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# A Cluster of Suspected Cases of Zika Leading to Uncommon Dengue Serotypes with Possible Coexisting Zika Virus in Northern Thailand, 2016

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**Abstract**

Due to high morbidity and mortality since 1949, dengue is one of the notifiable diseases routinely reported to the Ministry of Public Health. On 10 Apr 2016, five people with fever and rash from a village in Phetchabun Province were notified. Descriptive, case-control, and environmental investigations were conducted to verify diagnosis, describe characteristics of the outbreak, and determine risk factors. A confirmed case was a person with dengue-related symptoms, and dengue Immunoglobulin IgM, or dengue nucleic acids tested by reverse transcription polymerase chain reaction (RT-PCR). Controls were those without any symptoms and were randomly selected in the village. Of 12 dengue confirmed cases, there were six with DEN-3 and two with DEN-4 viruses. Living near cases (odds ratio = 11.1, 95% CI = 1.2, 98.3) and using home for community services (odds ratio = 9.2, 95% CI = 1.1, 79.6) were associated with dengue infection. One *Aedes aegypti* mosquito was identified with Zika virus by RT-PCR. A dengue outbreak related to serotypes DEN-3 and DEN-4 was confirmed with potential coexisting Zika virus in the village. Intensive vector control, elimination of mosquito breeding sites and health education provided in align with community participation controlled the outbreak.

**Keywords:** Dengue fever, Zika virus, outbreak, investigation, Lomkao District, Phetchabun Province

## Introduction

While half of the world population is at risk for dengue infection, the disease is commonly found in tropical and sub-tropical climates in Asian and Latin American countries.[1] Dengue virus is transmitted by *Aedes aegypti*, the same mosquito that spreads Zika virus. Both dengue and Zika virus are single-stranded RNA viruses and belong to genus *Flavivirus* in the family *Flaviviridae*.[2] Similar to other arbovirus infections, clinical manifestations of dengue and Zika virus infections include fever, skin rashes, conjunctivitis, muscle and joint pain, malaise, and headache, which are usually mild and last for 2-7 days[2,3].

In Thailand, the first dengue infection was reported during 1949 and the first dengue hemorrhagic fever (DHF) outbreak occurred in Bangkok during 1958.[4] At present, dengue is one of the notifiable diseases in the country, and causes high morbidity and mortality every year. During 2015, morbidity rate was 63.3 per 100,000 population and mortality rate was 0.1 per 100,000 population. The highest morbidity rate was observed among children aged 10-14 years.[5,6]

The severity of dengue infection had been reported to specific serotypes while severity also depends on several factors such as immune response and underlying conditions.[7-9] Out of four dengue serotypes, predominant serotypes in Thailand were DEN-1 in 2004 (56.4%), DEN-4 in 2007 (50.0%), DEN-1 in 2008 (57.4%) and DEN-3 in 2010 (38.7%).[10]

Regarding to Zika virus, the first human case was identified in Uganda during 1952 and outbreaks were reported in Africa and Asia in 1960-1980.[3] The disease re-emerged as a large outbreak of Zika virus and the associated microcephaly were reported in Brazil during 2015. In Thailand, Zika virus surveillance in humans was initiated since 2012, and an average of five confirmed cases of Zika virus were reported from the various parts of the country through the national surveillance system every year until 2015.[11] Two cases were reported in 2016 as of 18 Mar 2016.[12]

On 10 Apr 2016, a cluster of five people with fever and rash from village 4, Wang Ban Subdistrict, Lomkao District, Phetchabun Province (Village A) was reported to the Bureau of Epidemiology. In addition, outbreaks of dengue infection during 2010-2014 as well as an outbreak of Zika virus in humans during 2015 were reported to the provincial health office in Phetchabun. While clinical manifestations of fever and rash were consistent with dengue infection, the period of the outbreak was coincident with high transmission activity of Zika virus in the country as well. Hence, an investigation was conducted in the affected village on 12-18 Apr 2016 to verify the diagnosis, describe the characteristics of the outbreak, determine risk factors and recommend appropriate control measures.

## Methods

An investigation was jointly conducted by the Bureau of Epidemiology, the Office of Disease Control and Prevention 2 and local public hospitals using descriptive study methods to identify gap and potential risk factors. An analytic study was also performed to confirm the source of infection.

