response by the parasite to changing conditions brought about by drug pressure.

The clinical consequences for the individual of sub-clearance treatment in humans are unclear, despite being potentially manageable in areas with instant access to treatment, and will be hard to manage or even justify with increasing distance from health care. The epidemiological consequences are, however, clear: the longer the parasite remains the more it will transmit. Thus, although resistance might be slowed, transmission will probably increase. Targeting specific sub-groups potentially offers a way to circumvent this, but the feasibility and benefit of such an approach would require serious evaluation.

The second issue concerns the level of drug dose that can generate the required reduction of clinical disease without selection for the resistant parasites. Current wisdom suggests that sub-clearance drug doses select for drug resistance. The occurrence of residual sub-lethal levels of drug in treated individuals has already been theoretically shown to promote drug resistance [10]. However, drug dose *per se* is not the central issue, and drug half-life and the drug decay curve are of greater importance [8]. Slowly-metabolised drugs will increase the degree of drug exposure that parasites face, but drug concentration will inevitably decrease and offer a selective advantage to even partially resistant 'tolerant' parasites [12]. Short half-life sub-clearance doses will not impose the same pressure on the parasite population.

The third issue could be perceived as academic, but is likely to determine the actual impact of parasite ecology on the spread of drug resistance; it concerns the parasite's renowned phenotypic plasticity. Such plasticity would enable the parasite to respond to the immediate environment without need for mutation/selection events. The extent to which the parasite is able to survive in the face of drug pressure without recourse to resistance mutation will impact upon the relative selective advantage gained by fully resistant parasites, and hence upon the spread of resistance allele(s). Recent models have attempted to reflect more accurately the observed patterns of drug resistance, incorporating intermediate categories of 'tolerant parasites' in addition to the binary sensitive/resistant genotypes [8]. Such models make an initial attempt to loosen the strict population genetic framework of a mono- or oligogenic basis to resistance. Further development of such approaches will probably be highly fruitful.

In conclusion, although men are not mice, the proposal for sub-clearance treatment is based on sound reason and has precedents in other human pathogens [1]. The study reminds us how poorly we grasp the detail of malaria epidemiology and further highlights the yawning gap between basic science and policy in a field of extreme urgency. Surely, for the sake of science and public health, as suggested by the authors, the proposed benefits of sub-clearance treatment should be addressed in malaria.

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Letters

Why we should effectively treat malaria

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Goncalves and Paul [1] cogently discuss biological aspects of the suggestion put forward by Huijben *et al.* [2] that low and presumably sub-curative doses (see below) of antimalarial drugs could be a useful public health policy. This group has also discussed the possibility of using sub-curative doses elsewhere [3]. Huijben *et al.* justify this strategy for its putative benefit in reducing the spread of drug resistance, but the same suggestion of sub-curative regimens also occasionally arises in immunological arguments – where it has long been known that administering

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sub-curative drug dosages is sufficient to prevent death but does not impede the rapid, and highly beneficial, acquisition of protective immunity [4]. However, it would be ethically and operationally extremely difficult to deploy sub-curative regimens for reasons outlined below.

Huijben *et al.* refer to their doses as 'low' rather than 'sub-curative', but it is highly likely that low doses will be 'sub-curative' in a large number of patients. Malaria clones show great variability in their susceptibility to drugs (a 10 to 100 fold variation in IC_{50} was reported recently [5]) and individuals vary enormously in how they metabolise drugs: absorption, apparent distribution volume and drug elimination rate (which determines half-life) all vary substantially, a rule of thumb being over a three-fold range. Allowance is made for this variation by deploying drug regimens that are sufficiently high and/or frequent that they have a therapeutic 'margin of error' sufficiently wide that they can reliably clear most infections in most people; however, this is restricted by concerns over toxicity, and the vast majority of antimalarial drugs so far deployed subsequently had their dosages increased to achieve reliable cure [6]. Lower doses are therefore expected to be sub-curative. Furthermore, parasite clearance rates are highly correlated with drug effectiveness, and it is therefore unlikely that we could reduce clearance rates (identified as important by Huijben *et al.*) without simultaneously reducing the clinical efficacy of the drug. There is also an ethical imperative to clear parasites rapidly in order to alleviate symptoms.

Although some individuals die directly of severe malaria, a large number die from indirect causes – they survive the primary malaria infection but are weakened and die of a secondary cause such as severe diarrhoea or respiratory tract infection. It is generally thought that the prevalence of such indirect deaths is substantial [7]. Strong supporting evidence comes from interventions that temporarily block malaria infection, such as mass drug administration (e.g. intermittent presumptive treatment) and the provision of bednets. The results consistently show large reductions in all-cause mortality, suggesting that malaria is a contributory factor in a substantial proportion of childhood deaths [8]. It is therefore entirely plausible that some patients treated with sub-curative doses will have repeated episodes of recurrent malaria before succumbing to a fatal secondary infection. The 'experiment' of sub-curative doses was inadvertently performed with chloroquine (CQ) where, as resistance evolved, the drug dosages became clinically ineffective in a large number of patients. Although the aetiology is different (evolution of resistance versus deliberate choice of dosage regimen [2]), the consequences are the same – deployment of sub-curative regimens led to an initial rapid decline in the number of parasites before recrudescence two or more weeks later. The fact that CQ dosages had effectively become sub-curative was confirmed in Guinea-Bissau [9] where increasing CQ dosages restored clinical efficacy even against 'resistant' infections. The important point is the reaction of the malaria community, and this illustrates how difficult it would be to deploy deliberately sub-curative dosages – it is believed that CQ sub-curative dosages led to increased mortality [10] and that the deployment of sub-curative drug regimens amounted to 'medical malpractice' [11].

There are also practical problems in identifying an appropriate 'sub-curative' dosage. The best dose for preventing the spread of resistance is obviously zero, but the best dose for patients is fully curative. The ethical problem is therefore to quantify the relative 'value' of each effect and seek a trade-off between the two conflicting demands. Even if a specific sub-curative dosage can be identified, it is doubtful that this would be useful in practice – variation in human pharmacogenetics and parasite drug sensitivity will combine such that 'sub-curative' drug regimens are likely to be ineffective in a large number of cases, but fully-effective in a further large group of patients. It is not clear how this will affect the evolutionary and ethical arguments.

The application of evolutionary theory clearly has a role to play in infectious disease biology [12], but the use of sub-curative dosages to treat malaria is unlikely to gain ethical approval or community support. It might be possible to apply the reasoning to infections that are less lethal than malaria and/or which are treated in closely monitored hospital environments, and we await such applications with interest.

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