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First reported case of Zika virus infection associated with Guillian Barre Syndrome in Asia, Phetchabun Province, Thailand, 2016

(การสอบสวนผู้ป่วยโรคติดเชื้อไวรัสซิกาที่มีอาการแขนและขาอ่อนแรง ในอำเภอหล่มสัก จังหวัดเพชรบูรณ์ ประเทศไทย ปี พ.ศ. 2559)

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Abstract

Backgrounds: One suspected ZIKV patient with GBS was reported in Lomsak district, Phetchabun province that had prolong ZIKV outbreak in previous three months.

Methods: During investigation, we obtain patient's clinical data from medical records and relatives. The district level ZIKV surveillance system coverage was assessed by comparing number of reported cases with number of medical records meeting surveillance case definition. We interviewed related staff and some villagers about control measure implementation and assessed larva control in houses of recent confirmed cases or patients under investigation of ZIKV and in Lomsak hospital.

Results: The case was a 52-year-old Thai female presented

with rash and arthralgia for six days, followed by progressive muscle weakness one day later. Zika associated GBS was diagnosed by high protein and low cell count in CSF and positive urine PCR for ZIKV. Intravenous immunoglobulin was administered immediately after having CSF profile and 2 days later she got endotracheal tube intubation due to progressive muscle weakness which then resulted in respiratory failure. She had hospital acquired pneumonia and muscle atrophy during hospitalization. The patient was discharged and fully recovered in 3 months later. ZIKV surveillance system coverage was 61.22%. Assessment of control measures found several problems including inadequate skill of larva control of local staff and the fatigue of control system due to prolong outbreak situation.



◆ First reported case of Zika virus infection associated with Guillian Barre Syndrome in Asia, Phetchabun Province, Thailand, 2016	717
◆ สรุปการตรวจหาการระบาดของโรคในรอบสัปดาห์ที่ 46 ระหว่างวันที่ 18-24 พฤศจิกายน 2561	727
◆ ข้อมูลรายงานโรคเฝ้าระวังทางระบาดวิทยาประจำสัปดาห์ที่ 46 ระหว่างวันที่ 18-24 พฤศจิกายน 2561	731

Conclusion and Recommendations: This patient was the first reported case of Zika associated GBS in Asia. Improved surveillance coverage and proactive measures are needed to control ZIKV infection in this area.

Keywords: Zika virus surveillance system, Guillian Barre Syndrome, Lomsak district, Phetchabun

Introduction

Zika virus is an arbovirus of the flaviviridae family. It was isolated in 1947 from a febrile rhesus macaque monkey⁽¹⁾. Vector mediated transmission of Zika virus is Aedes mosquito which can contract Zika virus from infected human through blood feeding. Incubation period is 10 days on average in mosquito and 3–12 days in human (7 days on average)⁽²⁾.

Infected patient has clinical symptoms such as fever, rash, arthralgia, and non-purulent conjunctivitis. Some patients have retro-orbital pain and gastrointestinal symptoms⁽³⁾. It is estimated that 80% of infected human are asymptomatic, however they can transmit the disease⁽⁴⁾.

Zika virus infection can be diagnosed by polymerase chain reaction (PCR) for Zika virus laboratory test, primarily based on the detection of viral RNA from clinical specimens (blood, saliva, urine, cerebrospinal fluid, amniotic fluid, semen, and breast milk), or IgM for Zika virus⁽⁵⁾. However, IgM for Zika virus probably has false positive in other flavivirus patients⁽⁶⁾ such as dengue infection which has high incidence in Southeast Asia.

Zika virus can cause complication in baby born to infected mother. Newborn baby has microcephaly, and brain calcification resulted in neurological disorder. Another complication also found in Zika patients is Guillian Barre Syndrome (GBS) and other neurological diseases⁽⁷⁾.

