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Coping With Malaria While We Wait for a Vaccine

PETER WINSTANLEY

Department of Pharmacology and Therapeutics, New Medical Building, University of Liverpool, Liverpool L69 3BX, UK.

Malaria remains as much a scourge as ever. Of the four species of plasmodia capable of infecting man it is *Plasmodium falciparum* with which we have most problems because this species not only causes life-threatening illness but has also developed resistance to most classes of antimalarial drugs. Therefore, it is falciparum malaria that will be discussed here. Furthermore, although *P. falciparum* is a problem in much of the tropics, most cases and associated deaths are seen in sub-Saharan Africa: about 12 million cases and 1·2 million deaths annually (Anon. 1995). Most African nations are not only faced with many pressing healthcare problems (tuberculosis, diarrhoeal diseases and HIV to name but three) but also have extremely hard-pressed healthcare resources. Consequently, falciparum malaria in Africa will be the main focus of the present summary.

Although eradication of malaria was once a goal, the main target of control programmes over the last two decades has been reduction of the appalling mortality and morbidity figures cited above. Unfortunately it seems very likely that, over the next two decades, the trend is likely to worsen under the influence of global warming (and hence the possibility that malaria prevalence rates may rise) and the inexorable spread of multi-drug-resistant *P. falciparum*: it may be that we shall count ourselves lucky if we can hold mortality figures as they are, let alone reduce them.

Some of the Available Strategies

Plasmodium parasitaemia, particularly with *P. falciparum* is extremely (although variably) prevalent throughout tropical Africa: in parts of east Africa, for example, the prevalence rate can be as high as 80% in children at certain times of the year. Typically, only a proportion of children with parasitaemia develop symptoms and only a small proportion of these become severely ill or die (Marsh et al 1995). Africa is vast, and the epidemiology of clinical malaria is extremely complex; it is influenced to a large degree by factors like: variation in climate (mainly rainfall patterns); the biting habits of the predominant vector (usually the *Anopheles gambiae* complex); the culture and beliefs of the population, and their healthcare-seeking behaviour; availability and funding of healthcare; and access to means of travel. This, of course, is not an exhaustive list. Clearly, the relative importance of each factor in each geographical location would need to be addressed in a systematic manner for interventions to be chosen logically, but such data are lamentably incomplete and our attempts at control remain sub-optimal.

Certainly the "best" way to reduce malaria mortality figures for an average population in sub-Saharan Africa would be to tackle poverty, but more immediately-available targets include: reduction in transmission; mass chemoprophylaxis; effective treatment of non-severe disease (mainly based in out-patient departments); and improved treatment of severe disease (based in in-patient facilities).

Reduced transmission

Female *Anopheles* mosquitoes bite at night, and sleeping under nets reduces transmission. Herodotus, describing his travels around the Ancient World (The Histories), is the earliest author that I have been able to find who mentions the use of bednets (in the Egyptian delta) to prevent the nuisance of nocturnal insect bites. Bednets have had an established rational role in malaria prevention for about a century. More recently, dipping the nets in permethrin insecticide has been shown to be an effective means of reducing mortality in malaria-exposed African populations (Nevill et al 1996). The results of such work have been impressive. However, for such an intervention to be successful on a national scale, a number of factors would need to be addressed including adequate organization (including distribution, regular dipping and maintenance), adequate infrastructure (e.g. roads, networks of verbal/written communication) and adequate funding. Furthermore, several possible disadvantages will need to be considered before the intervention becomes generally adopted, such as diversion of funds from other national healthcare budgets (will supra-national funds be made available?) and the effects of interruption of the program on malaria mortality (will prevention of parasite transmission eradicate the development of immunity?)

Mass chemoprophylaxis

Chemoprophylaxis for foreign visitors to high transmission areas is standard practice, but such subjects are exposed for a finite period (commonly less than 4 weeks) and are able to bear the cost themselves. In contrast, African populations can expect to remain exposed to transmission throughout their lives and usually are unable to afford long-term antimalarial drugs. Certainly, the population acquires partial immunity to local strains of the parasite, so that continual exposure makes severe illness unlikely, but high-risk sub-groups remain. Furthermore, this partial immunity is bought at a terrible cost in childhood deaths. The high-risk sub-groups, particularly pregnant women, can usually be offered chemoprophylaxis because they self-present, making logistics manageable, they are at risk for a finite period and the programme can be kept cost-effective if the drugs are inexpensive (and costs are generally met by the State). However the scale of offering chemoprophylaxis to the whole under-5 age group is much larger: the pros and cons have been reviewed by Greenwood (1984).

