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Malaria in Southern Africa

P. V. ROLLASON

Hillside Pharmacy, Hillside Shopping Centre, Box 9002, Hillside, Bulawayo, Zimbabwe

I would wish you to see malaria through the eyes of one who deals with the disease every day of the week. The situation of a community pharmacist in a malarious area is very different from that of a researcher, or even a medical practitioner/prescriber. The disease presents itself to a community pharmacist as patients in a scare situation, bedevilled by confused utterances; scared because 600 people died of it in Zimbabwe in 1995; confused by so much differing advice on offer by everyone from the Professor to the next door neighbour. I will try to clarify the existing situation of the disease as seen in Southern Africa.

Vector Control

Urban areas, in some cases cities of a million or more people, are generally controlled at the start of the season by residual insecticide spraying undertaken by the local authority and concentrated on standing waters. Most of these major urban areas are situated on the highveld above 1000 metres altitude, which means in this part of Africa there is a very low risk of malaria. It is acknowledged that the altitude parameter of anophelene breeding varies as one moves nearer to the equator. In rural areas and especially those below 1000 metres, residual insecticide spraying is normally undertaken by central governments. Even when DDT was used, this presented no environmental hazard as the spraying was confined to dwellings both inside and outside. As a measure of its success, when the government runs out of money (far too frequently) and spraying at the beginning of the rainy season is reduced, morbidity and, distressingly mortality more than doubles. There has been encouragement for the greater use of bed nets, pre-soaked with pyrethrins where possible but this has not been very successful. It is general policy in Zimbabwe and its surrounding countries not to supply any form of chemoprophylaxis to constant dwellers in rural malarious areas. These people who are challenged daily with infected vectors, are regarded as being partial immunes, probably with a similar degree of success as would be achieved by most preventive drug regimes. But of course, urban high-veld dwellers visiting low-veld malarious areas need a preventive drug, and this is where a problem immediately arises. For example, a peasant family lives in a low-veld malarious area, Tjolotjo, but the father works at a factory on the high-veld in Bulawayo 100 km away. The family are partial immunes, but he is not. When he goes to visit them once in three or four months, he is advised to take his malaria tablets. But he says: "I do not need medicine; I am not sick. My wife and children do not take anything so why must I" He takes nothing and he gets malaria. Added to that, the confused story of prophylaxis and the various regimes on offer makes for a very difficult situation. There is also another point that should be mentioned: that of communication and knowledge of language and local customs.

We are experiencing more and more "Commuter malaria". Where I live on the high-veld in what is regarded as a non-malarious area, no prophylaxis is advocated and generally not used. However there are more and more cases of malaria being contracted in these areas, contrary to expectations. These are mosquitoes that go "walk-about". They travel in from malarious to non-malarious areas on buses, trains and bicycles, and do their damage on arrival. We had a fatal case of cerebral falciparum about three years ago in Bulawayo. The mosquito had hitched a ride in a boat trailer of some people who had been having a holiday on Lake Kariba, in the Zambezi valley. The trailer was parked on arrival home; the mosquito escaped and bit the lady who lived next door. She had not been out of the town for over two years, and yet she died from malaria because it had neither been suspected nor had it been thought of geographically for diagnosis. Another lady who collapsed seemingly from general malaise and possible malnutrition was given a routine blood test and surprisingly malaria was found. She was treated with chloroquine and fully recovered. The offending mosquito apparently came into town wrapped in the blankets of one of her employees returning to work after spending the Christmas holidays in a malarious area.

Treatment and Diagnosis

Probably of prime importance, however, is malaria treatment per se. I, of course, can only relate my own region's circumstances. Up as far as the Zambezi River, resistance to chloroquine, although known and documented, is generally isolated and not too significant. In fact chloroquine resistance is greatly over-estimated. Why should this be so? The answer to this vexed question (and I am sure this applies to many other parts of the world) is inaccurate diagnosis. Chloroquine is, as we know the drug of choice and is still remarkably effective. It is widely used, easily available and cheap. Some years ago it was decided to make chloroquine freely available to people especially in rural areas through local general stores so that when they felt that they were succumbing to malaria, they could easily buy treatment close to home. The normally recommended dose was well publicized and encouraged. It all went wrong. The people bought the chloroquine, but usually only two tablets to cure a headache or a hangover or conversely, a massive quantity to provoke an abortion. The amount used for the legitimate treatment of malaria was negligible. This has been partly overcome by confining the product to sale only in original packs of ten tablets, but obviously this is not the answer.

