutic efficacy study				In vitro tests and other studies	Funding sources	Comments
	Sentinel sites	Pf/Pv	Drug regimen	Study period/ frequency			
Timor-Leste	2 sites: Covalmina and Ailur districts	Pf	artemether-lumefantrine.		PCR for TES	GFATM	WHO technical support is required for PCR study. (support is also required for case management) Harmonizing TES study at the border between Indonesia and Timor Leste should be considered. Strong border collaboration needs to be established.
		Pv	chloroquine				

5. Discussion

Bhutan, Nepal, Sri Lanka and Timor-Leste required technical support on PCR analysis. It would not be cost-effective to establish PCR laboratory just for malaria efficacy study rather than upgrading the existing PCR laboratory in the country. It was suggested that India and Indonesia that have PCR facilities should provide support for analysis of PCR samples for these countries and WHO should facilitate transportation of samples.

India and Indonesia planned to strengthen national capacity in pharmacokinetic studies and molecular markers. It was recommended that WWARN should provide technical support on this issue. A training workshop on pharmacokinetic studies is proposed.

Border collaboration should be established in order to harmonize treatment regimens on both sides, to strengthen information sharing of TES at the sentinel sites at the international borders as well as to strengthen the malaria control programmes.

Information sharing within the SEA Region and with WWARN and networking on drug resistance monitoring were discussed during the

brainstorming session. It was recommended that the best way for information sharing is to organize an international meeting similar to this present meeting. A network has been established in the Mekong Region with strong participation from all Mekong countries.

It was suggested that India be the focal point for a network for South Asia (BBINS group including Bangladesh, Bhutan, India, Nepal and Sri Lanka). Indonesia and Timor-Leste should team up and collaborate with Pacific countries beyond SEA Region (i.e. Malaysia and Papua New Guinea) and Indonesia should be the focal point and involve other networks (ACTMalaria, APMEN, BIMST). The Coordinator of the Mekong Malaria Programme should facilitate networking of countries beyond the SEA Region.

The focal points for drug resistance monitoring and networking were proposed as follows:

- WHO SEARO - Dr Musfiqur Rahman.
- WHO MMP - Dr Delacollette and Dr Bustos.
- Bangladesh - Prof Emran-Bin-Yunus (Chittagong Medical College).
- Bhutan – Dr Thinley Yangzom (Malaria Programme Manager).
- India – Dr Neena Valecha (Deputy Director, National Institute of Malaria Research).
- Indonesia – Dr Desak Made Wismarini (Head, Sub-directorate malaria, MOH).
- Nepal – Dr GD Thakur (Malaria Programme Manager).
- Sri Lanka – Dr S Deniyage (Malaria Programme Manager).
- Timor-Leste – Dr Raul Sarmento (Malaria Programme Manager).

Commitments made by the participants:

(1) The country workplan on drug resistance monitoring to be finalized (with additional information) and circulated to participants and for the malaria programme managers to endorse within three weeks.

(2) Mapping of proposed sentinel sites in seven countries who participated in the meeting and those in Myanmar and Thailand will be developed by WHO-SEARO (Malaria Unit and Mekong Malaria Programme).

(3) Technical support (short term consultants) should be provided to countries by (1) India, and (2) Indonesia and (3) MARIB (Malaria Research Initiative Bandarban) in Bangladesh with financial support from WHO GMP.

(4) WWARN will support training on molecular markers, on request basis.

(5) WWARN will support artemisinin pharmacokinetic studies in India and Indonesia.

Recommendations

Recommendations to Member States

(1) Study drugs: Primaquine should be administered at the end of the study (Day 28) in vivax cases.

(2) In order to detect early warning sign of artemisinin resistant *P. falciparum*, patient follow-up at 72 hours after initial treatment is critical to detect patients with susceptible Pf resistant strains to artemisinins (i.e. delayed parasite clearance time on Day 3). It was recommended to record the time the drug is administered and slide taken during the first 3 days, until parasites are cleared.

