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Artemisinin resistance and the blame-game

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Dear Editor,

Pyae Phyo and colleagues [1] conclude that the increasing prevalence of K13 mutations is the decisive factor for the declining efficacy of mefloquine-artesunate (MAS3) reported on the Thai-Myanmar border. They then make an unsupported assertion that the definition of "artemisinin resistance" by ourselves [2] may have contributed to a failure to contain artemisinin-based treatment failures in the greater Mekong area. This has put us firmly in the distinguished company of 2 other independent groups who also critically assessed the term 'artemisinin resistance' and with whom we shared similar conclusions [2-4].

After all, it was our collaborative efforts that first established the molecular marker of increased *pfmdr1* copy number as being associated with treatment failures of artemisinin combination therapies (TFACT) [5]. Others confirmed our findings in different geographic areas (*e.g.* [6]). Some of our coauthors [5] at the time asserted without compunction that 'artemisinin resistance' would be unlikely to emerge in their lifetimes. They have not been accused of aiding the spread of parasites manifesting TFACT.

How have some later ideas in our opinion piece on 'anti-dogmatic approaches to artemisinin resistance' stood the test of time? We suggested that 'increased gametocyte production' may become 'a marker of slow parasite clearance phenotype' [2] and were gratified to see that some authors on Pyae Phyo's paper went on to observe that 'The higher proportions of pre-treatment and post-treatment gametocytemia in patients with slow parasite clearance suggest that artemisinin-resistance *P. falciparum* infections have a transmission advantage…' [7] despite our opinion being unreferenced.

We also suggested that because conventional ACTs use incomplete courses of artemisinins 'Contending that there is artemisinin resistance when cure of patients relies on the partner drug of an artemisinin is difficult to substantiate without additional studies' [2]. Once again, our suggestions have been borne out by the important finding that *kelch*13 C508Y in Cambodia is associated with increased IC_{50} values to piperaquine in DHA-piperaquine treatments – focusing attention on the partner in the ACT and not only the artemisinin component [8]. The use of longer courses of ACT further supported our suggestion that artemisinins are

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conventionally underdosed [9], including findings made by the same individuals [7] who now criticise the very publication in which that suggestion was made.

Defining the precise nature of a problem such as multidrug resistant malaria provides the greatest service to those trying to deal with it. Critically examining terms such as 'artemisinin resistance' cannot stifle thinking about multidrug resistant parasites. In contrast, as we have illustrated it stimulates studies on resistant phenotypes rather than stimulating their geographic spread, particularly in light of the dispersed global distribution of *kelch* mutations [10].

To manage the problem of multidrug resistance we need new antimalarial classes and new diagnostics that can tell us about drug resistance status as well as confirming infection with malaria parasites. But to underpin these advances, we need to understand better both the mechanisms of action of artemisinins and how resistance to this class develops. These advances need inclusive debates rather than exclusive crusades.

Conflict of interests: The authors state no conflicts of interests

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