The only place where accurate diagnosis of malaria can occur is in towns where there is a laboratory with a good microscope and above all a well trained technologist to read and interpret the blood slides. In most parts of the area this just doesn't happen. There was a World Health Organization (WHO) plan a couple of years ago to obtain some 2000 microscopes, to send them out to the rural areas to increase

diagnostic efficiency. There was no one to read the slides, even if they could have been prepared, there was no electricity for illumination and no microscopes working—they were either broken, stolen or sold. All this serves therefore to highlight a system that is prevalent throughout—presumptive diagnosis. This means in essence, that when a person feels unwell even with minor symptoms and has been in a malarious area, chloroquine is given in a full dose regime. If that person recovers, fine; it was malaria and has been dealt with. But so often he does not respond. Is the inference to be that chloroquine failed? Not at all—he has not had malaria but more than likely influenza, diarrhoea, dysentery or, particularly, tick fever. Fortunately chloroquine seems to have few side effects in an otherwise uncompromized person, and even skin itching although known, is nothing like as severe in my part of Africa as has been encountered in parts of West Africa. So, we have a system of basic misdiagnosis and this is very often classified as an example of chloroquine-resistant malaria. In fact the figures given for such resistance are so false that they are, in my estimation, about 50%. I have heard of quotes from other sources that the figures may be as high as 60% wrong. There is also another reason for confusion. Hardly any local medical practitioners and even some epidemiologists know what chloroquine resistance means. They are not aware of R1, R2 and R3 resistance, let alone the more recent WHO parameters of resistance estimation.

Diagnosis therefore is the kingpin of malaria containment. And there is much hope in this direction. The incidence of different malarial strains in Zimbabwe and Southern Africa generally is estimated roughly as *P. falciparum* 98%, *P. malariae* 1·5%, *P. ovale* 0·5% and *P. vivax* nil. The diagnostic system that measures the histidine rich protein of falciparum invasion by means of a dipstick procedure is therefore most valuable. I introduced this into Zimbabwe last year, and the manufacturers donated a set of 100 tests for trial. In the city of Bulawayo I worked with general practitioners, and when they had a case of suspected malaria, they telephoned me, and I went immediately to their surgery and did the test with them on the spot (an unusual role for a city pharmacist, but one that paid dividends!). Every diagnosis was deliberately confirmed by blood slides which could require a day or more to produce a result, but every single one was confirmed. The point here is that every positive case was commenced on treatment at once and results were 100% successful. Negative diagnosis required the doctor to think again and in every case another disease was found and then adequately treated. After a number of tests done this way, I gave the remainder to the local laboratory who conducted them for the general practitioners at no cost. They then purchased more, and the service was installed until (luckily at the end of the season) supplies from the manufacturer ran out. The USA could not cope with demand! There is now also an even cheaper ICT Rapid Malaria Test and, like the Parasight F test mentioned above, is specific for *P. falciparum* and these are just what we need. There should be just such a simple diagnostic system installed at every health clinic, every mobile health centre, and even with village health workers. Malaria would thus be much more accurately and efficiently dealt with, and a lot of unnecessary treatment and drug use avoided. Incidentally, the Parasight F test can even be done by someone who is illiterate, and takes less then ten minutes.

Coming now to the classic situation of *P. falciparum* malaria, what treatment policy is followed in Southern Africa? Chloroquine is still our number one drug. The drug of second choice and beloved by travellers from overseas to carry as a "stand-by" is pyrimethamine and sulphadoxine combination. The third line of treatment is mefloquine or halofantrine—the former not much used, the latter used generally successfully but now less popular because of its erratic absorption and its known cardiac side-effects. Quinine is still high on the list and used quite extensively. Most recently, artemisinin and derivatives, usually in the form of artemether injection, is being used by some doctors, generally with excellent results. So what problems do we have? With chloroquine, very few. We do know of resistance, we know where it occurs in isolated pockets but as yet these do not appear significant. We have found nausea and vomiting a problem especially when the initial dose of 600 mg base is taken but this is almost always overcome if administered with a glucose drink. Pyrimethamine–sulphadoxine is unquestionably an effective treatment, but has a complicating factor: after administration of the usual three tablet dose the patients symptoms usually improve quite soon—in 36 h or less—but when blood slides are taken parasitaemia remains higher than expected. Many practitioners are not aware that in the case of this drug the parasite load is reduced rather slowly, so they panic and rush to give quinine with all its nasty side effects, basically unnecessarily. Mefloquine is not much used for treatment, for no valid reason except perhaps expense. And as I mentioned, artemisinin is very successful in recalcitrant cases, a heavy parasite load and in the distressing escalation of cerebral malaria. Resistances to quinine and others, including mefloquine and halofantrine have not been recorded. Incidentally, very few doctors and even fewer patients are aware that cerebral malaria is as a result of either undiagnosed or inadequately treated *P. falciparum* malaria, and regard it as a special, different, fatal disease.

