The threat of antimalarial drug resistance

E. Ashley

Imperial College NHS Trust, London, United Kingdom

Abstract: History has shown us that wherever antimalarial drugs are deployed antimalarial drug resistance will follow. A pattern has emerged with the drugs falling to resistance first in South East Asia and subsequently in India, Latin America and Africa. The decline in chloroquine efficacy led to millions of avoidable deaths from malaria in sub-Saharan Africa throughout the 1980s and ‘90s.

Artemisinin based combination treatments (ACTs) are the recommended first line treatments for falciparum malaria worldwide. The unique properties of the artemisinin derivatives, in particular their ability to reduce peripheral blood parasitaemia rapidly, make them the most potent antimalarial drug class ever used. They are partnered with slower acting antimalarial drugs and given over 3 days. Resistance to both the artemisinin derivatives and their partner drugs (mefloquine and piperaquine) has emerged in South East Asia over the last decade. Now failure rates of the combinations exceed 30% at some locations. Alarmingly, malaria is on the rise again in western Cambodia where incidence rates had reduced dramatically over the last decade.

Genetic studies have identified several mutations in a gene encoding for a plasmodial kelch protein associated with artemisinin resistance. Sampling from several sites throughout Asia has suggested resistance may have emerged multiple times at different locations. This is unlike chloroquine resistance which is thought to have emerged only twice and then spread globally. This finding has implications for global surveillance and containment strategies. Newer antimalarial drug compounds are in development but are still several years away from registration. The most practical solution to contain the threat of antimalarial drug resistance before the death toll from malaria rises is to intensify our efforts to eliminate falciparum malaria.

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Declining efficacy of mefloquine-artesunate combination and relative role of drug-resistant molecular markers: Thai-Myanmar Border 2003-2013

A.P. Phyo

Shoklo Malaria Research Unit, Maesot Tak, Thailand

Abstract: Background: Mefloquine-artesunate treatment of Plasmodium falciparum malaria in the displaced population on the Thailand-Myanmar border led to a dramatic decline in transmission. Efficacy has fallen substantially in recent years, but the relative contribution of resistance to the individual drugs is unknown.

Methods: Patients with uncomplicated P. falciparum malaria receiving supervised mefloquine-artesunate treatment were followed for 42 days. Molecular testing was undertaken to determine baseline pfmdr1 copy number, K13 genotype and discriminate recrudescences.

Findings: 1005 patients were enrolled from 2003-2013, during which PCR-adjusted cure rate declined from 100% to 81.1%. The proportion of isolates with multiple pfmdr1 copies rose from 32.4% to 64.7% while infections with K13 mutation increased from 6.7% to 83.4%. K13 propeller mutations predominated after 2009. The PCR-adjusted failure rate of infections with both amplified pfmdr1 and K13 propeller mutation was 42.2% and the adjusted hazard ratio was 14.05 (p<0.001). Even without pfmdr1 amplification, K13 propeller mutation was a strong risk factor for recrudescence (AHR=5.73, p=0.009). The combined population attributable fraction of recrudescence associated with K13 mutation and pfmdr1 amplification was 82%.

Interpretation: Pfmdr1 amplification and K13 mutation act in combination to reduce the efficacy of mefloquine-artesunate but the rise in K13 propeller mutations was the decisive factor in the fall in efficacy to unacceptable levels. These findings confirm the strong link between artemisinin resistance and ACT failure, and demonstrate the relatively short timeframe in which ACT efficacy can be lost once artemisinin resistance is present.

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