Treatment of severe disease

Only a proportion of children with symptomatic falciparum

malaria go on to develop a severe or fatal illness (most commonly cerebral malaria, severe anaemia and metabolic acidosis—the three groups are not mutually exclusive), and so it may seem logical to concentrate resources trying to save these few. A moment's reflection reveals the difficulties of this approach, in that only a proportion of severe disease reaches hospital or health-care outposts (the proportion is, obviously, very variable depending on the proximity and standard of care offered; we usually have few data on proportions of malaria deaths occurring at home). Also, high-dependency care is, relatively, very expensive. Nevertheless, this is not to say that no attempt should be made to target this group: Marsh et al (1991) have calculated that a large proportion of severely ill children in their area are treated in hospital. Certainly the provision of simple measures, including administration of an effective parenteral antimalarial drug, dipstick measurement of blood sugar and 50% glucose, and safe blood transfusion, would save many lives and would probably be cost-effective in comparison with other interventions. Surprising though it may seem these, apparently basic, requirements are not universally available.

Further lives would probably be saved by provision of the following: increased nursing and medical staffing; diagnostic bacteriology (serious bacterial infections including bacteraemia and meningitis may co-exist with malaria); and a greater range of relatively sophisticated drugs (including parenteral anti-epileptics and newer antibiotics). However, these provisions are relatively expensive. Furthermore, it should be borne in mind that even when treatment budgets and staffing levels are high the mortality rate for cerebral malaria falls no lower than around 10% (Marsh et al 1995). Thus, ever increasing expenditure in this area could be expected to make only a limited improvement in mortality figures. Anathema though it might be to the practising physician (and I am one), when faced with difficult choices, planners may conclude that more lives could be saved by spending money in other areas of malaria control.

On the other hand, which parenteral antimalarial drug to choose for severe falciparum malaria (and how to give it) has received much attention in the last few years. If the simple process of changing drug could be shown to save lives, then this would probably be an affordable intervention. Quinine is currently the drug of first-choice in Africa, not because of its great potency, but because it is reliable (resistance has not been encountered). Unfortunately, quinine does not kill circulating parasites (Watkins et al 1991) which remain available to sequester in deep structures, possibly worsening outcome. The artemisinin-derivatives, on the other hand, have early effects on circulating ring-forms (Murphy et al 1995) and might be expected to reduce mortality. Unfortunately, randomized trials in Kenya (Murphy et al 1996) and elsewhere have failed to show such an effect on mortality, although artemether was at least as effective as quinine. A number of unanswered questions remain, including: what effect would artemisinin-deriv-atives have on mortality if given intravenously (artemether is given intramuscularly, and there are some concerns over its absorption) and does the use of artemisinins lower mortality in those children with uncomplicated disease, who may be at high risk of developing severe malaria (e.g. the very young, the anaemic and those with high circulating parasite loads)?

It is, of course, essential that fundamental research continues into the mechanisms (both molecular and pathophysiological) which underlie the development of severe disease. Improvement in understanding the problem will surely help us to tackle it more effectively.

Treatment of uncomplicated malaria

Throughout much of sub-Saharan Africa uncomplicated falciparum malaria is among the commonest causes of hospital attendance. Another way of looking at the same statement is that most cases of symptomatic falciparum malaria seek treatment: they may not necessarily attend hospital (distances may be too great and the waiting times too long) but may obtain their drugs from local shops (Mwenesi et al 1995). This group represents a self-selected opportunity for intervention. In practice, of course, treatment of symptomatic disease has long been the main malaria control measure employed in Africa. In my opinion this intervention is set to retain its pre-eminent place—so long as effective, practicable and affordable drugs are available. The importance of drug cost cannot be over-emphasized.

