

# Outbreak Investigation of Dengue with Unusual Manifestation, Ratchaburi Province, Thailand, March 2012

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## Abstract

More than 100 arboviruses can cause a systemic febrile illness with headache, arthralgia and rash. In March 2012, Bureau of Epidemiology was notified about a cluster of maculopapular rash with fever and poly-arthritis/-arthralgia in Ratchaburi Province. New cases were increasing although the local team implemented prevention and control measures. A joint investigation was later initiated to confirm the diagnosis of the outbreak. An active case finding was conducted, including an environmental survey and laboratory investigation. A case was defined as a person in 4 affected villages who developed undifferentiated maculopapular rash, with/without fever or joint symptoms during 1 February-23 March 2012. Of 33 cases identified, the first case developed symptoms on 11 February followed by his family members. Number of cases rose in 4 villages within a month, with attack rates between 0.1 percent and 2.5 percent. The first affected village was in the center of these villages. Eighty percent of cases were adults. Main clinical manifestations included generalized maculopapular rash (100%), fever (55%) and joint involvement (52%). In an environmental survey, the thicket, many mosquito breeding containers, abundant mosquitoes and no gathering activities of people in these 4 villages were reported. The villagers did not use Temiphos or *Poecillia* and any mosquito repellent. ELISA antibody test was positive for dengue virus IgM in 11 of 18 cases (61.1%). Entomological investigation found that 37 of 40 collected mosquitoes (93%) were *Aedes aegypti* and the RT-PCR identified dengue serotype 2 (DEN-2) in mosquitoes in 2 of 4 houses (50%). This unusual outbreak was in late summer and most likely caused by dengue infection, yet mostly affected adults. After strengthening prevention and control measures, the outbreak was subsided. Dengue prevention and control measures are very important because the people who previously infected with prevailing DEN-1 virus can develop the severe form of dengue hemorrhagic fever if they are re-infected with DEN-2 virus.

**Key words:** dengue, mosquito, maculopapular rash, poly-arthritis, poly-arthralgia

## Introduction

Arboviral diseases are any diseases caused by viral infections which are transmitted by arthropods.

Most of them spread by infected mosquitoes. More than 100 known arboviruses are capable of causing a systemic febrile illness that often includes headache,

arthralgia, myalgia, and rash. Although most arboviral infected patients are not severe cases and can expect a full recovery, some viruses also cause more severe, prolonged symptoms including severe joint pain<sup>(1-3)</sup>. In Thailand, common arboviral diseases which have been reported in rainy seasons, May-September, were dengue and chikungunya<sup>(4)</sup>. Ratchaburi province is one of the hyper-endemic areas of dengue, most common serotype in this province is serotype 1<sup>(5)</sup>. Only one chikungunya outbreak was reported in Ratchaburi province in 2009<sup>(6)</sup>.

However before the beginning of the rainy season, 2012, the Bureau of Epidemiology (BOE) was notified by Ratchaburi provincial health officers about a cluster of maculopapular rash (MP rash) with fever and poly-arthritis/-arthralgia in 4 villages of Ratchaburi Province. These clinical manifestations were not specific and could not lead to definite diagnosis of dengue or chikungunya or any other arboviral diseases. Moreover, new cases were still reported although the local Surveillance Rapid Response Team (SRRT) implemented initial prevention and control measures including thermal fogging, ultra-low-volume (ULV) fogging, and mosquito's larva elimination. A joint investigation was later initiated by BOE and local SRRT teams to identify disease etiology and diagnosis, to determine the extent of the outbreak and recommend appropriate prevention and control measures.

## Methods

### Descriptive study

Preliminary results of a local investigation team were reviewed to gain relevant information on the outbreak and an active case finding was conducted in a community survey. Medical records of possible OPD cases at Photharam hospital were reviewed.

The inclusion criteria of cases for the community survey were residents in Village 2, 3,4 and 7 of Klong Ta Kot subdistrict, Photharam district,

Ratchaburi province who developed at least 1 of 3 criteria:

- 1) undifferentiated MP rash
- 2) any new joint involvement
- 3) acute fever with any of dengue/ chikungunya signs and symptoms, excluding only fever with upper respiratory tract signs and symptoms

Criteria for including medical records in Photharam hospital in this review were any patients who lived in Klong Ta Kot subdistrict, Photharam district, Ratchaburi province and were diagnosed with any of ICD-10 (International Classification of Diseases-10) (Table 1)<sup>(7)</sup> from 1 January to 20 March 2012.

