A Field Trial of Pyrimethamine Combined with Dapsone in the Chemoprophylaxis of Malaria

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The use of pyrimethamine in combination with either sulphonamides or sulphones is now an accepted procedure in the treatment of malaria, particularly when dealing with *Plasmodium falciparum* infections resistant to chloroquine. It has not, so far, been used on a large scale in non-immune subjects for chemoprophylaxis, although resistance to pyrimethamine alone is widespread, but Lucas, *et al.* (1969) did demonstrate its effectiveness in suppressing parasitaemia in immune subjects.

An opportunity for a field trial occurred in the 1970-1971 malaria transmission season when 2 500 non-immune Africans from the Chilimanzi District of Rhodesia settled in Gokwe District.

Gokwe District, in the north-east of Rhodesia, is about 20 000 square Km in extent, and more than half is between 700 and 1 000 m. above sea level. Malaria transmission occurs in the lower lying parts of the district, and is known even on

the Charama and Mafungabusi plateaus more than 1 200 m. above sea level, transmission being highest during the wet season from December to April. The malaria parasite rate among the indigenous population is between 20 per cent and 30 per cent. Until 1960, it was sparsely populated, but in the past decade, increasing numbers of Africans living on the central plateau, who have never previously been exposed to malaria, have settled in the district, attracted by the fertile, virgin land.

In September, 1970, a headman and 2 500 followers moved from Chilimanzi District to a part of Gokwe District, situated approximately 18°S, 23°30'E. The soil here is Kalahari sand and there is no permanent surface water. To remedy this a large borehole was sunk, which fed six tanks three Km apart, each holding 30 000 litres of water. These tanks supply the needs of two-thirds of the population and the remaining third draw their water supply from three small boreholes.

Since all homes are situated within a reasonable distance of their water supply it was possible to divide the area into three approximately equal sections as follows:—

Section I — those people drawing their water from tanks 4, 5 and 6;
Section II — those drawing their water from tanks 1, 2 and 3;
Section III — those drawing their water from the smaller boreholes.

Distribution of Drugs

Three local Africans were employed to distribute the drugs, each taking one of the above sections. Each was responsible for covering his area once a week and administering tablets to every man, woman and child. To facilitate their task, the dose was fixed at one tablet per person per week, irrespective of age, each tablet consisting of:—

in Section I — 12,5 Pyrimethamine plus 100 mg Dapsone ("Maloprim")
in Section II — 25 mg Pyrimethamine
in Section III — 500 mg Calcium Gluconate (placebo).

Assessment

Prior to the start of the trial in January, 1971, 794 blood films were examined, representing a 30 per cent. sample of the population at risk. These people had no previous exposure to malaria and it was very early in the transmission season. It was therefore expected that all these blood films would be negative for malaria parasites, and such proved to be the case. A further 672 blood films were taken in February, and another 290 in April, at the end of the transmission season. In March, which is usually the peak month for malaria transmission, no routine blood films were taken; instead, each doser was instructed to look out for sick patients on his rounds and to take blood films from them.

Although the trial as such was restricted to three sections only, blood films were also taken from two other areas for comparison and these were added to the original three to make Sections IV and V.

Section IV is inhabited by indigenous Africans. It is separated from Section I by 8 Km. of supposedly uninhabited country, but this is no barrier. In April 1971, 35 children from Section IV were found to be attending school in Section I. Section IV was sprayed with BHC during February, but received no chemoprophylactic drugs.

Section V: this was settled at the same time as Sections I to III by about 200 Africans from Bikita District, an area of low malaria endemicity. They could not, therefore, be regarded as free from previous exposure to malaria. It was about 20 Km from Section III and no anti-malaria spraying was done, but the three dosers all joined forces and made a weekly journey there to administer pyrimethamine tablets. However, it was inevitable that the issuing of tablets here would not be very well controlled and the administration of drugs irregular when compared with Sections I, II and III.

Progress

Heavy rain in December, 1970, and early January, 1971, followed by spells of fine weather, made the first four months of 1971 a particularly favourable period for malaria transmission. During March, 521 slide positive cases were treated at Gokwe District Hospital, 80 Km away, and at the Baptist Mission Clinic 35 Km away. 200 cases were diagnosed on clinical grounds as suffering from malaria.

In view of this, calcium gluconate as a placebo was stopped in Section III at the end of February, and the inhabitants received 25 mg pyrimethamine weekly during March and April.

Results

These are shown in Table 1.

1 196 blood slides were taken and examined during the course of the malaria transmission