What follows is not meant to be a review of the Clinical Pharmacology of antimalarial drugs, but rather an attempt to put their usefulness into context in an African setting.

Chloroquine. In view of almost ubiquitous resistance throughout Africa, chloroquine cannot be recommended for non-immune patients with uncomplicated falciparum malaria. However, in many malaria-endemic countries, chloroquine remains the drug of first-choice. This is the product of extremely difficult health-care decisions on deployment of scarce resources—malaria is only one of many health-care problems, and even pyrimethamine–sulphadoxine (PM–SD) costs more than chloroquine.

Quinine. One might imagine that, faced with chloroquine-resistance, reversion to oral quinine therapy would be an obvious solution. Unfortunately quinine has the following major disadvantages: it is considerably more expensive than chloroquine; it must be given several times daily for at least 5 days; and it tastes appalling in the liquid suspensions needed for paediatric use. In consequence, although quinine is used for uncomplicated disease, availability is limited and compliance is poor.

Mefloquine. This synthetic drug has structural similarities to quinine. It is effective against *P falciparum* strains resistant to chloroquine and PM–SD, and is therefore extensively used in Indochina. Although mefloquine is marketed in some African countries, and is very potent against local *P. falciparum* strains, it is little used because it is unaffordable by the vast bulk of the population.

Halofantrine. Halofantrine is effective against many strains of *P falciparum* resistant to chloroquine, PM–SD and mefloquine, and is used extensively in parts of Indochina. Like mefloquine, halofantrine is rarely used in Africa because of its high cost.

Artemisinin and derivatives. Semi-synthetic artemisinin-derivatives are available in oral (and rectal) formulation, and

can be expected to be effective in an African setting. Their cost, which will be the critical determinant of their utility, is unclear at present but is likely to be relatively high. In contrast, artemisinin itself is cheaper to produce (it has merely to be isolated from plant material and formulated; no derivatization is required) and is extensively used for this reason in Vietnam. It is possible that oral/rectal artemisinin preparations may prove practicable for uncomplicated malaria in some parts of Africa, although the long treatment course needed to prevent recrudescence (5 days) is potentially a major disadvantage.

Pyrimethamine–sulphadoxine and other antifolate combinations. PM–SD is cheap, practicable (only one dose is needed) and highly effective in much of Africa. Not surprisingly this combination is fast becoming the drug of first-choice for uncomplicated disease. In much of Indochina, where parasites are often resistant to both PM and SD, PM–SD is clinically useless. Such resistance is unusual in Africa at the moment, but is confidently awaited and, unless an affordable replacement is available, the impact on mortality figures may well be major.

PM–SD is eliminated slowly (half-lives of 81 and 116 h respectively), which provides welcome chemoprophylaxis after treatment, but also favours the selection of parasites resistant to PM (Watkins & Mosobo 1993) and possibly also to SD. Rapidly-eliminated antifolate drugs are likely to exert less resistance selection pressure than PM–SD. Furthermore, *P. falciparum* resistant to PM retains sensitivity to other dihydrofolate reductase inhibitors. Chlorcycloguanil (the active metabolite of chlorproguanil) combined with dapsone is more potent in-vitro than PM–SD (Winstanley et al 1995) and is eliminated rapidly (half-lives lives of 12·6 and 24·5 h respectively). Consequently, our teams in Kenya and Malawi hypothesize that chlorproguanil–dapsone is at least as effective as PM–SD, that it exerts less selective pressure for resistance and that it will retain efficacy as PM–SD failure emerges. We are currently in the process of testing these hypotheses.

Conclusions

Ninety percent of global malaria mortality occurs in Africa. The absolute numbers of malaria deaths is likely to rise in the next decade. Insecticide-dipped bednets reduce malaria mortality, but the long-term sustainability of this intervention on a national scale has not been proved. Provision of antimalarial drugs for uncomplicated malaria is likely to remain among the more effective forms of malaria control.

Chloroquine is no longer reliable and pyrimethamine–sulphadoxine is the only affordable alternative presently available. However, resistance to pyrimethamine–sulphadoxine is likely to emerge within the next 10 years.

Effective, safe and affordable drugs for falciparum malaria are needed urgently.

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