Antimalarial drug resistance

Md Mushfiqur Rahman*, Leonard Ortega**, R M Rastogi* and Krongthong Thimasarn*

Abstract
Antimalarial drug resistance is of great concern in the WHO South-East Asia (SEA) Region. A high degree of resistance of *Plasmodium falciparum* to chloroquine and sulfadoxine-pyrimethamine is prevalent in this Region. Multidrug resistance is prevalent in some parts of the Greater Mekong Sub-region. Artemisinin and its derivatives in combination with other effective partner drugs, which showed fastest parasite and fever clearance time, have been introduced in all the countries in the Region. Emergence of artemisinin resistance at the Thai-Cambodia border has been reported recently. *Plasmodium vivax* is sensitive to chloroquine in all the countries except in Indonesia. WHO supports and coordinates global management of drug resistance. It provides technical and financial assistance for therapeutic efficacy studies that serve as the basis for updating malaria treatment policy. It supports national malaria control programmes and other partners in implementing strategies to contain and prevent further spread of artemisinin combination therapy (ACT)-resistant parasites.

Introduction
Malaria is endemic in all countries of the SEA Region except Maldives. Of the 1745 million total population in this Region, 76% are at risk of malaria. Antimalarial drug resistance is a major public health problem and is of great concern as it hinders the effective control of malaria. National malaria control programmes and research institutes in the Region, in collaboration with WHO, have intensified the monitoring of therapeutic efficacy of antimalarial drugs and provided evidence for the updating of national malaria treatment policy.

*Plasmodium falciparum* resistance to chloroquine and sulfadoxine-pyrimethamine is widespread in the Region. Multidrug resistance (resistance to three or more antimalarial compounds of different chemical classes) has been reported from the Greater Mekong Sub-region. *Plasmodium vivax*, the second most common parasite species in the Region, is still sensitive to chloroquine except in Indonesia where resistance is widespread. Chloroquine-resistant *vivax*, was also documented in India and Myanmar but not considered as a serious threat.

The most effective antimalarial drugs introduced for malaria control in the early 2000s are artemisinin and its derivatives. These drugs have the fastest parasite and fever clearance time compared to other antimalarial drugs. In order to prolong its effective life, WHO strongly recommended that artemisinin should be deployed in combination with other effective partner drugs (so called artemisinin based combination therapy – ACT). However, the use of ACTs is seriously threatened by the emergence of artemisinin resistance at the Thai-Cambodia border reported recently. The Thai-Myanmar border, Myanmar, Bangladesh and some north-eastern states of India are potentially vulnerable for the spreading of artemisinin-resistant strains through population movement across the international borders.

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*WHO Regional Office for South-East Asia
**WHO Country Office, Myanmar
WHO’s role in the global management of drug resistance is to develop, update and provide support for implementing standardized methods for assessing antimalarial drug efficacy on the basis of expert consensus and feedback from the field. For this, WHO has prepared guidelines for conducting drug efficacy trials at the country level and updating the same as and when required. All countries in the Region are following these guidelines for the routine drug surveillance system. It is found that the failure rate of the currently used ACTs is increasing on both sides of the Thai-Cambodian border, due mainly to local emergence of resistance to artemisinin derivatives. WHO is further investigating this problem and supports national malaria control programmes and partners in implementing strategies to contain and prevent the further spread of resistant parasites to neighbouring countries.

In 1977 the WHO Regional Office for South-East Asia (SEARO) initiated a special project “the Regional Collaborative Studies on Drug Resistant Malaria” to support Member States in conducting drug efficacy trial (both in vivo and in vitro tests). However following the termination of the project the work was meant to be carried out as routine activities by Member States. It was observed that drug resistance monitoring could not be sustained due to several operational factors. WHO developed standard protocols and template for therapeutic efficacy studies (TES) and supported countries to use the protocols. Three out of the five methods (in vitro test, in vivo test and genotyping) are being regularly applied by countries. Myanmar and Thailand that are participating countries of the Mekong Malaria Programme are doing well in terms of drug resistance monitoring. Following the
meeting organized by WHO in Bali, Indonesia in September 2010, other Member States in the SEA Region established a network of sentinel sites for TES that is now functioning. The network is important for long-term monitoring and understanding of the epidemiological pattern of drug resistance.

