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Experience with mass drug administration as a supplementary attack measure in areas of vivax malaria

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Mass drug administration was introduced in Syria to supplement DDT spraying after the main malaria vector Anopheles sacharovi *had developed considerable resistance to the insecticide. Mass administration of weekly doses of chloroquine and pyrimethamine was carried out in the Ghab area from August to October, the coverage obtained being over 80 % for most of the time. The number of cases with positive blood films declined rapidly from August onwards. Entomological observations showed that the house-resting density decreased shortly after the second round of DDT spraying but soon regained its previous level. Some relapsing cases were detected in 1969 but none were found in 1970, and it is considered that the possibility of relapses should not deter authorities from using mass drug administration in emergency situations.*

In recent years DDT resistance has developed in *Anopheles sacharovi*, the main malaria vector in Syria. At first, DDT was the only insecticide available locally and had to be used for residual spraying despite its reduced effectiveness. Mass drug administration was therefore introduced in some areas as a supplementary procedure.

Reports on the effectiveness of mass drug administration in areas of vivax malaria are scarce and the results from the Ghab area presented in this paper may be of some interest to other workers who face similar conditions in malaria eradication programmes elsewhere.

THE GHAB AREA

The Ghab area is situated in the middle of the Orontes valley, which runs north–south along a natural depression limited to the west by the Allaouite mountains and to the east by the fringe of the Syrian plateau. The area is approximately 60 km long and 20 km wide and in the past it was very marshy as a result of periodic flooding of the Orontes river; in recent years, following irrigation and drainage work, some very fertile land has been reclaimed. Consequently, the Ghab is now an area undergoing rapid development and many seasonal labourers and nomads migrate there during the warmest months of the year (July–August) and remain until the end of the malaria transmission season.

Malaria transmission persisted in the Ghab area until 1969 in spite of the attack measures used in the malaria eradication programme. Focal DDT spraying had been employed during 1964–66 but as the epidemiological situation became worse total-coverage spraying with DDT was carried out in 1967. Susceptibility tests in 1967 on *Anopheles sacharovi* indicated possible resistance to DDT.

Plasmodium vivax is the only *Plasmodium* species that has been reported from Syria in recent years.

MATERIALS

The drug regimen for adults consisted of weekly doses of 300 mg of chloroquine base and 25 mg of pyrimethamine base. Treatment was carried out for different periods in different areas, depending on local epidemiological and ecological situations.

The insecticide used for residual spraying was DDT 75% wdp, applied at approximately 2 g/m^2 twice a year.

SPRAYING AND MASS DRUG ADMINISTRATION CAMPAIGNS

In 1968, total-coverage spraying with DDT was continued in the Ghab area, the first spray round being applied in March–May. The degree of house coverage could not be determined as geographical

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reconnaissance had not been completed. Towards the end of July, most of the houses were replastered and whitewashed as usual; geographical reconnaissance was carried out shortly before the application of the second spraying round (mid-August to the end of September), and the coverage achieved in this round was 91.2%. Susceptibility tests carried out during the period 20 July–20 August 1968 demonstrated a high level of DDT resistance in the *A. sacharovi* population of the area (72.9% of 294 mosquitos survived when exposed to a 4.0% DDT concentration for 2 hours, and 37.3% of 77 specimens survived when exposed for 4 hours to the same concentration).

As DDT was the only insecticide available at the time, and as its efficacy against *A. sacharovi* was much reduced, plans were made to supplement its effect with mass drug administration. This was done between 3 August and 31 October 1968, when seasonal workers were arriving in the area: this period was chosen in order to reduce to a minimum the danger of a serious outbreak of malaria and the subsequent dissemination of the disease to other areas. The population to be protected amounted to 61 139 and the area was divided into 50 subsectors so that each agent was responsible for the treatment of an average of 1 200–1 300 people every week in each sector. During their weekly rounds, the agents were also requested to take blood films from all persons with fever, all newcomers, and all persons clinically suspected of having malaria. Instructions were given that medicaments were to be swallowed in front of the agent.

RESULTS

During the 13 weeks of this campaign the weekly population coverage exceeded 80.0% except for week 7, when only 62.4% of the inhabitants received the drugs (Table 1). Despite the dispersion of the population in the fields for harvesting, the administration of drugs was regular and the coverage reasonable.

The epidemiological situation rapidly improved after the introduction of mass drug administration and continued to improve thereafter. Table 2 shows that the number of positive cases rapidly declined from August 1968 onwards. At the same time there was a remarkable drop in the number of indigenous cases though transmission could not be interrupted completely during the period corresponding to the usual annual peak.

