

CHIKUNGUNYA INFECTION- AN EMERGING DISEASE IN MALAYSIA

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Abstract. Many countries neighboring Malaysia have reported human infections by chikungunya virus, a mosquito-borne togavirus belonging to the genus *Alphavirus*. However, although there is serological evidence of its presence in Malaysia, chikungunya virus has not been known to be associated with clinical illness in the country. An outbreak of chikungunya virus occurred in Klang, Malaysia, between December 1998 and February 1999. The majority of the cases were in adults and the clinical presentation was similar to classical chikungunya infections. Malaysia is heavily dependent on migrant workers from countries where chikungunya is endemic. It is speculated that the virus has been re-introduced into the country through the movement of these workers.

INTRODUCTION

Chikungunya virus is a mosquito-borne togavirus belonging to the genus *Alphavirus* and is responsible for extensive urban disease in Africa and Southeast Asia. It is known to cause severe arthralgia, often accompanied by arthritis and other systemic symptoms. Several other togaviruses such as O'nyong-nyong, Mayaro, Ross River virus, Barmah Forest virus, some strains of Sindbis and rubella have been associated with a similar disease syndrome. Chikungunya virus was first isolated in Tanzania during a 1952 to 1953 epidemic (Ross, 1956). The local tribal word *chikungunya* meaning "that which contorts or bends up" was given to the virus and the disease as an apt description of the clinical syndrome. Hammon *et al* (1960) documented the first appearance of the virus in Southeast Asia by isolation during an intense epidemic of dengue fever and dengue hemorrhagic fever in Bangkok, Thailand, in 1958. Clinically, the disease can resemble classical dengue fever and in dengue endemic countries, this can give rise to confusion and misdiagnosis. The virus continued to be active in Thailand until the 1970s, after

which it almost disappeared. The reasons for this decline were unclear because the mosquito vector, *Aedes aegypti*, was abundant and dengue transmission remained unabated. In 1988 evidence of chikungunya transmission in Thailand re-emerged, but the pattern was one of occasional outbreaks rather than severe epidemic disease. Besides Thailand, cases of chikungunya fever have also been reported in Cambodia (Chastel, 1963), Vietnam (Vu-Quidai and Kim-Thoas, 1967), and Myanmar (Khai Ming *et al*, 1974). A series of epidemics have been reported from Sri Lanka (Hermon, 1967), Calcutta (Shah *et al*, 1964), and the southern Indian cities of Madras, Vellore, Nagpur, and Maharashtra State (Myers *et al*, 1965; Padbidri and Gnaneswar, 1979). Antibody surveys indicated that chikungunya has also been active further east in the Pacific, including Indonesia (Slemons *et al*, 1984) and the Philippines (Campos *et al*, 1969; CDC, 1986; Macasaet *et al*, 1969; Manaloto *et al*, 1988).

Three alphaviruses (Getah, Bebaru and Sindbis) have been isolated in Malaysia, but they have not been associated with clinical infections, except a single case of mild fever attributed to Sindbis (Lim *et al*, 1972). A

serological survey for alphaviruses conducted by Marchette *et al* (1978) in Peninsular Malaysia showed that chikungunya antibody was detected in persons older than 20 years and proportionately larger number in the northern states bordering Thailand such as Perlis, Kedah and Kelantan. A second study by Marchette *et al* (1980) showed specific hemagglutination inhibition and neutralizing antibody in a chicken in Kelantan and a pig in Kedah, further supporting chikungunya activity along the Malaysia-Thailand border. They found that Malays, who are largely rural and aborigines, who are forest-dwellers, had higher frequencies of chikungunya antibody, and suggested that monkeys could serve as important vertebrate hosts. In their study conducted on Carey Island where monkeys are abundant in the mangrove and in plantations, chikungunya antibody was also demonstrated in plantation workers at a higher frequency. Despite the high antibody prevalence in man, there has been no report of clinical disease associated with this virus.

From 6th December 1998 to 28th February 1999, an outbreak of fever, rashes and joint pains occurred in Klang, 25 kms from Kuala Lumpur. Those affected lived in an area with poor sanitation and unsatisfactory refuse disposal. This paper documents the outbreak that was subsequently proven to be due to chikungunya virus.

