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FIELD TRIALS OF MASS ADMINISTRATION OF ANTIMALARIAL DRUGS
IN NORTHERN NIGERIA

by

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Introduction

The early success of residual insecticides gave rise to hope that malaria might be eradicated within a short period by the concentrated use of these chemicals alone. Further experience has thrown doubt on that, particularly with regard to the elimination of malaria from the tropical part of the African continent. In that area, holoendemic malaria is principally maintained by A. gambiae with A. funestus as a major additional vector. Considerable reduction in endemicity has been obtained by the efficient application of residual insecticides but generally transmission of malaria has continued and it has become apparent that additional measures will probably be needed if eradication is to be achieved. The possession today of a choice of potent antimalarial drugs encouraged the investigation of what help could be expected from them in furthering the ultimate object of malaria eradication. The present series of field investigations was initiated to discover what might be achieved in Northern Nigeria by a campaign of chemotherapy or chemoprophylaxis either independently or as an auxiliary to a scheme using residual insecticide to combat anopheline vectors.

The design of the investigations

Previous experience of mass chemotherapy in combating trypanosomiasis and leprosy was available in Northern Nigeria but in these instances medication was confined to those suffering from the diseases. There was also experience in the control of yaws in whole communities. To influence the prevalence of malaria in Nigeria would require antimalarials to be taken by all members of a community, fit as well as unfit. The previous experience in sleeping sickness, leprosy and yaws encouraged the hope that there would be no active opposition to such a regimen. It was, however, anticipated that the conservative peasantry of Northern Nigeria would not be enthusiastic takers of drugs.

It was regretfully decided that medicated salt was not a suitable vehicle for antimalarials in Northern Nigeria since salt was obtained from desert caravans as well as from sea-borne imports, and the amount eaten by different tribes varied considerably. It was also felt that the issue of a periodic supply of antimalarials to family or other groups would give small hope of regular and efficient individual medication, so that distribution to each member of the community was decided to be the only way to secure efficient administration. A routine of monthly administration was thought to be the utmost that could be operated in practice; the labour and the cost of weekly dosing would be beyond the region's resources.

With these considerations in mind three routines were initiated. With the aim of administering under most favourable circumstances a dose of antimalarials which had proved generally effective for the cure of malaria in clinical cases, it was determined to give adult-equivalent doses of 600 mg of chloroquine base together with 25 mg of pyrimethamine to two communities living in the area of the Western Sokoto Malaria Control Campaign, where a substantial degree of control of vector *Anopheles* had been obtained. To the inhabitants of the town of Argungu (10 000 population) this dosage was administered each month from June to October 1958 inclusive, viz. during the period of maximum transmission of malaria. To the inhabitants of the villages of Gulmare and Koci (1300 population) this dosage was administered at six-monthly intervals, coincident with the respraying of the villages with DDT (2 g per m²). It was hoped that these routines might eliminate the parasite reservoir from these populations and augment the effect of vector control so that malaria transmission would be interrupted and the populations freed of parasites. To complement these two routines, a third investigation was started at Tafashiya village (1000 population) in Kankiya District of Katsina Province, to explore what might be achieved by the barest possible drug routine, i.e. adult-equivalent doses of 25 mg of pyrimethamine issued once each month. For each investigation, considerable preparation was made. In the first place the co-operation of the local native authority, the Emir in Council of Katsina, Gwandu and Argungu respectively, was obtained. Thereafter the purpose of the investigation was explained to local councils and eventually to meetings of family heads. In each of the three areas, the response was uniformly favourable.

The next step was to prepare a comprehensive census by families for each area. The registers of these censuses had to be prepared in relation to the system of drug distribution to be operated so that the appropriate record would be available for each centre of drug distribution. In each case, the individuals of each family were grouped under the name of the house head, and the name, sex and age of each person were noted.

The local tax lists were the basis for the compilation of these censuses and made possible the identification of the householders: these men were the fixed points to which could be related the womenfolk of this changing polygamous society and around them, principally by the check of age and sex, could be grouped their children. To determine which "compounds"¹ ought to be recorded together, a preliminary sketch-map of the compounds in each locality proved helpful.

