EDITORIAL / VAN DIE REDAKSIE

Preventing malaria

The World Health Organisation has estimated that at any one time more than 100 million people in Africa suffer from malaria, i.e. approximately 1 in 3 people on the continent. The risk of dying of malaria, once it is contracted, is about 1 in 100. Neither AIDS nor tuberculosis in Africa compare with these awesome statistics. The situation is worse at present than it has ever been before.

There are several reasons for this deteriorating situation. These include the emergence of widespread chloroquine resistance, linked to the use of inappropriate drugs for malaria prophylaxis, and the spread of disease as a result of mass migration in the wake of civil war and famine. There is serious concern that quinine resistance may develop in Africa in the foreseeable future as it has in far-east Asia and the Amazon basin.

Most cases of malaria seen in South Africa, whether contracted here or elsewhere, are caused by *Plasmodium falciparum*. Within our borders the parasite is usually sensitive to chloroquine, except in the Ingwavuma and Ubombo areas. However, there is concern that this pattern of sensitivity may be changing for the worse. Only concerted scientific, public health and sociopolitical changes are likely to reverse this trend.

Over the past 2 years three meetings have been convened by a working group on malaria prophylaxis in order to develop a national strategy. Their recommendations are set out on pp. 126 - 129 of this issue of the *SAMJ*. The document reflects broad experience and considerable thought. People concerned with health policy and those from the pharmaceutical industry were included in the deliberations. The recommendations deserve careful attention. Because the situation is changing, any advice regarding malaria prophylaxis needs to be continually reviewed.

In developing their recommendations for this region and for travellers from South Africa going to other parts, the working group took the following into account:

1. The prevalence of chloroquine resistance of *P. falciparum* varies from country to country, and between regions within countries.

2. Chloroquine resistance of *P. falciparum* is widespread throughout sub-Saharan Africa north of the Limpopo River.

3. People living in what are known as unstable malarial areas need to take regular chemoprophylaxis. (An unstable area is one where malaria is seasonal and epidemic, and the local population is periodically exposed to malaria. In such a situation semi-immunity of individuals tends not to develop.)

4. People living for a number of years (between 3 and 5) in areas where malaria is stable are likely to be semi-immune, and they need not take chemoprophylaxis. (A stable area is one where transmission occurs throughout the year, and the population is exposed without break to infection. Provided people remain in the area throughout, they are likely to be semi-immune.)

5. Non-immune persons moving to a stable malaria area should take chemoprophylaxis. The exact length of time that prophylaxis is required before semi-immunity develops is not known.

6. Infants, young children and pregnant women are regarded as non-immune at all times, whether or not they live, or have lived, in stable malarious areas. They should receive malaria chemoprophylaxis wherever the possibility of exposure exists, and if possible they should be dissuaded from exposing themselves to malaria.

The report of the working party contains several principles and concepts pertaining to the prophylactic use of antimalarials:

- Drugs used in the prophylaxis of malaria should not, if possible, be the same as those used in the treatment of acute attacks of malaria.
- Pyrimethamine does not add materially to the prophylactic effect achieved by chloroquine alone (this refers to the South African experience).
- Proguanil has not been shown to be a consistently effective prophylactic agent, alone or in combination, on the African continent.

(The combination of proguanil and chloroquine is said to confer a higher degree of protection in chloroquine-resistant areas than chloroquine alone, but findings are not consistent. The combination is comparatively safe, and it can be used during pregnancy and childhood. However, because of lack of persuasive evidence supporting its efficacy in southern Africa and elsewhere on the continent, proguanil has not been registered in South Africa by the Medicines Control Council.)

- Maloprim (the combination of dapsone and pyrimethamine) has been associated with agranulocytosis in a small number of cases. (This risk appears to be greater when the recommended maximum prophylactic dose is exceeded, but agranulocytosis has also occurred in patients taking standard prophylactic doses.)
- There is no clear advantage in exceeding the recommended prophylactic dose of any of the antimalarial agents. This strategy was regarded by the working party as potentially unsafe and ill-advised.
- Doxycycline has proved a useful and effective prophylactic for travellers to chloroquine-resistant areas in far-east Asia. It may be used as an alternative to other agents when these are not available, or when they cannot be used because of toxicity or intolerance. (Doxycycline is contraindicated in pregnant women, in children less than 8 years of age, and in patients who are at risk of developing photosensitivity.)