Prophylaxis

Malaria is not a notifiable disease in terms of law and therefore incidences and geographical disposition can only be assessed by positive visits and voluntary reports. The Zimbabwe government has a research laboratory in Harare that concerns itself among other things with malaria, and there is a malaria unit within the Ministry of Health and Child Welfare. They both work in conjunction with the WHO sub-regional office in the same city.

In 1994 I was awarded an F.I.P., scholarship to research malaria incidence, treatment and prevention in Southern Africa, I concentrated on four countries—South Africa, Namibia, Botswana and Zimbabwe. South Africa is well involved in malaria work, and a special unit under the Medical Research Council employs more than twenty people concerned mainly in researching chloroquine resistance. Under the direction of Dr Brian Sharpe, they are also constructing malaria maps for the regions and I have been able to supply him with the Zimbabwe component. Namibia and Botswana have no research but generally follow WHO guidelines. Zimbabwe does more, although it does not have a specific biological research laboratory. Where treatment is concerned there is little difference within the four countries, drug availability

being the main limiting factor. However, where prophylaxis and particularly advice on prophylaxis is concerned there is utmost confusion. I must mention here South Africa's policy of recommending mefloquine as the main preventive drug to be used and registering it only for that purpose. It may not be used for treatment. A doctors prescription is required, costs are phenomenally high, and in spite of what the texts and promotion says, the incidence of unacceptable side-effects, especially in the first few weeks, is very high. This has, furthermore, led to a bad reputation for the drug among the lay public, and more importantly to poor compliance and thus increased risk. Contrary to this, we in Zimbabwe have used pyrimethamine-dapsone for over twenty years as our main preventative with excellent results and no known single case of agranulocytosis or resistance has been recorded. I was delighted to see acknowledgement of our use of this combination in the March 1995 edition of the British National Formulary. Proguanil and chloroquine is still used occasionally as prophylactic treatment but only where a patient shows a sulphonamide allergy to dapsone. Side-effects from this universally recommended regime of proguanil and chloroquine are much higher than generally acknowledged. This leads to poor compliance. Any patient who has to take sixteen tablets a week when he is not ill and then feels terrible, is not very likely to continue. Incidentally, whatever regime of prophylaxis is used, we advocate continuance for four weeks after leaving a malarious area, as generally we have no *P. vivax*. I found that Botswana was only recommending two weeks—I think they have now changed.

Titrating the dose of any drug for children is always somewhat hazardous. Age is the usual measurement but children vary tremendously in size and weight for age. Thus there is a tendency to marginally overdose. In one part of my country where the population is concentrated under one employer, pyrimethamine–dapsone is administered every Monday. On that day quite a number of children go blue from slight dapsone overdosage but it doesn't matter and simply acts as a proof that the dose has been taken. The origin of "Blue Monday" perhaps? I have records from the hospital that administers this whole area and even during this last bad season not one employee had malaria.

There is little doubt that in practice, the success of malaria

Table 1. Typical problems in malaria prophylaxis arising from case studies.

