CLINICAL CHARACTERISTICS AND METEOROLOGICAL PATTERNS OF ZIKA VIRUS INFECTION IN CHIANG MAI PROVINCE, THAILAND

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Abstract. Zika virus is an emerging mosquito-borne pathogen, with outbreaks occurring worldwide. However, clinical characteristics and meteorological patterns of Zika infection are not well established. In 19 cases of confirmed Zika infection in Chiang Mai from June - November 2016, rash was the most common (89%) symptom, followed by conjunctivitis (53%), fever (47%), arthralgia, headache and malaise/fatigue (each 37%), and myalgia (32%). Zika-infected subjects had visited a Zika virus-infected area within the previous two weeks or resided within a 100-m radius of an individual with Zika infection. Emergence of Zika virus cases followed onset of rainfall by approximately one month.

Keywords: Zika virus infection, clinical manifestation, meteorological pattern, Chiang Mai, Thailand

INTRODUCTION

Zika virus is an emerging mosquito-borne pathogen (arbovirus) in the genus *Flavivirus* and family Flaviviridae (Musso and Gubler, 2016).This virus was first isolated in 1947 by Dick *et al* (1952) from serum of a rhesus monkey in Uganda's Zika Forest and from mosquitoes in Africa in the following year (Dick *et al*, 1952; Musso and Gubler, 2016). Transmission occurs through the mosquito *Aedes* genus of the Culicidae family in a sylvatic cycle involving nonhuman primates (Haddow *et al*, 2012).The first epidemic outside Africa and Asia occurred in 2007 in the Yap Islands of Micronesia (Duffy *et al*, 2009). A Zika virus outbreak in French Polynesia from 2013-2914 involved over 28,000 cases (Musso, 2015). Zika virus has spread rapidly across Latin America and the Caribbean, and is now pandemic in over 20 countries (Fauci and Morens, 2016).

Three Zika virus cases were first reported in Ratchaburi Province, Thailand, in March 2012 followed by two cases in Lamphun and Si Sa Ket Province in 2013; and in 2015, there were two cases reported in Phetchabun Province (Buathong *et al*, 2015). These seven cases of acute Zika virus infection among Thai residents were from different regions of the country. In Chiang Mai Province, located in the north of Thailand, the first index case of Zika virus disease was in a traveler who had returned from an epidemic area of Phetchabun Province in June 2016, and an outbreak in Chiang Mai Province

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occurred after that. These local cases, combined with reports among travelers, provided evidence that Zika virus is present in a somewhat widespread fashion in Thailand (Bureau of Emerging Infectious Disease, 2014; Buathong *et al*, 2015).

However, studies on the clinical characteristics and meteorological patterns of Zika virus infection are limited (Duffy *et al*, 2009; Fauci and Morens, 2016). Few clinically suspected cases are laboratory confirmed (Cardoso *et al*, 2015). Furthermore, in all endemic or epidemic regions, Zika virus co-circulates with other arboviruses, including chikungunya and dengue (Cardoso *et al*, 2015). Thus, the aims of our study were to describe the clinical features and meteorological patterns of Zika virus infections in northern Thailand.

MATERIALS AND METHODS

Sample collection

This study was reported during the Zika outbreak occurring in Chiang Mai Province, Thailand from June to November 2016. We retrospectively collected clinical data of signs and symptoms from the Chiang Mai Provincial Public Health Office. A number of patients were tested for the presence of Zika virus by RT-quantitative (q)PCR in serum. However, all cases of infection with Zika virus infection were confirmed using RT-qPCR in urine. Demographic characteristics of the patients (age, occupation, location and type of house) were recorded.

Based on Chiang Mai Provincial Public Health Office guidelines, a full ethics review of the study was not required; however, verbal consent from all patients involved were obtained.

RT-qPCR assay

RNA from serum and urine was extracted using the QIAamp viral RNA Extraction Kit (QIAGEN, Hilden, Germany). RT-qPCR assay performed using an in-house method adapted US-CDC protocol (CDC, 2016) for detecting all known genotypes (genes E and NS2b) of Zika virus.

Meteorological measurements

The meteorological measurements were performed at the Northern Meteorological Center, Chiang Mai. Rainfall (mm), sunshine (hour), temperature (°C), and humidity (%) in epidemic areas were measured during March to November, 2016.