GBS caused by human's immune system attacks

their peripheral nerves⁽⁸⁾. GBS was triggered by several pathogens such as, HIV, Influenza virus, EBV, Zika virus or *Campylobacter jejuni*⁽⁸⁾. Clinical manifestations of GBS are ascending weakness, started with leg to arm and face, and tingling sensation. Around 25% of GBS patients may develop chest muscle paralysis cause respiratory failure. Diagnosis of GBS is based on symptoms and neurological findings with high level of CSF protein (cytoalbuminologic dissociation) and low cell count. Intravenous immunoglobulin (IVIg) administration and rehabilitation programs are gold standard of GBS treatment⁽⁸⁾.

Zika associated GBS was found in French Polynesia outbreak. Incidence of GBS was estimated at 0.24 cases per 1,000 infections. A case-control study in French Polynesia revealed a strong association between GBS and previous Zika virus infection (odds ratio was 34.1, 95% CI: 5.8–∞)⁽⁹⁾.

On 11th August 2016, Bureau of Epidemiology (BoE) received information from patient's relatives that a patient had muscle weakness and fever with rash in Hui-Rai subdistrict, Lomsak district, Phetchabun province. There was a prolonged Zika outbreak in Lomsak district. From 20th May–5th August 2016, there were 92 patients under investigation (PUIs) of Zika virus infection reported, 63 of them were confirmed (Figure 1) by case definition of Zika virus⁽¹⁰⁾ (Table 1), others were categorized as suspected case. Number of PUIs peaked in June. However, there was no previous report of Zika virus infection with neurological symptoms in Thailand. BoE and the Office of Disease Prevention and Control region 2nd jointly conducted an investigation during 19th–21st August 2016. The objectives of this investigation were to confirm diagnosis of Zika virus associated GBS, to describe the clinical manifestation, case management, and disease progression of the GBS case, to identify possible source of virus infection of the GBS case, and to assess and give recommendation on investigation and control measure of local teams.

Methods

Description of the GBS case

Medical records of the GBS case at Phetchabun hospital and Puttachinaratch hospital were reviewed by BoE teams for details of case's clinical manifestation and laboratory results. Physicians and case's relatives were interviewed to get details of exposure history, case management, and disease progression.

Identifying possible source of virus infection

Source of zika virus infection of the GBS case was explored by interviewing village health volunteers and case's relatives. Urine specimens were collected from case's relatives for urine PCR for zika virus. The team traced the possible source of zika virus that had contact with GBS case (index case) within 2 weeks before onset, and environmental survey near the index case's house and the house of patient who was a suspected source were conducted to identify the possible location of transmission.

Assessment of existing surveillance system and control measure in local area

Coverage or sensitivity of zika surveillance system in Lomsak district were assessed by retrieving all medical record (IPD and OPD) at Lomsak hospital during 1 July–15 August 2016 with following ICD 10 codes: A90 (Dengue fever), B05 (Measles), B06 (Rubella), B09 (viral unspecified), U06.9 (zika fever), and R21 (maculopapular rash). These medical records were reviewed to identify cases who met definition of patient under investigation (PUI) of zika virus infection (See table 1). The number of patient under investigations (PUIs) from medical review was compared with number of reported PUI/confirmed cases in the system of zika surveillance to determine the system's coverage.

The larva control was repeatedly assessed by survey. Purposive sampling was performed to select target places. Houses of recently confirmed zika and PUI cases, Lomsak hospital, and house of the GBS case were

surveyed. Family members were interviewed to determine the awareness regarding zika virus. Current control measures of larva survey and mosquito spraying were also assessed by interviewing related public health personnel, village health volunteers and villagers in the surveyed houses, including observed environment of these houses. Necessary control measures and health education were implemented after or during the assessment.

