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AFTERMATH OF A FIELD TRIAL IN SELF-ADMINISTERED
PYRIMETHAMINE IN A GHANAIAN COMMUNITY:
THE APPEARANCE OF P. FALCIPARUM RESISTANCE¹

by

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In an attempt to secure maximum benefit in the mass administration of the antimalarial drugs available, variations in single and combined drug dosage and technique of administration are being tested in the field. A preliminary account is set out in this report of the results of one such trial made in Ghana.

METHODS

At the malaria eradication pilot project in the Volta Region of Ghana, two small villages were placed on a weekly pyrimethamine regimen at a dosage of 12.5 mg for children under three years and 25 mg for all other age-groups. The trial was initiated by Dr I. H. Vincke, World Health Organization Malariologist and Team Leader to the project, principally as a field trial in self-administration of the drug. Assistance and co-operation of the Mass Education Division of the Department of Social Welfare and Community Development was obtained in the preliminary nominal population census, propaganda and education campaign, and in the earlier tablet distributions.

¹ This preliminary report is based on observations made jointly by the Malaria Unit, Ministry of Health, and the UNICEF/WHO-assisted pilot malaria project in the Volta Region of Ghana, led by Dr I. H. Vincke, and more recently by Dr H. van der Kaay.

Village I

At Akrofu Hewiofwe, population 721, pyrimethamine tablets were administered individually on 3 November 1958 (Week 0) while the pre-treatment malarionetric survey was in progress. After three similar weekly treatments one responsible member of each household was required, on the appointed day, to collect at the distribution centre the requisite number of tablets for the family in accordance with the ages listed on the household card. After a further three weeks of such direct management by the malaria project staff, tablet distribution was handed over to three teams of two volunteers (recorder and issuer) provided for the purpose by the three clans constituting the internal social organization of the village. The field trial continued on this wholly voluntary basis until Week 49 (October 1959) with only periodic supervisory visits from official personnel.

By Week 9 of the trial, sporozoite-positive A. gambiae were still being encountered at Akrofu Hewiofwe. It was considered that this may have been due at least in part to infiltration from a neighbouring untreated village one mile away on a third-class motor road.

Village II

This second village, Akrofu Agove, with a population of 356, was therefore placed on the same pyrimethamine regimen on 14 January 1959. Arrangements for voluntary tablet distribution were made, similar to those at Village I.

GENERAL ASSESSMENT OF RESULTS

At both villages, the pre-treatment malaria picture approximated that of holoendemicity, with P. falciparum predominating, and P. malariae not uncommon.

Village I

By Week 4, the parasite rate among the age-group 0-12 years at Village I had been reduced from 71.5% on 270 examinations to 6.6% on a sample of 151, and by Week 16 to 5.1%, with 10 positives among 196 examined. A check survey at Week 22 (3 April 1959) showed a parasite rate of 3.2% on a sample of 219 children aged 0-12 years (Table 1). Of the seven positives, however, only three were permanent residents, and after two consecutive directly supervised weekly tablet administrations, they were re-examined and found free from asexual parasites.

Village II

Here, the pre-administration (Week 0) parasite rate among 96 children aged 0-12 years was 59.3%, and by Week 6 this had fallen to 2.0%. Despite this reduction in the parasite reservoir, however, sporozoite positive A. gambiae were still being encountered at Village I eight weeks later in April 1959.

A re-assessment survey of both villages was made on 13-14 July 1959, i.e. on Weeks 37 and 26 for Villages I and II respectively, and the blood findings are set out in Table 2.

At Village I, blood films with malaria were encountered in all age-groups, with a total of 68 positives among 362 examinations and a crude parasite rate of 18.8%. Of the 68 positives, 12 showed P. falciparum crescents only; 16 had P. malariae (singly or mixed), and one showed P. ovale. The remaining 39 had P. falciparum rings.

Results at Village II were comparable, a crude parasite rate of 21.4 on a sample of 145 being contributed to by all the younger age-groups, while adults were all negative.

For purposes of comparison, parasite rates recorded among the age-group 0-12 years in the various check surveys are shown in Table 1 for the two villages. It was observed that the level of malarial infection for these ages was identical by Weeks 37 and 26 at Villages I and II respectively.

INVESTIGATION OF P. FALCIPARUM RESISTANCE

The above results did not become available until 14 days after the 13-14 July survey, but as many as possible of the persons then showing positive blood films were identified on 27 July. A thick film was taken (Day 0) and the appropriate dose of pyrimethamine was administered under junior staff supervision. On 30 July (Day 3) follow-up blood film examinations were made. Six schoolchildren were still positive for P. falciparum trophozoites (Table 3). One among them also showed scanty degenerating presegmenters of P. malariae, but no significance was attached to this. On Day 7 the P. falciparum infection was still evident in four of these children, but because the treatment on Day 0 had not been supervised originally by a senior officer, these four were re-treated on Day 7, again with the routine dose of pyrimethamine. Although the infections survived Day 7+3 in three cases, all P. falciparum rings were cleared by Day 7+6, i.e. by the sixth day after the second supervised dose of pyrimethamine.

