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**Summary**

Patients with *Plasmodium falciparum* infections in northern KwaZulu adjacent to the Mozambique border were treated with chloroquine 25 mg/kg. Persistent parasitaemias increased from nil in 1983 to 21,2% and 16,1% for hospital and field treatments respectively in 1987. After a change to sulfadoxine-pyrimethamine (Fansidar; Roche) treatment (adult 500 mg and 75 mg respectively) these rates fell in March 1988 to 6,9% and 0,4%.

Over the last 10 years the number of cases of malaria reported annually in KwaZulu has varied from 75 (1982) to 4 836 (1987) (mean 1 035). The majority of cases were found in the two northern districts of Ingwavuma and Ubombo that are situated adjacent to Mozambique. Transmission is seasonal and *Plasmodium falciparum* is responsible for 99% of infections. Intensive malaria control activities, including the application of residual insecticides to dwellings and the active detection and treatment of malaria infections, have been carried out for the past 30 years.

**Malaria detection and treatment procedures**

Over the last 20 years homesteads in malarious areas were visited every 4 - 6 weeks and blood smears were taken from residents with a history of illness resembling malaria and from those who had recently moved into and within the area. In addition, random blood smears were taken during these visits to make up a minimum weekly total of 10 smears for each of the 65 surveillance agents. Occasionally, when malaria transmission was intense, blood smears were taken from all residents of affected localities. Treatment with an adult dose of 4 Daraclor (Wellcome) (chloroquine 10 mg/kg, pyrimethamine 1 mg/kg) tablets was given at the time of taking the blood smear.

When malaria infections were found in blood smears, the individual was visited, usually within 7 - 10 days of the smear being taken, and given chloroquine 25 mg/kg, pyrimethamine 2,5 mg/kg over 3 days (curative treatment). These individuals were visited again after 2 - 3 weeks, another blood smear was taken and curative treatment was given again. If the retake smear was found infected it was considered a treatment failure and the treatment procedure was repeated until the individual became parasite-free. Similar retake smears were obtained from malaria patients treated in hospital after discharge and treatment was given to those found infected. During the first visit to infected individuals blood smears were also taken from adjacent residents in an attempt to trace and treat sources of infection. In hospitals severe infections were treated with quinine at an adult dose of 600 mg 8-hourly for 7 days.

From February 1987 treatment with Daraclor was replaced by chloroquine at 10 mg/kg and 25 mg/kg for initial and curative treatments. In recent years the annual blood examination rate in the Ingwavuma/Ubombo districts has been high during 1987 a total of 189 433 blood smears were examined from a population of 170 382 (counted during homestead visits).

In January 1988, after a review of the situation, it was decided to use Fansidar (500 mg sulfadoxine, 25 mg pyrimethamine per tablet; Roche) in place of chloroquine for the treatment of confirmed infections both in hospital and in the field. An adult dosage of 3 tablets was given in one dose.

**Results**

Before 1983 asexual *P. falciparum* parasites were rarely found in retake smears, and when present they were commonly related to vomiting soon after treatment. From 1983 parasites were found in increasing proportions of smears taken 2 - 3 weeks after treatment with chloroquine 25 mg/kg reaching 21,2% and 16,1% for hospital and field treatments respectively (Table I).

Less than 2% of infected individuals detected up to October 1987 could not be traced by field staff; these were included in total infections. During November and December 1987, 88 infections had not been found up to the time of analysis and were not included. Judging from the results obtained when smears were taken from all residents in a locality, it is conservatively estimated that at least 90% of symptomatic and 70% of asymptomatic infections actually present were detected, treated and reported by the health service during the period described.

Hospital authorities reported the appearance of R11 chloroquine resistance from 1984 and quinine was used to treat these infections. During December 1987, 16 deaths (1,2% of all infections) were reported by field health staff after their investigations of malaria infections. Most were related to delay in obtaining treatment and being severely ill on arrival at hospital and not to chloroquine resistance.

