

correlate. Gathering such data could take a few years and additional funding resources, but it is the best guarantee for achieving a taxonomic nomenclature that will last for many years to come.

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Letters

Sub-clearance treatment to slow malaria drug resistance?

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Huijben *et al.* [1] have recently made the provocative suggestion that sub-clearance drug treatment of clinical cases of *Plasmodium falciparum* malaria would prolong the effective life-span of the drug and should be preferred over the current treatment strategy that aims to eliminate all parasites as rapidly as possible. The article provides strong experimental data from a mouse model and is the latest in a growing literature with an evolutionary epidemiological framework that suggests that many of our current beliefs on the underlying causes of the spread of drug resistance and on resistance management are flawed or at best incomplete [2–5].

The basic underlying premise for this suggested change in approach to drug treatment is that within-host, among-parasite genotype interactions play a key role in the emergence of resistance [5]. Drug treatment that removes all sensitive parasites enables competitive release of any drug-resistant genotype [4] that, in the absence of treatment, would have been competitively suppressed by its drug-sensitive coinfecting parasite genotypes (i.e. cost-of-resistance) [2]. There is supporting evidence for both cost-of-resistance [6] and competitive release of resistant genotypes by drug treatment of *P. falciparum* infections [7] in naturally infected humans.

The development of models to predict the spread of drug resistance and guide treatment strategies has

burgeoned over recent years, generating a bewildering series of conditional and context-dependent predictions on how, where and when to use particular drug treatment strategies [2,3,8–10]. Sadly, the overwhelming conclusion is that the complexity of factors involved is such that unpredictable non-linear patterns of dynamics of resistance evolution are expected [3] and, *ipso facto*, current models cannot guide policy. With the recent push to deliver more accurate measures of drug resistance, high quality empirical data will become available; it is thus propitious to re-focus on resistance models and their role in guiding policy.

This latest work [1] emphasises the importance of within-host ecology, which has only slowly been incorporated into models [3]. The bold statement that sub-clearance drug use would slow down resistance spread throws up the promising possibility that the poor fit of models to empirical data could be due to parasite within-host ecology. Incorporating such detail into models thus seems necessary and, although currently embryonic, novel theoretical approaches uniting genetics and epidemiology within an evolutionary perspective are being developed [11].

Several issues, however, must be addressed if ever such studies are to make any impact on public health. A first concerns the epidemiological and clinical consequences of knowingly leaving a patient with circulating parasites. A second is how to gauge the actual sub-clearance level of drug required, and a third concerns the evolutionary

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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 frame-

work 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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