RESULTS

Cases

From June-November 2016,19 cases (6 males and 13 females) were investigated by the Chiang Mai Provincial Public Health Office. All 19 cases had laboratory confirmation of infection with Zika virus using RT-PCR in the urine (Table 1). Five (45%) patients were positive by RT-qPCR of serum. The youngest case was 9 years old and the oldest 74 years old, with a mean age of 36± 20 years. The most common occupations were contractor (32%), student (26%) and office worker (21%) (Table 1). The most common symptoms were rash (maculopapular or erythematous) (89%), conjunctivitis (53%) and fever (generally low-grade) (47%), arthralgias (37%), malaise/fatigue (37%).and myalgias(32%). Rash [on arms (100%), legs (94%) and trunk (94%), and face (76%)] appeared within 2 ± 1 days(mean ± SD) from onset of fever. One patient was hospitalized and two patients were pregnant. The peak of the Zika virus infection in Chiang Mai Province occurred in August, 2016.

The first locally acquired (index) case of Zika virus disease was reported

Table 1
Demographic characteristics, signs, symptoms and clinical course of 19 patients with Zika virus infection, Chiang Mai Provincial Public Health Office, Chiang Mai, Thailand, June 1, 2016 - November 20, 2016.

Characteristic	Number of patients (%)
Age (mean ± SD)(year)	36 ± 20
Female	13 (68)
Male	6 (32)
Occupation	
Office worker	4 (21)
Business person	2 (10.5)
Home worker	2 (10.5)
Student	5 (26)
Contractor	6 (32)
Number of people in household (mean ± SD)	4 ± 2
Pregnant	2 (10.5)
Hospitalized	1 (5)
Signs and symptoms	
Rash	17 (89)
Face	13 (76)[a]
Arms	17 (100)[a]
Legs	16 (94)[a]
Trunk	16 (94)[a]
Days from symptom onset to rash (mean ± SD)(day)	2 ± 1
Median time of rash (minimum, maximum)	2 (1, 4)
Fever	9 (47)
Conjunctivitis	10 (53)
Arthralgia	7 (37)
Myalgia	6 (32)
Headache	7 (37)
Malaise/fatigue	7 (37)
Limb swelling	2 (10.5)
Nausea/vomiting	1 (5)
Diarrhea	1 (5)
Positive by RT-qPCR in serum	5 (45)
Negative by RT-qPCR in serum	6 (55)
Positive byRT-qPCR in urine	19 (100)

[a]N = 17.

in a traveler returning from Phetchabun Province (epidemic area). Eleven (58%) cases had a recent travel history (within 2 weeks) to Zika virus infected areas. Nine (47%) cases resided within a 100-m radius of a patient with Zika virus (Table 2).

Meteorological patterns in the epidemic area

During the outbreak of Zika virus infection, there were two periods of different meteorological patterns (Fig 1). In the first period (March to May), only 0-2.76 mm

Table 2
Previous medical history of 19 Zika virus infected patients, Chiang Mai Provincial Public Health Office, Chiang Mai, Thailand, June 1, 2016 - November 20, 2016.

Previous medical history	Number of patients (%)
Contact with a person who is or has been traveling in an area of local transmission of Zika virus within the last three months.	5 (26)
Other family member with Zika virus infection during the past three months.	2 (10.5)
Recent travel history (within two weeks) to Zika-affected areas.	11 (58)
Living within a radius of 100 m from a Zika virus-infected individual's house.	9 (47)
Living in a tenement house.	2 (10.5)

