Measuring resistance to malaria

The paper by Randrianarivelosia and colleagues in this issue of the Journal (p. 47) describes the in vitro susceptibility of Plasmodium falciparum in Madagascar and the Comoros Union to three of the commonly used antimalarial drugs in the region — quinine, mefloquine and cycloguanil (the active metabolite of proguanil). Severe malaria in the Comoros Union and in Madagascar is invariably caused by P. falciparum, as it is in the rest of sub-Saharan Africa. All of 243 isolates assessed were sensitive to quinine, the drug recommended throughout the region for treatment of severe malaria. With regard to the two chemoprophylactic agents studied, all 67 isolates assessed were sensitive to cycloguanil and only 1 of 128 isolates was mefloquine-resistant. The mefloquine-resistant isolate was 1 of 110 evaluated from Madagascar; none of the 18 isolates from the Comoros Union was resistant. The authors argue that their findings confirm the sensitivity of the parasite to the 3 drugs most commonly used in their countries for both treatment and prophylaxis. They submit, on the basis of their findings, that treatment policy for uncomplicated malaria in the area is not addressed by this study. The authors refer to the presence of chloroquine resistance in the study area, particularly in the treatment of uncomplicated malaria, particularly chloroquine and sulfadoxine-pyrimethamine. However, the treatment policy for uncomplicated malaria in the area is not addressed by this study. The authors refer to the presence of chloroquine resistance in the study area, particularly in the Comoros Union, which is not surprising given its prevalence across almost all of sub-Saharan Africa. The efficacy of proguanil (cycloguanil)-based regimens cannot be concluded from this study alone.

It is also necessary to consider, in general, how feasible it is to extrapolate in vitro results to clinical outcome. As resistance means that there is a shift to the right in the dose-response (concentration-effect) relationship, it is to be expected that this might be reliably quantified in vitro. In vitro studies are not influenced by partial immunity acquired after repeated P. falciparum malaria infections (which do influence the in vivo response), and in vitro findings would therefore be as relevant to non-immune travellers, as to semi-immune locals. However, extrapolation of in vitro results to clinical outcome is not straightforward, for several reasons. In the first place, the authors have set drug concentration levels for each drug, above which the parasite is regarded as resistant and below which it is seen as being sensitive. But these levels are in the main arbitrary, and not universally agreed upon or in accordance with those set by others. Moreover, the results are critically dependent on precise details of the laboratory method; even minor changes in methodology might significantly influence the result. Unless the methods used for in vitro drug sensitivity testing are standardised between laboratories, subjected to robust quality assurance and monitored accordingly, comparison between laboratories cannot be made and general inferences that influence policy and clinical
decisions may not be derived. There are, in addition, inescapable limitations to extrapolating in vitro findings to the clinical situation. In vitro testing does not allow for drug behaviour in the body — the absorption, metabolism, distribution and elimination characteristics that significantly affect the antimalarial action of drugs. Nor can it take into account the complex immune response that takes place in conjunction with the drug action, including cytokine production, acute phase reactions, and the contribution of the spleen to the response in acute malarial infection. These are particularly important determinants of quinine effectiveness as quinine binds to acute phase reactants, resulting in a decrease in free quinine levels with increasing disease severity. This is one of the reasons for using a loading dose of quinine in severe malaria. Treatment failure from under-dosing and poor adherence, both widespread reasons for lack of antimalarial effectiveness, are not captured in either in vitro or in vivo studies.

For the findings from Antananarivo and the conclusions that have been derived from them to be persuasive, and for them to influence policy in their own countries and beyond, more is required than is reported in their paper. The drug concentrations that are set for defining resistance of P. falciparum would need to be defended against clinical evidence, and laboratory methodology, quality control and monitoring, all of which should be robustly applied. The efficacy of partner drugs used in combination regimens would also have to be reported, and the in vitro sensitivity of those drugs at greatest risk of developing resistance as a result of intrinsic mutations (such as atovaquone) or increased drug pressure (generally those antimalarials recommended for the treatment of uncomplicated malaria) should also be assessed. Every detail of the laboratory method would have to be standardised, within and between laboratories. If policy decisions are to be made from such findings the most important element is to show that sensitivity profiles are changing over time. More general agreement is needed on how in vitro laboratory findings might be used in deciding on policy change, and in comparing the situation between countries and regions. The World Health Organisation has developed guidelines for the conduct of in vitro drug sensitivity testing, and the use of the methodology for deciding policy; that need to be followed for the findings reported in this issue of the Journal to have general application. The laboratory approach must be affordable for it to take root in Africa. And finally, it should be remembered that drug resistance of the parasite is not the only explanation for a failed response in malaria.

If all these requirements can be met, and only if they can be met, the work of the Madagascar and Comoros Union scientists will come to be seen as an important foundational step in determining malaria drug policy on the African continent.

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