### Descriptive Study

A descriptive study on fever and rash was initiated by reviewing medical records of patients with dengue symptoms, dengue diagnosis, or international classification of diseases (ICD) 10 code of A97, who visited Lomkao District Hospital and Wang Ban Subdistrict Hospital in 2011-2015.

The national guidelines for prevention and control of Zika virus recommended that surveillance should be carried out in four groups in order to monitor for infection and microcephaly, to gather information on high-risk groups and areas, and to develop guidelines in setting control and prevention measures. The four groups placed under surveillance were pregnant women, general patients, infants with abnormal head (head size much smaller compared with other babies of the same age and gender)[13], and those who developed Guillain-Barre syndrome or neurological diseases after being infected. For these four groups, the definition of patient under investigation (PUI) was recommended as per the national guideline. Investigation and disease control for Zika virus infection should be undertaken among all PUIs (Figure 1).[14]

Following the national guideline[14] on surveillance of Zika virus infection, active case finding for suspected cases was carried out among patients at the hospitals for previous five years and people in Village A during 12 Mar - 28 Apr 2016. A suspected case was a person with fever and at least two of the following symptoms, or rash and one of the followings: headache, muscle pain, joint pain, vomiting and conjunctivitis in Village A during 12 Mar - 18 Apr 2016. A confirmed case was a suspected case who was tested positive for dengue, Zika or *Flavivirus* by immunoglobulin M (IgM) or reverse transcription polymerase chain reaction (RT-PCR).

### Laboratory Study

Following the national guideline[14] on active case finding and specimen collection for laboratory testing of Zika virus infection, urine and plasma specimens were collected from the suspected cases who were sick for less than five days and urine specimens from those with history of illness from five days to one month (Figure 2).

The specimens were tested for dengue and Zika virus by IgM or RT-PCR at the National Institute of Health and the Bamrasnaradura Infectious Diseases Institute. As a further step, urine and plasma specimens from all family members of the confirmed cases and all pregnant women in the village were sent to these two laboratories for testing.

### Analytic Study

A case-control study was employed to identify risk factors. A case was either a suspected or confirmed case while a control was a person in the same village without any symptoms. The case and control ratio was 1:1. Controls were selected by simple random sampling from the list of village residents with no specified symptoms. Crude odds ratio were calculated for all potential risk factors. All those with p-value lower than 0.05 were included in the multiple logistic regression model. The Epi Info version 3.5[15] was utilized to calculate the odds ratios (OR).

