Addressing Multidrug-Resistant Malaria in Asia

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Background

According to the World Health Organization’s Roll Back Malaria Initiative, there were 875,239 reported malaria cases and 4,508 associated deaths in the Mekong region of Southeast Asia during 2000. While improved access to prompt diagnosis and efficacious treatment has contributed to a decrease in the number of malaria deaths in Southeast Asia over the past decades, the recent emergence of multi-drug-resistant (MDR) malaria threatens to reverse these gains. Increased exposure of Plasmodium falciparum—the most deadly form of malaria—to sub-lethal doses of antimalarial drugs has resulted in resistance not only to traditional first-line drugs such as chloroquine and sulfadoxine/pyrimethamine (S/P), but also drugs such as mefloquine and quinine. Populations at risk for severe disease and death include children, pregnant women, people routinely in contact with forested areas where malaria-transmitting mosquitoes live, and people with limited access to health services (i.e. rural and mobile populations). Currently, the only individual drugs effective against MDR-malaria parasites are artemisinin derivatives such as artesunate. Efficacious drug-combination therapies have been developed, but they are often significantly more costly than treatment with individual drugs such as chloroquine or S/P. If steps are not taken immediately to address the root causes of drug resistance, these drug combinations will also lose their effectiveness in the near future.

Factors Contributing to the Emergence and Spread of Drug-Resistant Malaria

Drug management and quality. Fueling the emergence of drug-resistant malaria are various drug-use behaviors by both prescribers/dispensers and consumers that expose malaria parasites to sub-lethal doses of antimalarial drugs. Health care providers and merchants can contribute to the drug-resistance problem in several ways: prescribing/dispensing an antimalarial drug when a person does not have malaria; prescribing/dispensing the wrong drug when a patient does have malaria; and prescribing/dispensing the proper drug, but in an incorrect dosage. Patients can assist the process of parasite adaptation to these medicines by failing to complete the full drug course when they are ill. Self medication in the absence of a definitive diagnosis can also lead to the wrong drug being used in the wrong dose. This is especially problematic in border areas where patients may be avoiding the public health care system because they are in the country illegally or they do not speak the local language. Even if provider/dispenser and patient behaviors are ideal, malaria parasites can still be exposed to sub-lethal doses of antimalarial medicines if improper or counterfeit drug formulations are used to treat the disease. These drugs are readily available on the open market and often dispensed by untrained merchants in incomplete treatment regimens. In one study, 38% of “artesunate” samples from drug shop in Burma, Cambodia, Laos, Thailand, and Vietnam contained insufficient or no active ingredient.1

Economic pressures. Financial constraints on health services which have been exacerbated by the recent Asian financial crisis have resulted in budget reductions for malaria monitoring and control, operational research, and training. At the same time, decreasing economic opportunities have led to increasing population incursions into forest areas for informal income generating activities (e.g. hunting, gathering of forest products, clearing of land for agriculture).

Population movement. Mobile populations and expansion of areas under human habitation, especially encroachment upon forested land, have contributed to the spread of drug-resistant malaria from western Cambodia (marked with a star on the map above)2, where it emerged in the late 1980s, to other locations in Southeast Asia including eastern Burma and the border areas of Thailand. While the recent cessation of fighting in western Cambodia has decreased the number of refugees in eastern Thailand, the same conditions are likely to draw increased numbers of economic
migrants into western Cambodia in search of gems and forest products, putting them at risk for MDR malaria. At the same time, the current political and economic situation in Burma continues to force refugees and migrants into western Thailand in search of asylum and job opportunities. In recent years, increasing levels of drug-resistant malaria have been observed in several other countries in Southeast Asia where similar conditions (e.g. widespread and inappropriate drug use, poor drug quality, economic migration) also exist.

Controlling Drug-Resistant Malaria

Considering the cross-border nature of the MDR-malaria problem and the need for improved surveillance and disease-control capacity in Southeast Asia, a coordinated, regional approach is urgently needed to: (1) immediately contain the spread of MDR malaria; and (2) limit future emergence and spread of drug-resistant malaria. Specific efforts should focus on monitoring the current MDR-malaria situation and developing/implementing interventions, such as:

- Establishing a surveillance network in Southeast Asia (and possibly South Asia) for monitoring drug-resistant malaria especially in areas known to be "hot spots" and where there are high levels of migration (e.g. Burma-Thailand and Thailand-Cambodia borders);
- Conducting behavioral surveillance to assess how behaviors and practices related to migration, occupation, and dispensing/use of antimalarial drugs contribute to the emergence and spread of drug-resistant malaria;
- Monitoring the quality of antimalarial drugs available in the public and private/informal sector;
- Designing interventions aimed at health providers, drug dispensers, consumers, drug manufacturers, policy makers, and regulators in order to decrease inappropriate use of antimalarial drugs and improve the quality and efficacy of first-line drugs;
- Implementing interventions in areas that already have or are at high risk for MDR malaria; and
- Monitoring drug resistance, cure rates, case-fatality rates, drug quality, and behaviors in order to ensure that treatment protocols remain effective and that interventions to control MDR-malaria are successful.

