BODY OF REPORT

SEATO Medic Study No. 1	Epidemiology of Thai Hemorrhagic Fever
Project No. 3A 025601 A 811	Military Medical Research Program S. E. Asia
Task 01:	Military Medical Research Program S. E. Asia
Subtask 01:	Military Medical Research Program SEASIA (Thailand)
Reporting Installation:	US Army-SEATO Medical Research Laboratory APO San Francisco 96346
	Division of Medical Research Laboratories
	Department of Virology
Period Covered by Report:	1 April 1964 to 31 March 1965
Principal Investigator:	Major Scott B. Halstead, MC
Associate Investigator:	Dr. Charas Yamarat *
Assistant Investigator:	Miss Prabhasri Umpaivit
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Objective: To gather information on factors which influence and control the occurrence of mosquito borne hemorrhagic fever.

Description: Linear epidemiologic observations of hemorrhagic fever in Thailand together with an integrated program of laboratory and clinical studies have been undertaken since 1961. These studies are a collaborative effort of the US Army-SEATO Medical Research Laboratory, the Department of Microbiology of the Faculty of Public Health and the Children's Hospital. In addition, nearly every hospital.

* Professor and Head, Department of Microbiology, Faculty of Public Health, University of Medical Sciences, Bangkok

clinic and Maternal-Child Health Center, many pediatricians and Public Health Officers in Thailand have participated in this study.

Epidemiologic studies were divided into 4 parts:

Bangkok Area Study. Nineteen areas within Changwad Phranakorn were selected for study (17 within Bangkok municipality). Areas were chosen from approximately 2000 census enumeration districts by use of a random numbers table. Selected areas were located on a large scale city map and redrawn to include approximately 400 houses. Altogether, 44,018 persons resided in these areas, or approximately 3% of the 1960 Bangkok population. A profile of the ethnic and socio-economic characteristics of areas follows: Chinese-lower socio-economic, 6 areas; Thai-lower socio-economic, 4 areas; Thai and Chinese-low socio-economic group, 3 areas; Thai-middle socio-economic group, 3 areas; Thai and foreign-middle socio-economic group, 3 areas; Thai and foreign-middle to upper socio-economic group, 1 area; Chinese and Muslim-middle economic group, 1 area; and Thai-Chinese and foreign-upper income, 1 area. Bangkok, like most oriental cities, is difficult to classify in this manner as little urban stratification has occurred and most areas contain homes of rich and poor, Thai and Chinese, side by side.

Teams of 2 nurses or a nurse and nurse's aide were assigned to each of 5 areas. Each area was visited and mapped. Occupants were censused before and after the hemorrhagic fever outbreak of 1962. Households were classified by ethnic group and total monthly income.

Beginning in January 1962, 10-3-% of area houses selected randomly were visited and finger tip blood specimens were collected from occupants regardless of age. In November and December 1962, 1,888 persons were bled a second time.

From April 1962, each house in each areas was visited at 6 to 8 week intervals to inquire for occurrence of hemorrhagic fever. The clinic or hospital of admission was recorded and the diagnosis verified with the attending physician.

All sera obtained from a single area were tested simultaneously against dengue 1 and chikungunya antigens by hemagglutination-inhibition (HI) and complement-fixation (CF) at initial dilutions of 1:20 and 1:4, respectively.

In 5 areas, mosquito collections were made by members of Entomology Department.

Children's Hospital Out-patient Study. One out-patient with a fever of 38°C or higher was studied on Monday, Wednesday and Friday beginning April 1962 and continuing to December 1964. Acute and convalescent sera were obtained at approximately 2 week intervals in 95% of studied patients. Virologic specimens obtained also included throat and rectal swabs. In 1962, under the supervision

of Dr. Lowell Woodbury, WHO statistician, every fifth out-patient record was coded and recorded on IBM cards and diagnoses were classified by the International Intermediated List. Statistics for monthly OPD visits for a variety of febrile syndrome were thus available.

