Antimalarial and artemisinin resistance in the Greater Mekong subregion

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Antimalarial resistance is a global concern. Over the past few years, considerable effort and resources have been invested to monitor, detect and understand the basis for the different facets of emerging and increasing resistance of these antimalarial drugs. The development of new antimalarial agents has always been triggered by the development of resistance by the parasites.

The Greater Mekong Subregion (GMS) is known as the epicentre of \textit{P. falciparum} resistance to antimalarial drugs in South-East Asia. The \textit{in vivo} therapeutic efficacy studies (TES) of the WHO Mekong Malaria Programme (MMP) network have been monitoring the therapeutic efficacy of the first-line therapies to \textit{P. falciparum} and \textit{P. vivax} malaria with the use of a single standardized WHO \textit{in vivo} protocol across the six Mekong countries, and accurately checking the quality of data generated by studies carried out in strategically located sentinel sites. During the last decade, all six countries in the Mekong subregion, namely Cambodia, China, Lao PDR, Myanmar, Thailand and Viet Nam, have officially shifted to the use of artemisinin-based combination treatment (ACT), with the exception of Thailand that started using the artesunate-mefloquine (A+M) combination since 1995. China and Viet Nam, meanwhile, have also been using the five-day or seven-day artemisinin/artesunate monotherapy since the 1980s, as well as Myanmar and Cambodia in the private sector.

A WHO MMP informal consultation in January 2007 in Cambodia acknowledged the decreased sensitivity of ACTs for the treatment of \textit{P. falciparum} on the Cambodia-Thailand border triggering immediate in-depth research studies to confirm this worrisome situation. In addition to increased treatment failure rate, delayed parasite clearance was reported leading to the fear of reduced efficacy of the artemisinin component of the ACT. The Mekong Malaria Programme has been intensifying its support to 35 sentinel sites in the six countries since September 2007. The efficacy of antimalarial drugs was studied in \textit{P. falciparum} and \textit{P. vivax} patients against clinical symptoms and parasitemia with 28- or 42-day follow-ups, with adherence to standardized entry criteria, quality microscopy, data entry management and molecular genotyping techniques to differentiate true failures from re-infections. TES training workshops for field staff and country
monitoring visits to assess TES performance are being conducted in all countries to ensure proper implementation.

Results from the six GMS countries showed decreasing adequate clinical and parasitological response (ACPR) of ACTs\(^1\) especially in the border areas: in Kawthaung on the south eastern part of Myanmar bordering Thailand, the province of Ranong, where the cure rate to AS+M has been slowly declining since 2006. The Tak province bordering eastern Myanmar reported <90% ACPRs from 2004-2009. In the 2009 studies, the proportion of patients with longer parasite clearance (on Day 3 and beyond after 72 hours of treatment) to A+M was observed in sentinel sites along the western border of Thailand: with >15% Day 3 parasitemia in Tak, Kanchanaburi and in Ranong, whereas the neighbouring Kawthaung in Myanmar had 19% Day 3 parasitemia to dihydroartemisinin-piperaquine (DHA-PIP). On the other side of the eastern border of Thailand with Cambodia, results showed 90% cure rates to the A+M combination in Pailin and Pursat, and 34% Day 3 parasitemia to DHA-PIP in Pailin. Results also showed a longer parasite clearance time (25% Day 3 parasitemia) to 7-day artesunate (AS7) monotherapy in Yingjiang, Dehong county, Yunnan province of China bordering Myanmar, and in Binh Phuoc province in southern Vietnam bordering Cambodia, province of Snoul. Such worrying but yet preliminary results are currently being validated with in-depth studies on AS 7 monotherapy with pharmacokinetic assays. In the absence (yet) of molecular markers for artemisinin resistance, a top research and development priority, and an established in vitro threshold, measuring the parasite clearance time is now considered as an early warning signal to monitor failing ACTs or AS7. However, despite the early stage of developing resistance, there is yet no correlation between the prolonged parasite clearance time and the proportion of therapeutic failure of \(P.\) falciparum to ACTs. The current working definition of \(P.\) falciparum resistance to artemisinin is\(^2\): “an increase in parasite clearance time, as evidenced by \(\geq 10\)% of cases with parasites detectable on day 3 after treatment with an ACT (suspected resistance)” or “treatment failure after treatment with an oral artemisinin-based monotherapy with adequate antimalarial blood concentration, as evidenced by the persistence of parasites for seven days, or the presence of parasites at day 3 and recrudescence within 28/42 days (confirmed resistance)”.

There were several possible reasons raised for these ACT failures: failure of the partner drug mefloquine since pre-existing high level mefloquine in vivo resistance was documented in the past and is still being observed in vitro; the short half-life of artesunate relative to that of mefloquine, the latter drug being no longer very effective; under-dosing and poor compliance by both the patients and the public/private health practitioner despite treatment guidelines, the widespread uncontrolled use of substandard or counterfeit artemisinin derivatives or ACTs that created drug pressure against the artemisinins, and population movement across borders for socioeconomic and political reasons.

The varying topographies and drug policies of countries in the region, systematic findings and reports of substandard and


counterfeit drugs, injudicious use of medicines in the private sector, as well as the high degree of population mobility, justifies the need for periodic assessment of therapeutic efficacy of antimalarial medicines, sharing of efficacy surveillance data and more intensive intercountry crossborder collaboration. All countries need to be pro-active, as the TES provided early warning information on the emergence or spread of artemisinin resistance/tolerance from its initial foci on the Cambodia-Thailand border and now possibly spreading to other sites or emerging de novo in the Mekong region. This calls for harmonization and a careful implementation and review of country drug policies and case management in general in the GMS and beyond.