The Argungu investigation

This investigation was a formidable undertaking since it involved administering chloroquine and pyrimethamine at monthly intervals to about 10 000 people. The execution was the responsibility of the medical officer in charge of a medical field unit which is based on a health centre in the town, and he was able to make use of a proportion of the time of the auxiliaries of that unit for the undertaking. A superintendent of rural health and a health sister are also based at Argungu and lent assistance to the investigation. The town is the headquarters of its Emirate and the native authority co-operated throughout. On the advice of the native authority, the system of drug distribution adopted was by visiting each compound as early as possible in the day. Twenty-four hours' notice was given and it was expected that all the members of a "compound" would remain in its vicinity until the distribution was completed.

The preliminary census recorded 1356 households in Argungu. The records were made in 37 separate books, none containing more than 50 "compounds" and each confined to "compounds" in proximity to one another. In making the census each compound was given a number and that number was marked on the door-post of the entrance-hut ("zauri") to facilitate identification.

The drug distribution was done by five teams, each composed of a team leader (who determined the dose of the drug and who kept the records), a female community attendant (who served the females of each household), a native authority representative from the appropriate ward (who was familiar with the location of compounds) and one locally-recruited labourer. These teams distributed the drugs to individual compounds. It was determined that each team would deal with 50 households in one day, and on the first distribution this proved satisfactory and allowed issues to be completed in a week, each team distributing to just under 300 households in that period.

¹ A composite "house" divided into a number of individual huts and animal houses is called a "compound" in West Africa. It is occupied by one extended family.
(Editor's remark)

The routine developed was to issue a slip on the previous evening through the native authority ward representative to the householders whose "compounds" would receive tablets on a specific day. The members of these "compounds" were expected to remain collected in the vicinity of their homes until visited by the drug distributors and had to provide the drinking water to wash down their pills. Distribution started at first light, the ward representative moving ahead of the team to notify the next "compound" in turn of the team's approach. The team leader called forward individuals from his record, and the labourer and community attendant dispensed. Tablets were swallowed under supervision and the issue was noted in the record book. If there were absentees, a note was issued by the team leader instructing them to report to the health centre on their return to receive the medicines and a record of the absence was made. New residents in a "compound" were entered in the record book and received an issue of tablets.

It was found that infants and young children had to be given their medicine crushed and suspended in water. To cope expeditiously with this need, standard dosages were powdered in advance at the rural health centre and dispensed as individual powders. The speed at which a team could effect their daily task largely depended on the efficiency of the community attendant in feeding these powders to the younger customers.

At the second distribution it was found that on a schedule of 50 "compounds" per day the teams were not arriving at the last half of those warned sufficiently early to meet the need of a farming community anxious to get away to their fields during the wet season. Consequently the number of "compounds" to be visited was reduced to 25 per day with the consequence that teams were employed on distribution for two weeks in the month.

The dosage schedule adopted was as follows:

	Chloroquine (in mg of base)	Pyrimethamine (mg)
Infants	150.0	12.5
Children 1-5 years	300.0	12.5
Children 6-15 years	450.0	25.0
Adults (over 15 years)	600.0	25.0

The average monthly consumption was 31 600 tablets of chloroquine and 9000 tablets of pyrimethamine. This is greater than the estimated amount needed to protect the population of Argungu (estimated to be 10 600 persons, on the basis of a 2% annual increase since the 1952 census), but is not excessive since allowance must be made for double administration to those who vomit and to children who spill the drugs.

The highest number (625) of confirmed absentees was in the month of September (about 6%).

The population of Argungu has been under observation since 1952 in connexion with malarimetric assessment of the Western Sokoto Mass Malaria Control Campaign and its preceding pilot project. By the time of the present drug distribution, a considerable measure of malaria control had already been achieved by residual insecticide attack on the adult Anopheles. The measure of this success was determined in June 1958, immediately before the first issue of tablets, by examining a random sample of the Argungu population. Further random samples were examined throughout the distribution period and after it ended, so that about 12% of the total population were in fact examined over the period of the investigation. Table 1 shows the results of the examinations made in June 1958, before the first issue of tablets, in November 1958, after the final issue, and in March 1959, five months later.

