WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTÉ

CDS/SR/66.1

ENGLISH ONLY

SURVEILLANCE REPORTS

Mosquito-borne Haemorrhagic and dengue-like fevers

This is the first of Communicable Diseases Surveillance Reports which will appear periodically. These reports are the result of collaboration between various Units in the World Health Organization, particularly of Units in the Division of Communicable Diseases and the Vector Control Unit. They include information as reported to us by countries, WHO Regional Offices, WHO Reference and cooperating Laboratories and collected from Scientific Reports.

Surveillance Reports are distributed free of charge to all persons active in the medical and allied sciences who signify their interest in receiving it by writing to the Chief Medical Officer, Global Epidemiological Surveillance Unit, World Health Organization, Geneva, Switzerland.

Surveillance Reports are sent to the WHO regional offices and representatives in countries concerned and to the interested Panel Members of this Organization.

The purpose of Surveillance Reports is to provide a means for fast exchange of information, comments, and notes concerning surveillance of communicable diseases.

MOSQUITO-BORNE HAEMORRHAGIC AND DENGUE-LIKE FEVERS

Introduction:

Haemorrhagic syndrome is a common manifestation of arbovirus infections. However, until the outbreak of haemorrhagic fever in the Far East in 1930, no other disease of viral origin was known to be accompanied by haemorrhagic manifestations other than the well-known syndrome in yellow fever.

Later a disease similar to that in the Far East was reported from Norther and Eastern and South Eastern Europe. However, since 1954 outbreaks of mosquito-borne haemorrhagic fever have been reported in the Philippines and elsewhere in South-east Asia and at approximately the same time (1955) another type of haemorrhagic fever was recognized in South America (Argentina and Bolivia). These haemorrhagic fevers or syndromes are caused by different types of arboviruses with different epidemiology and ecology especially with regard to the vector and reservoir animals (Table 1).

Table 1. Haemorrhagic fevers in different geographical areas

Vector	Epidemic haemorrhagic fever	Virus	Geographical areas
Ticks	related to Russian spring-summer encephalitis: OMSK h.f. Kyasanur Forest disease	 Omsk virus KFD virus	 USSR India
	Crimean H.F.	Crimean virus	USSR
Mosquito	yellow fever	y.f. virus	Africa, South America
	Philippines, Vietnam, Malaysia, Singapore Thailand Burma, India	dengue group chikungunya	South-east Asia
Mites or rodent associated	haemorrhagic nephroso nephritis	?	Korea, East USSR, North, East, South-eastern Europe
	Bolivian h.f. Argentinian h.f.	Junín Tacaribe Machupo	South America

Common clinical features of epidemic haemorrhagic fevers are fever, haemorrhagic rash, bleeding (gastrointestinal tract, uterine, nasal), hypotension, thrombocytopenia, prostration, shock. These are frequently associated with death. Contrary to other haemorrhagic fevers leukopenia and hepatomegaly were often observed in mosquito-borne fever in South-east Asia but without albuminuria which is common in other types of haemorrhagic fever. A WHO Seminar on Mosquito-borne Haemorrhagic fever was held in Bangkok in 1964 and a "suggested definition and nomenclature for diseases suspected to be of dengue and chikungunya virus etiology" was adopted.

History

Mosquito-borne haemorrhagic fevers are of particular importance because since first recognized in 1954 in Manila they have been reported in many other areas in the Western Pacific and in South-east Asia where they have caused a great number of cases. In 1958, a haemorrhagic syndrome similar to the one reported in 1954 in Manila was observed in Bangkok. Later it was reported in Singapore (1960), South and North Vietnam (1960), Laos (1962) and finally in India (1963).

The first outbreak in India was reported from Calcutta in July-December 1963. Although no exact information is available, it is estimated that several thousand cases may have occurred. Hospital and burial records have shown that nearly 200 deaths by a haemorrhagic fever syndrome occurred.