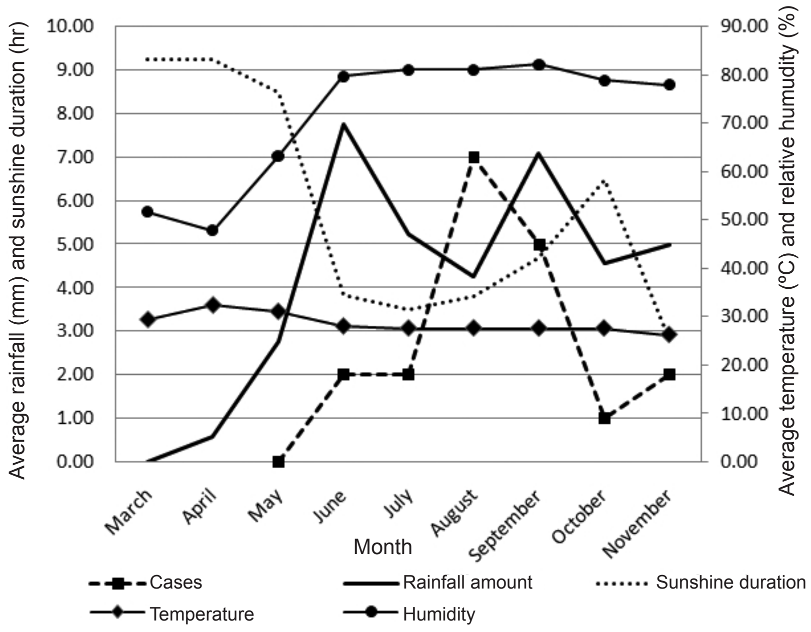

Fig 1–Monthly number of Zika virus cases, rainfall (mm), sunshine (hour), temperature (°C), and humidity (%) in epidemic area Chiang Mai, Thailand from March to November, 2016. Cases were from Chiang Mai Provincial Public Health Office and meteorological data from the Northern Meteorological Center, Chiang Mai.

of rainfall, with humidity ranging 47.9-63.1%, sunshine 8.5-9.3 hours, and temperature 29.4-32.4°C. In the second period (June to November), 4.26-7.76 mm of rainfall (average of 5.65 mm), with humidity ranging 79.8-82.2%, sunshine 2.8-6.5 hours, and temperature 26.3-27.6°C. Emergence of Zika virus cases followed onset of rainfall by approximately one month.

DISCUSSION

According to the CDC, the most common symptoms of Zika infection are fever, rash, joint pain, and conjunctivitis (CDC, n.d.). In our study, rash was more common than that (77%) reported in a surveillance series for Zika virus disease from Puerto Rico (Thomas *et al*, 2016). However, myalgia, arthralgia and fever in our study was less frequent than that (77%, 73% and 73%, respectively) reported from Puerto Rico (Thomas *et al*, 2016).

A Zika virus rash differs from a dengue fever rash, the latter appears in only about 50% of patients usually around the time of defervescence (days 5-7 after onset of fever) (Schwartz *et al*, 1996; Wilder-Smith and Schwartz, 2005). Whereas for Zika virus infection, a rash appeared in about 90% of cases, usually around day 2 after fever onset. Furthermore, the majority of Zika virus patients have normal leukocyte and thrombocyte counts, whereas dengue infection is characterized by marked leucopenia or thrombocytopenia (Schwartz *et al*, 1996; Wilder-Smith and Schwartz, 2005).These differences between Zika and dengue virus infection are used as an aid for differential diagnosis. Other symptoms such as headache, fatigue, myalgia and arthralgia occur in both Zika and dengue virus infections (Schwartz *et al*, 1996; Wilder-Smith and Schwartz, 2005; Meltzer *et al*, 2016).

Although symptoms of Zika virus disease are usually mild, most people fully recover without severe complications and hospitalization rate is low (Panchaud *et al*, 2016). However, Zika infection during pregnancy is correlated with congenital microcephaly, fetal malformation and fetal loss (Chan *et al*, 2016; Panchaud *et al*, 2016). Abnormalities among infants born from infected mothers consist of widespread brain calcifications and ventricular enlargement secondary to cerebral atrophy (Chan *et al*, 2016; Panchaud *et al*, 2016). In this study, the two Zika virus-infected pregnant mothers had no adverse pregnancy outcome and both infants were normal.

The first-line test and definitive diagnosis for Zika virus infection is made by identifying Zika virus RNA by means of RT-PCR (Gourinat *et al*, 2015). While 6 patients in our study cohort tested negative by RT-qPCR in serum, results were positive for urine of all patients. Viremia is transient, which may explain this result; thus, testing using RT-qPCR in serum is most reliable when performed within the first week of infection, whereas Zika virus RNA remains detectable for up to two weeks in urine (Lanciotti *et al*, 2008; Gourinat *et al*, 2015).

Previous exposure to a Zika virus-infected area was an important factor in becoming infected. Moreover, to the best of our knowledge, the present study is the first to observe a relationship between an outbreak of Zika virus infection and meteorological pattern. Because *Aedes aegypti* is the most common mosquito vector of Zika virus, reducing the mosquito habitats is a necessary control measure.

The weakness of the current study is the small sample size was a limitation of this study and our results need further confirmation and validation using a larger sample size and more extended longitudinal observation of meteorological patterns.

In summary, the most common signs and symptoms of Zika virus infections were rash, conjunctivitis and fever. Recent visit to a Zika virus-affected area and residing within the vicinity of an infected individual were risk factors for becoming infected. A particular meteorological pattern might play a role in the onset of Zika virus epidemicity.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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