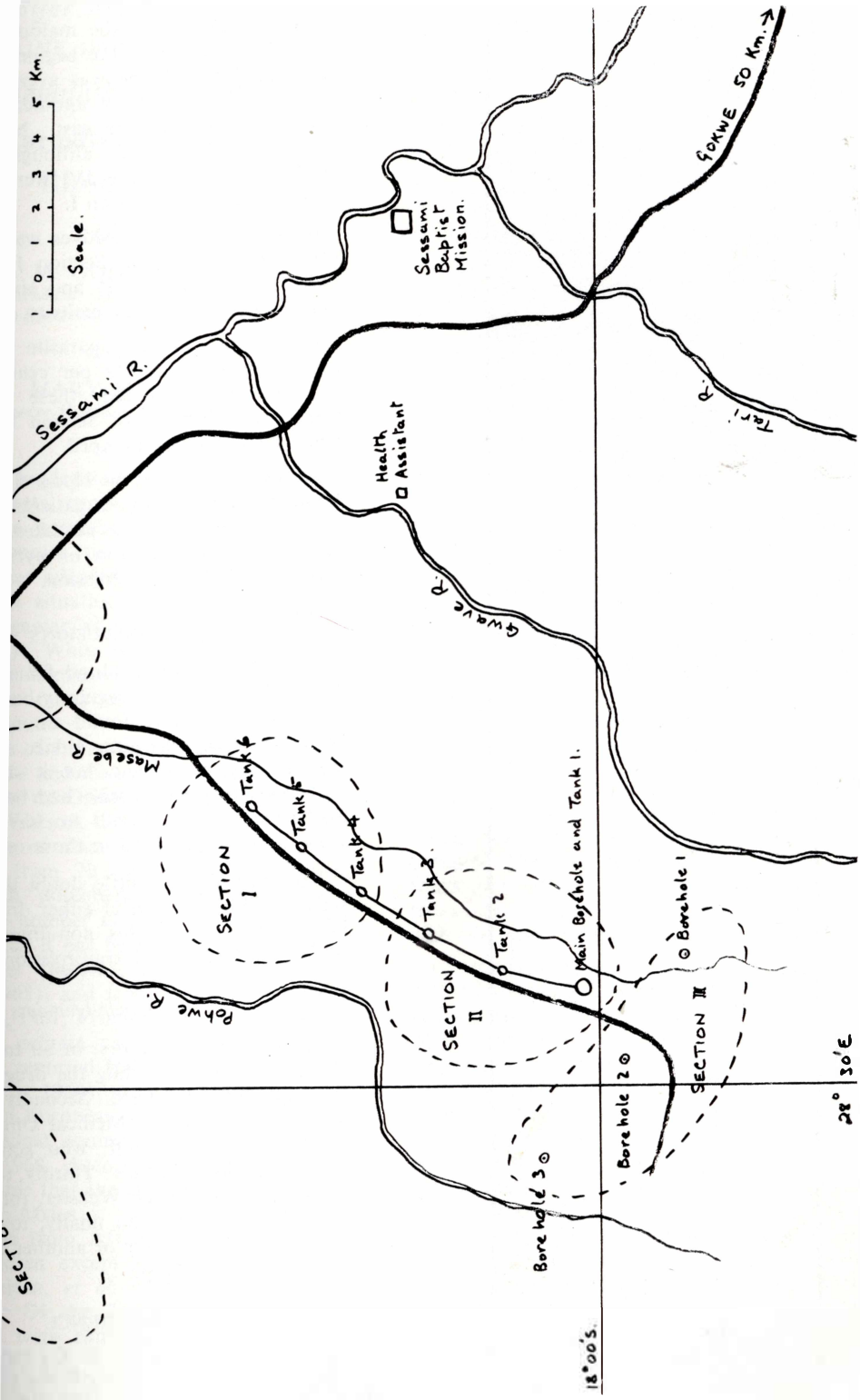
Scale.
1 0 1 2 3 4 5 Km.
Sessami R.
Sessami Baptist Mission.
GOKWE 50 Km.
Tarri R.
Health Assistant
Gwavi R.
Masebe R.
Tank 6
Tank 5
Tank 4
Tank 3
Tank 2
Main Borehole and Tank 1.
Borehole 1
SECTION I
SECTION II
SECTION III
Powe R.
Borehole 2
Borehole 3
18°00'S.
28° 30'E

Table 1

Results of Trial

AREA	TREATMENT GIVEN	JANUARY, 1971			FEBRUARY, 1971			MARCH, 1971			APRIL, 1971		
		Examined	+ve	Gameto-cytes	Examined	+ve	Gameto-cytes	Examined	+ve	Gameto-cytes	Examined	+ve	Gameto-cytes
I	Maloprim	124	Nil	Nil	346	4	1	20	Nil	Nil	105	Nil	Nil
II	Pyrimethamine	327	Nil	Nil	68	Nil	Nil	40	4	Nil	165	1	1
III	Calcium Gluconate January-February	343	Nil	Nil	258	1	Nil	20	6	2	20	Nil	Nil
	Pyrimethamine March-April												
IV	Nil (Indigenous Africans)	—	—	—	85	27	4	—	—	—	35	4	3
V	Pyrimethamine (Irregularly)	—	—	—	—	—	—	34	30	15	—	—	—

N.B. The only parasite found in this trial was *Plasmodium fuleiparum*.

season. In Section I, the maloprim-treated area, four of 346 taken at the beginning of February were positive, but one was a gametocyte carrier who actually came from another part of Gokwe District 60 Km to the east. No further parasitaemias were found, although four infected children from Section IV were found to be attending school in Section I.

In Section II five positives were found out of 273 examined; and in Section III seven out of 298: four in Section II and six in Section III were from clinically ill patients during March.

In Section IV the parasite rate in school children was 27/85 (32 per cent.) in February, and, as already noted, these children mixed freely with those from Section I; 4/35 (11 per cent.) being positive in April.

In Section V only 34 blood films were taken. These were all from ill patients during March, and 30 showed malaria parasites, indicating that the irregular distribution of pyrimethamine had had little effect on transmission.

Conclusions

Only three positive blood films were found in 471 subjects who had regularly been taking Maloprim, while 11 were found among 313 who had been on pyrimethamine alone. This difference may not be significant, but it should be noted that ten sick patients who had been taking pyrimethamine were found to have parasitaemia while none were found in those on Maloprim.

However, there is little doubt that the careful, regular administration of either drug did much to prevent malaria in this non-immune population during the early 1971 transmission season.

Acknowledgements

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REFERENCE

Lucas, A. C., Hendrickse, R. G., Okubadejo, O. A., Richards, W. H. G., Neal, R. A., and Kofie, R. A. (1969). *Trans. Roy. Soc. Trop. Med. Hyg.*, **63** : 216.