Results

Description of GBS case

The patient was a 52 years old Thai female. She started coughing, rhinorrhea and sore throat on 25th July 2016. On 2nd August 2016, she developed rash at face, trunk and lower extremity. She visited a private clinic and was diagnosed as measles. On 6th August 2016, she had joint pain and swelling. She visited Lomkaw hospital, a community hospital, and was diagnosed as viral infection rule out zika virus, but zika laboratory test was not performed. In the same day, she visited another community hospital, Lomsak hospital, and was diagnosed as viral exanthem. On 9th August 2016, she developed muscle weakness and numbness started from foot to knee. On 10th August 2016, she was unable to walk. Her relatives transferred her to Phetchabun hospital. Physicians suspected GBS. Lumbar puncture was performed and CSF test shown high protein (100 mg/dl) and low cell count (0-5 cell/mm³). On 11th August 2016, urine sample was collected for testing PCR for zika virus. Dengue NS1 Ag and rapid test for influenza were negative. Twenty grams intravenous immunoglobulin (IVIG) for GBS treatment was started immediately after having CSF profile, and a daily dose was given for 5 days (From 11th–15th August 2016). On 13 August 2016, she developed respiratory failure and received endotracheal intubation. She was referred to Puttachinaratch hospital (tertiary care hospital) on 15th August 2016. On the same day, her urine PCR result showed zika positive.

Patient was admitted in intensive care unit (ICU) for 18 days (15th August–2nd September 2016). During her hospitalization, she had muscle atrophy and an episode of nosocomial pneumonia. She received rehabilitation program and antibiotics. A tracheostomy was performed on 2nd September 2016 for prolong ventilation support. She was referred back to Phetchabun hospital on 2nd September 2016 for continuing antibiotics and rehabilitation program. On 10th October 2016, she regained spontaneous respiration and her skeletal muscles powers were also improved. On 4th November 2016, she was discharged from the hospital. Three months later, she was fully recovered. This case was classified as level 2 of Brighton criteria (Table 3).

Identified possible source of infection

Urine samples were collected from household contact of GBS case for zika virus PCR test, zika virus was detected in the sample of the case's older sister who had no clinical symptoms of zika virus infection.

The interview of GBS case's relatives revealed that the case often visited Grocery A store nearby her house to purchase food, and the grocery store was next to her older sister's house where she also paid frequent visit. They informed interviewers that there was a person in the same village, Mrs. K, who had fever with rash 1-2 weeks before the GBS case developing symptoms and often visited Grocery A before the onset of the GBS case.

Mrs. K had relatives in Ban-Tiew subdistrict where the highest zika burden was reported. Before her illness, she traveled to Ban-Tiew sub district around 3 times. Mrs. K had high grade fever with fatigue on 17th July 2016 (within 2 weeks before GBS case developed initial symptoms) and she still went to the grocery store every day. On 20th–21st July 2016, she developed rash, started from arm to leg then expanded to the whole body. She also had arthralgia at multiple joints. She was identified as a PUI case during the active case finding, and urine PCR for zika virus was performed on 22nd July 2016 (5 days after onset date), result was negative.

At the grocery store, there were many coconut shells with water and the mosquito larva container index (CI) was 31% (6/19).

Assessment of existing surveillance system and control measure in local area

During study period, 32 cases were identified as PUI cases from 47 OPD and IPD medical charts reviewed in Lomsak hospital. Among them, 13 cases were reported in zika surveillance system. These 19 underreported cases were mostly diagnosed as rule out zika virus infection and supposed to be reported. Therefore, the coverage of zika surveillance was 40.62 (13/32).

However, beside the 13 cases from medical charts review, there were 17 additional cases reported in zika surveillance system from Lomsak hospital. The medical charts of these cases were filled in the special outpatient department (OPD) unit designated for zika screening, but their ICD10 codes were not recorded in hospital database.

Result of larva survey results in houses of 2 recently confirmed cases, 2 recent PUI cases and Lomsak hospital were shown in Table 2. High larva index was found at a temple in Numkor sub district where was a resident place of a recent PUI case being surveyed, with container index of 77.00% (37/48), and at Lomsak hospital, household index (HI) was 100% (3/3) and CI was 41.18% (7/17).