MATERIALS AND METHODS

Outbreak profile

The onset of the first case was 6th December 1998 and the last case was 28th February 1999 (Fig 1). A resident of Taman Kem in Klang in January 1999 alerted the Klang Health Authority that at least 20 residents were ill with fever, rashes followed by swelling and joint pains in the hands and legs. The outbreak area was confined to 8 blocks of low-cost flat houses (572 units), 90 squatter houses and 4 blocks of 100 units of long houses. It was estimated that about 4,000 people were living in Taman Kem at the time of the outbreak. The sanitation was poor and refuse disposal system

was not satisfactory. Rubbish heaps were scattered around the area and the drains were clogged and filthy. Due to low water pressure the residents stored water in open containers. Active case detection was carried out in the epidemic area. Cases were treated as outpatients by general practitioners or in the Port Klang Government Health Center.

Patients

The total number of patients involved in the outbreak was 51. Thirty-two patients in the acute stage with fever and joint pains were admitted and 19 were treated as outpatients. Among the 32 admitted patients, 22 had adequate data for analyses.

Laboratory testing

The routine laboratory tests conducted were full blood count, ESR, renal profile and liver function tests. Standard serological tests were used for antibody to dengue, rubella, typhus, typhoid, Epstein-Barr virus, rheumatic fever, syphilis, and collagen diseases.

Alphavirus serology

Serological tests for the arthritogenic alphaviruses chikungunya, Ross River virus (RRV), Barmah Forest virus (BFV) and Sindbis were performed at the Western Australian Center for Pathology and Medical Research. Hemagglutination inhibition (HI) antibody was measured by standard methods using chikungunya, RRV, BFV and Sindbis hemagglutinins prepared from the supernatant of virus-infected Vero cells, and assayed using goose erythrocytes. IgM to these viruses was measured by an indirect immunofluorescent antibody assay. Antigen was prepared by infecting a Vero cell monolayer on a glass slide with virus and incubating at 35°C until discrete foci of infection were apparent, after which the slide was fixed in 100% acetone for 10 minutes at room temperature, before being stored at -70°C for future use. Ten microliters of patient serum was adsorbed with 50 ml goat anti-human IgG (PanBio, Australia) at 1 : 5 dilution and 50 µl of HUT 78 cell lysate (2

$\times 10^7$ cells/ml). This was then used for an indirect immunofluorescent assay, with detection of bound IgM by fluorescein isothiocyanate conjugated rabbit anti-human IgM (Dako, USA).

RESULTS

The epidemic curve (Fig 1) shows a fairly even spread of cases over the outbreak period with no obvious peak. The ages of the patients ranged from 16 to 59 years with the majority in the 30-39 years age group (29.4%) and the 40-49 years age group (31.4%). 76.5% were females and Indians formed the majority (72.5%)

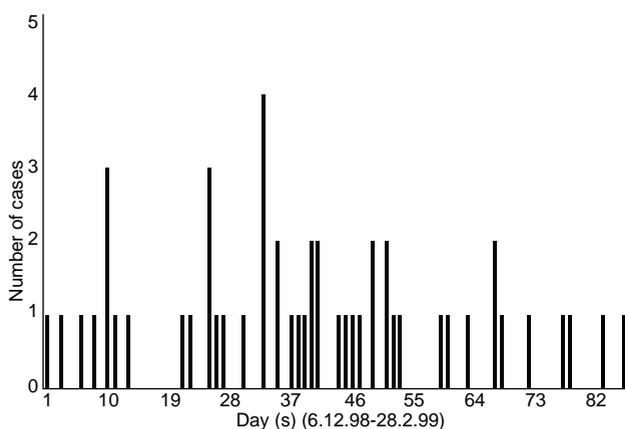


Fig 1—Epidemic curve of chikungunya infection.

followed by Malays (25.5%) and Chinese (2%). The patient composition based on race was consistent with the ethnic composition of the epidemic area.

Thirty-two patients were admitted with similar clinical triad of fever, rash and arthralgia but data were obtained from only 22 patients for analyses (Table 1). All the 22 patients were from the outbreak area and all had a history of fever lasting 2-5 days. The temperatures were high grade between 38°C to 40°C and in some patients, there were chills but no rigors. Myalgia was a common feature in up to 50% of them. In addition, backache was a frequent initial complaint with some being bedridden at home causing them to seek treatment later. A transient maculopapular rash lasting 2-3 days involving the trunk and limbs appeared from the second to seventh day. This rash was seen in 50% of admitted cases with a few complaining of it being pruritic. Up to 80% of patients had some form of joint involvement, either arthralgia or arthritis. The latter was a migratory polyarthritis of small joints of hands and feet, but it also involved large joints. Sore throat and retro-orbital pain as seen in other common viral infections were not prominent in this outbreak. Lymphadenopathy and hepatosplenomegaly were absent in all patients.