Details were available for 58 of 70 infections treated in hospital and 251 of 295 infections treated in the field during March 1988 after Fansidar (adult dose 1 500 mg sulfadoxine and 75 mg pyrimethamine) was substituted for chloroquine. Retake smears taken 2 - 3 weeks after treatment detected asexual parasites in 4 of 58 hospital treatments (6,9%) and 1 of 251 field treatments (0,4%). Although Fansidar was recommended for the treatment of moderately ill patients with confirmed infections and quinine as used previously for severe infections, it cannot be proved that these drugs were used for all infections treated in hospital.

**Discussion**

The results reported in this article, which include all reported infections, demonstrate the appearance and extent of *in vivo* resistance to *P. falciparum* in northern KwaZulu. It was not possible to obtain and examine further blood smears as required.
TABLE I. P. FALCIPARUM TROPHOZOITES FOUND AFTER TREATMENT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Year</th>
<th>Total No. of cases</th>
<th>Positive retakes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>1983</td>
<td>71</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>1984</td>
<td>489</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>1985</td>
<td>207</td>
<td>23.3</td>
</tr>
<tr>
<td></td>
<td>1986</td>
<td>240</td>
<td>21.2</td>
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<tr>
<td></td>
<td>1987</td>
<td>2017</td>
<td>21.2</td>
</tr>
<tr>
<td>Field</td>
<td>1983</td>
<td>130</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>1984</td>
<td>709</td>
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<td></td>
<td>1985</td>
<td>891</td>
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<td>1986</td>
<td>433</td>
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<tr>
<td></td>
<td>1987</td>
<td>2594</td>
<td>36.3</td>
</tr>
</tbody>
</table>

Retake A = after 10 mg/kg chloroquine; retakes 1 - 4 = after 25 mg/kg chloroquine repeated at each retake.

in protocols for standard in vivo tests; if undertaken a greater prevalence of resistance would probably be found. All infected individuals that could be traced were questioned about previous illnesses and malaria treatments. Field health workers would also have been aware of previous malaria infections. Re-infections with malaria within 6 - 12 months were rarely found.

Individuals with clinically moderate-to-severe infections, usually with recent acute onset, were treated at clinics and hospitals after either attending for treatment or being taken there by fieldworkers. Patients with asymptomatic and mild infections, commonly of longer duration, were treated at home by field staff. The lower relapse rate found after field treatment is probably related to the higher immunity to infection associated with these infections.

There was a considerable increase in reported infections from 201 during 1983 to 4699 during 1987. This was related to favourable climatic conditions, infected immigrants and the development of irrigation. The appearance of chloroquine resistance necessitated repeated treatment, which led to delays in obtaining cure and a resulting prolonged gametocytaemia.

The dramatic improvement in cure rate after the change from chloroquine to Fansidar treatment supports the hypothesis that chloroquine resistance was principally responsible for the failures in response after chloroquine treatment.

In vitro tests have confirmed the presence of chloroquine-resistant P. falciparum infections in Natal/KwaZulu. Chloroquine resistance is prevalent in Mozambique— in Maputo 94% treatment failures were reported among schoolchildren. It appears that resistant infections have been carried by some of the numerous migrants from Mozambique into KwaZulu. In Swaziland the prevalence is reported to be intermediate between Mozambique and KwaZulu. In contrast, few resistant infections have to date been detected in the eastern Transvaal (approximately 25 of 4883 infections detected in 1988) even among Mozambique migrants. This is possibly because they originate from districts isolated from the coastal cities where resistance was first introduced.

Visitors to malarious areas in southern Africa are advised to protect themselves against mosquito bites and to use chloroquine for prophylaxis. The latter may fail to prevent infection in localities with resistance but is likely to alleviate the severity of illness. Pyrimethamine was used in field treatments for its sporonticidal effect on gametocytes thus preventing further transmission in the mosquito. Since there is uncertainty concerning the pyrimethamine sensitivity of indigenous chloroquine-sensitive and -resistant parasites, Primaquine (ICI) is now being used in place of pyrimethamine in a single dose combined with schizonticidal drugs in order to ensure elimination of gametocytes in districts where chloroquine resistance is present.

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REFERENCES