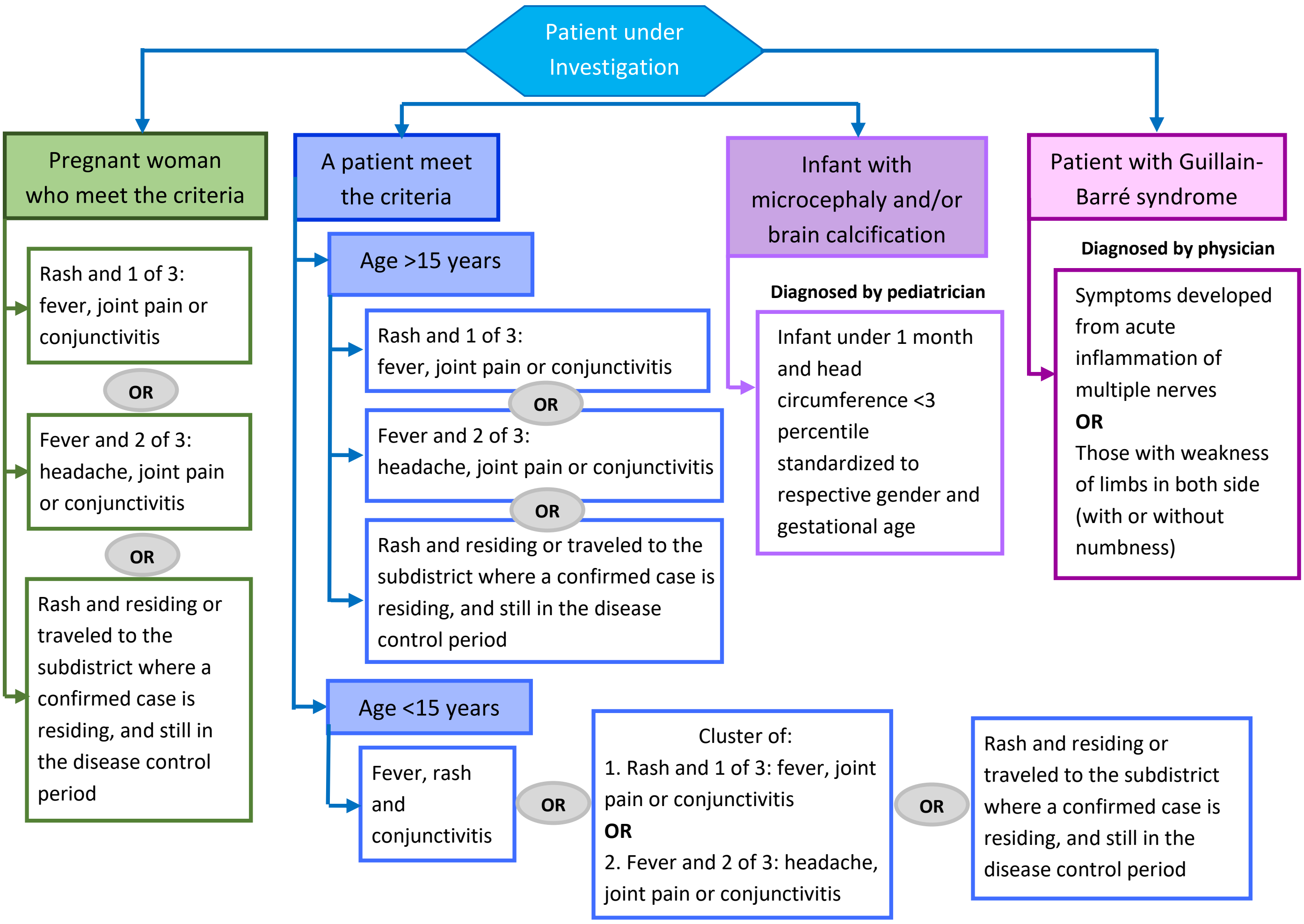
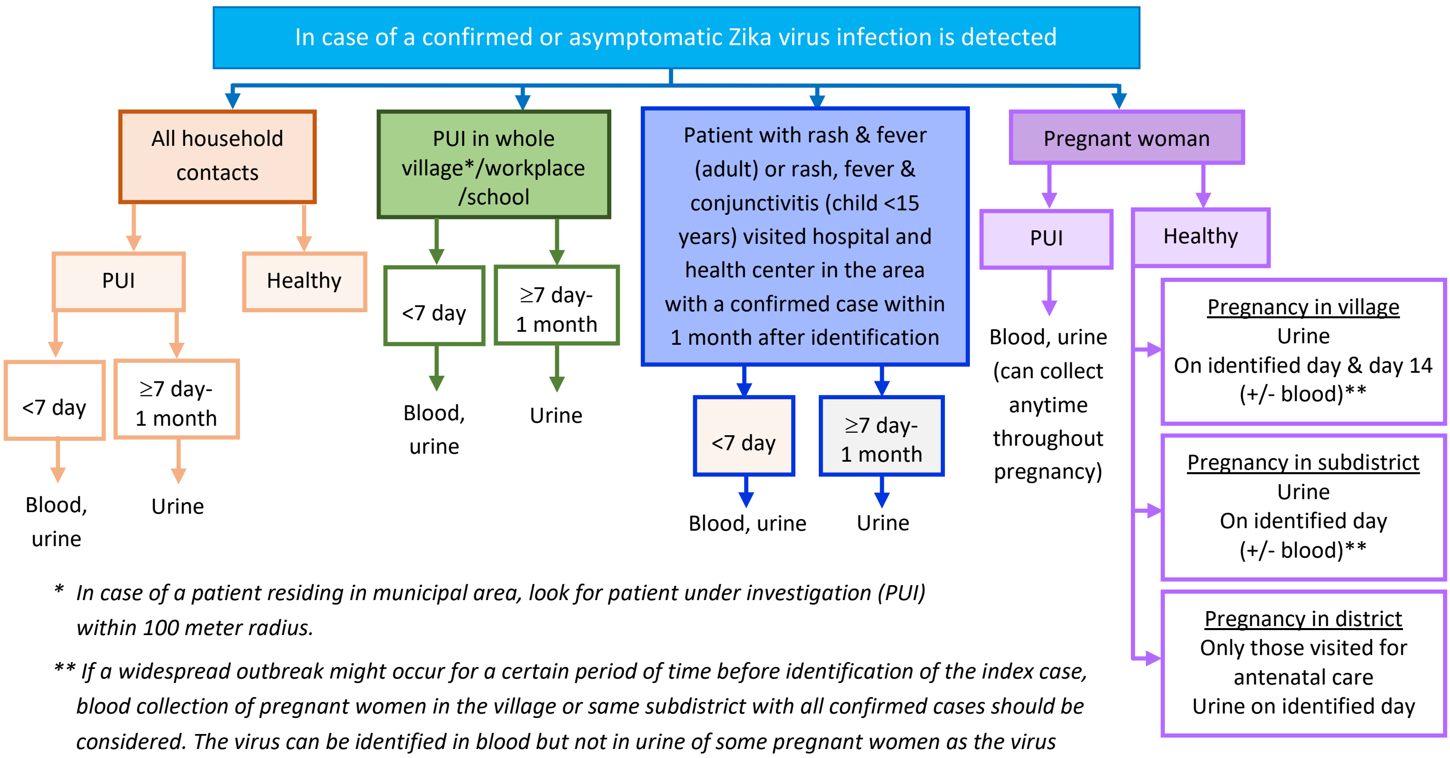