The outbreak in Calcutta had two phases: the first phase occurred between July and September and serological studies indicate that it was caused by a group B virus, probably dengue; the second phase, from September to the end of the year, was caused by chikungunya virus as shown by virus isolation and serology. Cases with haemorrhagic manifestations seem to have occurred more frequently during the first phase, although the chikungunya virus was isolated from some cases during the second phase of the outbreak also. In 1965, outbreaks of 48 cases (0 deaths) were reported in the East Godavari District and 1 case (1 death) in Nagpur City (both in Maharasthra State, India).

In April, May and June 1965 there was an extensive outbreak of dengue-like fever in Nagpur City and in some sectors about 40% of the population was affected. Several strains of chikungunya virus and one strain of dengue virus were isolated. Chikungunya infection was confirmed also serologically in several samples of paired sera from patients. In the first seven weeks of 1966 1 case of haemorrhagic fever (1 death) was again reported in Nagpur City.

From July to November 1964 an extensive outbreak of dengue-like fever took place in several cities in South-east Asia. Several hundred strains of chikungunya virus were isolated from patients and a number from Aëdes aegypti mosquitos. Chikungunya infection was confirmed in most serologically investigated patients. As a result of a random survey carried out in November 1964, it has been estimated that there were about 400,000 cases in Madras alone. During this epidemic there were 18 deaths out of 4,223 cases admitted to the Infectious Diseases Hospital. Three deaths were reported in infants under one year of age, 7 in children under 10, two in age group 10 to 20, none in age group 20 to 45, and 3 in persons older than 45 years of age, with case fatality rate 2.8% under 1 year, and 1.6% over 50 years. Out of these 18 deaths, 3 had haemorrhages, 5 died from peripheral circulatory failure, 3 had convulsions and others lung involvement. (R. Rao and others in Indian J. of Medical Res. Vol. 53, 1965).

In October 1964 a small outbreak of dengue-like disease occurred in Visakhpatnam and 10 or 12 deaths occurred. Dengue virus II was isolated from several patients and no evidence was found of the presence of chikungunya virus either serologically or by isolation. However in September 1965 another outbreak of dengue-like fever occurred and chikungunya virus was isolated from patients at that time.

In Vellore an epidemic started in August and ended in December 1965. Chikungunya virus was also isolated from patients. It has been estimated from epidemiological surveys that about 40% of the population suffered from the disease. Out of 11 infants from whom virus isolations were made in a study in Vellore, 10 had rash and 2 had haemorrhagic manifestations.

Similar outbreaks of dengue-like fever occurred also in other cities in India late in 1965.

In Ceylon a big outbreak of dengue-like fever was reported in the spring of 1965 and chikungunya etiology was confirmed by virus isolation and serology.

Serological studies carried out in South India and Ceylon with sera collected before the last epidemic of dengue-like fever caused by chikungunya virus have shown that no antibodies for this virus were present in persons younger than 20.

This indicates that chikungunya virus had not been present in this area for about 20 years before it appeared in the last epidemic.

In 1964, 1022 cases and 141 deaths caused by haemorrhagic fever were reported from hospitals in the Philippines. In the period from 1 January to 16 October 1965, 455 cases and 88 deaths were reported.

In Thailand, 2042 cases and 56 deaths from haemorrhagic fever were reported in 1964, and 2391 cases and 152 deaths in 1965. In the first seven weeks of 1966, 392 cases and 3 deaths have been reported. According to these recent figures a large outbreak can be expected in 1966.

In Tahiti (French Polynesia) 535 cases and no deaths were reported from dengue-like disease in 1965.

Negative reports were obtained from Hong Kong, the Republic of China (Taiwan), Western Samoa and Nepal.

In the Caribbean Region of the Americas, outbreaks of dengue have occurred in 1963 in Jamaica (1500 cases), in 1964 in Venezuela (16,000 cases), Dominica (about 300 cases), Puerto Rico, St Kitts-Nevis-Anguilla, Martinique (8-10,000 cases) and the Netherlands Antilles (about 8,000 cases). In Puerto Rico from August 1963 to February 1965, some 28,000 cases were reported. In Venezuela nearly 3,500 cases were reported in 1965. Cases were again also reported in Jamaica, Puerto Rico and in Antigua; in the Dominican Republic dengue is considered to be endemic although no cases were reported in 1965.

