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Simon V. Avery

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## Reply to “Chloroquine, an Antifungal but Also a Fertility Drug”

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We thank Kock et al. for highlighting their point to readers of our paper (1). Our paper does indeed include the suggestion that the results might have the potential for clinical application, including in malaria patients. The use of chloroquine (CQ) as an antifungal agent is not a new concept. Inhibition of opportunistic fungal pathogens such as *Cryptococcus neoformans* and *Histoplasma capsulatum* in the presence of CQ has been shown previously, *in vitro* as well as *in vivo* (2, 3). The experiments with other fungal pathogens described in our paper showed that the antifungal action of CQ could be enhanced in organisms with compromised cell walls. One logical next step would be to investigate this particular effect *in vivo*, during infection.

Previous studies indicate that the mechanisms of inhibition by CQ may differ between fungal species. For example, *C. neoformans* was inhibited by CQ-dependent increases in phagolysosomal pH which created an environment too alkaline for growth of this pathogen (3). Related mechanisms of CQ action are known in the malaria parasite (4). In the case of *H. capsulatum*, CQ acted by pH-dependent iron deprivation (2), and a similar mechanism was suggested for the model yeast *Saccharomyces cerevisiae* (5). More recently, however, thiamine transporters were found to be key targets of CQ action in *S. cerevisiae* as well as in cultured human cell lines (6). The latter mode of action may be particularly relevant to the findings we reported as it relies on direct interaction between CQ and the target organism, which should be exacerbated by increased CQ uptake in fungi with perturbed cell walls (1), rather than indirectly through an effect of CQ on host environment.

Fertility-promoting effects of CQ as described in the comments of Kock et al. have yet to be reconciled with the antifungal effects of this drug summarized above. Clearly, if clinical applica-

tion of CQ as part of an antifungal therapy is to be realized, we agree that it is important that possible issues such as those raised in the comments should be resolved. To that end, it will be helpful to characterize the relative antifungal and fertility-promoting effects of CQ across different CQ doses and in different fungi, including *in vivo*.

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