PREVENTION OF MALARIA TRANSMISSION WITH SINGLE DOSE OF PYRIMETHAMINE (DARAPRIM)

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Introduction

The success of residual insecticides in the prevention of malaria has been convincingly demonstrated in many parts of the world. Under certain conditions, however, this method has not given the desired results, either because the outdoor resting habits of the anopheline carrier enabled it to avoid contact with the lethal film, *e.g.*, *A. sergenti* in Jordan,[1] or because facilities for undertaking organised and widespread sprayings were too meagre to permit an adequate coverage of an intensely malarious region, *e.g.*, Equatorial Africa. Even in countries where malaria has been almost completely eradicated, the disease tends, for various reasons, to persist in small foci despite intensive sprayings. Lastly, because of the occurrence of resistance in anophelines to insecticides it is now considered necessary to eradicate malaria completely and speedily from a community while insecticides are still effective against the local carriers.

To meet these and allied situations, it is clearly desirable to develop an anti-malaria measure which would supplement residual insecticides or if necessary replace them. A field trial was accordingly planned to test whether the prolonged sporontocidal property of pyrimethamine could be utilized to serve this purpose.

Basic Consideration

To be successful, chemoprophylaxis requires a highly efficient organization for the repeated administration of drug. In this respect the situation has eased to some extent latterly as a number of the newer anti-malarials need be given only once a week or once a fortnight. Under rural conditions, however, the regularity of drug administration cannot be assured even at such intervals and, the scope of collective drug prophylaxis has, for this reason, remained considerably restricted. The situation, however, appeared more hopeful when one of us (M.K.A.) received a communication from Dr. G.R. Coatney[2] to the effect that "on a calculated basis following a single 25 mg. dose of pyrimethamine there would still be a suppressive amount (*i.e.*, 0.8 mg. of the drug) in the body after 52 days." The inference drawn from this observation was that if the amount remaining in the body proved effective against sporogenic cycle then a single dose of pyrimethamine would function as a "residual sporontocide" for at least 52 days. This time period, if confirmed in the field, would not only be much longer than that anticipated by Roberts[3] but would be sufficient to make the successful application of chemoprophylaxis in rural areas a feasible proposition.

Description of the Trial

Since the main object of the trial was to trace the effect of pyrimethamine on malaria transmission, it was felt that this purpose would be best served by making repeated observations on a small stable community. The trial, which lasted from July 1st to mid-October, was therefore, organized on a population of 1,289 in a group of four villages in the valley between Haripur and Havelian in the Hazara district of West Pakistan. Unlike the compact villages usual in this part of the country, the test villages consisted of a series of hamlets strung out in a row on the bank of a small river. A single dose of Daraprim (pyrimethamine) was given to the inhabitants of three of the villages namely Chamba, Dhaia and Dobandi, located in that order from north-east to south-west over a distance of about 3 miles, while the fourth village, called Nika Pa, which was the southern-most in the experimental area, received no treatment and was kept as control. Not only was spraying disallowed in these villages during the test season, but one of the factor that influenced their selection was that they had not been sprayed in previous years. The latter consideration greatly restricted our field of choice as spraying operations had been fairly widespread in this area. Another factor kept in mind was to select a more or less isolated block of villages so that the results would not be vitiated by the incursion of infected mosquitoes from the adjoining untreated areas. In this respect Chamba and Dhaia were ideally placed but Dobandi was not as the distance between the latter and the untreated village Nika Pa was less than ½ mile.

The drug was given in accordance with the dosage scale of 25 mg. to adults, 12.5 mg. to children from 7 to 12 years of age and 6.25 mg. to children aged 6 years and below. Particulars of every individual in the test and control villages were noted in separate registers and the dosage given to each person was recorded at the time

TABLE I.—POPULATION AND TREATMENT FIGURES.

Name of Village	Population	Number received treatment	Number who avoided treatment	Percent missed treatment
TEST				
Chamba	601	592	9	1·5
Dhaia	274	262	12	4·4
Dobandi	186	160	26	14.0
CONTROL				
Nika Pa	228	Nil.	—	—

the drug was administered. This procedure ensured not only a reliable record of pyrimethamine administration, but also an up-to-date census of the population under test.