Village health volunteers mentioned that they did larva survey and managed containers by turning them upside down. However, we found that the house owners turned some of them back to the previous position since they want to use those containers. The village health volunteers did not advise people in community to store the containers properly in the place where they could not fill by rainfall or use other appropriate methods. In addition, the village health volunteers could only perform larva survey in some houses, especially confirmed case houses, as other house owners often deny them from entering their properties.

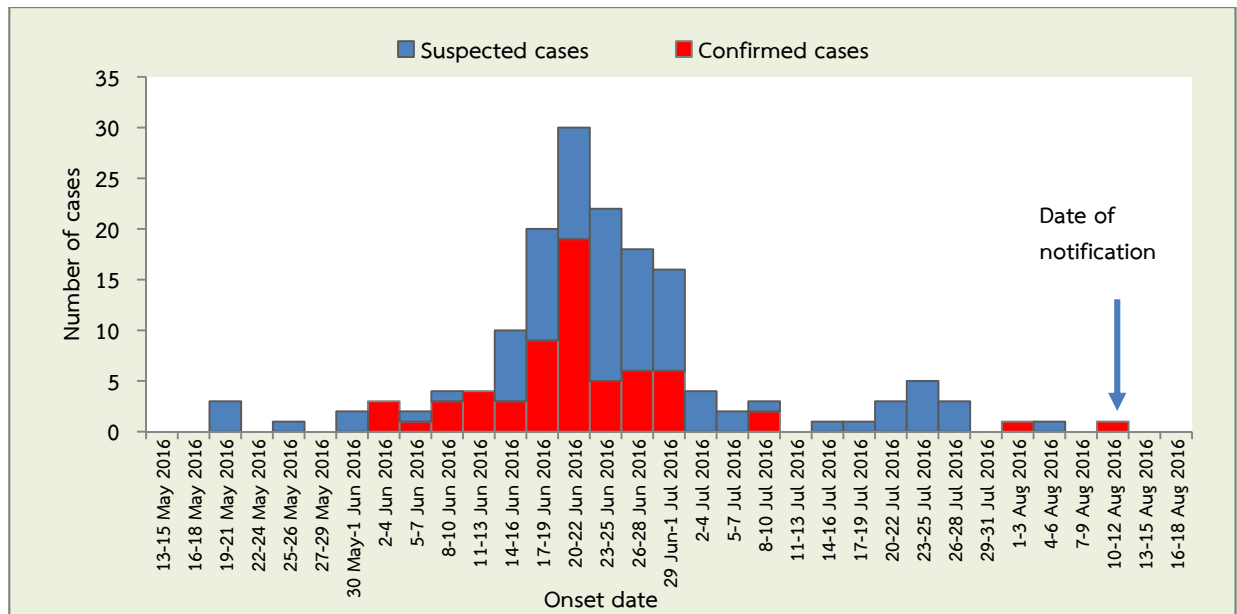


Figure 1 Situation of Zika virus infection in Lomsak district, 20 May–5 August 2016

