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INTRODUCTION

Malaria control operations, essentially begun in Thailand in 1950, were converted into an eradication program in 1958, but total coverage was not achieved until 1965. The control program and early phases of the eradication program were clearly instrumental in dramatically reducing malaria incidence from a mortality rate of 195.0/100,000 population in 1950 to 18.2/100,000 in 1964. After two full years of operations, the total coverage program, which was initiated with a greatly reduced malaria incidence, had been unable to interrupt malaria transmission in Thailand. Three factors were alleged to be the cause:

1. Exophilic and exophagic habits of the two principal vectors, Anopheles minimus and A. balabacensis balabacensis, that prevent residual spraying of dwellings from disrupting the host-vector-parasite relationship insofar as these vectors are concerned.

2. High rate of migration, by laborers living in difficult-to-locate temporary shelters, into and out of hyperendemic areas.

3. High incidence of chloroquine-resistant Plasmodium falciparum strains, which are responsible for the continued presence of a large reservoir of infection.

While these assumptions may be valid, they are based on scanty factual evidence. To define specific causes of failure to interrupt malaria transmission and to develop alternative eradication measures, negotiations between the Thailand Mission of the U.S. Agency for International Development (USAID/T) and the National Malaria Eradication Project of Thailand (NMEP/T) cooperatively created the Thailand Malaria Operational Research Unit (TMORU), to be administered by the U.S. Public Health Service (PHS) as part of its PASA responsibilities for administering overall USAID-supported global malaria eradication activities. As originally conceived, TMORU was to be staffed by a five-man U.S. team, comprised of two epidemiologists, two entomologists, and an operations specialist and supported by a small staff of subprofessional personnel provided by NMEP/T. The team was to be primarily responsible for defining alleged problems hindering malaria eradication in Thailand and for developing possible solutions.

A secondary role of TMORU was to serve as liaison between the NMEP/T and such other research groups involved in studies of malaria as the Southeast Asia Treaty Organization (SEATO), the Faculty of Tropical Medicine in Bangkok, and the Institute for Medical Research in Kuala Lumpur.

On September 21, 1967, the epidemiologist team leader arrived in Thailand to activate TMORU.

ACTIVITIES

Administrative, Logistical

Such basic equipment as microscopes, tents, and portable generators were procured from NCDC. Glass slides, standard antimalarials, and such surplus heavy laboratory equipment as a refrigerated centrifuge and two vehicles were provided by NMEP/T. In addition, future needs of recently developed antimalarials for evaluation against local strains of falciparum malaria will be furnished by pharmaceutical companies.

An entomology technician, hired by USAID, is the field supervisor. Additionally, NMEP/T has provided two insect collectors and two microscopists. Much time was devoted to training these technicians to work as a team in the field. Emphasis was placed on developing greater knowledge of all aspects of malariology so that independent judgment could be based on broader comprehension of the studies being pursued.

Survey for Study Sites

During the first two months of TMORU field activities, major time was devoted to inspecting possible study sites in Regions I, IV, and V. The only criteria were a reported high rate of transmission and some assurance that local transmission was occurring. During these survey trips, epidemiologic data relating to occurrence and incidence of malaria were collected. Preliminary entomologic studies were conducted to determine the transmission potential. When possible, active case detection (ACD) smears were collected to ascertain the current status of malaria in such areas.

Of more than eight proposed sites visited, the most promising was a Royal Thai Government (RTG) forest preserve near Siracha, in which the Shaving Board Factory of Siracha has the option to cut timber. In the forest preserve, the Shaving Board Company maintains a working force of approximately 500 people (workers and dependents). This site possesses one of the highest attack rates for malaria of any area in Thailand. In this microcosm, a well-defined area 7 to 8 miles in diameter, are represented the major technical problems to malaria eradication in Thailand at the present time.