Every effort was made to administer the drug to the maximum number of persons. In this respect we were fairly successful, as will be seen from Table I which shows that the percentage of persons who avoided treatment was reasonably low except in Dobandi.

Assessment

To assess the effects of pyrimethamine, malariometric data and figures for malaria incidence were collected simultaneously from all the villages under observation.

Spleen rates were taken at the beginning and again at the end of the malaria season in mid-July and mid-October, respectively, but examinations for parasites were conducted every month from July to October. Special efforts were made to examine the maximum number of infants, as it was felt that the occurrence or otherwise of malaria transmission could be best deduced from infection in this group, there being no facilities for mosquito dissection.

As regards malaria cases, two methods were used for obtaining the figures. First, a treatment centre was established in a centrally placed village which was accessible equally to all the inhabitants of the experimental area. Every patient reporting at this centre with fever had a blood slide examined for malaria parasites and was given a single dose of amodiaquine (Camoquine) in the scale, 600 mg. of active base to adults, 400 mg. to children from 5 to 15 years, 200 mg. to children under five years. Camoquine was selected for clinical treatment, because it was considered least likely to affect the sporontocidal action of pyrimethamine. The treatment centre proved very popular attracting nearly all the malaria cases that occurred in the neighbourhood.

The second set of figures was collected during special rounds when all the villages were searched on one specified day for malaria cases by house-to-house enquiry. Unfortunately, the idea of undertaking such rounds, which came to be designated "Malaria Census," struck us late in the season, the first one being on the 5th of September, while the three subsequent rounds were carried out regularly every two weeks.

Malariometric Data

In Table II are given the spleen rates of children from three to nine years of age and in Table III parasite rates in children and youths of varying age groups.

From a study of the July spleen rates in Table II, it will be seen that although the rates in different villages varied, all of them belonged to the meso-endemic class. The spleen rates increased progressively in the villages from north to south, indicating that the northern group, comprising Chamba and Dhaia, was relatively less malarious than the southern group of Dobandi and Nika Pa. Particular importance was, however, attached to the latter two villages inasmuch as they were both equally malarious, and any variation in the rates during or after the malaria season could

TABLE II.—SPLEEN RATES IN CHILDREN FROM 3 TO 9 YEARS OF AGE.

Name of Village	JULY					OCTOBER				
	No. exam.	No. positive	Spleen rates	A.E.S.	S.I.	No. exam.	No. positive	Spleen rates	A.E.S.	S.I.
TEST—										
Chamba ..	158	24	15.18	1.5	22.77	132	4	3.03	1.0	3.03
Dhaia ..	79	18	22.78	1.8	41.00	81	8	9.87	1.0	9.87
Dobandi ..	56	24	42.75	1.5	64.13	52	6	11.53	1.7	19.60
CONTROL—										
Nika Pa ..	69	28	40.58	1.4	56.84	65	25	38.46	1.2	46.15

A. E. S. — Average enlarged spleen. S. I. — Splenometric Index.

TABLE III.—PARASITE RATES.

MONTH AND AGE GROUPS	CHAMBA			DHAIA			DOBANDI			NIKA PA (Control)		
	No. examined	No. positive	Parasite rate	No. examined	No. positive	Parasite rate	No. examined	No. positive	Parasite rate	No. examined	No. positive	Parasite rate
JULY												
0 to 1 year ..	17	0	0	6	0	0	4	0	0	3	1	—
1 to 9 years ..	195	10	5.13	94	4	4.26	44	3	6.82	65	7	10.77
10 to 16 years ..	53	0	0	18	0	0	8	0	0	15	2	13.33
AUGUST												
0 to 1 year ..	5	0	0	3	0	0	3	0	0	3	1	—
1 to 9 years ..	138	5	3.62	60	4	6.67	49	3	6.12	59	10	16.95
10 to 16 years ..	129	0	0	12	0	0	6	0	0	11	1	9.09
SEPTEMBER												
0 to 1 year ..	9	0	0	6	0	0	7	1	14.29	2	2	—
1 to 9 years ..	161	4	2.48	80	4	5.00	58	7	12.07	47	11	23.40
10 to 16 years ..	27	0	0	13	0	0	9	0	0	7	2	28.29
OCTOBER												
0 to 1 year ..	10	0	0	6	0	0	7	0	0	3	0	0
1 to 9 years ..	160	1	0.63	97	0	0	63	2	3.17	68	7	10.29
10 to 16 years ..	52	0	0	23	0	0	20	0	0	13	0	0

only be occasioned by the effects of pyrimethamine.