**Figure 1. Criteria of patient under investigation for investigation of Zika virus infection in Thailand, specified by the Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, 2016[10]**




* *In case of a patient residing in municipal area, look for patient under investigation (PUI) within 100 meter radius.*

** *If a widespread outbreak might occur for a certain period of time before identification of the index case, blood collection of pregnant women in the village or same subdistrict with all confirmed cases should be considered. The virus can be identified in blood but not in urine of some pregnant women as the virus can stay longer in blood and can still transmit the infection.*

**Figure 2. Guideline on active case finding and specimen collection for confirmed cases and asymptomatic infection of Zika virus infection by the Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, 2016[10]**

### Environmental Study

In order to find the source of infection, an environmental survey was carried out in the village by the investigation team. Using the Thai national guidelines issued in 2016[14], an environmental survey for mosquito larvae was performed in 100-meter radius around the houses of suspected and confirmed cases. House index (HI) and container index (CI) were calculated for days 0, 3, 5, 7, 14, 21 and 28, started from the day when a case was discovered. HI is the percentage of houses infested with larvae and/or pupae, and CI is the percentage of water-holding containers infested with larvae or pupae.[16] In addition, mosquitoes and larvae were trapped and tested for dengue and Zika virus by RT-PCR in the laboratory of Vector Borne Disease Control Center of Phetchabun Province.

## Results

### Descriptive Study

Reviewing the medical records in the hospitals for cases with fever and rash revealed that dengue clusters during 2011 and 2013, one rubella case during 2013 and two Zika virus infections during 2014 were reported in this area.

A total of 32 suspected cases were identified in Village A of Petchabun Province during 1-28 Apr 2016. The male-to-female ratio was 1:1.6 and the mean age was 24 years, with a range of 4-76 years. The index case was a student and 37.5% of the suspected cases were students as well. The most common clinical manifestation was rash (87.5%) (Figure 3). The majority (79.2%) of the rashes were maculopapular rash and 20.8% had erythema for 1-5 days, with average of two days. Rash was found mostly over the chest and back (51.6%). About 43.8% of cases had joint pain for 1-4 days (average 2 days). Almost all cases had fever (84.4%) and some had conjunctivitis (31.3%).

The index case was a 13-year-old girl and developed symptoms on 10 Mar 2016. Before the semester break, she travelled to the school in the subdistrict to receive her examination result eight days prior to disease onset. The school reported that no students got ill with fever and rash. She was completely recovered on 17 Mar 2016, without visiting a hospital or clinic. Later on, the district hospital identified four children with fever with rash in the same community.