Hospital Data Collection. A nurse-epidemiologist made regular weekly (1962) or monthly (1963-4) visits to each of 22 hospitals in the Bangkok-Thonburi metropolitan area. Name, age, sex, ethnic group, street and house address were recorded for patients with a discharge diagnosis of hemorrhagic fever.

Once each year every registered hospital in Thailand with more than 12 beds was requested to submit name, age, sex, ethnic group and date of admission of all patients with the diagnosis of hemorrhagic fever admitted within the calendar year. In 1962, replies were obtained from 102 hospitals outside Bangkok and Thonburi while in 1963, 75 hospitals replied. No systematic serologic verification of these diagnoses was attempted.

Study of Disease in Caucasians. Specimens from Caucasian patients were contributed by the Joint U.S. Military Advisory Group-U.S. Embassy Dispensary, The Bangkok Sanitarium and Hospital, the Bangkok Nursing Home and the Bangkok Christian Hospital, US medical facilities at Don Muang Airport, Takli, Udorn, Korat, Chachengsao and Ubol and the Peace Corps.

Progress: Epidemic patterns of hemorrhagic fever in Thailand. Shown in Figure 1 is the monthly distribution of hospitalized hemorrhagic fever for 1958-1964 for the Bangkok-Thonburi municipal area. Biannual epidemic surges are evident.

Seasonal Occurrence. Closer examination of Figure 1 shows the relationship of epidemic perios to seasonal rainfall in Thailand. The annual monsoon generally commences in late May or early June and ends in October or November.

Mosquito Vector. The relationship of hospitalized hemorrhagic fever in 1962 to populations of Aedes aegypti has been illustrated in the FY 64 report of SEATO Medic Study No. 40. Hospitalized dengue and chikungunya virus infections (hemorrhagic fever)correlate seasonally with the Aedes aegypti population. Both viruses have been recovered almost exclusively from this species in Bangkok (see SEATO Medic Study No. 7).

Etiologic Association with Multiple Viruses. Studies have demonstrated the association of hospitalized hemorrhagic fever with dengue viruses of multiple types and with the group A virus, chikungunya. Table 1 shows chikungunya and dengue virus isolations from humans with a clinical diagnosis of hemorrhagic fever in 1962.

Mild and Severe Disease Associate with Dengue and Chikungunya Viruses. From the Children's Hospital study, monthly percentages of hemorrhagic fever cases caused by chikungunya and dengue viruses were calculated. These percentages