Table 2 summarizes the reports on mosquito-borne haemorrhagic fever and dengue-like fevers in 1965. It also illustrates the need for more complete reporting of these diseases.

Mosquito vectors

Abundant evidence is now available to incriminate mosquitos of the genus Aëdes as both natural and experimental vectors of dengue and chikungunya viruses and dengue-like diseases and haemorrhagic fever. Aëdes aegypti, Aë. albopictus and Aë. scutellaris may act as vectors of these dengue fevers not only in areas where the disease has been long endemic but in areas into which the disease has been imported. An example of the latter instance are the severe dengue outbreaks in Greece in 1927 and 1928, in Japan during World War II and in the Caribbean.

TABLE 2

MOSQUITO-BORNE HAEMORRHAGIC FEVER AND DENGUE-LIKE FEVER

REPORTED TO WHO IN 1965

COUNTRY	Haemorrhagic fever		Dengue-like fever	
	Cases	Deaths	Cases	Deaths
WPRO				
American Samoa			-	-
Australia			2	-
British Solomon Islands			-	-
Cook Island			-	-
Fiji			32	-
Guam			-	-
Gilbert & Ellice			-	-
Hong Kong	neg. reports		-	-
Nauru			-	-
New Zealand	-	-		
Niue			-	-
Papua & New Guinea			16	-
Philippines				
Port of Manila	258	15		
Philippines	455	38		up to 16.10.65
Tahiti			535	-
Tonga			-	-
Western Samoa			-	-
SEARO				
India	49	1		...
Pondicherry			92	...
East Godavari			5460	...
West Godavari			1	...
Nagpur City			1	...
Nepal	-	-		up to 18.6.65
Thailand				
Bangkok & Thonburi	1417	31		
Thailand	974	121		
AMRO				
Antigua			8	-
Jamaica			36	-
Dominican Republic			Considered endemic no figures available	
Puerto Rico			89	-
Venezuela			3471	-

No figures are available for Dominica and St. Kitts-Nevis-Anguilla although epidemics are known to have occurred.

... Data not available

It can also be noted that the recent epidemics of dengue in the Western Pacific and South-east Asia have been expanding into whatever areas Aëdes (Stegomyia) are present and have now reached Ceylon.

Chikungunya vectors

In East Africa, chikungunya virus has been isolated from wild-caught Aë. aegypti, Aë. africanus, Culex fatigans and several Mansonia species. Laboratory and field evidence indicate that Aëdes (Stegomyia) species are most probably the vectors in nature.

In Bangkok, Thailand, several isolations of chikungunya virus have been made from pools of wild-caught Aë. aegypti, while but a single isolation was made from an extremely large number of C. fatigans pools; outside Bangkok, virus has been recovered from pools of C. tritaeniorhynchus and C. gelidus. It should be noted that C. tritaeniorhynchus is the prime vector of Japanese B encephalitis.

The epidemiology of chikungunya infection is further complicated by the evidence that there is also a transmission cycle other than man-mosquito-man; this was first noted in Africa when viremia was found in monkeys and neutralizing antibody in chimpanzee serum. The susceptibility of several African primates to chikungunya virus has been demonstrated.

In Thailand, the situation has been shown to be even more complex; chikungunya antibody was found in three out of nine horses sampled; a later survey of a number of domestic and wild animals around Bangkok showed horse, pig, water buffalo, monkey, rabbit, calf, dog, cattle and bats all to be positive for chikungunya antibodies in roughly that order of frequency.

Dengue and haemorrhagic fever vectors

As early as 1906 Aë. aegypti had been suggested as a vector of dengue and by 1916 dengue was transmitted by Aë. aegypti in human volunteers. Eventually, such experimental transmission was also demonstrated with Aë. albopictus and Aë. scutellaris while other species of mosquitos were found to be refractory.