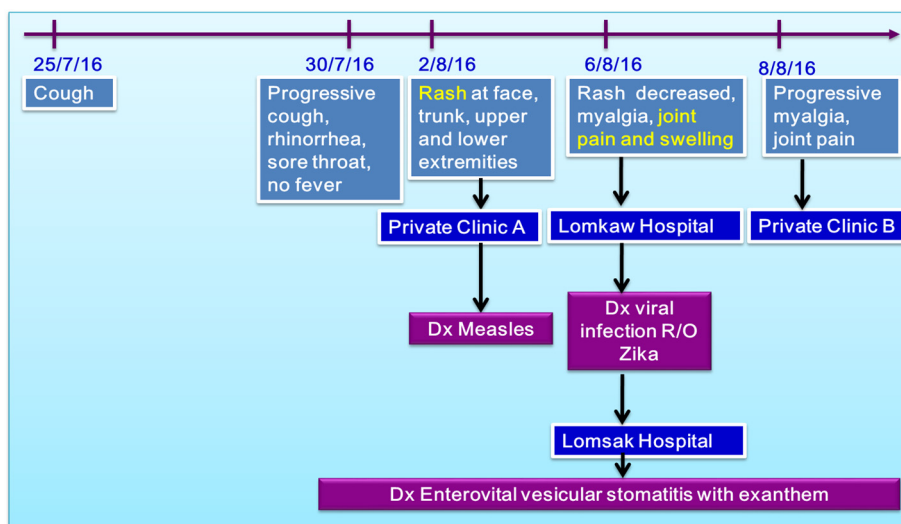


Figure 2 Timeline of clinical information of GBS cases, 25 June–8 August 2016

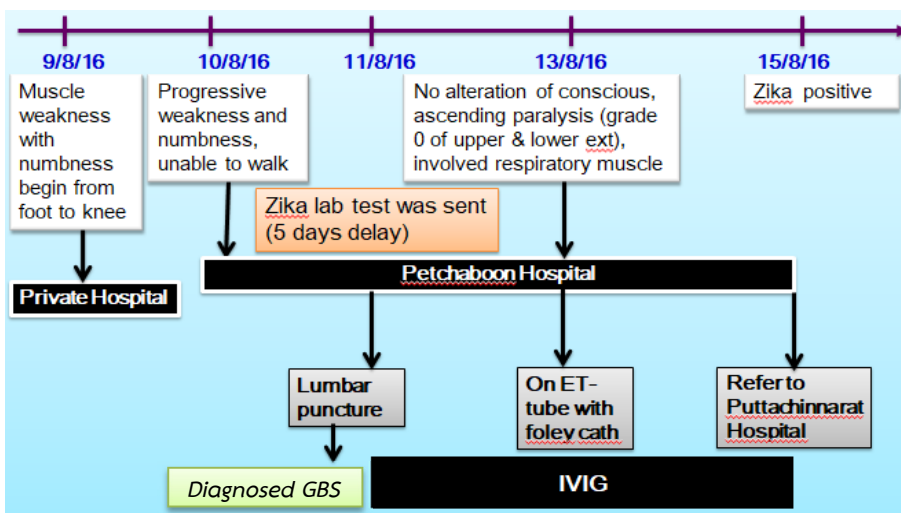


Figure 3 Timeline of clinical information of GBS cases, 9–15 August 2016

Local teams performed ultra-low volume spray (ULV) into zika case's house and the whole village. Vehicle-mounted motorized ULV was used first, then portable backpack ULV were used in the house and surrounding area. Vehicle-mounted motorized ULV can only access to areas with good road condition.

Most villagers knew there was a zika outbreak in their village through announcement from village health volunteers and public health officers while they performed mosquito spraying, however, they were not aware of current control measures in this area.

Table 1 Case definition of Zika virus⁽¹⁰⁾

Topic	Definitions
Patient under investigation of Zika virus infection (PUI)	<p><i>Patient age > 15 years with</i></p> <ol style="list-style-type: none"> 1. Maculopapular rash with at least one symptom, fever, arthralgia and conjunctivitis 2. Fever with at least two symptoms, headache, arthralgia and conjunctivitis 3. Maculopapular rash who stay or had history of travelling to confirmed case's outbreak area (sub-district level) that was still in the active phase <p><i>Patient age < 15 years with</i></p> <ol style="list-style-type: none"> 1. Fever with rash with conjunctivitis 2. Cluster of patient with maculopapular rash with at least one symptom, fever, conjunctivitis and arthralgia or fever with at least two symptoms, headache, arthralgia and conjunctivitis 3. Maculopapular rash who stay or had history of travelling to confirmed case's outbreak area (sub-district level) that was still in the active phase <p><i>Pregnancy woman with</i></p> <ol style="list-style-type: none"> 1. Maculopapular rash with at least one symptom, fever, arthralgia and conjunctivitis 2. Fever with at least two symptoms, headache, arthralgia and conjunctivitis 3. Maculopapular rash who stay or had history of travelling to confirmed case's outbreak area (sub-district level) that was still in the active phase <p><i>Neonatal microcephaly</i></p> <p>Neonatal aged not more than 1 month with head circumference less than 3rd percentile for age and sex</p> <p><i>Gullain-Barre Syndrome or Acute Inflammatory Demyelinating Polyradiculoneuropathy</i></p>
Suspected case	PUI who has clinical onset within 2 weeks before or after the onset of the confirmed case and stays in the same village or have epidemiological linkage with the confirmed case, without specimen collection for zika virus detection or collect specimen with inappropriate timing.
Confirmed case	<ol style="list-style-type: none"> 1. PUI who has positive laboratory results, PCR for zika virus, in blood, urine, or other secretions 2. Neonatal microcephaly with positive result for zika IgM
Asymptomatic infection	A person who does not have any symptom or have some symptom but does not meet the criteria of PUI but showed positive laboratory result for zika virus (zika virus PCR)