Additionally, the area has the following advantages:

1. The location and identity of laborers are known; clandestine operations apparently do not exist.
2. The area is easily accessible during dry season and accessible by heavy company truck during rainy season.
3. Full cooperation of management, particularly the medical staff, has been offered, and a company medical clinic is available to hospitalize malarious patients enabling close follow-up required for drug studies.
4. A. b. balabacensis is the probable primary vector with A. minimus the probable minor secondary vector.

Drafting of Research Protocols

Based on the information collected from the survey of possible study sites, research protocols for proposed entomologic and parasitologic studies were drafted. Plans for entomologic studies were formulated with assistance of the PHS entomologist at the Malaria Eradication Training Center (METC), Manila, who served as consultant to TMORU for two weeks in February 1968.

Shortly after field studies were initiated by TMORU, it became apparent that well-controlled drug studies, if undertaken in the field, would be practically impossible because of the mobility of patients living in hyperendemic areas. To resolve this problem, establishing a prison-volunteer project (discussed in later section of this report) was proposed to the Director of NMEP/T. Accordingly, research protocols concerning evaluation of chemotherapy in Thai prison volunteers were also drafted and submitted to NCDC.

TMORU Studies through June 30, 1968

Entomologic

Preliminary entomologic studies (survey for vectors) were conducted to determine the transmission potential in proposed study sites. At the same time, attempts were made to evaluate the best method for catching adult anopheline mosquitoes. Methods including man-biting, animal-biting, man- and animal-baited net traps, and miniature

NCDC light traps were used. Limited results obtained by the close of the reporting period indicated that vectors are extremely difficult to find in areas other than developing or virgin-forested areas and that baited net traps and animal-biting collections consistently resulted in higher numbers of anophelines caught (Table 1).

Parasitologic

Currently, primaquine and pyrimethamine are used in Thailand as sporontocidal agents. Primaquine 30 mg plus chloroquine 600 mg (base) is the presumptive treatment regimen in Zone Pakchong; in the other zones of Thailand, pyrimethamine 50 mg is used rather than primaquine. Primaquine, 15 mg/day for 5 days combined with the standard 1.5 gm chloroquine, constitutes the radical treatment regimen used throughout Thailand. The present use of these two drugs as sporontocides was based on the marked sporontocidal effects demonstrated in studies conducted in the early 1950's, utilizing strains of chloroquine-sensitive falciparum malaria. As far as can be determined, no studies have been made to demonstrate whether sporontocidal effect is present when these drugs are used against the local chloroquine-resistant strains. To provide the needed answer, such a study was initiated.

To date, eight falciparum patients have been treated with a single presumptive treatment dose--four with chloroquine 600 mg (base) + pyrimethamine 50 mg and four with chloroquine 600 mg (base) + primaquine 30 mg. Of these eight patients, only one had clearance of patent parasitemia by day 5. This patient, given pyrimethamine, was the only one whose post treatment follow-up smears showed gametocytes. Of the other seven patients, six were still symptomatic on follow-up day 7 when radical treatment was administered. Apparently, a single presumptive dose is inadequate to cope with falciparum strains in Pakchong. Because of lack of sufficient clinical response to a single dose of presumptive treatment, this study has been discontinued. No conclusion concerning the sporontocidal effect of presumptive treatment with either primaquine or pyrimethamine could be made because of inability to follow these patients for more than a week, which is too short a time for development of gametocytemia.

In 1965, Harinasuta et al. reported on 42 cases of falciparum malaria treated in a Bangkok hospital with the 1.5 gm regimen of chloroquine. Of the 42 cases, 40

TABLE 1
 TMORU Entomologic Activities, May and June 1968

Pathum Thani					
Hours	Bulb	Light Trap		Water Buffalo- Baited Net Trap	Man-biting
		C*	A*		
1900-2130	Yellow	11	0	<u>A. argyropus</u> 3	No anophelines
	Regular	28	0	<u>A. sinensis</u> 5	
2130-2400	Blue	57	0	<u>A. vagus</u> 2	
	Regular	146	0	<u>A. annularis</u> 1	
2400-0230	Red	16	0	<u>A. campestris</u> 2	
	Regular	42	0		
0230-0500	Green	35	0		
	Regular	47	0		
1900-0500	Regular with dry ice	237	4**	(No collections attempted)	(No collections attempted)
	Regular without dry ice	153	0		