USAID Approach and Partners

Starting in FY 1999, USAID began providing support to strengthen national and regional capacity to monitor and respond to drug-resistant malaria in Southeast Asia. At the country level, USAID is working with national malaria programs, the World Health Organization (WHO), the Kenan Institute of Asia, and other partners in both Cambodia and Thailand (U.S. Government regulations currently prohibit direct support being provided in Burma.) Specific activities include: improving the diagnosis of P. falciparum, including the use of dipsticks, so that the newer and more-costly drugs are used judiciously; providing effective combination therapies to vulnerable populations; expanding the use of insecticide-impregnated mosquito nets to limit transmission of malaria and the need for antimalarial drugs; and monitoring drug resistance, drug-use practices, and drug quality. In the future, interventions to limit the emergence and spread of drug resistance will be applied and monitored for effectiveness.

At the regional level, USAID is also supporting the WHO Southeast Asia and Western Pacific Regional Offices in New Delhi and Manila, respectively, the Centers for Disease Control and Prevention in Atlanta, the Rational Pharmaceutical Management Project, the U.S. Pharmacopeia Drug Quality and Information Project, and the Asian Collaborative Training Network for Malaria (ACTMalaria) as part of the Mekong Roll Back Malaria Initiative. These partners are providing technical assistance related to strengthening national and regional capacity for monitoring drug-resistant malaria, drug quality, and drug-use practices and developing/implementing control measures where appropriate. USAID has also initiated efforts to monitor drug-resistant malaria in South Asia (through the Environmental Health Project) and other parts of Southeast Asia (through WHO) to determine if the problem is severe enough to justify intervention.
**Expected Outcomes**

- Enhanced capacity of National Malaria Programs and other local institutions to monitor: the emergence and spread of drug-resistant malaria; drug-use practices; and drug quality.

- Enhanced capacity of National Malaria Programs and other local institutions to use surveillance data to change health policies (as needed) and develop/implement effective control strategies for drug-resistant malaria.

- Improved collaboration among health officials and scientists in Asia. Improved collaboration among health officials and scientists in Asia.

**Illustrative Results to Date**


2000: Inter-country agreement on standardized methodology and frequency for surveillance of drug-resistant malaria in Southeast Asia.

2001: Standardized, regional training on surveillance of drug-resistant malaria conducted by ACTMalaria; assessment of a pharmaceutical plant producing artemisinin-based drugs for the region.

2002: First round of drug-resistance surveillance initiated in Cambodia, Laos, Thailand, and Vietnam; Initial assessments of other facilities producing antimalarial drugs and possible field sites for routine monitoring of antimalarial drug quality; study of antimalarial drug use practices conducted in western Cambodia; inter-country agreement on standardized methodology and frequency for surveillance of drug-resistant malaria in South Asia.

2003: Training on drug quality surveillance conducted and antimalarial drug quality monitoring initiated in Cambodia, Laos, Thailand, and Vietnam; treatment policy for malaria updated in Cambodia based on drug-resistance information; antimalarial drug resistance studies conducted in Nepal (Jhapa district) and neighboring district (Dharjeeling in West Bengal) of India.

2004: Standardized surveillance for antimalarial drug resistance initiated at two sites each in Papua New Guinea and the Philippines; treatment policy for malaria updated in Thailand based on drug-resistance information; study of antimalarial drug use practices conducted in eastern Thailand; review of drug resistance, drug use, and drug quality data from the Mekong sub-region.

**Footnotes:**


2 In the late 1950s, chloroquine-resistant *P. falciparum* emerged in the same general region of Cambodia and spread to other parts of Asia and Africa over the next 30 years.

3 The Government of Japan is also supporting these malaria activities in Cambodia and Burma. In Thailand, other partners under the USAID Border Action Against Malaria project include Kenan Institute of Asia, the Faculty of Tropical Medicine at Mahidol University, the Armed Forces Research Institute of Medical Sciences (AFRIMS), the Shoklo Malaria Research Unit (SMRU), and local malaria units. In addition, the Gates Foundation provided $4 million to SMRU and Mahidol University in 2001 to address the MDR-malaria problem in western Thailand.

4 The Mekong Roll Back Malaria Initiative is coordinated by the two WHO regional offices since the countries (Burma, Cambodia, China, Laos, Thailand, and Vietnam) span their two regions. Other donors for malaria activities in the Mekong region include the European Commission and Japan.