The first actual isolation of dengue virus from wild-caught mosquitos was reported in 1960. These isolations, in the Philippines and in Thailand, resulted from investigations being carried out on the outbreaks of haemorrhagic fever which were first reported in Manila in 1954 and whose first sizeable outbreak occurred in 1956 and in Bangkok in 1958. The predominant mosquito species in the

Manila urban area were *Culex pipiens fatigans* and *Aë aegypti*, while in Bangkok *C. fatigans*, *Aë aegypti* and *C. tritaeniorhynchus* were most frequently found. Dengue type III was isolated from a pool of Manila *Aë aegypti* and isolations of dengue type II were made from pools of wild-caught Thai *Aë aegypti*.

Despite the recentness of these isolations, abundant epidemiological evidence had previously indicated that outbreaks of fevers caused by dengue and chikungunya virus could occur where *Aëdes* mosquitos were present and found in large numbers and would not occur in areas where they were either absent or found only in small numbers. Laboratory investigations had also shown that dengue virus would multiply in the body of the mosquito which could then transmit it following a period of incubation.

Following the first isolations of dengue virus from wild-caught mosquitos in the Philippines and Thailand, it was noted that haemorrhagic fever did not occur in areas where *Aë aegypti* was absent and only *Aë albopictus* present. As an example, *Aë albopictus* is a common pest mosquito in Hong Kong while *Aë aegypti* is completely absent. While dengue has frequently been reported from that city, there have been no cases of haemorrhagic fever. Despite this several researchers believe that *Aë albopictus* which, as noted above, has been demonstrated as capable of transmitting dengue, may have a role in the transmission or maintenance of etiological agents. The possibility of a transmission cycle involving monkeys or other animals is now under investigation.

Dengue in South-east Asia, had, in the late 19th century and early part of the 20th, been primarily a rural disease presumably transmitted by indigenous *Aëdes* species such as *Aë albopictus*. As urbanization intensified in this century and cities grew, *Aë aegypti* spread and increased its numbers in these cities with resulting epidemics of urban dengue disease. To-day, in Thailand and to a lesser extent in other countries of South-east Asia, *Aë aegypti* has spread even to small villages of a few tens of houses. In Thailand as well, haemorrhagic fever has begun to appear in rural towns and villages as well as in the largest population centres such as Bangkok and Chiengmai.

Haemorrhagic fever first appeared as an epidemic disease in Singapore in 1960, and mosquito virus surveys were begun in the same year. Dengue virus was recovered several times from pools of wild-caught *Aë aegypti* and on one occasion, for the first time, from *Aë albopictus*. While almost ten times as many *C. pipiens fatigans* were processed as *Aë aegypti*, no virus isolations were made from the former species.

Following the outbreak of haemorrhagic fever in Calcutta in 1963, a survey was made of *Aëdes* mosquitos in that City. *Aë. aegypti* and *Aë. albopictus* were both found to be common and, in addition, tolerant to DDT. Type IV dengue virus has been isolated from wild-caught *Aë. aegypti* in Vellore in Southern India.

Summarizing the work on isolation of virus from naturally infected mosquitos in the Philippines, Thailand and Malaysia, frequent isolations of both dengue and chikungunya have been made from *Aë aegypti*. A very few have also been made from *Aë. albopictus*, *C. gelidus* and *C. tritaeniorhynchus*. The latter was not, however, found capable of transmitting dengue experimentally despite its efficient role in transmitting other viruses. While *C. pipiens fatigans* was both the most common mosquito in these collections and the most common in the cities of South-east Asia, it is again emphasized that it has no apparent role in the transmission of dengue and haemorrhagic fever.

Both on the basis of epidemiological evidence and virus isolations, *Aë. aegypti* was incriminated as the vector in the recent dengue epidemic which occurred in the Caribbean and on the North-east coast of South America.

Dengue-like fevers have been known in the South-east Asia Region for more than 70 years, but epidemiological retrospective enquiries made in Bangkok (Thailand) have shown that no case histories resembling haemorrhagic fever can be found in the period from 1930 to 1954. This supports the opinion that a new disease or a syndrome has appeared or that the disease existing in the area for decades has changed its picture and become more serious.

Several theories explaining these events have been expressed:

(a) the possibility that new virulent mutants of dengue viruses have appeared;

(b) the introduction or modification of some environmental factor not yet known into the area, such as an increased urbanization;

(c) the changes in the degree of dengue endemicity or, perhaps, the introduction of a new serological type of dengue virus able to cause a damaging immunological response in patients previously infected with other dengue virus strains.