Data abstraction form was used in data collection which included demographic data, exposure factors, onset date of illness, clinical signs and symptoms of patients, laboratory results, diagnosis and treatment.

### Environmental study

An environmental survey was carried out in Village 2, 3 and 4, Klong Ta Kot subdistrict, Photharam district, Ratchaburi province to observe human behavior, mosquito habitat, mosquito breeding containers including mosquito larvae in water containers. Moreover, adult mosquitoes were collected, direct landing catches of mosquitoes from human bait, inside and outside of 4 patients' houses for species identification at Thailand National Institute of Health.

**Table 1** ICD-10 coding used for including medical record

| ICD-10 code | Titles  |
|-------------|---|
| A90         | Dengue fever  |
| A92         | Chikungunya fever   |
| B05         | Measles   |
| B06         | Rubella   |
| L50         | Urticaria   |
| R21         | Rash and other non specific skin eruption   |
| Y400-599    | Drug medicaments and biological substances causing adverse effects in therapeutic use |

### Laboratory investigation

#### Human serum samples

Human serum samples were collected from 18 villagers and tested with following techniques;

- Rapid screening test (ELISA test kit) for Rubella and Dengue virus (DENV)<sup>#</sup>
- ELISA IgM and IgG for DENV, chikungunya virus (CHIKV) and Japanese encephalitis virus (JE virus)\*
- RT-PCR for CHIKV, DENV and Alpha-virus\*
- Viral isolation for Flavivirus and Alphavirus\*
- Viral genomic detection by Next Gen Machine<sup>§</sup>

All acute serum samples were collected within 3 days of fever onset and convalescent serum samples were collected 14 days after the onset.

#### Entomological laboratory investigation

All collected adult mosquitoes were sent for mosquito species identification and testing by Real Time PCR for CHIKV and DENV\*.

#### Data analysis

This study used proportion to present the result of quantitative data analysis. Median with range was used in age variable analysis.

## Results

### Descriptive study

In the community survey, 33 patients met the case definition. Based on medical record review, there were 13 OPD patients diagnosed with the diseases classified in ICD-10 coding criteria but only 4 of them met the case definition. As such, a total cases in this outbreak remained 33 as the 4 OPD cases had already been identified in the community survey.

This outbreak occurred in Village 2, 3 and 4, Klong Ta Kot subdistrict, Photharam district, Ratchaburi province. The first case was a 59-year-old Thai male in Village 3 which was surrounded by others-2, 4 and 7 (Figure 1). He developed symptoms on 19 February 2012 and the next two cases -including the index case- were his family members, living in the same house. Number of cases rose in 4 villages within a month. The four cases in Village 4 were in the same family living under the same roof. No gath-