TABLE 1. RESULTS OF SURVEYS OF THE CHILD POPULATION OF ARGUNGU TOWN OVER THE PERIOD OF THE INVESTIGATION

	Age-groups	Date of surveys					
		June 1958		November 1958		March 1959	
		Positive/ examined	per cent.	Positive/ examined	per cent.	Positive/ examined	per cent.
Spleen rates	Under						
	12 months	-	-	0/16	0.0	2/23	8.7
	1- 2 years	5/17	29.4	0/42	0.0	6/32	18.7
	3- 4 years	8/17	47.1	2/52	3.8	4/24	16.6
	5- 7 years	7/20	35.0	10/80	12.5	20/66	30.3
	8-10 years	4/10	40.0	4/51	7.8	9/48	18.8
	11-15 years	1/ 9	11.1	0/12	0.0	1/ 5	20.0
<u>P. falciparum</u> gametocyte rates	Under						
	12 months	0/ 3	0.0	0/16	0.0	0/15	0.0
	1- 2 years	4/18	22.2	0/55	0.0	1/21	4.8
	3- 4 years	2/18	11.1	4/66	6.1	1/10	10.0
	5- 7 years	3/20	15.0	3/87	3.4	2/36	5.5
	8-10 years	0/11	0.0	0/55	0.0	0/36	0.0
	11-15 years	0/ 9	0.0	0/21	0.0	1/ 7	14.3
Crude parasite rates excluding cases showing only "crescents"	Under						
	12 months	1/ 3	33.3	0/16	0.0	1/15(a)	6.7
	1- 2 years	4/18(b)	22.2	1/55	1.8	6/21	28.6
	3- 4 years	6/18(b)	33.3	4/66	6.1	4/10	40.0
	5- 7 years	7/20	35.0	7/87	8.0	8/36(b)	22.2
	8-10 years	2/11	18.2	2/55	3.6	8/36	22.2
	11-15 years	3/ 9	33.3	0/21	0.0	3/ 7	42.8

Note: All infections are due to P. falciparum except that marked (a). Those marked (b) are mixed infections of P. falciparum and P. malariae.

The contrast between the November and June rates is a measure of the success of the chemotherapy in reducing the prevalence of malaria. That reduction was not sustained after the discontinuance of medication. By March 1959 the parasite rates had returned more or less to the pre-treatment levels. This is in part explicable by the fact that Argungu lies on the very edge of the area of mosquito control so that its inhabitants are exposed to infection whenever they travel north of the town. They may also be infected in the town by invading infected vectors but we have no evidence that this occurs.

The Gulmare and Koci investigation

As at Argungu, the population of Gulmare and Koci had been observed in connexion with routine malarionetric assessment of the Western Sokoto Pilot Project and Mass Campaign. A substantial reduction in the malarionetric indices had been achieved by October 1957 but a big reservoir of parasites remained. The villages had been protected by six-monthly applications of DDT since early in 1954.

As at Argungu, chloroquine and pyrimethamine were administered to the inhabitants of these villages at the same adult-equivalent doses. However, the drugs were administered only at six-monthly intervals coincident with the spraying of these villages with residual insecticide.

The system used to distribute the antimalarials in these villages was to summon the population by households to one of five distribution points where one senior and one junior officer issued the medicines. After some experiment it was found possible to issue the complete dose at once and for it to be swallowed under surveillance. A special distribution under the supervision of a health sister was organized for a small group of "purdah" women. The whole operation could be completed in one working day. The results of issues made in November 1957, in May and November 1958, and in March 1959 are shown in Table 2.

The crude parasite rate (excluding crescents) in October 1957, before the first medication, was 58.3% in the child population of the villages. Following the November 1957 and May 1958 distributions, this rate stood at 12.7% in July 1958, and rose slightly to 21.1% by October of that year. The further November medication reduced it to 1.8% as determined from blood slides collected at the end of that month, about a fortnight after the drug distribution. That rate represents 10 infected children. Those 10 infections were believed to be eliminated by individual treatment with the regimen dose of chloroquine and pyrimethamine in early January 1959, after which their blood was negative at a check examination. Two months later, 12 children with trophozoites were found, representing a rate of 3.1%. Six of these had been positive after the November medication but were thought to have been cleared in January. Six seem to have been true new infections, contracted since November, i.e. in a period of four months.