Problem	Answer
During a bad season should one increase the preventive dose of pyrimethamine–dapsone to one tablet every five days rather than the usual seven days?	No. The difference in serum levels between five and seven days is only about 2% and compliance on a five day dosage is likely to be nil.
Should one add chloroquine to pyrimethamine–dapsone during the bad season to get better protection?	Not a bad idea, but the dose of chloroquine should be taken when the effectiveness of pyrinethamine dapsone is running out, that is five days later, and compliance is likely to be very poor.
A patient has an allergy to sulphonamides and seemingly to chloroquine, reacts badly to proguanil, and has minor psychiatric problems treated with tri-cyclic anti-depressants. What preventative would he take?	Possibly tetracycline i.e. doxycycline 100 mg day^{-1}.
A woman is three months pregnant and has to visit a malarious area. What must she take?	Pyrimethamine–dapsone all through pregnancy. She should also have a folic acid supplement, 5 mg daily, and we suggest also 250 mg vitamin C.
An epileptic lady is treated regularly with phenobarbitone and clonazepam. What preventative should she take?	We suggest pyrimethamine-dapsone, but starting four weeks before entering a malarious area to allow time for dose adjustment of her epileptic drugs, (it was found necessary to slightly increase her dose of clonazepam).
A child aged about eleven presented every few weeks with recurrent falciparum malaria was treated in turn with chloroquine, quinine, and halofantrine; but why the recurrence?	The most likely explanation was a constant re-challenge as he lived on the borders of a malarious area, but there is also the possibility of inadequate dosage through considerable vomiting that was not compensated for.
An elderly Zimbabwean lived back in the UK for ten years then returned to Africa. She brought proguanil and chloroquine which she took although she was in a non-malarious area and did not need to. She developed very bad mouth sores and aphthous ulcers.	We took her off all medication and she was fine. Although she had lived here previously she was scared because of all the stories she had heard in the UK about Southern Africa.

(In passing, no inoculations whatever are needed for travellers to Zimbabwe and nearby countries unless coming through Zaire when yellow fever is good. We had one poor man who had been bludgeoned by his doctor into having eight different inoculations—including rabies—all unnecessary!).

chemoprophylaxis depends on compliance with the medication dosage provided. Many people, especially travellers, carry stand-by medication when visiting malarious areas. Upon feeling unwell the medication is taken and all too frequently incorrectly. For example, a course of three tablets of pyrmethmine-sulphadoxine will be carried for just such an eventuality, but the person feels only a little ill, but suspects malaria—is not sure—so takes one tablet just in case. Similar scenarios occur with chloroquine. Money also plays an important part: in Zimbabwe, pyrimethamine-dapsone costs the patient about ZIM$16·00 for 20 tablets—enough for five weeks prevention for four people. Proguanil–chloroquine, to cover the same number of people for the same period, would cost about ZIM$650·00; mefloquine would be ZIM$945·00—40 and 60 times the cost of pyrimethamine-dapsone, respectively! Which would you choose, given that the results are reasonably equivalent? Especially if you live there and have a monthly income of abound ZIM$1000·00 per month. Perhaps now you can see the popularity of pyrimethamine–dapsone as our malaria preventative.

Following along this line, I wonder what your opinion would be of a general practice doctor who himself lives in a seasonal malarious area and recommends to his patient no chemoprophylaxis at all. He maintains it suppresses the disease and masks its diagnosis. He has limited diagnostic facilities and certainly no dipstick test. Table 1 poses a number of problems encountered in malaria prophylaxis and are all case studies—actual occurrences that we have had to deal with.

I have not mentioned the possibility of a vaccine which so many of you are deeply concerned with. There is good reason. It will, with all respect, have very little impact on us at all. With a population of about 11 million variously exposed to malaria, no one or no country will be able to periodically vaccinate everyone against malaria by virtue of practicality and finance. As far as we can assess the situation the vaccine will be of value to the fairly well-off traveller as cover for a short period.

Conclusions

In summary, Southern Africa has a bad enough malaria situation, but chloroquine still works and other drugs are available and effective. There is much more interaction between neighbouring countries now than ever before and are working now on a malaria 6-year plan, possibly financed by Australia, to co-ordinate work on this disease and its containment. This scheme will be centred on Harare, Zimbabwe.

I was, however, interested in news recently of an idea to genetically engineer anophelene mosquitos so that they give a bite which introduces a protective protein, and hence limits the disease. The idea of millions of flying vaccinations is mind boggling. The Swiss have recently come out with a little electric device which sends out a supersonic noise that repels mosquitos. But when questioned as to what happened with anopheles which do not buzz, and therefore may not react accordingly, they were not quite sure. We always tell our visitors that the malarial mosquito does not buzz, has stripes or spots, sticks her backside in the air to bite and only does so at sunset or later. So if they are having a sundowner drink and come across such an animal which they cannot see or hear, they should certainly kill it! And the best malaria preventive of all is gin and tonic. The tonic water provides quinine and if you have enough, the gin results in alcoholic mosquitos who get so drunk they don't know what they are doing!