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An Extended Field Trial of Pyrimethamine Combined with Dapsone in the Prophylaxis of Malaria

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INTRODUCTION

Pyrimethamine has been in use as a prophylactic drug against malaria for a quarter of a century, and in general it has proved both reliable and inexpensive. However, there has been an increasing frequency of reports of tolerant strains of malaria parasites in different areas of Africa. There is, in fact, good reason to believe that such tolerant strains exist in Rhodesia — particularly in the Zambesi Valley and areas to the north of the main watershed.

The emergence of the pyrimethamine tolerant strains has led to extensive use of chloroquine as a suppressive drug. This use has been widely criticised on the grounds that such usage may lead to the selection of a chloroquine resistant strain of malaria parasite. It is conceded that such a possibility exists, but there is no evidence that such selection has yet occurred in Africa. However, chloroquine remains the most important and effective drug available for the treatment of overt malaria, and therefore it would be unwise to continue using it as a prophylactic or suppressive drug if an acceptable alternative is available. For those reasons, much attention has been given to the investigation of other possible drugs and to the development of drug combinations. The first combination to be used was a combination of pyrimethamine with chloroquine, and subsequently pyrimethamine was combined with sulphonamides and with sulphones.

Lucas *et al* demonstrated the efficacy of a combination of pyrimethamine (12,5 mg) with Dapsone (100 mg) given weekly as a casual prophylactic, and their results have been confirmed by other workers including Harwin who reported on preliminary trials of this combination drug in Rhodesia in a population of 2 000 non-immune people. This combination drug is now available commercially in most malarious countries of the world.

The dosage levels for the combination have been determined largely on the dapsone content, and the manufacturers have determined that a safe plasma level of dapsone is 2 000 ng ml. Above this level toxic manifestations may appear. After a single oral dose of 100 mg in an adult, an average plasma level of 1 200 ng ml will be reached within eight hours. Maximum excretion of the drug occurs within six days and thereafter no further urinary excretion occurs. On day six the plasma level will have fallen to 10 ng ml. A single adult dose of 100 mg therefore gives maximum therapeutic effect whilst allowing a margin for safety.

From the established adult dosage it is possible to rationalise a formulation for children. In the past, the dosage schedules employed were based on the weight or age of the child concerned. However, Catzel has shown that it is more realistic to relate the paediatric dose to surface area of the body. According to his concept, the dosage for children 12, 7 and one year old of average weight, would be as follows:

Age	*Weight (kg)*	*% of adult dose*
Adult	65	100
12 years	40	75
7 years	23	50
1 year	10	25

However, Catzel was discussing general principles of paediatric dosage and his comments were not directed to malaria prophylaxis. Therefore it was decided to evaluate the efficacy, under practical field conditions, of the pyrimethamine-dapsone combination at dosages determined by Catzel's principles.

OBJECTIVES

A trial of the efficacy of pyrimethamine in combination with dapsone for the prevention of malaria was initiated immediately prior to the start of the malaria transmission season of 1973-74. The objectives of the trial were:—

(i) as stated above, to assess the value of paediatric doses derived from general dosage schedules suggested by Pincus Catzel;

(ii) to establish the practicability of control of malaria transmission using prophylactic drugs under local conditions in a large area with a large and unsophisticated population;

(iii) to ascertain whether a fortnightly regimen of drug administration would be as effective as a weekly one;

(iv) to confirm the acceptability and safety of the drug in a semi-immune population (supplementing a similar trial by Major General du Preez of the South African Medical Corps in non-immunes);