It is also of interest that there was a substantial degree of reduction of the rate of liver enlargement in children in Gulmare-Koci. In children of 3-4 years of age, the rate of hepatomegaly was 33.3% and 29.4% in 1957 and 1958; it fell to 8.9% in 1959. The relevant figures for children of 5-7 years of age were 43.8% in 1957, 33.1% in 1958 and 3.7% in 1959.

TABLE 2. RESULTS OF SURVEYS OF THE CHILD POPULATION OF GUIMARE-KOCI
OVER THE PERIOD OF THE INVESTIGATION

Age-groups	Date of surveys									
	1957 October		1958 July		1958 October		1958 November		1959 March	
1. Spleen rates										
Under										
12 months	2/ 29	6.9	2/ 31	6.5	1/ 29	3.4			1/ 9	11.1
1- 2 years	9/ 61	14.8	3/ 43	7.0	3/ 53	5.6			2/ 40	5.0
3- 4 years	21/ 51	41.2	8/ 83	9.6	7/ 66	10.6			6/ 70	8.6
5- 7 years	108/153	70.6	33/148	22.3	23/181	12.7			22/124	17.7
8-10 years	54/121	44.6	17/120	14.2	8/ 99	8.1			5/ 82	6.1
11-15 years	11/ 43	25.6	2/ 63	3.2	4/ 64	6.3			0/ 22	0.0
2. <u>P. falciparum</u> gametocyte rates										
Under										
12 months	2/ 32	6.3	0/ 33	0.0	3/ 31	9.7	1/ 31	3.2	0/ 9	0.0
1- 2 years	14/ 86	16.3	0/ 58	0.0	9/ 56	16.2	11/ 58	19.0	1/ 57	1.8
3- 4 years	6/ 72	8.3	11/ 99	11.1	7/ 69	10.1	14/ 79	17.7	1/ 82	1.2
5- 7 years	22/161	13.7	9/150	6.0	22/191	11.5	33/191	17.3	1/128	0.8
8-10 years	11/122	9.0	5/122	4.1	2/110	1.8	5/111	4.5	3/ 87	3.4
11-15 years	4/ 64	6.3	3/ 65	4.6	4/ 78	5.1	3/ 82	3.7	0/ 30	0.0
3. Crude parasite rates (excluding cases showing only crescents)*										
Under										
12 months	2/ 32	6.3	0/ 33	0.0	5/ 31	16.1	0/ 31	0.0	0/ 9	0.0
1- 2 years	35/ 86	40.7	4/ 58	6.9	14/ 56	25.0	1/ 58	1.7	1/ 57	1.8
3- 4 years	37/ 72	51.4	18/ 99	18.2	13/ 69	18.8	3/ 79	3.8	2/ 82	2.4
5- 7 years	134/161	83.2	26/150	17.3	50/191	26.2	6/191	3.1	5/128	3.9
8-10 years	77/122	63.1	11/122	9.0	20/110	18.2	0/111	0.0	3/ 87	3.4
11-15 years	28/ 64	43.7	8/ 65	12.3	11/ 78	14.1	0/ 82	0.0	1/ 30	3.3

* All infections were due to P. falciparum except 12 where P. malariae was the only parasite present. Thirty-nine were mixed infections of P. falciparum and P. malariae.

In the columns corresponding to each age-group, the first double figures represent the number of positives out of the number examined. The second figure refers to the relevant percentage.

The Tafashiya investigation

The 25 mg tablet of pyrimethamine is small and tasteless and so it is the easiest of all antimalarial drugs to administer on a large scale. There is virtually no "consumer resistance" to be overcome and even toddlers swallow these tablets without fuss. This enabled two assistants to distribute tablets to the Tafashiya population of 1000 persons in two working days of each month. The distribution took place at two points in the village consecutively, the inhabitants coming forward in family groups and swallowing the tablet before moving from the distribution point. On the second day absentees were rounded up.

Dosage was confined to two schedules, all under five years of age receiving half a tablet and all aged five and over one tablet. Drinking water to wash down the pills was provided at the distribution points.