The map shows the levels of efficacy (Adequate Clinical and Parasitological Response – ACPR) of ACTs in the SEA Region from 2002-2009.

**Status of antimalarial drug resistance, by country**

**Bangladesh**

Emergence of drug resistance is posing a serious problem in Bangladesh. The degree of resistance of *P. falciparum* to chloroquine (CQ) has increased tremendously. Both in vitro and in vivo studies were carried out. Studies carried out from 1979 to 1995 showed an increasing trend of high degree of resistance from 10% to more than 70%. Chloroquine and sulphadoxine-pyrimethamine combination (CQ+SP) also showed more than 25% resistance against *P. falciparum*. Oral quinine plus SP combination showed variable degree of resistance from 13% to 30% against *P. falciparum*. Intravenous quinine showed acceptable level of resistance, which was only 6%. Mefloquine was not used routinely in Bangladesh but resistance of *P. falciparum* was found in in vivo test (treatment failure rate of 27%) and in vitro test (61% of total isolates studied). The efficacy of artemether-lumefantrine (an ACT) against *P. falciparum* was very high (ACPR about 93%) in 2005. The 42-day TES of ACT in 2007 revealed 99%-100% efficacy. The Malaria Control Programme switched from CQ to artemether-lumefantrine in 2004 but the widescale implementation of this combination started in 2007. This combination was tested again in a 28-day study during 2009 and results showed 98%-100% ACPR. The TES on *P. vivax* was not carried out as there were very few *vivax* cases, and no evidence of chloroquine-resistant *P. vivax* had been found in the country.

**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) at the southern district bordering India. The WHO study protocol was followed. All patients were followed up for 28 days and all *falciparum* cases are hospitalized for three days. Artemether-lumefantrine was introduced as the first-line treatment of uncomplicated *falciparum* malaria cases in 2004. The combination was tested annually from 2005 to 2009. Chloroquine for treatment of *P. vivax* cases was also tested annually from 2004 to 2009. Artemether-lumefantrine against *P. falciparum* and chloroquine against *P. vivax* provided very high (100%) ACPR but total cases studied were low especially during the last two years due to reduction of malaria incidence. An in vitro study was not conducted.

**India**

Chloroquine-resistant *falciparum* was reported throughout the country especially the northeastern states where high degree resistance was documented. Sulfadoxine-pyrimethamine-resistant *falciparum* was also reported but was found to be focal in distribution. The country switched the first-line treatment for uncomplicated *falciparum* malaria to ACT (artesunate + sulfadoxine-pyrimethamine) in 2008 in areas with high drug resistance and the regimen was implemented countrywide in 2009.

Drug resistance monitoring is being carried out regularly by the malaria control programme in collaboration with the National Institute of Malaria Research. Therapeutic efficacy studies were conducted on both *P. falciparum* and *P. vivax*. Eleven and two sentinel sites were assigned for *falciparum* and *vivax* cases, respectively. The most recent study conducted in 2009-2010 revealed that the
efficacy of currently used ACT (artesunate + sulfadoxine-pyrimethamine) on *falciparum* malaria was high (94%-100%) and the efficacy of chloroquine for treatment of vivax was 100%. Parasite clearance time and gametocytaemia pattern were studied. At some sentinel sites less than 80% of *falciparum* cases had the parasite cleared after 48 hours of initial treatment. Genotyping (MSP2) was done to differentiate between recrudescence and new infections. Molecular markers (Pfcrt k76t and dhfr) were studied at all sentinel sites.