In the control village Nika Pa, the spleen rates as well as splenometric indices displayed a minor fall in October instead of the expected rise, due probably to the prompt treatment of malaria cases. In the test villages, on the other hand, the fall in October rates was considerably steeper which could have been brought about only by the interruption of transmission. This is clear from a study of the ratio of July to October splenometric indices which in the control village was 1.2:1 against 7.5:1, 4.2:1 and 3.3:1 in the test villages Chamba, Dhaia and Dobandi, respectively.

Table III shows that malaria infection (*P. vivax*) occurred in one infant in the control village in July, actually on the second day of that month. Malaria transmission was, therefore, already taking place in the experimental area when pyrimethamine was being distributed. In August the same infant was again found to harbour *P. vivax* but in September two other infants in this village were infected, one with *P. vivax* and the second with *P. falciparum*. Thus, out of a total of four infants in the control village, malaria infection occurred in three while the fourth might or might not have been infected as he could not be examined in September and October.

In contrast to this, there was no infection in infants in Chamba and Dhaia, indicating the absence of transmission in these two test villages. In Dobandi, on the other hand, *vivax* infection was found in one infant on 7th September, *i.e.*, in the tenth week after the distribution of the drug. Allowing for the two incubation periods, this infection may be traced to potent gametocytes that were circulating in the blood round about the second week of August. The sporontocidal effects of a single dose of pyrimethamine can thus be reckoned to have lasted for approximately 42 days which is ten days short of the time-period given by Coatney.[2]

The parasite rates amongst older children in the different villages conf rmed to the findings in infants. Thus, in the control village, the rates in children aged 1 to 9 years displayed a definite rise in August which ended in a peak in mid-September. Species distribution of *P. vivax* and *P. falciparum* shown in Table IV was also of the order usually encountered in a normal seasonal malaria outbreak.

In the test villages, Chamba and Dhaia, the rates in the same age groups remained stationary in August while in September instead of a rise they displayed a fall. This finding together with the fact that no *P. falciparum* infection was found in either of the villages was an added evidence pointing to complete interruption of transmission. In Dobandi, on the other hand, the August rates were low but in September not only did the rates rise markedly but also there was one *P. falciparum* infection. Unlike control village, Nika Pa, however, the steep September rise in Dobandi was followed by an equally precipitous fall in the rates in October indicating that transmission in the latter village supervened too late in the season to bring about the usual cumulation of malaria infection and the rise in *P. falciparum*.

Turning to the parasite rates in the age group 10-16 years it was not always possible to sample an adequate number of persons. However from a study of the available figures in Table III it will be seen that only the control village showed infection in this group.

Incidence of Malaria

Figures for malaria cases from the two sources, namely, the treatment centre and the malaria census, are shown in Table V. These figures portray almost the same picture as that presented by the parasite rates. For here also, the incidence of the disease was low in Chamba and Dhaia, higher in Dobandi but much higher in the control village. Species distribution also conformed to the pattern seen in the parasitic survey, all cases in Chamba and Dhaia being benign tertian while in Dobandi two out of 15 cases were malignant tertian. In the control village, on the other hand, *P. falciparum* prevailed in a much higher proportion as will be seen from the figures presented in Table VI.