### Laboratory Study

Samples from 32 suspected cases were tested and 12 (37.5%) were tested positive for dengue by IgM or RT-PCR. Of these, four (33.3%) cases were found to have *Flavivirus* by IgM while six cases (50.0%) were identified with DEN-3 virus by RT-PCR and two cases (16.6%) had DEN-4 by RT-PCR. None of them were found to have Zika virus. There were two pregnant women in the village and both of them tested negative for dengue and Zika virus.

Hence, 12 cases were confirmed to have dengue infection in this outbreak. The attack rate was 8.5% among 142 residents in the village. The outbreak started on 14 Mar 2016 and ended on 30 Apr 2016, with the peak in mid-April (Figure 3). After monitoring for 28 days from the onset of the last case, since there were no new case, the outbreak was declared an end.

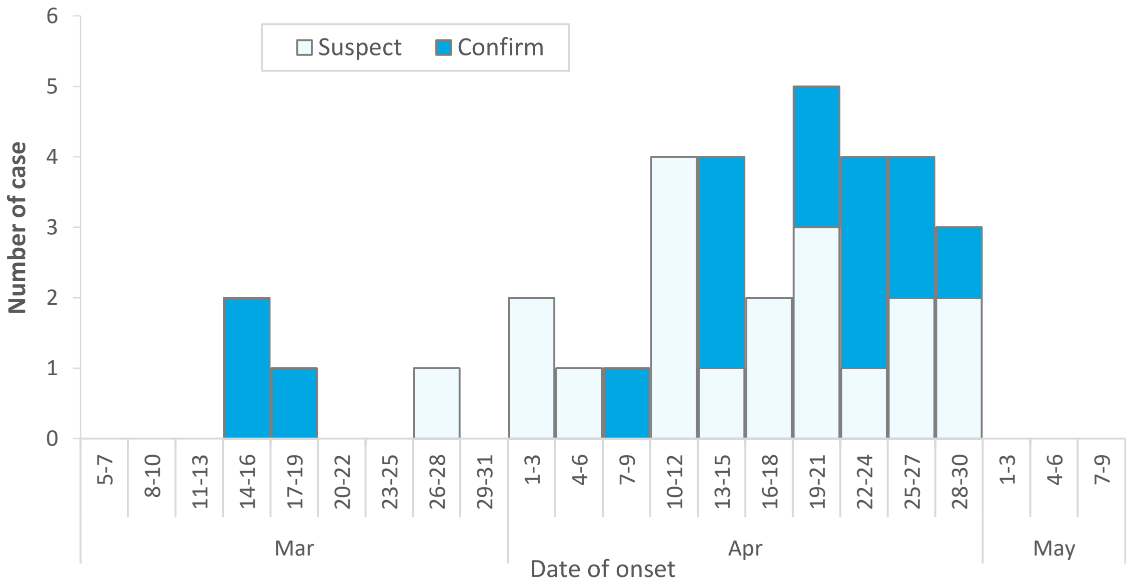



**Figure 3. Number of dengue cases by date of onset in a village, Lomkao District, Phetchabun Province, Thailand, 3 Mar to 8 May 2016 (n = 32)**

### Analytic Study

In order to identify the potential risk factors for dengue virus infection, all 12 dengue confirmed cases and 20 suspected cases were included in the analysis. In univariate analyses, four statistically significant risk factors were: being a student (OR = 31.2, 95% CI = 1.7-563.2), having a suspected case in the family (OR = 23.0, 95% CI = 1.3-420.4), living within 100-meter radius of a suspected case's house (OR = 2.9, 95% CI = 1.0-8.7), and using home as a grocery shop or for community service (OR = 8.5, 95% CI = 2.3-32.2). A multivariate analysis revealed that living within 100-meter radius from a suspected case's house (Adjusted OR = 11.1, 95% CI = 1.2-98.3, p-value = 0.03) and using home as a grocery shop or for service (Adjusted OR = 9.2, 95% CI = 1.1-79.6, p-value = 0.04) were factors associated with dengue infection (Table 1).

### Environmental Study

The time of the outbreak was at the end of summer and approaching the rainy season. There was a forest and a river running near the village. The village was far from schools. Containers with water were observed in an antique shop, and there was a home-made tamarind pickle shop. These pickle pots were used for one week and then left empty until the next batch of tamarind was available. Since there was no cover for the pots, water might collect in the vacant pots (Figure 4).

