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Controversies in Tropical Medicine

Counter Perspective: Artemisinin Resistance: Facts, Fears, and Fables

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It would indeed be wonderful if concerns over artemisinin resistance were a false alarm, or that the current levels of resistance could not be exceeded.[1] However, are we "wrong to be distracted" by increasing evidence of resistance to the key drug for the treatment of severe and uncomplicated falciparum malaria emerging from the very place where resistance to chloroquine and sulfadoxine-pyrimethamine emerged before? Our slow and ineffective responses to those disasters cost the lives of millions of people—mainly children in Africa. Only a small fraction of the world's malaria burden occurs in mainland South-East Asia, yet that is where the resistance comes from. In an increasingly interconnected world, ignoring the potential for rapid spread to infect India and Africa seems worse than unwise. That is why everything that can be done should be done to curb spread and eliminate foci of artemisinin resistance in Asia.

Now to those other "messy inconsistencies"; in areas where parasite clearance rates have slowed markedly failure rates to artemisinin combination treatments (ACTs) have risen, and have prompted changes in policy. On the North West border of Thailand failure rates with artesunate-mefloquine now exceed 30%. The apparent paradox of reduced clinical efficacy without marked changes in *in vitro* susceptibility is explained readily by loss of ring-stage susceptibility to artemisinins without major changes in susceptibility of the trophozoite and schizont stages[2]; this results in delayed parasite clearance and reduced overall parasiticidal effect. Most *in vitro* tests evaluate predominantly the drug susceptibility of these more mature parasite stages. The second point that worse resistance to artemisinin may not occur is something we should all hope for, but certainly should not rely upon. The third point that ACT failures can result from resistance to the partner drug is true, but does not explain current therapeutic responses. When ACTs were first introduced in 1994 failure rates with mefloquine alone on the North West Thailand border were approaching 50%, yet the additional 3 days of artesunate reduced this to a failure rate of ~5%.[3] Today susceptibility to mefloquine has returned to levels similar to those in 1994, yet failure rates are six times higher. Clearly this is because of resistance to artemisinin and not just to mefloquine. Yet the two are linked as declining artemisinin susceptibility means that the partner drug in an ACT must remove a greater proportion of the infecting parasites to effect cure, and this increases the selection pressure for the emergence of partner drug resistance.

Given the potentially devastating consequences of losing our front-line antimalarial drugs, raising the alarm is surely the right thing to do. Let us hope the response is effective for, if I remember correctly, the wolf did eat the flock.

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