### Indonesia

The country has a long history of drug resistance since 1978. Widespread drug resistance of both *P. falciparum* and *P. vivax* to chloroquine has been reported throughout the country. This is the most important barrier to malaria control in the country. Drug resistance monitoring is being conducted on a regular basis on both parasites on currently used treatment regimen. Moreover, alternative drugs and potential drug combinations are also being studied in order to provide information for subsequent drug policy revision. There are six sentinel sites for drug efficacy studies. During 2000-2004, the ACPR of chloroquine for treatment of vivax malaria was 80%-90% except in S. Lampung district where the ACPR was only 33% in 2002 indicating high chloroquine resistance. Amodiaquine, as an alternative drug for treatment of vivax malaria was studied in Bangka district; the ACPR was 97%. Artesunate + amodiaquine (as an ACT) was deployed as the first-line treatment for uncomplicated *falciparum* malaria in 2004. During 2003-2005, the combination with dosage of amodiaquine at 30mg/kg BW was relatively more efficacious than that of 25mg/kg BW (ACPR higher than 90% and 80%-90%, respectively). In 2005, a comparative study between artesunate + amodiaquine and dihydroartemisinin-piperaquine for *falciparum* malaria was carried out in Timika, Papua district. The ACPRs were 52% and 84% respectively. A high degree of resistance of both vivax and *falciparum* malaria in Timika, Papua district was found. In two studies conducted in 2007 high relapse rates were observed in vivax cases treated with artemether-lumefantrine and artesunate + amodiaquine when compared to dihydroartemisinin-piperaquine. Based on these findings, the national drug policy was changed in 2006 and dihydroartemisinin-piperaquine became the first-line treatment for any uncomplicated cases of all four parasite species and for treatment of malaria in the second and third trimesters of pregnancy.

### Nepal

Malaria is endemic along the southern districts bordering India. *P. vivax* is the predominant species (80% of the total malaria cases). Drug resistance monitoring started in 1978 and both in vivo and in vitro studies were conducted with the primary focus on *falciparum* resistance. Chloroquine-resistant *falciparum* was first reported in 1984 and subsequently resistance was reported from several districts. In 1996-1997, sulfadoxine-pyrimethamine (SP) that replaced chloroquine lost its efficacy. In 2000, the late treatment failure rate of *falciparum* cases treated with sulfadoxine-pyrimethamine was found to be 57%. In 2003, the efficacy of SP was found to be very low in Jhapa district. This led to revision of national treatment guidelines and adoption of ACT as the first-line treatment of uncomplicated *falciparum* malaria in 2007. Artemether-lumefantrine that was chosen as an ACT was studied in Jhapa district in 2007 and in Dhanasho district in 2008: high efficacy (ACPR 100%) was reported. Chloroquine for treatment of vivax malaria was studied intermittently, i.e. in Kanchanpur district in 2003 and Dhanusha and Dadeldhura districts in 2008, and Kanchanpur district in 2009: results showed a high cure rate (ACPR 100%). The fixed sentinel sites have not been fully established. The country is considering increasing the number of sentinel sites and engaging more partners and setting up a region-wide drug resistance monitoring network.
Sri Lanka

The country reported high proportion of P. vivax (95%) cases. However, the country monitored the efficacy of both P. falciparum and P. vivax against antimalarials. Chloroquine-resistant falciparum was reported in 1984 following two focal falciparum outbreaks. There were several reports of chloroquine resistance in 1996, 2003 and 2004. The first case of sulfadoxine-pyrimethamine-resistant falciparum was reported in 1992. The national malaria treatment guidelines were revised in 2008 and artemether-lumefantrine was adopted for treatment of all falciparum cases as a strategy for malaria elimination. No case of chloroquine-resistant vivax has been reported 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 3 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 due to the low number of malaria patients.

Timor-Leste

Being a newly established country that lacks national capacity, drug resistance monitoring is not conducted. Based on information from the nearby areas of Indonesia where high degree and widespread drug resistance to both species were reported, the National Malaria Control Programme adopted artemether-lumefantrine as the first-line treatment for uncomplicated falciparum malaria in 2007. National capacity in drug resistance monitoring is yet to be established.

Countries in the Greater Mekong Subregion

There are six countries in the Greater Mekong Subregion, namely Cambodia, Lao PDR, Myanmar, People’s Republic of China (Yunnan Province), Thailand and Viet Nam. Resistance to several antimalarial drugs of different chemical classes was reported in the region. Consequently, in order to strategically respond to the problem a network of drug resistance monitoring was established as a part of the Mekong Roll Back Malaria Initiative. All six countries are actively participating in drug resistance monitoring and networking. There are currently 34 fixed sentinel sites that are functioning well. The key factors that have contributed to success include: regular funding; having fixed sentinel sites; good data management; technical support; and regular and effective information-sharing. Countries have been maintaining sentinel sites for several years now, and have contributed significantly in providing evidence for updating the malaria treatment policy.

References and bibliography

