

Comment letter

Title: Antimalarial resistance unlikely to explain UK artemether-lumefantrine failures

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Sutherland et al. focus on antimalarial resistance when explaining the failure of artemether-lumefantrine to cure falciparum malaria in four travellers returning from Africa (1). Recurrence in non-endemic settings certainly indicates therapeutic failure, and increasing failures in an endemic area can be a sign of antimalarial resistance (2).

But was this 'cluster' of failures a likely indicator of rising levels of resistance? We consider it very unlikely. Artemisinin-combination therapies do not cure 100% of patients (3); in large trials and extensive surveys in malaria-endemic regions, and smaller-scale work in non-immune populations, artemether-lumefantrine efficacy is approximately 96% (3, 4)(5). Pharmacological factors clearly play a role in recrudescences (6). Furthermore, suppose 400 UK travellers are treated with artemether-lumefantrine annually, with 1% experiencing recrudescence (both conservative estimates). Although this averages only four recrudescences per year, we still expect a 'cluster' of four recrudescences in four months approximately every two years, because randomness is clumpy, and all four-month windows are counted (7).

Consistent with this, there was no robust clinical or laboratory evidence in the case descriptions indicating resistance to artemether-lumefantrine components. Almost no phenotypic data were available relating to parasite responses (parasite clearance rate (8), in vitro susceptibility to lumefantrine and artemisinins, and day 7 lumefantrine levels). Of the molecular markers described only *K13* (no mutations), *pfmdr1* and *pfprt* have been validated by transfection and/or independent association studies. All parasites carried *pfmdr1* haplotypes containing ancestral alleles at the key N86 and D1246 residues (9, 10) and cannot be considered as 'resistant' unless we also define ancestral *P. falciparum* as lumefantrine-resistant – which is clearly inappropriate. *pfmdr1* gene amplification, a mutation genuinely associated with lumefantrine resistance, was not assessed.

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42 For these reasons, the possibility that these cases represented resistant parasites appears
43 remote and, practically, retreatment with artemether-lumefantrine would have been
44 justified in our view. In African children retreatment of recurrences (including
45 recrudescences) with the same ACT provides similar efficacy to 'rescue' treatment (11).

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47 Although we disagree with the authors in terms of the likelihood that resistance explains
48 these cases, we do agree that ongoing studies of resistance are needed. While
49 lumefantrine (and mefloquine) fortunately work particularly well against the chloroquine-
50 resistant parasite populations dominant across Asia and Latin America (excepting
51 mainland Southeast Asia), things are different in Africa where ancestral chloroquine-
52 sensitive parasites have resurfaced following chloroquine withdrawal. While not resistant
53 *per se*, these parasites are naturally less sensitive to lumefantrine, a factor potentially
54 contributing to reports of lower cure rates with artemether-lumefantrine in endemic areas
55 (12) and returning travellers (13). Such parasites respond well to artesunate-amodiaquine,
56 but the best way to use these two ACTs providing opposing selective forces over an
57 extended period remains ill defined, particularly in areas with falling transmission. Potential
58 options include multiple first-line therapies, which modelling predicts will delay the
59 emergence of resistance to both artemisinins and their partner drugs (14), or ACTs
60 containing two partner drugs ('triples') (15, 16). Despite the evidence that ACTs remain
61 highly efficacious across Africa, experience tells us we need to stay ahead of the game.

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63 **References**

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