Entomological studies

Entomological observations started on 20 July 1968 but because of staff limitations were confined to window-trap observations, bait-captures in fixed indicator districts, and spot checks. The data obtained (Onori & A. R. Zahar, unpublished data, 1968) show that there was a reduction in the house-resting density shortly after the second round of DDT spraying (Table 3). The number of mosquitos caught per trap, however, increased temporarily but with increased mortality. Part of the decrease in the window-trap collection at the end of the study might have been a result of the drainage works carried out in that period, which dried out the main breeding areas along the Orontes river. The house-resting and biting densities increased again slightly after a brief reduction following the second round, and by October had almost regained their original level. An appreciable proportion of gravid females were obtained from the sprayed premises (59% of half-gravid and 82% of gravid females) by spray captures and window-trap observations one month after the second round of spraying.

The consolidated results of the susceptibility tests carried out (24 September–15 October) after the second application of DDT were as follows:

Exposure	*Corrected mortality and number exposed*
4.0% DDT, 2 h	25.8% (89)
4.0% DDT, 4 h	45.9% (74)

In comparison with the results obtained in July (prior to the second round of spraying), the mortality after 2 hours was almost the same but the mortality after 4 hours had decreased considerably.

Relapses after mass drug administration

In 1967, when DDT was used without mass drug administration, there were 559 cases of malaria in the Ghab. In 1968, there were 470 cases and 192 of these were classified as relapses, although the latter had not been detected by surveillance operations during the previous year. In 1969, only 114 relapsing cases were found, and 92 (80.7%) of them had received drugs in the mass administration programme, but it is not known whether they had missed some rounds of medication: 22 (19.3%) of the cases had not been recorded as present when administration was carried out. Since mass drug administration involved weekly house visits, the blood examination rate was consistently higher during the months when it was in progress (Table 1).

Table 1. Number of people and percentage coverage obtained during the 13 weeks of mass drug administration carried out in the Ghab area of Syria from 3 August to 30 October 1968

Week of treatment	Population treated	Coverage (%)
1	51 152	83.7
2	55 417	90.6
3	56 448	92.3
4	56 931	93.1
5	52 518	85.9
6	54 556	89.2
7	38 155	62.4
8	49 277	80.6
9	54 283	88.8
10	53 254	87.1
11	54 676	89.4
12	50 526	82.6
13	49 947	81.7

DISCUSSION

Mass drug administration alone, or as a supplement to the use of insecticides against adult mosquitos has been widely used in the eradication of falciparum malaria (Clyde, 1961; de Zulueta et al., 1961, 1964; Rieckman, unpublished data, 1968; Macdonald et al., 1968).

The value of mass treatment is still uncertain in areas where vivax malaria is prevalent since information is lacking on the quantitative effect of mass drug administration on the parasite reservoir. For instance, it is not known how many of the cases treated by the usual drug regimens are likely to relapse and at what intervals such relapses might occur (Macdonald et al., unpublished data, 1967).

The studies referred to in this paper seem to indicate that mass drug administration at weekly intervals can be used profitably in areas of vivax malaria as a temporary supplement to insecticidal attack on adult mosquitos where the insecticide has failed, or might be expected to fail, to interrupt transmission.

The effectiveness of the first spraying round of 1968 with DDT may have been affected by the

Table 2. Number of positive and indigenous cases and the blood examination rates (BER) obtained in the Ghab area in 1967, 1968, and 1969 [a]

Month	1967			1968			1969		
	No. of cases	Indigenous	BER	No. of cases	Indigenous	BER	No. of cases	Indigenous	BER
January	4	3	0.5	1	2.2	2.2	—	—	2.7
February	5	2	2.4	—	—	2.3	1	—	0.7
March	1	1	2.2	1	—	1.5	2	—	2.1
April	—	—	2.3	9	—	1.9	8	—	3.1
May	2	—	1.9	38	2	2.5	23	—	2.3
June	1	—	1.2	80	18	2.2	42	—	4.2
July	3	—	1.6	179	120	3.5	27	—	3.5
August	14	2	1.3	101	74	4.6	8	—	3.6
September	26	17	1.5	34	26	6.4	2	—	4.0
October	261	221	2.1	12	7	9.6	1	—	3.7
November	178	165	2.9	11	11	4.8	—	—	3.2
December	64	52	2.7	4	3	4.8	—	—	2.3
Total	559	463	22.5	470	262	47.4	114	—	36.4

[a] In 1968 DDT was applied in March-May and again from mid-August until the end of September; mass drug administration was carried out between 3 August and the end of October. In 1969 dieldrin spraying was carried out in May and in August.