A total of 10 houses and a temple were surveyed for HI and CI in Village A. The highest HI (26.6%) was spotted within 100-meter radius of the suspected cases (average HI 13.1%) while the highest CI was discovered in another house with 11.5% (average CI 4.5%). No mosquito larvae or pupae were found either in the temple or containers around the temple.

**Figure 4. Home-made tamarind pickle pots in a village, Lomkao District, Phetchabun Province, Thailand, 2016**

Six *Aedes aegypti* and one *Culex* mosquitoes were trapped from seven areas near the suspected cases' houses. Among them, Zika virus was detected in the salivary gland of one *Aedes aegypti* by RT-PCR.

## Actions Taken

In addition to strengthening of surveillance and active case finding, we coordinated with local authorities to identify more budget for the disease control team. Activities on vector control, health education, repellent distribution, and use of insecticides and ultra low volume fogging for adult mosquitos were enhanced. Unused water containers were destroyed and chemical control was implemented at 100-meter radius of the cases' houses. Health personnel from other districts and the Vector Borne Disease Control Center 2.2 in Phetchabun checked for HI and CI on 0, 3, 5 and 7 days after the outbreak alert. Concept of community participation was emphasized in parallel with enhancing control measures until 28 days after the onset of the last case.

**Table 1. Univariate and multivariate analysis on risk factors for dengue infection in a village, Lomkao District, Phetchabun Province, Thailand, March - April 2016**

| Factor | Univariate | | Multivariate | |
|---|---|---|---|---|
| | Crude Odds Ratio | 95% CI | Adjusted Odds Ratio | 95% CI |
| Being a student | 31.2 | 1.7-563.2 | 8.0 | 0.6-99.2 |
| Having a suspected case in the family | 23.0 | 1.3-420.4 | 0.4 | 0.02-8.6 |
| Living within 100-meter radius of a suspected case's house | 2.9 | 1.0.-8.7 | 11.1 | 1.2-98.3 |
| Using home as a grocery shop or for services in community | 8.5 | 2.3-32.2 | 9.2 | 1.1-79.6 |

## Discussion

Through identification of *Flavivirus* and dengue serotypes DEN-3 and DEN-4, an outbreak of dengue virus infection was confirmed in the Village A of Lomkao District, Phetchabun Province. The clinical manifestations of fever, maculopapular rash generally on large areas of body and joint pain were consistent with those of dengue and Zika virus infections[2,3].

The index case and 37.5% of the suspected cases were students. The period of outbreak from Mar to Apr 2016 corresponded with the semester break of the schools, February to May. This result was consistent with the previous knowledge showing that dengue virus infection most frequently occurs among those aged 5-14 and 15-24 years old, and 50% were students.[17] This could be explained by the fact that in general, children tend to have a lower rate of immunity to dengue infection.[18] Despite this, an increasing trend of dengue infection had also been observed in older age groups.[19]

Although dengue virus infection in Thailand generally revealed serotypes DEN-3 (30.9%) and DEN-4 (29.5%) in the previous decade,[6] a higher number of DEN-1 (79.6%) and DEN-2 (10.7%) serotypes were reported during 2014 (35.7%).[20] Especially in the northern region, DEN-2 and DEN-1 had been most frequently reported in 2013 (DEN-1 41.5%) and 2014 (DEN-1 79.5%). The fatality rate for DEN-4 was 50%. Many severe cases were reported in 2014 as people were not immune to the new serotype.[21,22] However, one study in 2014 reported that serotypes DEN-3 (46.6%) and DEN-4 (31.0%) were predominant in the northeastern Thailand.[18] This outbreak occurred in a northern village, and DEN-3 and DEN-4 serotypes were identified, which exhibited a discrepancy with the prior national data of dengue infection and yet, consistent with the findings in the northeastern area due to geographical proximity.

All the cases identified in this study, including DEN-3 and DEN-4 serotypes, presented as mild infections. A previous study in Thailand stated that DEN-2 and DEN-3 infections were two times more likely to result in severe infection compared with DEN-4.[7] While DEN-2 was noted to be more pathogenic in some studies[23,24], DEN-1 may also lead to severe disease, as shown in a study conducted by Balmaseda A, et al[25]. Despite that, DEN-4 was related to mild infections in some reports[26,27].