Table 1
Symptoms and signs of chikungunya infection.

Symptoms	Present		Absent	
	No.	Percentage (%)	No.	Percentage (%)
Fever	22	100	0	0
Myalgia	11	50	11	50
Sore throat	2	9	20	91
Backache	11	50	11	50
Headache	11	50	11	50
Retro-orbital pain	3	14	19	86
Rash	11	50	11	50
Small joint only	0	0	0	0
Large joint only	4	18	0	0
Small/large joint	14	64	0	0
No joint symptoms	4	18	0	0

Routine laboratory tests showed that the total WBC count was in the normal range with the platelet count being above 130,000/mm³ in all patients. The follow-up counts did not show any change. The ESR was moderately elevated at 70 mm/hour. The renal function and liver enzymes were normal.

All patients were treated symptomatically with analgesics and anti-pyretics and were discharged well although two patients continued to have arthralgia beyond two weeks after discharge. In some cases, the arthralgia persisted for longer than six months. In those who had arthralgia beyond six months, hydroxychloroquine was prescribed for 3-6 months.

Six patients were initially tested for alphavirus antibodies. All showed high HI titers (1:160->1:640) and positive IgM to chikungunya virus. Most also showed high titers to Sindbis and some had significant HI titers to RRV. However, IgM tests were negative for all alphaviruses other than chikungunya, and these other reactions may be due to past Sindbis infection and/or cross-reacting IgG. Serological tests for the other potential infectious causes and for autoimmune diseases were negative. Samples subsequently obtained from a further 19 patients showed 13 with high HI titers and a positive IgM to chikungunya virus. A further two patients had high HI titers but a negative IgM, perhaps due to deterioration of IgM during transport between Malaysia and Australia. Four patients had negative HI titers and IgM and may have been sampled too early in the course of the illness.

DISCUSSION

Although there has been serological evidence of chikungunya activities in Malaysia, no documented case of clinical disease has been reported until now. This present epidemic took place in a known dengue-prone area where the *Aedes* mosquito index had been high since December 1998 with an *Aedes* survey reading of 3.2 on 26th January 1999 and 2.7 and 2.3 on 3rd February. The source of the mosquito

breeding was mainly in uncollected rubbish and water storage containers. The situation was worsened because of many construction sites abandoned due to the economic recession in the country at that time and found to be breeding mosquitos.

In the serological survey conducted by Marchette *et al* (1980), chikungunya virus was found to be active in the states of Perlis, Kedah and Kelantan which are adjacent to the Malaysia-Thailand border. Chikungunya antibody was found more frequently in the 0-19 year-age group. However, in the more urban areas of Malaysia, there was almost a complete absence of chikungunya antibody in children and young adults. Prior to this outbreak, there was no evidence of transmission of chikungunya virus within urban areas or any areas south of the border regions. Marchette *et al* (1978) had speculated that the introduction of the virus from contiguous epidemic could result in a widespread epidemic of the disease since *Aedes aegypti* was prevalent in all urban areas. That is presumed to have been the origin of this outbreak in Klang.

Malaysia is heavily dependent on migrant workers from neighboring countries, including those in which chikungunya virus is endemic. It has been estimated that there are almost 2 million migrant workers in the country, of whom half may have entered illegally. Therefore there was a substantial risk of a viremic worker introducing this virus into new areas within Malaysia.

Once the outbreak was confirmed to be mosquito-borne, epidemic control measures, including public health education and active case detection, were initiated. House to house fogging was conducted and active source reduction brought the epidemic to an end within a few weeks.

Since the re-introduction of the virus during this outbreak, the disease has become endemic in Malaysia. This demonstrates that if all the necessary epidemiological factors are in place, a disease such as chikungunya can re-emerge and become a public health concern.

ACKNOWLEDGEMENTS

This project is funded by a grant from the Ministry of Science, Technology and the Environment, Malaysia (IRPA R&D Grant No. 06-02-03-0307). We wish to thank the Ministry of Health, Malaysia, for allowing us to help in the investigation of this outbreak.

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