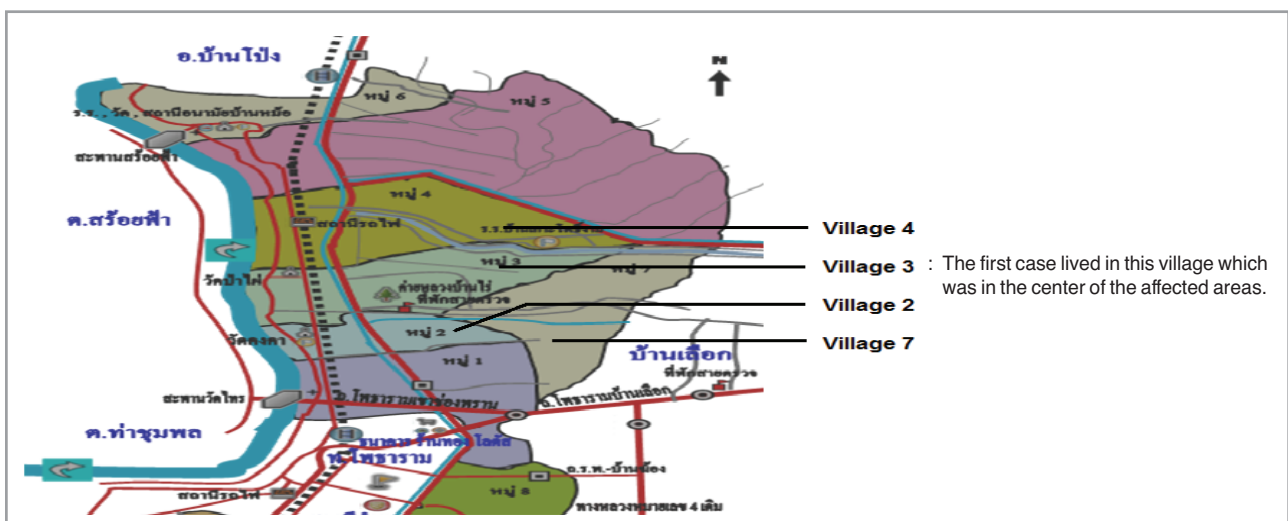


Figure 1: Map of affected village (Village 2, 3, 4 and 7) in Klong Ta Kot subdistrict, Photharam district, Ratchaburi province

Remark: # Bureau of Epidemiology team,  
\*Thailand National Institute of Health  
§ Japan National Institute of Health

ering activities of people in these 4 villages were reported. As the distances between the houses of the first and the others were within 300 meters, the infection seemed to jump from one village to another (Figure 2) forming many small clusters of cases (Figure 3). The local SRRT had implemented prevention and control measures, including thermal fogging, ultra-low-volume (ULV) fogging and eliminating mosquito's larva since March 9 before the Bureau of Epidemiology team joined an investigation on March 20.

Village 2 had the highest attack rate (12/474:

2.5%), followed by Village 3 (16/1,042: 1.5%), Village 4 (4/1,545: 0.3%) and Village 7 (1/1,302: 0.1%). The proportions of affected houses to the total number of houses in respective villages were in the same rank of order of the attack rates of cases, 7.3, 2.9, 0.6 and 0.3 percent respectively.

Eighty percent of cases were in adulthood with the highest proportion among the 31-60 year age group (Figure 4). The median of age was 35 years old (range: 8 months - 68 years). Male to female ratio was 1 to 2.6.

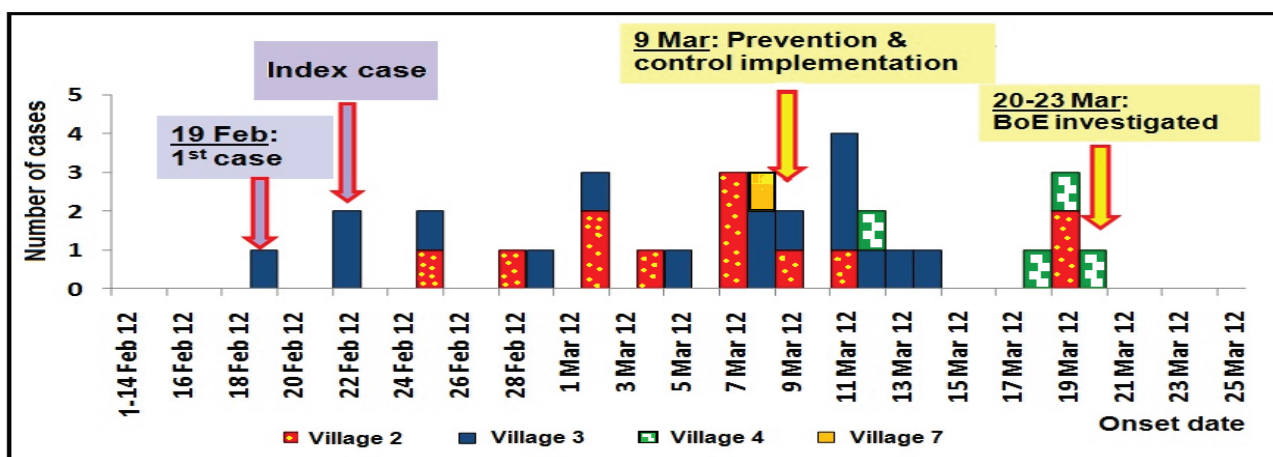


Figure 2 Number of maculopapular rash cases by onset date in Village 2, 3, 4 and 7, Klong Ta Kot subdistrict, Photharam district, Ratchaburi province, 1 Feb-23 Mar 2012 (N = 33)