Table 2 Assessment of larva survey of local team in recent confirmed, PUI cases' house, and Lomsak hospital in Lomsak district, Phetchabun province, 2016

Areas	Date of start control measure of local teams	Date of start survey by BoE teams	HI (%)	CI (%)
House of confirmed case				
Village 4 th Hui Rai subdistrict	15 August 2016	20 August 2016	1/5 (20.00)	7/58 (12.06)
Village 3 rd Hui Rai subdistrict	15 August 2016	20 August 2016	2/10 (20.00)	2/108 (1.85)
House of PUI cases				
Village 12 th temple in Num Kor subdistrict (Dx DF on 15 August 2016)	No control measure before survey	21 August 2016	1/1 (100.00)	37/48 (77.08)
Village 4 Ban-Tiew subdistrict (Dx DF)	6 July 2016	20 August 2016	1/2 (50.00)	1/35 (2.85)
Lomsak hospital	No control measure in staffs' houses	20 August 2016	3/3 (100.00) (Staffs' houses)	7/17 (41.17)

Table 3 Case definition of Guillian Barre syndrome (Brighton criteria) compare with findings from reported GBS case in Thailand ⁽¹⁵⁾

Criteria	Level 1	Level 2	Level 3	GBS case
Clinical	<ul style="list-style-type: none"> – Bilateral and flaccid weakness of the limb – Decrease and absence deep tendon reflex in weak limb – Absence of identified alternative diagnosis for weakness – Monophasic illness pattern with nadir follow by clinical plateau 	<ul style="list-style-type: none"> – Bilateral and flaccid weakness of the limb – Decrease and absence deep tendon reflex in weak limb – Absence of identified alternative diagnosis for weakness – Monophasic illness pattern with nadir follow by clinical plateau 	<ul style="list-style-type: none"> – Bilateral and flaccid weakness of the limb – Decrease and absence deep tendon reflex in weak limb – Absence of identified alternative diagnosis for weakness – Monophasic illness pattern with nadir follow by clinical plateau 	<ul style="list-style-type: none"> – Bilateral and flaccid weakness of the limb – Absence of identified alternative diagnosis for weakness Monophasic illness pattern with nadir follow by clinical plateau (Classified as level 2)
Laboratory	<ul style="list-style-type: none"> – Cytoalbuminologic dissociation (high protein) - Electrophysiological findings consistent GBS 	Cytoalbuminologic dissociation (high protein)	-None	Cytoalbuminologic dissociation (high protein)

Discussion

Description of GBS case

The patient was diagnosed as zika virus associated GBS from clinical presentation and laboratory diagnosis, CSF profile and urine PCR for zika virus. This is the first reported zika associated GBS case in Asia. The confirmation of zika infection was delayed for at least 5 days due to late request of laboratory test though zika was suspected in the area affected by a prolonged outbreak. This zika associated GBS case had severe clinical manifestation, and did not respond well to IVIG. The patient was fully recovered after 3 months. On average 2/3 GBS patients get fully recovered after one month⁽⁸⁾. The first report of zika related GBS came from French Polynesia in 2014. There were 42 zika cases with GBS, 38% of cases were admitted in ICU and 24% had tracheostomy⁽¹²⁾⁽¹³⁾.