(3) PCR technique is mandatory for TES of *P. falciparum* in order to distinguish reinfections from recrudescence. Bangladesh, Bhutan, Nepal and Timor-Leste do not have capacity for PCR analysis. Paired blood samples (collected in filter papers) should be sent as follows:

- National Malaria Research Institute (NIMR) in New Delhi to support PCR analysis of Nepal.
- Prof. Harald Noedl (Malaria Research Initiative Bandarban) to assist Bangladesh and Bhutan.
- Indonesia (Ekjman Institute) to support Timor-Leste.

(4) The concerned countries should budget for the cost of PCR analysis which is approximately US$ 30 per pair of samples.

(5) Upgrading the existing PCR laboratory in Nepal and setting up of a PCR laboratory in Sri Lanka should be explored on a long term basis, as a part of health system strengthening.

(6) All study drugs should be of good quality, i.e. meet GMP (good manufacturing practices) criteria. Exception is given to dihydroartemisinin-piperaquine which is the newly WHO recommended combination and is not yet fully pre-qualified.

(7) Countries should include budget for drug resistance monitoring and related training courses in the GFATM proposal or the WHO country budget (in particular in the next biennium 2012-2013) for support of international meetings and consultants.

Recommendations to WHO

(1) SEARO and Country Offices should coordinate and support transportation of samples. WHO HQ (GMP) is requested to absorb the cost if the sample size is small (cost less than US$ 500)

(2) WHO HQ (GMP) should share information on rapid test to detect G6PD deficiency.

(3) WHO HQ (GMP) and SEARO should support training on good clinical practice (GCP) for all Member States in collaboration with TDR. A suitable training centre should be identified for this purpose.

(4) A follow-up meeting should be organized in early 2012 at the latest in order to review the drug resistance situation in the SEA Region based on the studies proposed in the workplan. WHO GMP is requested to financially support the meeting.

Annex 1

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Annex 2

Agenda

(1) Opening ceremony

(2) SEAR situation:

- Meeting rationale
- Overview of the malaria situation and drug resistance in SEAR.
- Lessons learnt from Mekong Region: artemisinin resistance and its containment project on the Cambodia-Thailand Border

(3) Technical issues to strengthen drug resistance monitoring:

- Update on diagnosis, treatment and new tools
- Update on *in vivo* WHO *P.falciparum* and *P. vivax* therapeutic efficacy protocols including selection of *P. falciparum* and *P. vivax* sentinel sites, *in vivo* and *in vitro* procedures and frequency of studies
- Overview of molecular markers to monitor drug resistance.
- Presentation (and discussion) of the WHO protocol template research proposal form if submitted to WHO
- Clarification and decision on critical technical elements

(4) Presentation on malaria situation and treatment policy by country:

- Bangladesh, Bhutan
- India, Indonesia,
- Nepal., Sri Lanka, Timor-Leste

(5) Country presentations: Monitoring *P. falciparum* and *P. vivax* resistance to anti-malarial drugs: Results from the most recent studies in SEAR countries:

- Bangladesh, Bhutan,
- India, Indonesia,
- Nepal., Sri Lanka, Timor-Leste

(6) Breakout session: Individual country workplan development

(7) Presentation of country workplan (TES and resistance studies).

(8) Networking of drug resistance monitoring

(9) Conclusions and recommendations.

(10) Closing ceremony

The rapid spread of resistance to several antimalarial drugs has led to the revision of the national treatment guidelines and intensification of monitoring of therapeutic efficacies of currently used antimalarial drugs. The recent emergence of artemisinin resistance in the Greater Mekong Sub-region necessitated the strengthening of drug resistance monitoring and networking for effective information exchange that is essential for tracking the spread of the resistance. Several new tools have been developed and are deployed for drug resistance monitoring.

A workshop on Malaria treatment policy and drug resistance monitoring in countries of the South-East Asia Region was organized in Bali, Indonesia from 15-17 September 2010. Seven Member States (Bangladesh, Bhutan, India, Indonesia, Nepal, Sri Lanka and Timor-Leste) participated. The primary aims of the workshop were to update and revitalize the national therapeutic efficacy studies and drug resistance monitoring for strengthening treatment of malaria in Member States. The current national treatment guidelines were reviewed. Lessons learnt from the Mekong Malaria Programme on early signs of artemisinin resistance, maintaining quality drug resistance monitoring and networking were shared. Several technical and operational recommendations were made to Member States and WHO.

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