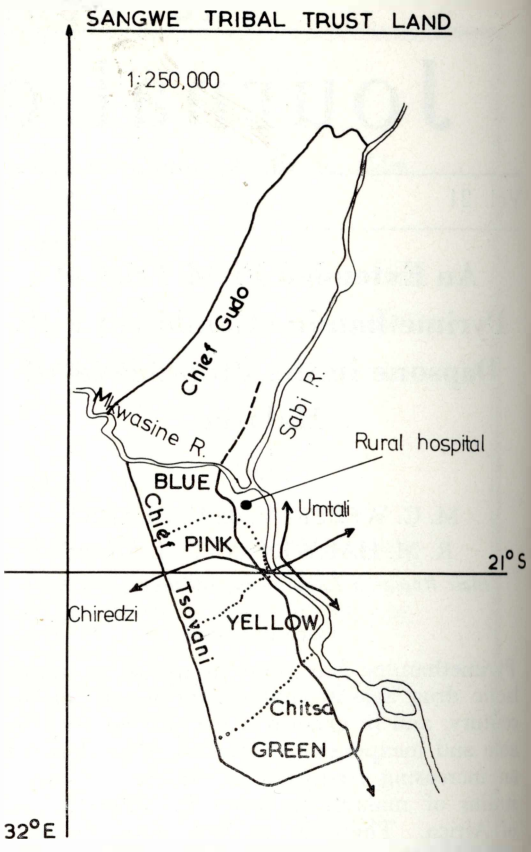
(v) to substantiate or otherwise, unsupported reports of the persistence of gametocytaemia if a dose lower than recommended was used.

DESCRIPTION OF THE AREA

The area chosen for the trial was the southern half of the Sangwe Tribal Trust Land in the region of 21°S and 31°8'E. It covers approximately 260 square km of hot, arid scrubland bordered on the north and east by the Mkwasine and Sabi Rivers and on the south and west by the Gona-re-Zhou Game Reserve and Chiredzi Intensive Conservation Area, respectively. The mean altitude is approximately 300 m above sea level.

The resident population of the selected area was found to be slightly in excess of 9 000 and to have an age distribution which was strongly biased towards the younger age-groups, with over half the total population being under the age of 12 years. The agricultural output of the area is limited and most of the inhabitants depend for their livelihood on wage-earning as labourers on neighbouring irrigation estates.

There is a prolonged dry season through winter and early summer, and malaria transmission is largely limited to the later summer months during the rains, at which time it is intense. The trial was conducted between October, 1973, and May, 1974, inclusive, and by chance it coincided with one of the wettest seasons on record. The rains, normally lasting from December to March, started in mid-October and persisted until early May. Evidence from all surrounding areas and from those people in the tribal area who initially refused prophylaxis showed that it was an exceptionally severe season for malaria.



Sangwe Tribal Trust Land falls under African Tribal Chiefs Gudo and Tsovani and Headman Chitsa. Chief Gudo's area, lying to the north of the Mkwasine River, was not included in the trial. On the South bank of the Mkwasine River is the Sangwe Rural Hospital which serves the whole Sangwe Tribal Trust Area, including that portion omitted from the trial. Records of clinical "fever cases" were available from the Rural Hospital for the whole of Sangwe.

MATERIALS AND METHODS

Past experience has shown that malaria control by means of massive drug administration is

TABLE I.

DOSAGE SCHEDULE

	Pink Zone	*Blue Zone*	*Green Zone*	*Yellow Zone*
Drug used	Pyrimethamine/ Dapsone	Pyrimethamine Dapsone	Pyrimethamine Dapsone	Pyrimethamine
Frequency	Weekly	Weekly	Fortnightly	Weekly
Dosage: Adult	1 tablet	1 tablet	1 tablet	2 tablets
5 - 10 years	½ tablet or	½ tablet	½ tablet or	1 tablet
2 - 4 years	10 ml syrup	5 ml syrup	10 ml syrup	10 ml syrup
Under 2 years	5 ml syrup	2,5 ml syrup	5 ml syrup	5 ml syrup

feasible only if an active well-organised campaign is pursued. It is useless to ask the populace to attend weekly at a given locality to receive their drugs; rather it is necessary to employ personnel specifically to make weekly rounds of the villages and houses, and ensure that every person present is dosed. This method was employed on the previous drug trial in Gokwe District,[2] however, it was by no means certain that it would be successful when a larger population was involved.

Although the primary concern was the effect of the drug on children, it was not practicable to exclude the adults from the trial and the whole population falling under Chief Tsovani and Headman Chitsa was treated.