At a time when the parasite appears to be gaining the upper hand it is encouraging that a new drug for prophylaxis is on the horizon. This is mefloquine, an analogue of quinine. Mefloquine is currently being widely tested in this country in a surveillance study of persons travelling to areas with *P. falciparum* resistance.

The early results seem promising. Nevertheless, there are safety issues. Confusion and even toxic encephalopathy have been described with mefloquine, and it shares the propensity of quinine occasionally to cause hypersensitivity thrombocytopenia. Caution is necessary when it is administered to the elderly, to patients with heart disease, and to patients receiving other medicines. It should not be given to pregnant women or very young children. Underlying epilepsy may be aggravated.

In the longer term, malaria will be conquered by advances in public health and by a better understanding of the mechanisms of infection (in both the anopheles and humans) and resistance. Until then, it is important that this country invest effort and resources in epidemiological, pharmacological, surveillance, information, vaccine and eradication programmes. Immediate advice to health professionals on drug treatment and prophylaxis is available from either the Transvaal Pharmaceutical Society (TPS) (Tel: (011) 339-4831) or the University of Cape Town Department of Pharmacology's Medicines Information Centre (Tel: (021) 47-1250, ext. 291 or 427).

It is important that people travelling for more than a short period in high-risk areas carry the means to treat themselves when immediate access to therapy is not assured. The WHO has recommended Fansidar or quinine, or a combination of these, for this purpose.

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Malaria — are we giving travellers adequate and accurate information?

Many members of the travelling public think that the information given to them about malaria by travel agents, airlines and the medical and pharmaceutical professions is inadequate. Indeed, given the large numbers of travellers who are regularly referred by their medical advisors and, to a lesser extent, by pharmacists to the Department of National Health and Population Development or other agencies for advice about malaria prophylaxis, little or no interest is shown by the medical profession in this topic. It is little wonder, therefore, that preventable malaria deaths occur from time to time because of ignorance on the part of both patients and attending doctors. This state of affairs is not unique to South Africa. An American study[1] showed that of 68 American travellers who died of malaria, 77% did not take chemoprophylaxis, 13% took inappropriate chemoprophylaxis, and 40% of the cases were misdiagnosed.

South Africa's prolonged isolation on all levels is responsible for today's lack of general awareness of the international travel explosion which has taken place during the last few decades. Not only do people travel more; they travel increasingly to tropical areas, formerly the hunting grounds of the few wealthy enough to afford such visits. The number of cases of malaria and other travel-related infections seen by doctors practising in non-malaria areas has escalated accordingly. In such areas malaria is no longer a rarely seen disease to be shied away from and referred to a centre with expertise in tropical diseases. It is the duty of the profession to inform itself about appropriate prophylaxis and treatment, the former admittedly no longer a simple matter, especially as some commonly recommended drugs such as proguanil and mefloquine are not readily available in South Africa.

The Department of National Health and Population Development has published a leaflet which provides basic information on malaria for the general public and a more detailed booklet[2] aimed at the medical and paramedical professions. However, neither of these excellent publications appears to be widely distributed. On a recent visit to Kenya, I saw no malaria warnings on my departure from, or arrival at Jan Smuts Airport, our principal international gateway. I did not look very hard, but then neither do the great majority of travellers who have other things on their minds. Such warnings must therefore be displayed prominently. Better still, a small red slip that alerts the traveller to the prevalence of malaria in certain areas and the need for precautions could be inserted into travellers' passports by the passport control officers.

Travel agents are in business to 'sell' travel, not to frighten prospective clients away with horror stories about malaria. Understandably therefore, the dangers of malaria and other exotic infections tend to be played down in favour of the various attractions to be experienced. Nevertheless, many travel agents do indeed alert their clients to a need for malaria precautions when visiting certain travel destinations. But, while travel agents are frequently called upon to give travel-related health advice, they are not qualified to provide anything but the most basic information.