Figure 3 Map of Cases' house in Village 2 and 3, Klong Ta Kot subdistrict, Photharam district, Ratchaburi province

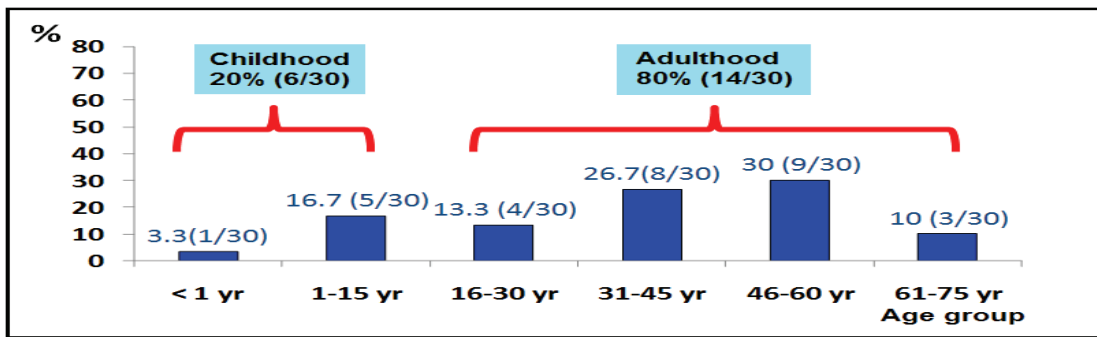


Figure 4 Proportion of cases by age-group in Village 2, 3, 4 and 7, Klong Ta Kot subdistrict, Photharam district, Ratchaburi province, 1 Feb- 23 Mar 2012 (N=30)

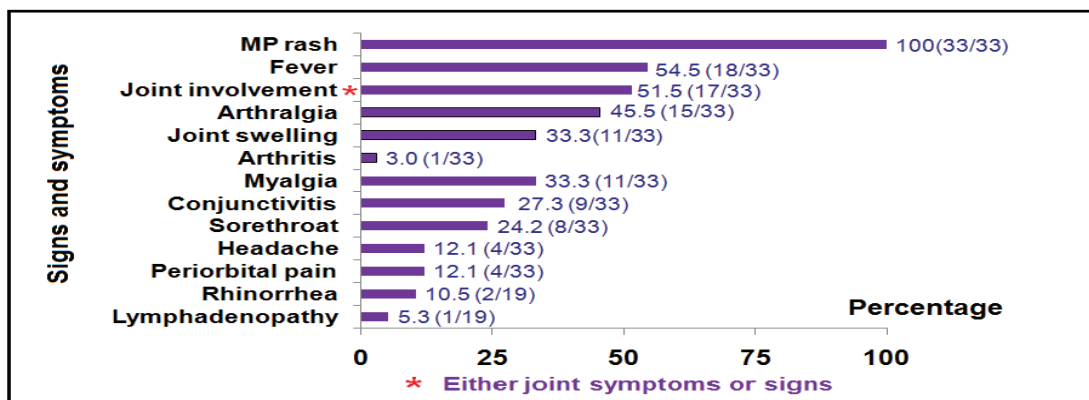


Figure 5 Proportion of clinical manifestation among cases in Village 2, 3, 4 and 7, Klong Ta Kot subdistrict, Photharam district, Ratchaburi province, 1 Feb- 23 Mar 2012 (N=33)

Top three common clinical manifestations were MP rash (100%), followed by fever (54.5%) and joint symptoms (51.5%) (Figure 5). Thirty percent of cases had all these 3 symptoms, 24 percent of cases had rash and fever, 21 percent of cases had rash and joint symptoms, and 24 percent of cases had only rash.

The sequence of signs and symptoms development among 15 cases whose complete data illustrated that a common pattern started with fever followed by rash and joint symptoms, respectively in about 27 percent of the patients. The second common pattern was fever and then developed rash for 20 percent of the patients. Of these 15 cases; fever emerged as the first symptoms in 9 cases (60%).