It was decided to use four different treatment schedules, three of the combination drug and one using pyrimethamine by itself. The combination drug on test was administered either as tablets each containing 12,5 mg pyrimethamine and 100 mg dapsone, or as a syrup containing 0,6 mg ml of pyrimethamine and 5 mg ml of dapsone, and the pyrimethamine was administered either as 25 mg tablets or as a syrup containing 6,25 mg ml. The area was divided into four zones, one for each dosage schedule and each identified by a colour. These zones were treated as follows:

Pink Zone: The test drug was administered weekly at a dosage of one tablet for adults and children over ten years of age, half tablet or 10 ml syrup for children aged between two and ten years, and 5 ml for infants under the age of two years.

Blue Zone: The test drug was again administered weekly, but the dose for children was changed, those aged five to ten years receiving one half tablet or 10 ml syrup; those aged two to four years receiving 5 ml of the syrup and infants under two years of age receiving only 2,5 ml.

Green Zone: The test drug was used at the same dosage as in the pink zone, but the people received the drug each fortnight, not each week.

Yellow Zone: Pyrimethamine, by itself, was issued weekly at a dosage of two tablets for any person over ten years of age, one tablet for children five to ten years old, 10 ml syrup for children aged two to four years, and 5 ml syrup for infants below the age of two years.

It was not possible, with the resources available, to include the adjoining area, under Chief Gudo, in the trial area, and this area was thus used as a control. In this area which was close to the rural hospital, supplies of chloroquine were made readily available without charge, to treat any overt malaria cases.

Five local, suitable persons were employed from October, 1973, to distribute the drugs to the people. A zone was allotted to each of four of them; the fifth was stationed at the rural hospital and ordered to take blood films from anybody from within the trial area or from Chief Gudo's area, who reported with fever or symptoms suggestive of malaria. He also acted as reserve in case one of the other four should be unable to carry out his duties. These five young people were inevitably dubbed "pill-pushers."

A register was drawn up for each area showing the names of all persons resident, and quantity of drug to be administered to each person. If any individual was absent at the time of a visit, or failed to receive his dose, this absence was recorded in the register.

Surveys in Sangwe during the previous dry season had shown a parasite rate of 11,2 per cent. with a gametocyte rate of 5,6 per cent. indicating the probability of a high transmission rate during summer. With the population grouped in small settlements, and in view of this high transmission rate, it was decided to estimate the prevalence of malaria before, during and after the trial by using the staged cluster sampling method prepared for malariometric surveys in Rhodesia by Lobel (personal communication), based on his experience in malaria epidemiology in South America.

The object is to examine a number of people randomly chosen from each cluster which falls within the sampling scheme, with the cluster in this instance being the village. In this way it is possible to obtain a better cross-sectional sample of the population than with the 10 per cent. sampling often recommended for malaria surveys. In order to obtain sufficient numbers, 30 persons were to be examined from each cluster and among this number were to be representatives of each age group.

From an initial estimate of the population, a sampling interval (SI) was obtained where

$$SI = \frac{\text{Total population}}{\text{No. of clusters (villages)}} = \frac{9\,000}{70} = 130 \text{ approx.}$$

Each sample of people to be examined was chosen from the cluster or village whose population, when added to the cumulative total population for the area fell after the sampling interval of 130. In this specific trial, a random number between 1 and 130 was selected and added to the SI of 130. In this case it gave a number greater than 171 so villages A_1 and A_2 were eliminated as the total number of residents of these two villages did not reach this figure (refer Table II). Thus one sample was taken from the next village A_3 and two samples from the large village A_4. Thus after each 130 people, 30 were examined, giving a total sample of over 18 per cent. of the population.

On reaching the sampling area the number of people present was determined, and if this number was greater than the cluster, adults were left to the end. Although children outnumbered adults, they were divided into four age groups; consequently the adult group was always the largest.

Sampling was carried out on three occasions; October, 1973 (pre-treatment), January, 1974 (mid-season), and May, 1974 (post treatment).