The benefits of malaria chemoprophylaxis should not be overestimated. It is an unfortunate fact that it is no longer possible to provide travellers with a safe, fully effective antimalaria drug regimen. Some travellers return home and develop malaria despite meticulously observed prophylactic programmes. A few will even die. This is an acceptable risk associated with travel just as illness and death are a risk of many other recreational and occupational activities. It is not acceptable, though, for travellers to become ill because of a lack of accurate information. Such information must be made available to the public. Medical practitioners are the most appropriate source of this information, because the complexities of travel itineraries, travellers' health profiles and the geographically varying epidemiology of malaria frequently necessitate individually tailored advice instead of standard across-the-board recommendations. No one knows a patient better than his own doctor, who is in the best position to advise on drug interactions and adverse effects, contraindications to malaria exposure or certain antimalarials, and the interaction between malaria and other underlying diseases or physiological conditions to which the patient may be subject. A complicated case of malaria, not uncommonly seen in our largely non-immune travellers, is a medical emergency and only the doctor can provide immediate medical care. His receptionist, his nurse or some semi-administrative health authority or academic can do nothing in this regard. It is essential that the doctor knows which antimalarial drug, if any, the patient was taking prophylactically. Without this information it is difficult to avoid toxicity as a result of overdosage, or the use of a drug to which the patient's parasite is resistant. The patient may be comatose and unable to provide this information. It will, however, be in the patient's record if the doctor himself did the necessary pre-travel counselling.

What then should the prospective traveller be told about malaria?

1. Chemoprophylaxis prevents many, but not all, cases of malaria.

2. Chemoprophylaxis, when it does not prevent malaria, may reduce its clinical severity.

3. Chemoprophylaxis should be augmented by one or more antimosquito measures such as the use of protective clothing, mosquito repellants, insecticides, bed net, and door and window screening.

4. Some conditions are associated with a greater risk of serious malaria and persons with conditions such as pregnancy or splenectomy should ideally avoid malarious areas.

5. Pregnant women who cannot avoid travel to malarious areas must practise chemoprophylaxis with antimalarials recommended for use in pregnancy; the potential hazards of malaria to themselves or their unborn infants are greater than those associated with the drug.

6. An episode of illness during or after travel must be promptly investigated for the possibility of malaria, despite any antimalarial precautions that may have been taken.

7. The option of stand-by treatment (self-medication) must be considered for all travellers planning to spend 2 weeks or more in an area where access to medical care is not readily available.

It must be kept in mind that malaria remains endemic in 99 countries and that more than 2 billion people are therefore exposed to malaria infection.[3] It has been estimated that nearly 120 million clinical cases occur annually and that there are 300 million parasite carriers globally, mostly in Africa. The malaria mortality rate is estimated to be in excess of 1 million annually. These statistics serve to underline the need for travellers to take the necessary precautions.

No medical practitioner can afford, therefore, to be without an authoritative and up-to-date information resource on malaria and other potential health hazards

which may affect the travelling public. The World Health Organisation publishes such an annually updated guide at especially low cost to developing countries.[4]

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Transfusion of malarial or other parasites in blood

No cases of the transmission of malaria or other protozoal or metazoal parasites through blood transfusion appear ever to have been reported in South Africa, though it seems improbable that none has ever occurred. Admittedly malaria is nowhere holoendemic here, and its most severe ravages have tended to occur during epidemics, when those harbouring the parasites are unlikely to donate blood. On the other hand, it is unlikely that none of the potential blood donors who carried out military service in northern Namibia and southern Angola ever became infected with a malarial parasite. It is true that *Plasmodium falciparum*, once properly treated, is unlikely to recur without reinfection, and that the local populations which might afford a reservoir for parasites are principally negative for Duffy receptors and hence unlikely to harbour *P. vivax*;[1] but one might have expected at least a few cases of *P. malariae* to slip through and give trouble later.