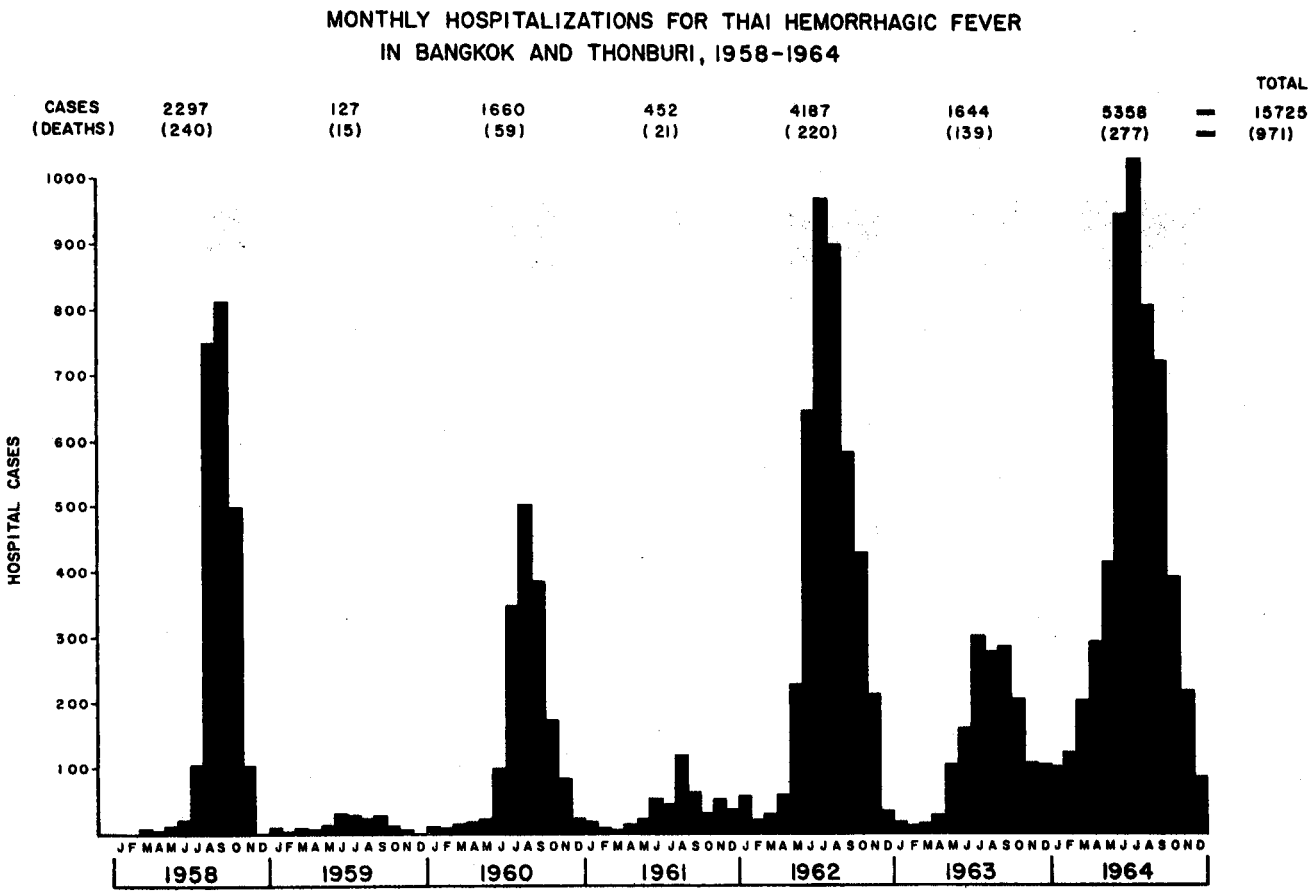
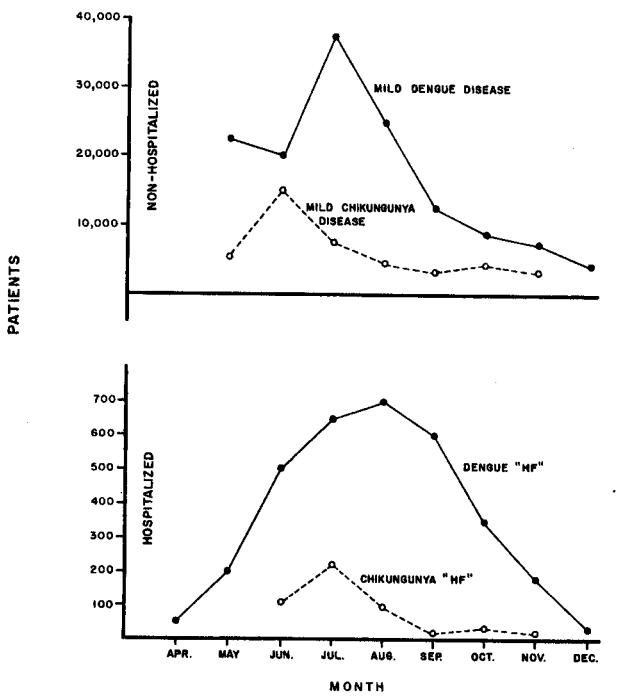


Table I

VIRUSES RECOVERED FROM 154 HOSPITALIZED HEMORRHAGIC FEVER PATIENTS, BANGKOK, 1962

	d1	d2	d3	d4	Chikungunya
Viruses recovered	9	10	3	0	9
% Recovery	5.8%	6.5%	1.9%		5.8%