(d) The change of mosquito species density might also be a factor in causing epidemics.

In spite of the increasing amount of clinical, virological, immunological and epidemiological information collected in recent years, in individual countries of the South-east Asia Region, the information available is still too incomplete to permit us to analyze and synthetize sometimes conflicting data, especially on the following aspects:

(1) The role of chikungunya virus in the pathogenesis of haemorrhagic fever syndrome. Are the cases with definite haemorrhagic syndrome, sometimes fatal, which were described in the recent outbreak in Madras and caused by chikungunya virus, similar to or different from the cases of haemorrhagic fever reported in other parts of India and elsewhere in the Region?

(2) Do we have sufficient evidence that no child of European origin infected by dengue or chikungunya viruses, has developed an illness with symptoms of haemorrhagic fever or rather is the number of European or American children in South-east Asia too small and are these children living in different environmental conditions with regard to repeated exposure to the infection?

(3) Can haemorrhagic fever syndrome appear in areas where only one type of dengue group virus or chikungunya has been circulating in the human population in the last 3 to 5 years?

Recent outbreaks of dengue-like fevers with relatively frequent joint or arthritis manifestations and a long convalescent state clearly demonstrate the public health and economic importance of these diseases.

Alarming evidence of the changing picture of the disease and the possibility that severe manifestation can be more widespread not only in South-east Asia but also in other parts of the world, urges an increasing effort to study this complicated and difficult problem from all points of view:

(a) <u>clinical</u> and pathophysiological,

(b) <u>laboratory</u>, basic virological and immunological research,

(c) <u>vector</u>, its genetics, ecology and control, and

(d) <u>epidemiology</u>

The epidemiological studies should be oriented in different ways:

(a) in limited geographical areas (city or small part of a big city only), every case of dengue-like fever in the family or in the neighbourhood of the case of haemorrhagic fever will be studied very carefully and in one or more cities epidemiological investigations should utilize laboratory (virus, serology) and vector study methods. Agglomeration of haemorrhagic fever cases in small areas of a city will be used for a complete study of host, family or environmental factors.

(b) the second orientation of epidemiological studies being of a long-term surveillance type, is concerned mostly with the follow-up of the spread of infection in the human population of a given area and all conditions which are influencing this spread. To enable a global surveillance system to be built up, all cases of haemorrhagic fever and outbreaks of dengue-like fevers should be reported to WHO.

(c) Epidemiological studies will also be carried out in the receptive areas (in neighbouring South-east Asia):

1. where at the present time only one type of dengue group or chikungunya virus is circulating or had circulated recently;
2. in the area or areas where for a long period of time (one or two decades or more) there is no evidence that dengue group or chikungunya viruses have circulated in the human population, but where Aëdes aegypti is present.

Epidemiological (surveillance) studies can provide in advance important ecological information which will facilitate the better understanding of the whole process of spread of infection and possible control and preventive measures. Studies on the vector or vectors have already begun as will be described below.

Control

The WHO Seminar on Mosquito-Borne Haemorrhagic Fevers in Bangkok in October 1964 considered the various possibilities for control of the disease including vaccines. They reached the conclusion that "other than the control of the vector, Aëdes aegypti, no adequate preventive or control measures are available to deal with epidemics of dengue or chikungunya in urban areas.

No vaccine has as yet been developed that is considered suitable for use in areas of the outbreaks."