In addition to attempting to assess the value of the prophylaxis by malariometric surveys in the population, further assessment was also possible by monitoring for active cases of malaria. The "pill pushers" were issued with equipment for taking blood slides and they were requested to take thick blood films from any person showing any clinical illness. Similarly, any person attending the rural hospital who showed any sign or symptom that could be attributed to malaria also had a blood film taken. Any case proven to be malaria was investigated and cross-checked with the register to determine his dosage history, if any.

Field difficulties were encountered in the trial. Prior to starting the distribution of drug, meetings were held with the chiefs, headmen and kraal heads. At these meetings convened by the District Commissioner, all details of the trial were discussed in an endeavour to overcome the fears and superstitions of the tribespeople who are largely unsophisticated peasant farmers. Initially, they were suspicious and truculent with superstitious fears of having blood films taken. However, as the trial progressed, their attitudes changed and excellent co-operation was achieved before the worst phase of malaria transmission started in December, 1973. In fact, a number of the inhabitants initially refused treatment on religious or on other grounds, but as the season progressed, more and more of these people requested to be included in the trial when they realised that the treated people were protected, whereas they themselves were contracting malaria.

TABLE II.

RESULTS OF MALARIOMETRIC BLOOD-FILM SURVEYS IN SANGWE TRIBAL TRUST LAND.

	Examined	*Positive*	*Parasite Rate %*
Pre-treatment.			
October, 1973.			
Pink Zone	228	10	4
Blue Zone	347	13	3
Green Zone	327	53	16
Yellow Zone	350	23	6
Mid-Season.			
Feb./March, 1974.			
Pink Zone	146	5	3
Blue Zone	91	2	2
Green Zone	336	35	10
Yellow Zone	166	3	2
Chief Gudo	331	174	52
Post-treatment.			
May, 1974.			
Pink Zone	447	6	1
Blue Zone	401	13	3
Green Zone	422	43	10
Yellow Zone	73	5	7

Note: Refer to Table I for dosage. No drugs administered in Chief Gudo's area.

Other difficulties encountered were the distance of the trial area from the administrative centre in Salisbury, and the abnormally heavy rainy season. In the extremely wet conditions travel, even by bicycle, was difficult and the "pill pushers" were often obliged to do their rounds on foot. Under the circumstances their morale remained remarkably high.

Results

The results of the blood film surveys are shown in Table II. They may be summarised by saying that, despite the known heavy transmission which occurred during the season, the prevalence of malaria in the treated area remained low, whereas the prevalence in the adjacent untreated area was 52 per cent. at the mid-season survey, and there were a number of cases of active malaria proven from this untreated area. Unfortunately, it was not possible to give pre-treatment and end-of-season survey results for this untreated area, but it is reasonable to assume that the prevalence of malaria at the start of the season was no higher in this area than it was in the treated zones. The individuals from whom positive blood films were taken in the end-of-season survey were checked against the registers of treatment for each of the test drug zones. In the Pink Zone (test drug, weekly, higher paediatric dose) there were six such positive blood films. Four of these showed *Plasmodium falciparum* parasites with two having rings only, one having rings and gametocytes, and one having only gametocytes. Of the other two, one had *P. malariae* and one *P. ovale* parasites. In the Blue Zone (test drug, weekly, lower paediatric dose) there were 13 positive blood films. However, of these there were ten people who had missed more than one dose of the drug, and only one had taken all doses. All these people showed *P. falciparum* parasites. In the Green Zone (test drug, fortnightly) 43 positives were found in 422 people examined. Of these 43 positives, two were *P. ovale* and one was *P. malariae*. The remaining 40 were *P. falciparum*, and of these 15 showed gametocytes, and the remaining 25 had ring forms only. Four of the 43 had no record of treatment, i.e., they were not listed in the register, and a further 11 had missed one or more doses. No detailed investigation was made of the positives from the Yellow Zone in which pyrimethamine alone was used.