FIGURE 2: MONTHLY ATTACK RATES OF HEMORRHAGIC FEVER AND MILD DISEASE CAUSED BY CHIKUNGUNYA AND DENGUE VIRUSES (ESTIMATES) BANGKOK, 1962

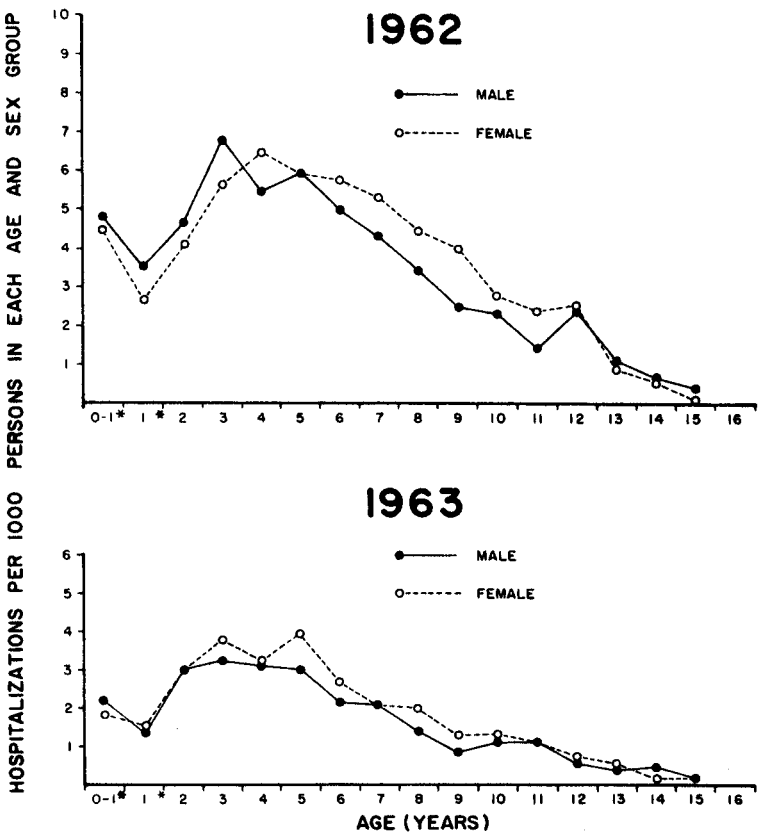


were multiplied by monthly admission figures for all Bangkok-Thonburi hospitals. Figure 2 shows estimated hospital admissions due to chikungunya and dengue viruses.

Mild disease occurrence was estimated by totalling monthly visits for all Children's Hospital out-patients in all diagnostic categories represented in the PUO samples. The per cent of confirmed dengue or chikungunya illnesses in the monthly sample were calculated from virologic studies. These figures were then multiplied by monthly pediatric out-patient visits for all Bangkok and Thonburi Hospitals. This resulted in an estimate of dengue and chikungunya disease seen in hospital OPD's. In order to estimate the total magnitude of disease requiring a visit to a physician, OPD figures were multiplied by a factor of 2.5 (in the Bangkok Area Study it had been observed for every patient receiving a treatment at a hospital OPD there were 1.5 who were treated by private practitioners). This factor may be low, but it is the best estimate available. Monthly estimates of mild dengue and chikungunya infections are shown in Figure 2. Total disease for the period April-December 1962, inclusive, was estimated at 200,000.

As a measure of the accuracy of estimates of mild disease, two additional sources of information are available. First, the number of mild chikungunya and dengue out-patient infections at Children's Hospital is substantiated by analysis of monthly OPD visits. By counting excess respiratory disease above 2,5000 visits per month, and excess PUO's above 100 visits and OPD hemorrhagic fever not admitted for the period April to December, there were slightly over 13,000

FIGURE 3. AGE SPECIFIC HOSPITALIZATION RATES FOR MALES AND FEMALES, THAI HEMORRHAGIC FEVER, BANGKOK-THONBURI, 1962-3.



