

The status of drug-resistant malaria along the Thailand-Myanmar border

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Emerging *Plasmodium falciparum* resistance to artemisinin derivatives continues to be a major global public health concern. There is a limited window of opportunity to contain resistant parasites before they spread around the world. Artemisinin-based combination therapies (ACTs) are recommended by WHO as the first-line treatment for uncomplicated malaria, and the scale-up of these highly effective medicine combinations has been integral to the remarkable recent successes in the fight against malaria. No other antimalarial medicines are available at present with the same level of efficacy and tolerability as ACTs.

The study entitled *Emergence of artemisinin-resistant malaria on the western border of Thailand: a longitudinal study* by Nosten and colleagues (Lancet, 5 April 2012) contains important evidence about the existence of artemisinin-resistant *P. falciparum* parasites in parts of western Thailand. The findings further deepen the concern WHO and other partners have had about emerging artemisinin resistance along the Thailand-Myanmar border. In light of this study, WHO reiterates its call to the global malaria community and donor organizations to urgently scale up efforts to prevent and contain artemisinin resistance in both Thailand and Myanmar, and to intensify ongoing efforts in the Greater Mekong sub-region.

The four countries most affected by the emergence of artemisinin resistance are Cambodia, Thailand, Viet Nam and Myanmar. Of these, Myanmar has by far the greatest malaria burden. Over 40 million people, or an estimated 69% of the Myanmar population, reside in malaria-endemic areas, and 24 million live in high-transmission areas. For 2010, Myanmar reported 650,000 malaria cases and 788 malaria-related fatalities in the public sector. Given its extensive migrant population, the widespread use of oral artemisinin-based monotherapies, and its geographical proximity to India, Myanmar is critical to the success of efforts to prevent the emergence of artemisinin resistance globally.

In settings with artemisinin resistance, ACTs may take longer to cure patients but they continue to be the most effective treatment for uncomplicated malaria. The large majority of patients with delayed response to artemisinins are still being cured with the help of the partner drug in the combination. In Myanmar, the three registered ACTs are still highly effective in all the sentinel sites where their efficacy was monitored (>95%). However, the emergence of resistance at new locations in the Greater Mekong sub-region is disconcerting, and WHO is also concerned about the weakening efficacy of partner drugs in Cambodia and Thailand.

Global Plan for Artemisinin Resistance Containment

WHO first issued a warning about the threat of artemisinin resistance in the Greater Mekong sub-region in 2005, after routine efficacy studies showed that the *P. falciparum* parasite was taking longer to clear from the bloodstream of patients. The first cases of *confirmed* artemisinin resistance were found in western Cambodia, along the Cambodia-Thailand border in late 2006. Following this, in early 2007, WHO convened a meeting of partners, which resulted in the development of the Artemisinin Resistance Confirmation, Characterization and Containment project (ARC3), funded by the Bill & Melinda Gates Foundation.

WHO subsequently scaled up its monitoring for signs of emerging resistance in the Greater Mekong sub-region, and found evidence of *suspected* resistance in Myanmar, Viet Nam, and along the Myanmar-China border. Up to today, however, only cases found in Pailin and Tasanh (western Cambodia) and in Wang Pha/Mae Sot (western Thailand) have matched WHO's working definition of *confirmed* artemisinin resistance.

In 2010, WHO embarked on the development of a *Global Plan for Artemisinin Resistance Containment* (GPARC). The plan was drafted following a consultation with all constituencies of the Roll Back Malaria Partnership, as well as a range of donor organizations and industry partners. Launched in January 2011, the GPARC called on the global health community to take urgent action to protect the efficacy of ACTs, contain artemisinin resistance in existing 'hotspots' and stop its spread around the world. WHO appealed to both malaria-endemic countries and donor organizations to adapt the global plan into operational programmes at the national level.

WHO emphasized the relevance of the GPARC to all malaria-endemic countries, not just those where resistance had already been confirmed or suspected. The total funding requirements for GPARC implementation were estimated at 175 million USD globally, with just over 100 million USD for programme support. Thus far, there has been only limited earmarked funding for GPARC-related programmatic activities, while prevention and containments efforts have been restricted to the Greater Mekong sub-region.

In Myanmar, studies conducted in townships in the eastern part of the country - along the border with Thailand - have found evidence of suspected artemisinin resistance. In line with GPARC recommendations, the government developed the Strategic Framework for Artemisinin Resistance Containment in Myanmar (MARC), with support from WHO and a number of international donors. The containment programme started in 2011, and results from the first year of activities will be presented in June 2012. However, Myanmar currently faces a substantial funding gap, which prevents it from moving forward with full implementation of the MARC.

At present, containment activities are also ongoing in Thailand, Cambodia and Viet Nam, with Viet Nam also in urgent need of financial assistance to scale up both basic malaria prevention and control interventions and containment efforts. WHO is currently working with affected countries to develop a Regional Framework to Contain Artemisinin Resistance for South East Asia, which will be discussed on 24-26 April, 2012 in Bangkok, Thailand during a high-level WHO-ASEAN

expert meeting on antimalarial drug resistance. During the same meeting, four donor organizations - AusAID, DFID, USAID and the Bill & Melinda Gates Foundation - are expected to present an assessment report about recent progress in drug resistance containment in the Greater Mekong sub-region.

A molecular marker has not yet been identified for artemisinin resistance so it is not clear whether the drug-resistant parasites identified in western Thailand by Nosten and colleagues have emerged independently, or have spread from western Cambodia. WHO urges research partners to conduct further scientific studies to arrive at a more conclusive definition about the origin of resistant parasites.

Conclusion

The Lancet article by Nosten and colleagues serves as a reminder that the threat of artemisinin resistance in the Greater Mekong sub-region requires an urgent and concerted international response. The international media attention generated by this study provides an opportunity for affected countries, WHO, and other development partners to push for a greater recognition of the importance of antimalarial drug resistance monitoring, as well as a scale-up of containment efforts in affected countries. WHO urges donors and funders to come forward and provide urgent financial support to Myanmar and Viet Nam to scale up malaria prevention and control efforts, intensify containment activities and monitor for the possible spread of resistance.

Funding is also needed to increase cross-border collaboration between these countries and to harmonize malaria-related activities in the region. In addition, advocacy efforts will need to be intensified to remove oral artemisinin-based monotherapies from markets around the world once and for all. With malaria designated as one of the key priorities on the UN Secretary General's five-year action agenda (2012-2017), there is an unprecedented opportunity to fully implement the global malaria strategy - including the GPARC - and to push back against the emerging threat of antimalarial drug resistance.

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