Among 17 cases with joint involvement, only 3

cases could provide the information about positions of joint involvement. In both small and large joints, two-third of them (66.7%) had metacarpophalangeal joint, wrist joint, and knee joint involvement; one-third of them (33.3%) had plantar, ankle, sacroiliac, shoulder and interphalangeal joint involvement. One of those who had joint involvement had polymigratory arthritis.

#### Environmental study

The landscape of the villages was dominated with thickets. Although the local SRRT provided prevention and control measures including thermal fogging, ultra-low-volume (ULV) fogging, and mosquito's larva elimination, a large number of mosquitoes, especially *Aedes aegypti*, could be observed in/around the of



houses during the daytime survey. There was no common place for villagers to join activities together e.g., market in any of Village 2, 3, 4 and 7. No gathering activity of people in each village occurred prior to the outbreak. Low social contact between households were reported.

Most villagers, particularly men, did not stay at home during day time. During SRRT did mosquito fogging most of the houses consequently remained closed and, therefore, hampered its effectiveness.

The villagers did not apply larvicidal chemical (Temiphos) and *Poecillia* in their water containers. House index (HI) in 4 houses of Village 2 was 75 percent (3/4) and the container index (CI) was 50 percent (4/8).

### Laboratory study

#### Human serum samples

Nine acute serum samples and 13 convalescent serum samples were collected. Among these samples, there were 4 paired serum samples. The results of rapid screening test (ELISA test kit) in 8 samples showed past rubella antibody (25%), acute dengue infection (12.5%), recent dengue infection (25%) and past dengue infection (50%).

Laboratory confirmation test results; ELISA an-

tibody test for DENV, CHIKV, and JEV infection in 18 samples; showed evidence of either DENV infection or flavivirus genus infection (61.1%) (Table 2) yet without any trace of CHIKV and JEV. The others laboratory confirmation test results of all 8 acute serum samples, viral isolation for Alphavirus / Flavivirus (4 samples) and RT-PCR test for CHIKV / DENV (8 samples), were negative. Moreover, the viral genomic detection (in 4 acute serum samples) also failed to identify any of the viruses.

#### Entomological laboratory investigation

It was found that 92.5 percent (37/40) of mosquitoes were *Aedes aegypti*. Other species of mosquitoes included *Aedes albopictus* (2.5%), *Armigeres subalbatus* (2.5%), and *Mansonia uniformis* (2.5%). The results of Real Time-PCR showed Dengue serotype 2 in *Aedes aegypti* in 2 out of the 4 houses of the patients.

## Discussion

Mosquito-borne viral diseases were most likely a diagnosis of patients in this outbreak. It can be explained by the observed characteristics of the outbreak, the pattern of cases distribution in this subdistrict with many small clusters of cases<sup>(3)</sup>. In addition the jumping pattern of disease spreading from Village 3 to others in its vicinity had been observed without any other linkage between the affected households.

Top three clinical signs and symptoms of the cases were generalized MP rash, fever, joint involvement which were not specific to either Alphavirus or Flavivirus infection<sup>(8,9)</sup>. Both can be transmitted by mosquitoes<sup>(1-3,8-12)</sup>.

In Ratchaburi dengue is hyper-endemic and chikungunya outbreak is sporadic<sup>(4)</sup>. However, two of the prominent symptoms - MP rash (100%) and joint involvement (51.5%) - as well as the high proportion of the affected adult (80%) - indicate the possibility of chikungunya.

**Table 2** The results of ELISA antibody test for DENV infection (n=18)

| Interpretation                                | Number of positive samples (%) |
|---|--------------------------------|
| Acute infection (primary)                     | 1 (5.6)                        |
| Acute infection (secondary)                   | 4 (22.2)                       |
| Acute infection (either primary or secondary) | 2 (11.1)                       |
| Recent infection (primary)                    | 0 (0.0)                        |
| Recent infection (secondary)                  | 4 (22.2)                       |
| No DENV infection                             | 4 (22.2)                       |
| Uninterpretable                               | 3 (16.7)                       |
| <b>Total</b>                                  | <b>18(100.0)</b>               |

On the contrary, evidence of DENV infection or flavivirus genus infection was reported only by the serological examination in both acute or convalescent serum samples (61.1%) without any further confirmation by RT-PCR and viral isolation in acute serum samples. The negative results of RT-PCR and viral isolation, possibly could be attributed by neutralization of viral pathogens by IgM antibody, very low viral load in samples and/ or viral degradation at 4°C<sup>(7)</sup>. With high profile of vectors of DENV / CHICKV infection in the study area including those carrying DENV serotype 2 in the 2/4 patients houses, dengue infection emerges as the most likely culprit.