Age-sex population estimated from registered live births and infant mortality figures Ministry of Public Health. Demographic data for other age groups obtained from 1960 Thailand Population Census.

Table 2

HEMORRHAGIC FEVER AND RACE IN HOSPITALIZED HEMORRHAGIC FEVER PATIENTS AND IN BANGKOK SAMPLE, 1962

	Census sample*	Hospitalized HF	HF in areas sample
% Thai	55.7	55.0	57.6
% Chinese	40.0	44.0	42.4

* 3% of Bangkok municipal population (1960).

Table 3

THE OCCURRENCE OF HEMORRHAGIC FEVER PER 1000 DENGUE HI ANTIBODY CONVERSIONS IN SEVERL INCOME GROUPS. BANGKOK AREA STUDY, 1962. BASED UPON PRELIMINARY REPORT.

Total Monthly Income (Baht)	Estimated dengue infections	Hosp. HF	Ratio Hosp. HF infections	Hosp. and non-hosp. HF	Ratio
2,500+	960	3	3.1/1000	16	16.6/1000
1,500-2,500	1,483	8	5.3/1000	21	14.1/1000
700-1,500	7,230	28	3.8/1000	75	10.4/1000
100-700	3,299	24	7.2/1000	44	10.3/1000

such patients in 1962. Second, in 1962 dengue and chikungunya virus transmission rates in Bangkok estimated from HI conversions of susceptibles were 30% and 25%, respectively. Other studies have suggested that clinical disease to virus infection ratios for both dengue and chikungunya viruses is nearly 1, hence huge numbers of illness might reasonably have occurred during the epidemic.

Age and Sex Distribution. Shown in Figure 3, are age specific hospitalization rates in 1962 and 1963 males and females living in Bangkok and Thonburi at the time of onset of hemorrhagic fever. From Figure 3 it appears that hemorrhagic fever is only a disease of children. However, adult cases have been reported and may be reported more frequently in the future as doctors treating adults examine more carefully for this condition.

Age specific death rates in residents of Bangkok and Thonburi for 1962 and 1963 vary between 5-10% but do not show a significant trend for any particular age group.

Incidence of Hemorrhagic Fever in Ethnic Groups. The occurrence of hemorrhagic fever in ethnic groups was studied by comparing the per cent distribution of Thai and Chinese in the Bangkok Area Study with the distribution of ethnic groups among hospitalized hemorrhagic fever patients and with the occurrence of hemorrhagic fever in ethnic groups in study areas. These data, summarized in Table 2 show a virtually identical distribution of ethnic groups in all 3 populations. Since disease mortality rates in Chinese and Thai are similiar it may be concluded that there is not difference in disease severity in these two ethnic groups.

Table 4

ACCUMULATION OF DENGUE HI ANTIBODY WITH AGE AND SEASONAL DENGUE VIRUS INFECTION RATE IN 6 SELECTED STUDY AREAS, BANGKOK, 1962

Areas	Predominating Ethnic and Economic group	% Antibody in Jan. - Feb. 1962 by age group					Dengue virus infection Rate in 1962
		0-4	5-9	10-14	15-19	20+	
3	Thai, middle class'	22	59	78	92	90+	33%
5	Thai, lower class	39	61	70	85	95+	30%
7	Thai, lower class	41	61	69	86	94+	35%
18	Chinese-Thai, upper class	16	14	44	87	90+	10%
19	Chinese, lower class	35	50	-	-	-	20%
20	Thai,low-middle class	23	62	86	86	90+	25%

Table 5

ACCUMULATION OF CHIKUNGUNYA HI ANTIBODY WITH AGE IN 6 SELECTED STUDY AREAS OF BANGKOK, 1962

Area	Predominating Ethnic and Economic group	% Antibody in Jan. - Feb. 1962 by age group				
		0-4	5-9	10-14	15-19	20+
3	Thai, middle class	14	31	46	67	75
5	Thai, lower class	14	32	54	61	74
7	Thai, lower class	16	46	61	75	81
18	Chinese-Thai, upper class	0	8	11	50	58
19	Chinese, lower class	5	20	-	-	-
20	Thai, low-middle class	16	40	68	80	86