Table 3. Entomological indices, Ghab area, July-October 1968

Window trap observations						House-resting densities		Bait capture – Kabr Fedda				Overnight collection in unsprayed tent		
Date	Total no. collected	Average no. of *A. sacharovi* per 10 traps per day	Total no. dead at collection and after 24 hours	Total no. alive after 24 hours	Percentage dead in traps	Date	Kabr Fedda	Date	Average no. of *A. sacharovi* per man/night			Date	Kabr Fedda	Horat
									Man in house	Man outside	Baited net			
3– 7 Aug.	107	26.8	18	89	16.8	5 Aug.	5.7 [a]		–	–	–	24/25 July	–	30
10–14 Aug.	99	24.8	19	80	19.2	14 Aug.	12.3 [a]	13/14 Aug.	8	1	15	30/31 July	8	–
17–21 Aug.	83	22.0	17	71	19.3							6/ 7 Aug.	–	10
												13/14 Aug.	57	–
After the second DDT spraying round														
24–28 Aug.	32	8.0	6	26	18.8	28 Aug.	6.2	27/28 Aug.	0	0	4	20/21 Aug.	–	0
31 Aug.–4 Sept.	53	13.3	15	38	28.3	–	–	10/11 Sept. [b]	1.75	2.3	7	27/28 Aug.	11	–
7–11 Sept.	62	15.5	28	34	45.2	11 Sept.	7.4	24/25 Sept. [c]	0.21	0	4	3/ 4 Sept.	–	7
14–18 Sept.	61	15.3	10	51	16.4	–	–					10/11 Sept.	7	–
21–25 Sept.	21	5.3	4	17	19.0	25 Sept.	8.0					17/18 Sept.	–	19
												24/25 Sept.	13	–
												1/ 2 Oct.	–	24

[a] By hand capture as mosquitos were needed for susceptibility testing.
[b] Rainfall occurred in the first half of the night.
[c] Irregularities as new staff were being assigned for training.

replastering and limewashing of houses; in view of this and the occurrence of DDT resistance in the *A. sacharovi* population, it was not surprising that the number of indigenous cases jumped from 2 in May to 120 in July. Later, however, as a result of mass drug administration and the application of the second spraying round, the number of indigenous cases fell considerably towards the end of the year.

Although the second spraying round was carried out more thoroughly than the first one and was not disturbed by replastering of houses, the entomological data indicate that although the densities of mosquitos did not reach the levels recorded prior to the second round, they were high enough to ensure the continuation of transmission in the area. Although the susceptibility tests carried out after the second spraying round confirmed the presence of DDT resistance, the reduction in mosquito densities suggests that the population of *A. sacharovi* in the Ghab area was heterogeneous and that a proportion were still susceptible to DDT.

In order to see how much of the reduction in malaria was a result of mass drug administration and how much was related to the residual effect of the second round of insecticide spraying, all the positive cases found from 15 April to the end of October were recorded individually according to the first day of onset of fever. Altogether 57 localities had positive cases in 1968; the number of malaria cases increased during the application of the first spraying round, which was very much protracted, and reached a maximum between 21 June and mid-July.

Malaria transmission in the Ghab area, as well as in other parts of Syria, normally reaches its peak in autumn (see Table 2, 1967 figures). In 1968 the large number of malaria cases in July may have included a large number of relapses in addition to new infections; in August the majority of the cases resulted from new infections and it appeared probable that an epidemic would develop. Instead, there was a dramatic fall in the number of cases soon after the introduction of mass drug administration (3 August), so that when the second round of DDT spraying started on 13 August only a few cases were recorded.[1]

It is probable, therefore, that the reduction in the number of cases in the Ghab area in 1968 can be attributed almost entirely to the mass drug administration since the residual effect of DDT would not have been evident before completion of the second spray round (beginning of September). Practically all of the malaria cases reported in the Ghab area after 1 September were in three large villages (Salhab, Kalat Madik, and Skalbieh) where mass drug administration had not been carried out.

The experience gained in the Ghab area confirms that relapses may occur with the drug regimen used for the local strain of vivax malaria. In our trial it was impossible to determine the relapse rate with accuracy as it was not known how regularly the prescribed drugs had been taken in 1968. No relapses were reported from the Ghab in 1970, indicating that relapses may occur only for a short period. The trial shows, however, that the possibility of relapses should not deter authorities from using mass drug administration under special circumstances or in emergency situations.