GBS might cause mortality in case of delay diagnosis and treatment⁽¹⁴⁾. Normally, IVIG or plasma exchange should be administrated within 10-14 days

from onset of initial infection symptoms⁽⁸⁾. This case got IVIG on 17 days after cough and 9 days after having rash, and the IVIG was applied just 2 days after development of weakness. The interval between onset of initial symptom and development of weakness could be long, thus, use of IVIG following neurological symptoms may not fall into the 14 days golden period, and cause difficulty to achieve desired outcome.

Mrs. K probably had epidemiological linkage with GBS case because she visited the grocery store near the GBS's house often, even after onset of her symptoms. Before the onset, she went to Ban-Tiew subdistrict where the hardest hit area of this zika outbreak was. Mrs. K had typical symptoms of zika infection but negative for urine PCR for zika, however, according to guideline zika infection cannot be ruled out with negative test result, given low viral load in clinical specimen impairing sensitivity of PCR, and IgM/IgG cross-reaction with Dengue in our region⁽⁶⁾.

Environmental survey in Grocery A found larva in the backyard (CI = 31%, 6/19) and many garbage. Grocery A may be a possible location of transmission to this GBS case.

Assessment of existing surveillance system and control measure in local area

Low coverage of zika surveillance system in Lomsak district may be caused by lack of co-operation between the hospital teams and the surveillance team (in district health office). Impaired surveillance system resulted in lower case confirmation, lack of control measure in some cases and caused prolong outbreak. Moreover, since effective control of zika outbreak is labor intensive and requires large amount of resources, especially in the situation that the outbreak was not detected in the early stage, like in Lomsak district, this prolong outbreak caused fatigue of the outbreak control system. Therefore, there was silent transmission in various areas as reflected from the environment survey result.

The methods used for larva control in this area was similar to other areas in Thailand that use village health volunteers to help in larva control of the houses under their responsibility and focus more on environmental sanitation than using larvicides. However, community engagement level was inadequate as many house owners refused to participate in larva control. Moreover, both the village health volunteers and the villagers need more knowledge to choose appropriate options in larva control.

Limitations

Further active case finding and environmental survey were limited by time. Comprehensive system evaluation was not performed due to constraint on available resource.

Recommendations

Ability of case detection should be improved by giving health care workers more training on zika virus

and GBS, and references such as reporting flow chart. Coverage of zika surveillance system in Lomsak district should be improved by periodic monitoring and evaluation of the system performance.

Health education on zika virus and container management should be provided to villagers. Public health officer should be encouraged to provide more guidance to village health volunteers on larva control and monitor its quality.

Collaboration with village health volunteers in outbreak area should be strengthened to screen for early symptoms such as fever or rash, and notify local health officer. Health officers should provide mosquito repellent and perform mosquito spraying upon notification of early cases, then collect specimens if they turn to PUI

And vigorous detection and control of zika virus nationwide should be emphasized to reduce the zika burden and its severe complication.

Conclusions

This was the first case of zika virus associated GBS in Asia. Patient had critical situation and required intensive care despite administration of IVIG. Prolong Zika outbreak in these areas may be caused by inadequate control measure of general public, impaired surveillance coverage and inadequate vector control. Enhancing zika virus surveillance system and improve knowledge and raising awareness among general public are needed to control zika virus outbreak and decrease incidence of zika associated GBS.