If control of this group of diseases is then dependent upon control of the vector there are two main lines of control which might be considered: the first is to reduce the population of the vector to a point where transmission of the disease would be interrupted; the second, to attempt the eradication of the vector. In considering the second of these possibilities, i.e. eradication, one has a precedent in the hemisphere-wide Aë. aegypti eradication programme which was initiated in the Americas in 1947. This programme is aimed at the elimination of Aë. aegypti as the urban vector of yellow fever in South and North America and the Caribbean. The mosquito has been eliminated from most of South America, Central America and all of Mexico - a total of 18 countries and territories. An eradication programme has just been initiated in the United States. Despite the very considerable success already achieved, eradication has not been successful on the North-east coast of South America and on several islands of the Caribbean and there have been a number of re-infestations of areas from which the mosquito had already been eliminated. These set-backs have been due both to administrative failures in the organization of certain campaigns and to the appearance of a very high level of insecticide resistance. In a recent review of the extent of this resistance, it was observed that susceptibility tests done in 64 localities in 16 countries and territories covering almost all the Caribbean area, indicate that there are now no known populations in this area which can be considered susceptible to either DDT or dieldrin. In fact, most of the reintroductions which have occurred, have been of strains of the species which are resistant to DDT and dieldrin; in some places tolerance to malathion, diazinon and to some degree fenthion, has also developed.

Inasmuch as such a high degree of insecticide resistance has been found to occur in the western hemisphere, the Organization has initiated a global survey of insecticide susceptibility in order to determine the present extent of resistance in those parts of the world where Aëdes (Stegomyia) species are either now vectors of disease or might become so should the diseases be introduced. A centre in Paris has been designated to receive eggs collected from the field and to test the emerging larvae for resistance. It has already been determined that resistance to the chlorinated hydrocarbon insecticides is widespread in the Western Pacific, South-east Asia and to a lesser extent in Africa. It is thus most unlikely that any of the insecticides in this group could be utilized in a wide-scale campaign. Much of this resistance has undoubtedly occurred due to exposure to DDT or dieldrin.

Another serious limitation upon considering any eradication campaign in South-east Asia for the moment is the lack of sufficient information on the vector mosquito or mosquitos, including as basic a question as their distribution and density. In order to remedy this serious lack of information, the Organization has also commenced a global survey on the distribution and density of Stegomyia mosquitos. It is apparent that the group, and especially Aë. aegypti is extremely dynamic at least in some parts of its range. However, in the Mediterranean basin, genes for insecticide resistance do not appear to be frequent and in many countries including Greece, Italy, Israel, etc. the species has disappeared despite the absence of any insecticide campaigns aimed specifically at this mosquito. Part of the reason for this disappearance has been the general increase in the level of environmental conditions including a great increase in piped water supplies. Aë. aegypti, Aë. africanus, and several other of the Stegomyia group appear to have originated in Africa, south of the Sahara; in this area they are found both in urban centres and in the smallest of villages, both associated with man and breeding in the rain forest, feeding on primates and other animals. In South-east Asia, the distribution of Aë. aegypti is probably broader than has been previously thought and just as urbanization has resulted in a great increase in numbers of C.p. fatigans, this species as well has increased, probably at the expense of Aë. albopictus. It is clear that as a preliminary step to any sizeable control programme, even one aimed at only reducing the mosquito population to a point at which transmission of disease will no longer take place, far more information must be obtained on the ecology and population dynamics of Aë. aegypti and albopictus. Only when such information is available can a scientifically based control programme be initiated, aimed at reducing the vector population and stopping transmission. To this end, the Organization is establishing an Aëdes Research Unit in Bangkok to undertake studies on the population dynamics, ecology, distribution, vectorial capacity, behaviour and insecticide susceptibility of Aë. aegypti and albopictus. At the same time advantage is being taken of the WHO scheme for the evaluation and testing of new insecticides to examine, with a high priority, new larvicides and new larvicide formulations which may have a substantial toxicity to Aëdes larvae coupled with a sufficiently low mammalian toxicity to enable them to be considered for application to drinking water - apparently the common source of Aë. aegypti breeding in South-east Asia and the Western Pacific. Based on the genetic and behavioural studies which will be carried out by the Aëdes Research Unit, consideration will also be given to the utilization of other control techniques such as the sterile male technique, biological or genetic control.

Concomitant with the above, health education programmes must emphasize the need for encouraging the public to assist by eliminating the domestic and peri-domestic breeding places of Aëdes larvae. It is recognized, however, that such education would necessitate changing many traditional practices of water storage which are not even completely eliminated by the introduction of piped water supplies; it is for this reason that much reliance must still be placed on insecticidal control or other control methods based on the studies now begun.