However, this is an unusual dengue infection outbreak because it occurred in summer and mostly among adult patients with prominent chikungunya-like clinical manifestation of generalized MP rash plus joint involvement.

This outbreak spread in Village 2, 3, 4 rapidly due to high mosquito larva index, the environment was prone to mosquito breeding, the eradication of larvae and mosquitoes was not successful without strong collaboration with the villagers.

Dengue prevention and control measure in this area is very important because the patients who have been infected with any serotype of DENV will have partial immunity to prevent the other serotype infection<sup>(2,3,13)</sup>. After that brief period of immunity these patients will become susceptible host for DENV reinfection and developed dengue hemorrhagic fever (DHF)<sup>(1-3,13)</sup>.

Moreover DENV serotype 1 prevails in Ratchaburi province<sup>(5)</sup> thus the patient once infected with DENV serotype 1 will have even higher risk to develop severe form of Denque haemorrhage fever-DHF if they are reinfected with DENV serotype 2<sup>(13)</sup>.

### **Actions taken**

Implementation of prevention and control mea-

asures were repeated and included thermal fogging, ultra-low-volume (ULV) fogging, mosquito's larva source reduction, mosquito repellent distribution and educated health volunteers and villagers. There was no new case detected after outbreak interventions.

### **Limitations**

This study was a retrospective study, so it is subject to information bias. The case patients might be unable to recall their clinical symptoms in the past. Although a case definition as the one who had any clinical signs and symptom was used, all cases reported having MP rash. This might be because MP rash is an easy sign for anyone with mild symptoms to observe. Most of the villagers were not home in the day time so their family members became a proxy. Most houses were closed in day time and hampered the evaluation of the true HI and CI. Virus from patients could not be identified and some specific viruses that can cause fever with rash and joint pain, e.g. Sindbis virus, Ross River virus were not included.

### **Conclusions**

This was the unusual dengue infection outbreak, as the infection affected mostly adult populations and occurred in summer; its two of the prominent clinical manifestations were chikungunya-like generalized MP rash and joint involvement. The outbreak spread in 4 villages with attack rate between 0.1 and 2.5 percent. The previous prevention and control measures were not effective because of the unfavorable environment and limited local cooperation. After strengthening prevention and control measures, the outbreak was subsided and no new case was reported.

### **Recommendations**

The SRRT should provide health education for the villagers in this subdistrict regularly to encourage the people about the importance of dengue preven-

tion and control measures, especially in the coming rainy season.

Laboratory investigation should be improved to early detect new pathogens that may mimic symptoms of known pathogens in the country.

Further study about unusual manifestation of dengue infection in other setting should be conducted.