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แนะนำการอ้างอิงสำหรับบทความนี้

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การสอบสวนผู้ป่วยโรคติดเชื้อไวรัสซิกาที่มีอาการแขนและขาอ่อนแรง ในอำเภอหล่มสัก จังหวัดเพชรบูรณ์ ประเทศไทย ปี พ.ศ. 2559

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³ สำนักงานควบคุมป้องกันโรคเขต 2 จังหวัดพิษณุโลก

บทคัดย่อ

บทนำ: สำนักระบาดวิทยาได้รับรายงานว่ามีผู้ป่วยสงสัยว่ามีการติดเชื้อไวรัสซิการ่วมกับมีอาการแขนและขาอ่อนแรงที่อำเภอหล่มสัก จังหวัดเพชรบูรณ์ ซึ่งมีการระบาดอย่างต่อเนื่องของโรคติดเชื้อไวรัสซิกาในช่วง 3 เดือนที่ผ่านมา

วิธีการศึกษา: ในการสอบสวนได้เก็บข้อมูลผู้ป่วยจากการทบทวนเวชระเบียนและสัมภาษณ์ญาติของผู้ป่วย ทำการประเมินความครอบคลุมของการรายงานผู้ป่วยซิกาในระบบเฝ้าระวังในระดับอำเภอ ร่วมกับประเมินการควบคุมโรคในพื้นที่ โดยสัมภาษณ์วิธีการควบคุมโรคจากเจ้าหน้าที่ อาสาสมัครสาธารณสุข และประชาชนในบ้านที่ลงสุ่มสำรวจ ได้ทำการสุ่มสำรวจลูกน้ำยุงลายในบ้านที่เพิ่งพบผู้ป่วยยืนยันและผู้ป่วยเข้าเกณฑ์สอบสวนโรคติดเชื้อไวรัสซิการวมถึงโรงพยาบาลหล่มสัก

ผลการศึกษา: ผู้ป่วยเป็นหญิงไทยอายุ 52 ปี อาการเริ่มด้วยมีผื่นและปวดข้อ 6 วันตามด้วยอาการแขนและขาอ่อนแรง 1 วัน แพทย์พบว่าผู้ป่วยติดเชื้อไวรัสซิการ่วมกับมีภาวะ Guillian Barre Syndrome (GBS) จากผลการตรวจน้ำไขสันหลังและการตรวจพบสารพันธุกรรมไวรัสซิกาจากตัวอย่างปัสสาวะ แพทย์ได้ฉีด Immunoglobulin (IVIG) ทางหลอดเลือดดำเป็นเวลา 5 วัน ในระหว่างนั้นผู้ป่วยยังคงมีอาการอ่อนแรงเพิ่มขึ้นเรื่อย ๆ และมีภาวะทางเดินหายใจล้มเหลวเฉียบพลัน 2 วันหลังจากเริ่มให้ IVIG จึงต้องใส่ท่อช่วยหายใจ ระหว่างนอนโรงพยาบาลผู้ป่วยมีภาวะติดเชื้อในปอดและกล้ามเนื้อฝ่อ ผู้ป่วยออกจากโรงพยาบาลและอาการดีขึ้นใน 3 เดือนต่อมา ผลการประเมินความครอบคลุมในการรายงานผู้ป่วยเข้าสู่ระบบเฝ้าระวังไวรัสซิกาของอำเภอพบว่าค่อนข้างต่ำ (ร้อยละ 61.22) การประเมินการควบคุมโรคในพื้นที่พบปัญหาในหลายด้าน รวมถึงทักษะที่ไม่เพียงพอในการทำลายลูกน้ำและความล่าช้าของระบบในการควบคุมโรคจากสถานการณ์การระบาดที่ยาวนาน

สรุปผลและข้อเสนอแนะ: ผู้ป่วยรายนี้เป็นผู้ป่วยรายแรกในทวีปเอเชียที่วินิจฉัยว่าเป็นโรคติดเชื้อไวรัสซิการ่วมกับมีภาวะแขนและขาอ่อนแรง (GBS) การปรับปรุงระบบเฝ้าระวังซิกาและการควบคุมป้องกันโรคสามารถควบคุมและป้องกันโรคติดเชื้อไวรัสซิกาในพื้นที่นี้ได้

คำสำคัญ: ระบบเฝ้าระวังซิกา, ภาวะแขนและขาอ่อนแรง, Guillian Barre Syndrome, อำเภอหล่มสัก, จังหวัดเพชรบูรณ์