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Maximising the public health benefit of antimalarials

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Artemisinin combination therapies (ACTs) are integral to current malaria treatment strategies. They effect rapid and complete clearance of multidrug-resistant strains of *Plasmodium* spp, decrease the transmission potential of the parasite, and limit the emergence of de novo resistance.

In *The Lancet Infectious Diseases* today, Smithuis and colleagues[1] report the results of a factorial, open-label, randomised controlled trial at three sites in Myanmar (Burma) in which 808 patients with uncomplicated *Plasmodium falciparum* malaria were first allocated to one of four fixed-dose ACTs (artesunate–mefloquine, artesunate–amodiaquine, dihydroartemisinin–piperaquine, or artemether–lumefantrine) or a loose combination of artesunate and mefloquine. The study shows that all of the combinations are associated with rapid parasite clearance and, with the exception of artesunate–amodiaquine, low rates of recrudescence. How, therefore, should policymakers decide between one highly efficacious regimen and another?

The primary goal of antimalarial treatment should always be to safely eradicate asexual parasites from the host. After this, the most important consideration is to maximise the benefit to public health as gauged by a regimen's ability to limit the emergence and spread of antimalarial resistance and decrease transmission to the mosquito vector. However, the empirical assessment of these properties is not straightforward.

Compared with loose formulations, fixed-dose ACTs have the potential to improve adherence to curative treatment and reduce the risk of parasite exposure to unpartnered artemisinin derivatives, therefore prolonging the useful lifetime of these important drugs. Of the fixed-dose combinations, those with long-acting partner drugs such as mefloquine or piperaquine also provide an extended period of post-exposure prophylaxis, reducing the overall frequency of recurrent infections and allowing greater time for haematological recovery.[2] However, this benefit might be countered by a long tail of subtherapeutic drug concentrations promoting greater selective pressure for the spread of resistant parasites.[3]

In individuals who are not immune, mature infectious *P falciparum* gametocytes are usually detected after the onset of symptoms.[4] Variations in the gametocytocidal activity of antimalarial regimens might therefore translate to tangible differences in the probability that

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a given infection is transmitted. Artemisinin derivatives have potent activity against stage I–III gametocytes but are ineffective against mature, infectious forms. In the study by Smithuis and colleagues, gametocyte carriage was almost three-times higher after dihydroartemisinin–piperaquine compared with fixed-dose artesunate–mefloquine,[1] a finding that has now been replicated in several randomised trials.[5–7] The relative transmissibility of these gametocytes is unknown.

Primaquine has activity against all gametocyte stages and can substantially reduce the risk of *P falciparum* gametocyte carriage.[8] In a second round of randomisation, the authors allocated patients to schizonticidal treatment with or without a single 0·75mg base/kg dose of primaquine. Since gametocytes are non-pathogenic and primaquine is not active against asexual stages of *P falciparum*, this treatment had no potential to directly benefit the individuals in the study. Impressively, Smithuis and colleagues show that this dose of primaquine almost completely eliminates the risk of subsequent gametocyte carriage, therefore negating the differences in the gametocytocidal activity of the ACTs. Concerns remain about the potential for a one-off dose of primaquine to induce haemolysis, especially in glucose-6-phosphate dehydrogenase (G6PD) deficient individuals.[9] Other than a mild truncation of haematological improvement after treatment with primaquine, the investigators did not detect any significant adverse effects, although this was not the primary endpoint and the prevalence of G6PD deficiency in the study population was unknown.[1]

A single dose of primaquine has no effect against the hypnozoites of *Plasmodium vivax* and indeed heterologous recurrence with vivax malaria was common in this study.[1] Previous work suggests that this finding is likely to be due to a substantial, but underappreciated, burden of concomitant blood-stage *P vivax* infection in patients with falciparum malaria in coendemic regions.[10,11] Although Smithuis and colleagues show that the long-acting ACTs, artesunate–mefloquine and dihydroartemisinin–piperaquine, are associated with lower rates of heterologous recurrence,[1] this suggests suppression of the first of several potential liver-stage relapses and thus post-treatment prophylaxis might offer only temporary relief.[12] Such high rates of co-infection provide a strong rationale for a unified treatment strategy in which all G6PD-replete patients with microscopically confirmed malaria in regions where *P falciparum* and *P vivax* are both endemic receive a full course of primaquine to sterilise circulating gametocytes and rid the liver of *P vivax* hypnozoites.

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