In the course of the above investigations some evidence of irregular ingestion of the pyrimethamine tablets was uncovered, and this was made known to the village leaders, but no further action was taken at that stage. Twelve weeks later (Weeks 49 and 38 for Villages I and II respectively), on 5-6 October 1959 the situation was re-assessed. All available personnel were deployed on examination of the blood films so that initial parasitological results could be available within three days. Crude parasite rates of 49% were observed at both villages (Table 4), while for the age-group 0-12 years the rates were 62.1 and 57.8% respectively, comprising all three species of malaria parasites normally encountered in Ghana. All reported blood film results were based on examinations carried out by the senior staff.

At Village II attempts were made immediately to find the positives of all ages, collect new blood films (Day 0) and treat them under supervision with the standard dose of pyrimethamine. Follow-up by blood film examinations was made on Days 3 and 6 after treatment. At Village I the same procedure was followed three days later among schoolchildren only.

The results of these investigations are summarized in Table 5, where failure of P. falciparum trophozoite clearance by Day 6 is shown for 52 individuals. In view of results obtained by the Malaria Unit in other observations on P. falciparum clearance times in Ghana after single 25 mg doses of pyrimethamine, the findings set out in Table 5 are presented as evidence of P. falciparum resistance to that drug in the two villages under discussion.

CROSS-RESISTANCE IN P. FALCIPARUM TO LAPUDRINE¹

Recent trials have shown that in Ghanaian schoolchildren asexual forms of P. falciparum are cleared by Day 2 after a single 20 mg dose of Lapudrine (Charles, 1959). Robertson (1957) has reported cross-resistance to Lapudrine in the early exo-erythrocytic forms of a proguanil-resistant Malayan strain of P. falciparum. Because of this, the following preliminary results obtained with Lapudrine at Akrofu Hewiofwe are of interest.

From amongst the children infected with pyrimethamine-resistant P. falciparum at Village I, nine were chosen at random eight days after a supervised 25 mg dose of pyrimethamine. New blood films were taken (Day 0) and they were each given 20 mg of Lapudrine orally. The results of their follow-up examinations are shown in Table 6. All but one were positive for P. falciparum rings on Day 3, though generally at very much reduced densities, and on Day 6, six were still showing the presence of asexual parasites.

¹ Lapudrine N¹-3:4 - dichlorophenyl-N⁵-isopropyl diguanide - is a derivative of proguanil found to be highly active against P. gallinaceum and P. relictum. It was investigated by D. G. Davey in 1946 (Ann. Trop. med. Parasit. 40, 52 and 453) and used in a trial in East Africa by Robertson (see under references) who reported that, weight for weight, it is more persistent and more active than proguanil. (Editor's remarks)

COMMENTARY

In view of the findings reported here, the distribution of pyrimethamine at Akrofu Hewiofwe and Akrofu Agove was discontinued in October 1959, and observations on the phenomenon of pyrimethamine resistance in P. falciparum are being continued at those villages.

It is already clear that the popularity of the malaria preventive trial in these two villages had not waned. Householders continued conscientiously to collect their weekly quota of drug to the last, but there is conclusive evidence that they have not all ingested their tablets regularly. Not only P. falciparum, but P. malariae and P. ovale were also present. This irregularity in self-administration of the tablets might have contributed to the emergence of resistance.

The results shown in Table 1 suggest that at least in Village I self-administration of the tablets was faithfully practised up to Week 22. Even after such an interval, however, and before the appearance of P. falciparum resistance, gland-infected anopheline vectors were still being collected in the village. This appears to cast some doubt on the value of 12-week courses in similar mass drug programmes under tropical African conditions.

SUMMARY

In two villages in the Volta Region of Ghana, a trial in mass use of weekly self-administered pyrimethamine failed to maintain the earlier encouraging results recorded.

Resistance of P. falciparum to pyrimethamine was apparent after the thirty-seventh and twenty-sixth weeks at the two villages respectively. This, together with cross-resistance to Lapudrine, was confirmed 12 weeks later.

REFERENCES

- Charles, L. J. (1959) Drugs and combinations of drugs in malaria, AFRO/Mal/4/12, Mimeographed document.
- Robertson, G. I. (1957) Experiments with antimalarials in man. III. Experiments with Compound 5943, Trans. roy. Soc. trop. Med. Hyg. 51, 457.