Incidence of Hemorrhagic Fever in Various Income Groups. Table 3 shows dengue infection rates for several income groups calculated from dengue antibody conversions (HI negative to HI positive) were multiplied by total persons in the group. Hospitalized patients and total hemorrhagic fever diagnoses are then expressed as a rate. Hospitalization rates in the upper income group are slightly below that of lower income groups while rates for total HF diagnoses were similiar in all groups. This discrepancy could be explained if dengue infections were somewhat milder among upper income families or alternatively, if upper income group children were more likely to be cared for in private clinics or at home.

Urban patterns of spread of hemorrhagic fever. Tables 4 and 5 illustrate the pattern of distribution of dengue and chikungunya HI antibody among residents of 6 Bangkok Study areas in January and February, 1962. Antibody occurrence is arranged by age of residents. It can be seen that chikungunya transmission rates in preceding years had been lower than dengue and that the accumulation of antibody to both chikungunya and dengue were relatively low among the residents of the only upper income area included. This area (#18) is characterized by well-screened houses set in the middle of large walled-in compounds. Relative differences in the immunologic experience of people in different areas of the city may explain the "brush-fire" type of urban epidemiology noted in out study. Districts which are hyperendemic for hemorrhagic fever in one year may have low endemicity the following year.

A second characteristic of the urban epidemiology of Thai hemorrhagic fever is the focal spread of cases. It has not been uncommon to find that all cases occurring in a Study Area were localized to a group of 50 or 100 houses.

A third phenomenon, perhaps related to the focal nature of case occurrence, is the occurrence of multiple cases in a family. In the period April 1962 to July 1964, 271 families out of 7,336 (3.7%) in the Bangkok-Thonburi Study Areas had one or more cases (Table 6). There were 46 secondary cases in these families. If one considers only hospitalized cases, there were 105 primary cases in 7,336 families (1.4%) and 12 secondary cases. "Secondary" attack rates are obviously considerably higher than primary rates. How much of the multiple diagnosis is due to suggestion or anxiety on the part of physician or parent is impossible to determine.

Summary and Conclusions: Much of the data presented above must be evaluated tentatively. Serologic data, for example, is difficult to interpret. Does a negative ($< 1:20$) HI test for dengue mean that the individual has never been infected with dengue or that infection was remote ? Neutralization tests in tissue culture are in progress, but, until the full spectrum of distinct dengue virus types has been identified it is difficult to evaluate neutralization test data.

Within the limits thus imposed, a number of interesting observations can be made from these studies. First, it is evident that dengue and chikungunya are not only ubiquitous infections but cause much disease of moderate severity in

Table 6

MULTIPLE OCCURRENCES OF HEMORRHAGIC FEVER IN THE SAME YEAR AMONG 27 FAMILIES, BANGKOK STUDY AREA, 1962-4

Number of Cases/Family	Occurrence	DISPOSITION		
		Non-hospitalized	At least 1 member hospitalized	All individuals hospitalized
1	236	147	-	89
2	28	15	4	9
3	3	2	0	1
4	4	2	2	

Bangkok.

The focal nature of dengue (and chikungunya ?) urban hyperendemicity (HF outbreaks) is worthy of note and suggests a method of epidemic control based upon the location of early cases of hemorrhagic fever and thorough eradication of Aedes aegypti in the patient's home and a surrounding group of 50-100 houses.

High rates of multiple hemorrhagic fever cases within families is compatible with almost all theories of the pathogenesis of hemorrhagic fever, i.e,, a mutant virus is the case, the immunologic status of the patient is important or inherited factors influence the severity of infection. A higher attack rate of hemorrhagic fever in families in different years compared with controls, however, would tend to suggest that similarity of genetic factors was operative. These calculations have not been made. Failure to find significant differences in incidence of hemorrhagic fever in various ethnic or income groups suggests that nutritional or genetic status has no effect on the course of dengue infection.

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