Boontoey (Pakchong)					
Hours	Bulb	Light Trap		Animal (ox) Biting	Man-biting
		C*	A*		
1900-2130	Yellow	1	0	1900-2200 hr.	(No collections attempted)
	Regular	4	0		
2130-2400	Blue	1	0	<u>A. subpictus</u> 9	
	Regular	6	0	<u>A. vagus</u> 2	
2400-0230	Red	0	0	<u>A. barbirostris</u> 2	
	Regular	0	0		
0230-0500	Green	0	0		
	Regular	0	0		
1900-0500	Regular with dry ice	31	0	1900-2200 hr. <u>A. subpictus</u> 6	1900-2000 hr. <u>A. subpictus</u> 1
	Regular without dry ice	8	0	<u>A. barbirostris</u> 1	<u>A. philippinensis</u> 1
1900-2200	Battery too weak			(No collections attempted)	<u>A. vagus</u> 1 <u>A. philippinensis</u> 2 <u>A. peditaeniatu</u> 1

* C = culicines
 A = anophelines

** A. annularis 3
A. ramseyi 1

were not cured. The majority of the resistant cases reported can be classified according to the WHO category as RI (clearance of asexual parasitemia within 7 days followed by recrudescence). Since 1965, field surveys for chloroquine-resistant falciparum malaria have been conducted by Basu and by Bourke et al. These surveys from three different hyperendemic areas of Thailand showed a resistance rate ranging between 51 and 69 percent. The final follow-up smear taken in these field studies ranged only from day 8 to day 11 (day of treatment being day 0). The studies cited showed, however, that the rate of chloroquine resistance in Thailand is high and the distribution widespread. The question of whether current radical treatment has any effect on reducing infective reservoirs needs to be answered. To assess the responsiveness of the Thai falciparum strains to radical treatment, which would also accurately indicate the chloroquine-resistance rate, the study has been divided into two parts. The TMORU is investigating this problem in "problem areas," and NMEP/T personnel will conduct similar studies in each of the 30 zones of Thailand. The two complementing studies will emphasize the following:

1. Each dose of drug will be administered individually.
2. Follow-up of each case will be at least once weekly for a minimum period of 1 month.

By the end of the reporting period, two passive case detection (PCD) posts--one at the zone office in Pakchong and another at the market area of Boongtoey, Village No. 1, Canton Musi--had been established. TMORU technicians working in these two posts had taken smears from 256 people. Of this total, 58 had falciparum malaria with a slide positivity rate (SPR) for falciparum of 22.6 percent. Daily administration of radical treatment was begun on 34 cases chosen on the basis of some assurance that follow-up for 1 month might be possible. At the end of the reporting period, of the 34 patients, follow-up for more than 3 weeks had been possible only in 12 cases. Significantly, not one of the 12 patients was cured. Smears from 2 of the 12 were still positive by day 7. In the remaining 10 patients, smears were negative in 3 to 5 days, but recrudescence of patent parasitemia occurred between days 11 and 15.

Results of the study from NMEP/T personnel were unavailable at the close of the year.

Proposed Studies

Since well-controlled study of new antimalarials in the field is not feasible because of a highly mobile population, negotiations between the Director General of Prisons and NMEP/T finally resulted in joint approval of a Thai Prison-Volunteer Project for chemotherapeutic evaluations. Accordingly, protocols dealing with the proposed studies were prepared and submitted to NCDC for approval:

1. The study of malaria in Thai Prison Volunteers.
2. The response to standard antimalarials by five strains of chloroquine-resistant falciparum malaria from Thailand.
3. The evaluation of sulformethoxine plus pyrimethamine against chloroquine-resistant falciparum malaria in Thai Prison Volunteers.
4. The evaluation of sulfalene combined with trimethoprim for treating chloroquine-resistant falciparum malaria in Thailand.