Of the other protozoal or metazoal conditions which might be transmitted thus, the distribution of African trypanosomiasis[2] is uncertain and does not occur in sufficient density for its possible presence in blood donors here to be worth considering; filariasis[3] is rare in this country, and leishmaniasis[2] of the southern African type, confined to desert areas, is unlikely to have crossed the border. Conversely, toxoplasmosis[4] may be encountered wherever there is a large feline population, and babesiosis[5] wherever ixodid ticks are found and biliary fever occurs in dogs.

Protozoal diseases include some of the most insidious and dangerous ones able to be spread by blood transfusion. They are often not easily recognised as having been transmitted by that route except where transmission occurs outside the areas where they are ordinarily present. Transfusion leishmaniasis became conspicuous when it occurred in Sweden,[2] and its very rarity led to similar cases being suspected in the USA[6] and France.[7] *Babesia microti* may be transmitted during blood transfusion in its intra-erythrocytic form. The severity of disease is often increased where there is splenic impairment. It is likely, should transfusion babesiosis occur in or in the vicinity of malarious areas, that it would be mistaken for malaria. *Toxoplasma gondii* is one of the causes of infectious mononucleosis. It is an obligate intracellular parasite of white cells, and though transmission has not been found to occur following the transfusion of whole blood,[4] infection can certainly result from the administration of leukocyte preparations in patients with leukaemia.[8] African trypanosomiasis, unlike the South American variety, has been reported to follow blood transfusion only in children in endemic areas.[9]

Although all these conditions, with the exception of microfilariasis (and transfused microfilariae cannot mature in the human body), are serious, they are too rare and sporadic to be important. The one possible exception is babesiosis, but *Babesia* is hardly ever found in man except after splenectomy, and splenectomised persons are not acceptable as blood donors. The combined significance of all of these diseases is far outweighed by that of transfusion malaria, which may be due to any one of the four species which affect man.[10]

As might be expected, transfusion malaria is most severe and most easily recognised in a patient who has not previously been exposed to the disease. One reason for this is, of course, the absence of any kind of protective antibody; the other is the lack of cellular immunity. In naturally acquired malaria, the cellular immune system is primed early on when the liver cells are invaded by sporozoites before the inception of the true blood phase. Secondary invasion of the liver by merozoites may occur with *P. vivax*, *P. malariae* and *P. ovale*, but never with *P. falciparum*, which is consequently far more frequently responsible for fatalities than the other species are. The parasite most frequently responsible for the disease, however, is *P. malariae*,[11] which can persist asymptomatically in infected persons for many years. It is likely that much the same holds for *P. vivax* and *P. ovale*. Relapses caused by these three parasites, to which tissue immunity will develop if the recipient survives the initial post-transfusion attack, therefore tend to be relatively benign.

From 1972 to 1981, 26 cases of transfusion malaria were reported in the USA; 9 cases were due to *P. malariae*, 8 each to *P. vivax* and *P. falciparum*, and only one to *P. ovale*,[12] which is in any case the rarest of the parasites and is not infrequently mistaken for *P. vivax*. It was later held that about 50% of these cases could have been prevented by proper interrogation of the donors.[13] This series was later expanded, and it was found that of the 3 deaths among the 47 patients with transfusion malaria between 1972 and 1988, *P. malariae* was responsible for one and *P. falciparum* for two.[14]

Despite its unfamiliarity in South Africa, transfusion malaria is a disease about which one should be wary, especially in the light of increasing contacts with countries to the north, in many of which the frequency of the disease approaches holo-endemicity and where at least *P. falciparum* often displays a high rate of resistance to the 4-aminoquinolines commonly used in the treatment here. The blood transfusion services of South Africa have all adopted stringent policies with regard to the acceptance of potentially malarious donors, and this accords with what is presently being advocated in other countries.[13] Their effectiveness will depend, however, on the frankness and often the understanding of the donor. Medical practitioners who advise patients before visits to malarious areas, especially in south-east Asia, should secure reliable information about the drugs of choice for prophylaxis and treatment there. Above all, anyone known ever to have harboured *P. malariae* must be discouraged from ever donating blood again.

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