TABLE 1. SHOWING RESULTS OF PERIODIC PARASITOLOGICAL SURVEYS ON AGE-GROUP 0-12 YEARS AT VILLAGES I AND II BEFORE (WEEK 0) AND AFTER INITIATION OF A SELF-ADMINISTERED WEEKLY PYRIMETHAMINE FIELD TRIAL

	Village I (721 pop.)						Village II (356 pop.)			
	3 November 1958						14 January 1959			
	Wk 0	Wk 4	Wk 16	Wk 22	Wk 37	Wk 49	Wk 0	Wk 6	Wk 26	Wk 38
No. exmd	270	151	196	219	196	203	96	50	105	95
No. pos.	193	10	10	7	55	126	57	1	30	55
Parasite rate %	71.4	6.6	5.1	3.2	28.1	62.1	59.3	2.0	28.4	57.8

TABLE 2. SHOWING PARASITOLOGICAL FINDINGS ON WEEKS 37 AND 26 RESPECTIVELY AFTER WEEKLY SELF-ADMINISTERED PYRIMETHAMINE AT TWO VILLAGES IN GHANA

Age (years)	Village I: Week 37			Village II: Week 26		
	Number examined	Positive		Number examined	Positive	
		No.	%		No.	%
0 < 2	29	5	17	15	4	27
2 < 5	35	10	29	26	7	27
5 < 10	99	28	28	54	17	31
10 < 15	70	16	23	11	2	18
15 < 20	18	3	17	4	1	25
20 +	111	6	5	35	-	-
Total	362	68	19	145	31	21

TABLE 3. SHOWING RESULTS OF PARASITOLOGICAL FOLLOW-UP BEFORE AND AFTER A SUPERVISED DOSE OF PYRIMETHAMINE IN 63 VILLAGERS POSITIVE FOR P. FALCIPARUM TROPHOZOITES ON 13/14 JULY 1959

Village	Day 0 27 July 1959		Day 3 30 July 1959		Day 7 6 August 1959	
	Exam.	Pos.	Exam.	Pos.	Exam.	Pos.
Village I	45	26	40	5	5	3
Village II	18	6	17	1	1	1
Total	63	32	57	6	6	4

TABLE 4. SHOWING PARASITOLOGICAL FINDINGS ON WEEKS 49 AND 38 RESPECTIVELY AFTER WEEKLY SELF-ADMINISTERED PYRIMETHAMINE AT TWO VILLAGES IN GHANA

Age (years)	Village I: Wk 49			Village II: Wk 38		
	Number examined	Positive		Number examined	Positive	
		No.	%		No.	%
0 < 2	24	15	62	9	5	55
2 < 5	32	24	75	27	15	56
5 < 10	96	57	59	46	28	60
10 < 15	47	22	47	14	7	50
15 < 20	9	5	55	4	3	75
20 +	73	15	20	35	8	23
Total	281	138	49	135	66	49

TABLE 5. SHOWING RESULTS OF A SUPERVISED TRIAL OF PYRIMETHAMINE
P. FALCIPARUM TROPHOZOITES ON WEEKS 49 AND 38 RESPECTIVELY AFTER
WEEKLY SELF-ADMINISTERED PYRIMETHAMINE AT TWO VILLAGES IN GHANA

Age (Years)	Day after treatment with pyrimethamine*		
	Day 0	Day 3	Day 6
	No. positives** treated	Pos./Exmd	Pos./Exmd
0 < 2	4	4/4	3/4
2 < 5	7	5/7	6/7
5 < 10	59	38/50	37/43
10 < 15	13	6/12	6/12
15 < 20	1	1/1	-
20 +	2	1/2	0/2
Total	86	55/76	52/68
Percent. positive	100.0	72.4	76.5

* 0-3 years, 12.5 mg; over 3 years, 25 mg

** Selected for asexual P. falciparum infection

TABLE 6. SHOWING FAILURE OF A SUPERVISED 20 MG DOSE OF LAPUDRINE TO CLEAR P. FALCIPARUM TROPHOZOITES RESISTANT TO PYRIMETHAMINE AT AKROFU HEWIOFWE, VOLTA REGION, GHANA

No.	Age (years)	Parasite Density (per mm ³) before and after supervised treatment with Lapudrine					
		Day 0*		Day 3		Day 6	
1	6	F 480	Fg 20	F 20	Fg 20	F 20	Fg 20
2	6	F 560	Fg 20	F 500	Fg 20	F 20	Fg 20
3	8	F 480		F 20		F 20	Fg 20
4	8	F 400		Neg.		Nil	Fg 20
5	8	F 160		F 40	Fg 20	F 20	Fg 20
6	8	F 160		F 20		Nil	Fg 20
7	9	F 1200		F 20		F 20	
8	10	F 160		F 120		Not examined	
9	10	F 2400		F 400		F 800	
PDI		3.55		1.37		1.50	

PDI Parasite density index

* All these children had received 25 mg pyrimethamine 7 days previously

F Falciparum trophozoites

Fg Falciparum gametocytes