Further assessment of efficacy was available from the investigation of the histories of cases of overt malaria reported to the hospital or to the "pill pushers" on their rounds. Between the start of the trial in October, 1973, and December, 1973, 29 active fever cases were detected. Of these 28 were from the untreated Gudo's area, and only one from the treated area. This one case could not be traced. In January, 1974, communications with Gudo's area were cut by the flooded Mkwasine River, and thus admissions to the hospital from this untreated area ceased. However, in the first four months of the year, there were 30 fever cases reported from the trial area. Blood films were taken from all these, but only 16 were proven to be malaria. Of these, three could not be traced, and they must be presumed to be newcomers to the area, and twelve were proven to be residents who had returned to the tribal area after working on the adjacent irrigation estates. Thus there were only two cases which could be considered to be "breakthroughs". One of these had missed several doses of drug and there was thus only one case where the person had apparently been on regular prophylaxis. The numbers treated in the four zones were:—

Pink Zone	1 290
Blue Zone	1 528
Green Zone	1 280
Yellow Zone	1 172
Total	5 270 treated

The estimated population of Chief Gudo's area was 3 500. Since there were 20 cases from Gudo's area (up to December) and possibly two from the treated zones, it would appear that the probability of contracting malaria in the untreated area was over 20 times higher than in the treated zones.

Discussion

It is most important when considering the results of this trial, to remember that it was conducted in an area of seasonal but intense malaria transmission, and in addition, during a very wet season in which malaria transmission was abnormally severe.

The results of the blood film surveys give limited information. The relatively low prevalence of parasitaemia during and after the trial in all four of the treated zones, when compared with the high prevalence in the untreated Gudo's area, is clear evidence that the drugs had marked prophylactic effects. In the Green Zone, which had a fortnightly dosage schedule, the prevalence of malaria remained at a higher

level than in the other treated zones. Since the pre-treatment prevalence was also higher in the green zone, no definite conclusion can be drawn, but there is some indication that the fortnightly dosing was less efficient than weekly dosing. There was also an apparently high prevalence of persisting gametocytaemia in people who received the combination drug at fortnightly intervals.

It could be argued that because almost all people living in the four treatment zones received treatment, transmission would be inhibited and the results would be biased in favour of the drug treatment. However, the reports and follow-up investigations of malaria cases within the treated areas demonstrated that if the drugs were not taken the chances of contracting malaria were very high, whereas only one person, who was recorded as taking all drug doses, contracted the disease. It is presumed that the people from neighbouring untreated areas, constantly visiting in the treated area to attend beer drinks or other celebrations, provided sufficient parasite reservoir to maintain a high transmission.

The "pill pushers" were instructed to maintain a constant vigilance for side-effects of the drugs, or for reports of such side-effects. In addition, technicians from Salisbury visited the area frequently, and they also searched for any reports of side-effects. There was no suggestion that any of the 5 000 people receiving prophylactic drug suffered any side-effects whatever. It is thus possible not only to conclude that the drug is safe, but, with the results available, also to conclude that an efficient and safe paediatric dosage has been demonstrated. It is therefore, our recommendation that the dosage schedule for this combination of pyrimethamine and dapsone should be:—

Adults and children ovr 10 years old	— 1 tablet each week
Children 5-10 years	— ½ tablet each week
Children 6 months-5 years	— 5 mls syrup
Infants under 6 months	— 2,5 mls syrup

It may be coincidental that, during the trials, an outbreak of cholera occurred in surrounding areas including Chief Gudo's area. No persons treated with the combination drug contracted cholera. However, there were insufficient cases for statistical evaluation.

Finally, it may be mentioned that the goodwill that developed in the populace was so great that many of the suspicions and the distrust of authority, other than the tribal authority, were overcome. The benefits to be derived from this will extend much further than the protection against malaria.

Summary

A proprietary combination of pyrimethamine and dapsone, was used in the Sangwe Tribal Trust Land in the Rhodesian Lowveld, between October, 1973, and May, 1974, in an attempt to control the incidence of malaria.

The season proved to be an exceptionally wet one and conditions for malaria transmissions were therefore unusually favourable. In spite of this, with good organisation it was possible to achieve a satisfactory level of control of transmission.

After some initial resistance the local population readily accepted the drug.

A satisfactory paediatric dosage regimen was established.

Some degree of control was achieved by issuing Deltaprim fortnightly but a weekly issue appeared preferable.

When the test combination was given fortnightly there appeared to be a higher incidence of gametocytaemia.

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