The value of mass drug administration as a supplementary attack measure in areas of vivax malaria has yet to be explored under normal epidemiological conditions but the high rate of relapses after its cessation would necessitate an adequate surveillance system. It might prove very useful as a temporary measure to reduce the reservoir of infection in a community exposed to a vector that could not be controlled by the available insecticide and before other attack measures could be introduced. In 1963 an epidemic of malaria in Basrah city (Iraq), whose vector was a DDT-resistant strain of *A. stephensi*, was controlled by six rounds of mass drug administration (600 mg of chloroquine base and 50 mg of pyrimethamine base per adult, at fortnightly intervals) despite the fact that the average coverage of the population per round of chemoprophylaxis did not exceed 50% (Lepeš, personal communication). Naturally, the success of mass drug administration depends largely on satisfactory planning and good population coverage. If properly supervised and combined with active surveillance activities it has other advantages: in the Ghab area it resulted in an increase of the number of blood slides collected, the blood examination rate reaching its highest level during the months of mass drug administration. The weekly screening of the population for persons with fever or for clinically suspected malaria cases leads to early detection of cases and to the early commencement of radical treatment. This is perhaps as important in interrupting transmission as the mass suppressive chemotherapy itself, at a time when the problem is restricted to a few cases, which constitute a small but persistent reservoir of infection.

[1] A graph showing the number of cases in relation to the date of onset of fever has been deposited in the WHO library. Single copies can be obtained on request to the Chief Librarian, World Health Organization, 1211 Geneva 27, Switzerland.

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RÉSUMÉ

RÉSULTATS D'UN TRAITEMENT MÉDICAMENTEUX DE MASSE ADMINISTRÉ COMME MESURE COMPLÉMENTAIRE D'ATTAQUE DANS DES RÉGIONS DE PALUDISME À *PLASMODIUM VIVAX*

L'auteur expose les résultats obtenus en Syrie en complétant par une campagne intensive d'administration de médicaments une attaque imagocide menée dans des zones de paludisme à *Plasmodium vivax* où le vecteur, *Anopheles sacharovi*, était devenu résistant au DDT à un moment où l'on ne disposait d'aucun insecticide de rechange. Il semble que dans les conditions locales un traitement « suppressif » à la chloroquine et à la pyriméthamine (posologie pour l'adulte: 300 mg de chloroquine base et 25 mg de pyriméthamine base par semaine) ait, en combinaison avec l'attaque imagocide, endigué une flambée de paludisme et considérablement favorisé l'interruption de la transmission.

On a des raisons de penser que le succès de l'opération est imputable presque entièrement au traitement médicamenteux de masse dont ont bénéficié en moyenne 80 à 85% des habitants, et non à l'action du DDT sur la population locale d'*A. sacharovi* résistante à cet insecticide.

Parmi les malades ainsi traités en 1968, certains ont fait des rechutes quelques mois après l'interruption de la médication, sans qu'il soit possible de déterminer le taux exact de récidives. En 1969, les rechutes ont pu être dépistées facilement grâce à des opérations de surveillance bien menées et la transmission n'a pas repris dans les zones intéressées depuis l'application à deux reprises, en 1969, d'un insecticide efficace, la dieldrine. On n'a observé aucune rechute en 1970. Ainsi, les rechutes enrigistrées à la suite d'un traitement médicamenteux de masse n'enlèvent rien à l'intérêt de cette mesure auxiliaire, particulièrement en présence d'une situation d'urgence.

En Syrie, les deux mesures ont été mises en œuvre simultanément au moment où le réservoir de l'infection ayant déjà été ramené à un niveau assez bas, une stratégie efficace s'imposait pour son élimination définitive. Il semble que les résultats les plus satisfaisants soient obtenus en confiant la surveillance aux agents qui administrent les médicaments. L'examen systématique hebdomadaire de toute la population pour le dépistage des cas fébriles ou des cas cliniques suspects augmente considérablement les chances de découvrir et de traiter précocement tous les cas résiduels de paludisme.

REFERENCES

Clyde, D. F. (1961) *Amer. J. trop. Med. Hyg.*, **10**, 1

Clyde, D. F. (1967) *Malaria in Tanzania*, London, Oxford University Press

Macdonald, G. et al. (1968) *Bull. Wld Hlth Org.*, **38**, 743

Zulueta, J. de et al. (1961) *E. Afr. med. J.*, **38**, 1

Zulueta, J. de et al. (1964) *E. Afr. med. J.*, **41**, 102