With this simple system, distribution started in June 1958 and has continued at monthly intervals since. Attendance has been fair. Absentee rates have been as follows: June, 12.5%; July, 8.8%; August, 6.2%; September, 6.2%; October, 8.9%; November, 15.8%; and December, 18%.

Unfortunately, P. falciparum resistant to pyrimethamine became established under this routine (Archibald, 1960) and it was consequently discontinued early in 1959. Throughout the investigation the Tafashiya population received the drug with keenness even after its effectiveness had virtually disappeared.

Discussions

In carrying out this investigation the advantage in ease of acceptance of the small tasteless tablet of pyrimethamine was immediately obvious. There were substantial difficulties with toddlers taking chloroquine and a number of them vomited that drug. At Argungu, too, aversion to the chloroquine-pyrimethamine routine grew during the five months in a degree not indicated by the absentee rates. An increasing effort was required to collect straying people, anecdotes of ill effects began to circulate, and there was evidence of "palming" of tablets. The staff engaged at Argungu greeted the end of the period of routine administration with undisguised relief.

Although the taste of chloroquine is an important disadvantage, the size of its tablet and the number being given were also disadvantages, especially when frequent administration was attempted. During 1959, when a combined chloroquine-pyrimethamine tablet became available, we met much less objection to this medication.

No objection was made at Tafashiya to the monthly pyrimethamine routine, although the absentee rate increased markedly in November and December. However, the selection in so short a time of a resistant strain of one parasite demonstrates the inherent difficulty of using pyrimethamine for mass administration.

The effectiveness of the respective routines is the true measure of their value but the practicability of applying them is an important consideration in determining their place in malaria eradication. At Tafashiya, the distribution to a population of 1000 persons occupied two men for two days; at Argungu, 10 000 persons occupied 20 people for an average of six working days; at Gulmare-Koci, 1300 persons occupied 10 people for one day. The comparison as to the staff required for each routine was:

Argungu:	1 distributor/day per 84 persons per month
Gulmare-Koci:	1 distributor/day per 130 persons every six months
Tafashiya:	1 distributor/day per 250 persons per month

The advantage in economy of staff of the Gulmare-Koci routine is obvious. This routine also has the advantage that the six-month interval allows a small team to cover a substantial population in a cycle of six months (approximately 150 000 could be served by a 10-man team). The Argungu routine in contrast would need four teams of 20 to cover 150 000 people. Also, administration once in six months causes little upset to a community in contrast to the disturbance of a monthly routine. In short, the Gulmare-Koci routine is promising and further trials of it are intended. Its success is obviously dependent on coincident vector control; the contrast between the reappearance of infection at Argungu and the relative absence of reinfection at Gulmare-Koci indicates the limitations of chemotherapy when vector control is not adequate.

The Argungu result is encouraging in the degree of success achieved by the chemotherapy but we do not consider that the routine used there could be adopted on a much more extended scale. The return of parasites to pre-chemotherapeutic levels in four months, not of maximum transmission, indicates the predominant importance of vector control.

It was strongly brought out during this series of investigations that small tasteless tablets had substantial advantages in mass acceptance. Conversely, the fairly large and bitter chloroquine tablets used in this investigation were troublesome to administer.

The investigation also brought out that a small but not insignificant number of individuals do not become parasite-free on the chloroquine dosage given. That the drug has been swallowed has been determined to our satisfaction, but we do not know whether it has been absorbed or whether these unresponsive individuals are especially susceptible to malaria so that they might need unusually high drug doses to overcome their infection, or indeed whether a proportion of insusceptible parasites may not be present. Such individuals appeared at all three of the locations investigated and in all three sites certain of those individuals received personal attention but proved difficult to become parasite-free. The problem posed by these persons has yet to be solved.

Summary

Three trials of mass chemotherapy of malaria in Northern Nigeria are described, two being supplements to a residual insecticide campaign. These two schemes succeeded in reducing the reservoir of malaria parasites to a low level, but the third scheme using a low dose of pyrimethamine at monthly intervals, without antimosquito measures, resulted in the emergence of resistant P. falciparum.

REFERENCE

Archibald, H. M. (1960) The appearance of P. falciparum resistant to pyrimethamine in a Northern Nigerian village, W. Afr. med. J. 9, 21