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เดือนมีนาคม 2555 สำนักกระบาดวิทยาได้รับรายงานว่ามีกระระบาดของไข้ผื่นร่วมกับอาการทางข้อ ในพื้นที่ 4 หมู่บ้านของ จังหวัดราชบุรี ซึ่งภายหลังการดำเนินมาตรการควบคุมป้องกันโรคของหน่วยงานในพื้นที่ยังมีผู้ป่วยรายใหม่เกิดขึ้นอย่างต่อเนื่อง สำนักกระบาดวิทยาจึงเข้าร่วมสอบสวนเพื่อหาสาเหตุ ประเมินสถานการณ์โรค และหาแนวทางการป้องกันควบคุมโรคที่เหมาะสม โดยศึกษากระบาดวิทยาเชิงพรรณาค้นหาผู้ป่วยเพิ่มเติมในชุมชนและทบทวนเวชระเบียนผู้ป่วย โดยใช้นิยามได้แก่ ผู้ที่อาศัยในหมู่บ้านทั้ง 4 แห่งที่มีผื่นไม่ทราบสาเหตุเกิดขึ้น ระหว่างวันที่ 1 กุมภาพันธ์ - 23 มีนาคม 2555 นอกจากนี้ยังสำรวจสิ่งแวดล้อมเก็บตัวอย่างยุงจากบ้านของผู้ป่วยเพื่อชนิดและหาเชื้อไวรัสในยุง รวมทั้งเก็บตัวอย่างซีรัมผู้ป่วยเพื่อหาเชื้อไวรัสที่ติดต่อดโดยแมลง ส่งตรวจที่กรมวิทยาศาสตร์การแพทย์ การศึกษารายงานผู้ป่วยตามนิยาม 33 ราย ผู้ป่วยรายแรกเริ่มมีอาการเมื่อ 11 กุมภาพันธ์ 2555 จากนั้นมีการระบาดเกิดขึ้นภายในครอบครัว ต่อมาภายในเวลาประมาณ 2 สัปดาห์ มีการระบาดเกิดขึ้นในพื้นที่ 4 หมู่บ้าน ผู้ป่วยส่วนมากเป็นวัยผู้ใหญ่ (80%) อาการหลักได้แก่ ผื่นผิวหนัง (100%) ไข้ (55%) และอาการทางข้อ (52%) จากการสำรวจสิ่งแวดล้อม พบหมู่บ้านแรกที่มีผู้ป่วยเกิดขึ้นอยู่ใจกลางของหมู่บ้านทั้ง 4 แห่ง ทุกหมู่บ้านมีต้นไม้ขึ้นหนาแน่น พบบึงและแหล่งเพาะพันธุ์เป็นจำนวนมากบริเวณรอบบ้าน คนในชุมชนไม่ได้ใส่ทรายอะเบท ปลาหางนกยูงเพื่อทำลายลูกน้ำในแหล่งน้ำต่าง ๆ บริเวณบ้าน รวมทั้งไม่ทายากันยุง จากการสัมภาษณ์ไม่พบการทำกิจกรรมร่วมกันของคนในชุมชน ผลตรวจทางห้องปฏิบัติการพบภูมิคุ้มกันต่อไวรัสเดงกีชนิด IgM ในผู้ป่วย 11 ราย จาก 18 ราย (61.1%) การศึกษาทางกีฏวิทยาพบว่า ยุงเกือบทั้งหมดที่สำรวจเป็นยุงลาย (93%) และพบไวรัสเดงกี ซีโรทัยป์ 2 ในยุงลายจากบ้านผู้ป่วย 2 ใน 4 หลัง (50%) การระบาดของผื่นผิวหนังครั้งนี้จะมีสาเหตุมาจากการติดเชื้อไวรัสเดงกีมากที่สุด ผู้ป่วยส่วนมากเป็นวัยผู้ใหญ่ จำกัดอยู่ในพื้นที่ 4 หมู่บ้าน โดยพบอัตราป่วย ร้อยละ 0.1 - 2.5 มาตรการควบคุมป้องกันโรคที่ได้ดำเนินการก่อนหน้านี้ไม่ได้ผล เนื่องจากสภาพแวดล้อมไม่เอื้ออำนวย รวมทั้งคนในหมู่บ้านไม่ตระหนักถึงความสำคัญของมาตรการ ภายหลังการเพิ่มความเข้มข้นของมาตรการควบคุมป้องกันโรค การระบาดจึงยุติและไม่พบผู้ป่วยรายใหม่ มาตรการควบคุมป้องกันการระบาดของโรคในพื้นที่มีความสำคัญมาก เนื่องจากผู้ป่วยที่เคยได้รับเชื้อไวรัสเดงกีแล้วครั้งหนึ่งสามารถที่จะติดเชื้อไวรัสเดงกีซีโรทัยป์อื่นซ้ำและมีอาการรุนแรงได้ โดยเฉพาะอย่างยิ่งถ้าเคยรับเชื้อเดงกีซีโรทัยป์ 1 มาก่อนแล้วได้รับซีโรทัยป์ 2 ซ้ำ อาจเป็นไข้เลือดออกชนิดรุนแรงได้

**คำสำคัญ:** เดงกี, โรคติดต่อโดยยุง, ผื่นผิวหนัง, อาการทางข้อ