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Controversies in Tropical Medicine

Perspective: Artemisinin-Resistant Malaria and the Wolf

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The emergence of artemisinin-resistant malaria has been widely reported in scientific journals as well as the lay press. But how strong is the scientific evidence?

It makes sense that artemisinin-resistant malaria would be emerging. Falciparum malaria has become resistant to every other drug.[1] Why should artemisinin be different? Furthermore, artemisinin resistance seems to be developing in the same geographical area along the Thai–Cambodia border that spawned chloroquine, sulfadoxine-pyrimethamine (SP), and mefloquine resistance.[2]

The strongest argument that resistance has emerged is that parasites are now being cleared from circulation more slowly than before by artemisinin combination treatments (ACTs).[2,3] Artemisinin, when first introduced, cleared parasites faster than any other drug. Furthermore, the delayed parasite clearance time (PCT) is associated with a specific parasite genotype.[4]

In addition, the most commonly used ACT in Thailand, artesunate-mefloquine, has begun to fail.[5]

Taken together, these observations support a narrative, where resistance to a drug that is critical to global malaria control has emerged in a known hotbed of antimalarial resistance and will inexorably develop into a global pandemic of falciparum superbugs unless critical scientific, programmatic, and funding resources are redirected to Southeast Asia for containment.

This narrative belies messy inconsistencies.

First, there is very little evidence of ACT clinical failure caused by artemisinin resistance. For every previous antimalarial drug (including quinine, chloroquine, mefloquine, and SP), the definition of drug resistance included clinical failure.[6] In contrast, virtually all of the reported subjects with increased PCT after ACT treatment were clinically cured. Furthermore, the parasite isolates from these patients were sensitive to artemisinin *in vitro*.[2,3,7] *In vitro* resistance to artesunate monotherapy has been documented, but only in two patients with modest elevations in the concentration that inhibits response by 50% (IC_{50}).[7] There is not a single example, to my knowledge, of any other infectious agent being called drug-resistant without this clinical or *in vitro* evidence.

Second, the increased PCT might not be a harbinger of worse things to come. Infectious agents often show modest resistance to drugs, but this modest resistance never increases. The best example is *Pneumocystis jiroveci*.[8]

Third, the focus on artemisinin resistance takes attention away from the fact that ACT failures can be caused by partner drug resistance. World Health Organization-approved forms of artemisinin therapy are all combinations of an artemisinin derivative and a partner drug, and they are usually administered for 3 days. However, 3 days of treatment with either artesunate or artemether monotherapy may only cure a minority of patients.[9,10] Thus, when resistance to the partner drug emerges, ACT failures will be common. Because mefloquine monotherapy was widely used before the introduction of artesunate-mefloquine (the most common ACT in Thailand), ACT failures in Thailand could largely be caused by mefloquine resistance.

Fourth, both Thailand and Cambodia have, in recent years, made great strides in controlling malaria, with perhaps only about 200,000 cases per year total in both countries. Fears of artemisinin resistance wrongly distract the world's attention from sub-Saharan Africa and India, where malaria affects at least 1,000 times more people.[11]

In summary, delayed PCT could be a harbinger of disaster. Or it could be a false alarm. Is delayed PCT the wolf's snout peeking out from grandmother's nightgown? Or is it just crying wolf?

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