

The importance of scientific debate in the identification, containment and control of artemisinin resistance

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Dear Editor,

The Introduction to the paper by Phyto and colleagues [1] contains the statement “However, the link between K13 polymorphism and treatment failure was not clearly established and some authors have contested whether use of the term artemisinin resistance is justified [16-18]. This uncertainty may have contributed to the failure to contain artemisinin resistance in the greater Mekong area.” Our paper [2] was one of those cited in this statement (it was #17) and we are deeply concerned that our attempts to improve the standard of scientific debate surrounding resistance to artemisinin combination therapies (ACTs) appears to have been misinterpreted as being retrogressive and even as having “contributed to the failure to contain artemisinin resistance”.

Our paper [2] used pharmacological modelling to investigate the likely properties of infected red blood cell (iRBC) clearance dynamics post-treatment. Notably, we never “contested whether use of the term artemisinin resistance is justified” and explicitly stated (page 6343 of [2]) that “K13 mutationsappear to virtually remove parasite hypersensitivity in the early ring stages, allowing its detection through increased iRBC clearance rates”. Briefly, we argued in our paper that: (i) artemisinins have been historically under-dosed: 2mg/kg was initially suggested because no increase in clearance rates occurred at higher doses [3]. Artemisinins are currently dosed at 4 mg/kg but the lower previous doses may have contributed to resistance emergence. (ii) Splitting current daily ACT regimens into twice-daily half doses, was rejected on the basis that clearance rates did not increase [4]; again, we were concerned that sub-optimal dosing regimens may lead to resistance [5]. (iii) That substantial levels of artemisinin resistance in sequestered parasite stages would not manifest as reduced iRBC clearance rates. (iv) That heritability estimates of iRBC clearance rates are

methodologically compromised and should be interpreted with extreme caution (SI of [2]); we are disappointed that Phyto et al chose not to point the CID readership to this work and blandly self-cited that clearance rate “was found to be heritable”. In summary, we showed that regarding iRBC clearance rates as sensitive or specific measures of drug efficacy and resistance could lead to a potentially highly damaging level of complacency about current dosing regimens and patterns of existing drug resistance and that an informed, evidence-based debate is required to ensure this threat is properly addressed.

Finally, any implication that our work might have “contributed to the failure to contain artemisinin resistance” is easily refuted by the timing: our paper was published online in August 2015, long after the WHO had finalised its plans for artemisinin containment [6,7], and after the time period of 2003-2013 discussed by Phyto et al. In fact, the debate around “containment” centred on three questions (1) is it feasible to eliminate the “resistant” populations? (2) Is it cost effective to do so? (3) Are resistance mutations confined to these areas? The answer to all three questions should have been unambiguously affirmative for “containment” to proceed and, for the record, we took no part in this debate or surrounding discussions.

We confirm that none of us have any potential Conflicts of Interests related to the contents of this letter.

References:

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