In addition, mosquito-infested places with high HI and CI were detected within 100-meter radius of the suspected cases' houses, which was higher than the standard criteria specified by the Bureau of Epidemiology (Table 2). High density of mosquito breeding sites was augmented by the analytic findings that living near the suspected cases' houses and using home to provide community services were associated with dengue infection. The houses attached to a shop or a service delivery place are liable to be crowded with visitors and tends to be a source for dengue outbreak, especially if the area is populated with high number of mosquitoes. Potential breeding sites in close vicinity were associated with outbreak spots and found to advance the outbreak as reported previously.[28,29]

Since *Flavivirus* was identified by IgM in four cases, antibody testing of dengue virus could be confounded by cross-reactivity with other *Flaviviruses* when a person was infected with or vaccinated against other *Flaviviruses* such as Zika virus, yellow fever or Japanese encephalitis, especially during the acute

**Table 2. Environmental targets for larva survey of Zika virus infection, specified by the Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand, 2016[10]**

| No. | Target | General Areas | Municipal Areas | Bangkok and Pattaya City |
|---|---|---|---|---|
| 1. | HI and CI 0% within 5 days | - Whole village<br>- If a suspected or confirmed case's house is close to other villages, mosquito larva control must be done in half of each village located within 100 radius meter.<br>- Within 100 meter radius of the case's regular route if the case go out of the home after onset of symptoms | - Within 100 meter radius of a case's house<br>- Within 100 meter radius of the case's regular route if the case go out of the home after onset of symptoms | - Within 100 meter radius of a case's house<br>- Within 100 meter radius of the case's regular route if the case go out of the home after onset of symptoms |
| 2. | HI and CI <5% within 14 days | - Whole subdistrict where the case is residing | - Whole community or village where the case is residing | - |
| 3. | HI and CI <5% within 28 days | - Whole district where the case is residing | - Whole subdistrict where the case is residing | - Whole community where the case is residing |

phase of infection[30]. Furthermore, *Aedes aegypti* mosquito in the affected area was found to have Zika virus. Identification of two Zika infection in 2014 by reviewing of medical records and findings of Zika virus infection in Phetchabun Province from other studies[31,32] were in supportive as evidences of existing Zika virus in the area.

Due to the facts mentioned above, the findings suggested a dengue outbreak with potential coexisting of Zika virus in the area. Co-infection of dengue and Zika viruses was observed among two patients in New Caledonia during 2014[33] and a traveler returning from Haiti in 2016[34].

## Conclusion

The identification of *Aedes aegypti* mosquitoes in conjunction with the epidemiological findings confirmed a dengue outbreak related to DEN-3 and DEN-4 serotypes, and potential coexiting Zika virus in Village A of Lomkao District, Phetchabun Province.

## Recommendations

The remarkable fact was that the dengue outbreak occurred among students during the semester break although being a student was not a significant factor in the multivariate analysis. This highlighted the importance of implementing the vector control program in the communities during semester breaks in addition to the routine campaigns in schools.

Furthermore, results of dengue serotyping could pinpoint the potential source of endemic area as well as predict the severity of involved cases. Hence, the serotyping of the infected cases should be performed in the future investigations of dengue outbreaks.

While HI and CI are definite and simple indicators for entomological surveillance to predict the vector population, these should be carried out to prioritize areas for vector control as well as be vigilance with routine environmental surveys for potential outbreaks. Since HI and CI must be zero within five days in the affected village and less than 5% within 14 days in the subdistrict as per the national guideline[14], strict mosquito control measures were recommended to the related public health offices. Proper sanitation and elimination of mosquito breeding sites especially in houses with high HI and CI, and the service delivery places was educated to the local public.

## Limitations

As the study was carried out among patients with clinical symptoms, asymptomatic cases were not included in the study and the findings might not represent the actual disease prevalence in the area. However, since the identified risk factors were related to the residence, recall bias was less likely to exist in this study.

As the *Flavivirus* was detected by IgM, the United States Centers for Disease Control and Prevention recommended that testing of acute specimens should be conducted by the molecular testing such as RT-PCR for confirmation of Zika virus infection in the future studies[36].

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