The above studies, requiring some 60 volunteers, will commence in September 1968. As a result of these studies, an alternative treatment regimen will probably be selected for field use to replace quinine in treating chloroquine-resistant falciparum malaria in Thailand.

Meetings Attended

During the fiscal year, the TMORU team leader attended two meetings:

1. The Fifth Malaysia-Thailand Border Meeting on Malaria and Public Health, November 23-25, 1967, at Penang.
2. A seminar and laboratory meeting on parasitology and tropical medicine, May 31-June 2, 1968, at Singapore.

PROBLEMS

Staffing

Professional

The inability to provide TMORU with staff in addition to the team leader precluded comprehensive studies on the overriding question of persistent malaria transmission in Thailand. Instead, studies pursued were based on contingency planning and, therefore, were fragmentary and limited to certain aspects of the total problem while the key problem--that of association of vector and man--remained neglected. This frustrating situation was a direct result of the usual administrative delay in processing nominees for overseas assignment. This delay enabled the USAID Mission to eliminate unfilled TMORU positions through the "BALPA" exercise.

Subprofessional

Technicians provided by NMEP/T, while proficient in the work for which they were trained, nevertheless lack the broad background and experience required for meaningful, minimally supervised, investigational field work in malariology. The time-consuming need for constant and close supervision is mandatory. Much time was therefore devoted to instructing these field technicians in other aspects of malariology. This effort should result not only in more efficient use of technicians to meet current TMORU needs, but also in future benefits to NMEP/T by having a core, albeit small, of more broadly trained and versatile field technicians.

Field Logistical Problems

Transportation

One primary requirement for effective use of field technicians is adequate means of transportation for each individual. The most practical way is to provide motorbikes to enable them to cover greater distance and reach more remote areas in studies in which contact of patients is essential. Presently, for various administrative reasons, TMORU has been unable to procure motorbikes. The much costlier alternative is to request additional vehicles; unfortunately, none of the technicians currently can operate vehicles. To remedy this situation, TMORU is continuing to try to obtain

the needed motorbikes and, where possible, to provide driving instruction for technicians. Until this problem is solved, accumulation of cases for study in the field will be needlessly slow.

The full impact of monsoon rains on non-surfaced roads is yet to be experienced; but because of unusually early rain in some localities, certain proposed study sites were rendered inaccessible to vehicles. This problem is acute for TMORU, and, on a much larger scale, for NMEP/T, whose routine activities are also drastically limited. The need to investigate and solve this problem by TMORU, therefore, is justified as another aspect of operational research. Specifically, and conditional on added staff, a determination will be made on where and how to procure the most practical vehicle to negotiate roads impassable to jeeps.

Population Migration

The migration of transitory laborers is associated with areas undergoing development, such as clearing of virgin forest for farming and tin or gem mining. Malaria transmission is most active in such areas. TMORU attempts to study patients in such situations are extremely handicapped; since more than 60 percent of the population are migrants, following up patients for at least 3 weeks after treatment is difficult. In Thailand, a malarious patient, once asymptomatic, seldom stays in one location.

PROPOSED COURSE

Clearly, USAID/Thailand will not support TMORU as originally indicated. Therefore, the team leader and sole member of TMORU will depart Thailand in June 1969, unless some arrangements can be made with AID/W for funding and staffing of TMORU as a centrally-funded activity. In the meantime, to realize even a modicum of results from an otherwise totally frustrated effort, the following course is proposed:

1. Major efforts will be made to complete drug studies against Thai strains of falciparum malaria as outlined in the protocols. This will include controlled studies in prison volunteers as well as subsequent field trials in problem areas.

2. The PHS Malaria Advisor will be transferred from Region II to Bangkok to assist TMORU as a junior entomologist in field investigations. This will consist of supervision of existing Thai field personnel and limited entomologic study directed toward the main goal of demonstrating where transmission of malaria is occurring and why.

3. The NCDC Malaria Eradication Program will propose that AID/W make TMORU a malaria eradication operational research activity with central AID/W funding, effective July 1, 1969.