Discussion

Judging from the results of observations on the control village, malaria may be said to have prevailed in the experimental area in a moderately severe form during the season under review. It is, therefore, particularly significant that, in such a year, a single dose of pyrimethamine should have succeeded in eliminating transmission in two out of thr e test villages throughout a season of 3½ months. In the third test village, Dobandi, a break-through occurred about 42 days after the administration of pyrimethamine but conditions there were peculiar. In the first place, no less than 14 per cent of its inhabitants had missed the drug, vide Table I. Secondly, owing to its location, the village was exposed to the invasion of infected mosquitoes from the adjoining untreated sector to a greater extent than the other two test

TABLE IV.—SPECIES DISTRIBUTION OF *P. vivax* AND *P. falciparum* IN CHIDREN AGED 1 TO 9 YEARS IN THE CONTROL VILLAGE.

Niki Pa	*P. vivax*	*P. falciparum*	Mixed *vivax* and *falciparum*	Total
July	9	1	..	10
August	10	1	1	12
September	9	5	1	15
October	3	4	..	7
	31	11	2	44

TABLB V.—INCIDENCE OF MALARIA.

Name of village	Population	Cases treated in Treatment Centre					Cases found during Malaria Census					Total from cases both sources	Incidence ratio per 1000 population
		July	Aug.	Sept.	Oct.	Total	5th Sept.	19th Sept.	3rd Oct.	16th Oct.	Total		
TEST—													
Chamba	601	0	1	1	—	2	1	1	1	0	3	5	8.32
Dhaia	274	0	1	0	0	1	1	3	0	0	4	5	18.25
Dobandi	186	0	1	9	2	12	2	1	0	0	3	15	80.65
CONTROL—													
Nika Pa	228	1	8	16	6	31	5	3	3	1	12	43	188.60

TABLE VI.—SPECIES DISTRIBUTION IN MALARIA CASES IN THE CONTROL VILLAGE NIKA PA.

Species	Treatment Centre Figures					Malaria Census Figures				
	July	August	Sept.	Oct.	Total	5 Sept.	19 Sept.	3 Oct.	16 Oct.	Total
P. vivax	—	6	7	2	15	4	2	1	—	7
P. falciparum	—	1	7	4	12	1	1	2	1	5
P. malariae	1	—	—	—	1	—	—	—	—	—
Mixed *P. vivax* and *P. falciparum* ..	—	1	2	—	3	—	—	—	—	—
	1	8	16	6	31	5	3	3	1	12

villages. Thirdly, it had the highest spleen rates indicating that pyrimethamine was probably exposed to the severest infection pressure there.

From the available evidence it is impossible to deduce which of these factors, singly or jointly, caused the break-through of transmission in Dobandi. The question is, however, of considerable practical importance and deserves further investigation as connected with it is the problem whether higher dosage or more frequent administration of pyrimethamine than that used in this trial will be necessary to prevent a break-through of transmission in villages with high spleen rates. Satisfactory results have been recorded from a single dose of pyrimethamine (Daraprim) in a hyperendemic area in Kenya[4] but in that trial the sporontocidal action of the drug was not especially investigated.

Our trial has the merit of demonstrating the value of sporonotocide as a preventive of malaria transmission but only in an area of moderate endemicity with a short malaria season. We recognize that pyrimethamine has the risk of uncovering resistant strains of parasites but the potential advantages of the method are so patent that it deserves an extensive trial despite the possibility of this complication. To reduce the chance of resistance, this drug may perhaps, be reserved exclusively for malaria prevention as pointed out by Covell et al., [5] although it would be difficult to say how effective this precaution would be considering that a single dose of the drug has been reported to have caused the appearance of a resistant strain in Kenya.[4]

Summary

1. A field trial to test the utility of a single dose of pyrimethamine as preventive of malaria transmission is described. The dosage scale given was 25 mg. to adults, 12.5 mg. to children from 7 to 12 years of age, and 6.25 mg. to children aged 6 years and below.

2. The trial covered a small community kept under continuous observation over a malaria season. No evidence was forthcoming of malaria transmission in two out of the three test villages for $3\frac{1}{2}$ months but transmission broke through in the third village.

3. Under the conditions of the trial, the sporontocidal action of the single dose of pyrimethamine was found to last a minimum of 42 days even in the most adverse local circumstances.

4. It is concluded that this method of control deserves trial in other areas as its potential advantages outweigh its possible drawbacks, namely, the practical difficulties in organizing mass chemoprophylaxis and the risk of bringing resistant strains to surface.

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