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Field Epidemiology Training Program, Bureau of Epidemiology
Department of Disease Control, Ministry of Public Health, Thailand
Tel: +6625903894, Fax: +6625903845, Email: osireditor@osirjournal.net, http://www.osirjournal.net

Epidemiological Features of Japanese Encephalitis among Acute Encephalitis Syndrome Cases in Myanmar, 2014-2016: Implications to the Vaccination Program

Yamin Thaung[1,*], Witaya Swaddiwudhipong[2], Htun Tin[3], Panithee Thammawijaya[2], Phanthanee Thitichai[2], Thuzar Chit Tin[3]

1 Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand

2 Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand

3 Department of Public Health, Ministry of Health and Sports, Myanmar

*Corresponding author, email address: dryaminthaung@gmail.com

Abstract

Japanese encephalitis (JE) was confirmed in Myanmar since 1974 and sporadic outbreaks have been reported. A descriptive study was conducted to determine the epidemiological characteristics of JE among acute encephalitis syndrome (AES) cases during 2014-2016 and identify potential risk factors for JE infection. The reported AES cases increased from 252 in 2014 to 1,911 in 2016. The annual proportion of JE among AES cases were 22.1-22.6% during 2014-2016. The highest proportion of JE among AES case was found in Rakhine State (44.6%) in 2016. Proportions of JE among AES cases were high in the rural areas, and in children aged 1-14 years. None of AES cases had previous JE vaccination prior to onset. JE infection was confirmed in 53.4% of serum and 47.0% of cerebrospinal fluid specimens obtained 3-7 days after onset of illness. In multivariate analysis, people aged one year and above, living in rural areas (Adjusted odds ratio = 2.9, 95% CI = 2.2-4.0) and having chickens and/or ducks in/nearby house (Adjusted odds ratio = 1.4, 95% CI = 1.0-1.9) were significantly associated with JE positivity among AES cases. An effective immunization campaign should be implemented nationwide, with prioritization given to the most affected areas and those aged 1-14 years.

Keywords: Japanese encephalitis, AES, vaccination, Myanmar

Introduction

Japanese encephalitis (JE) is a vector-borne zoonotic viral disease. It is transmitted to humans through the bite of infected *Culex* species mosquitoes, particularly *Culex tritaeniorhynchus*. Pigs, ducks and chickens are the amplifier hosts and humans are the incidental or dead-end hosts.[1-4] Less than 1% of people develop clinical illness after they are infected with JE virus (JEV). The case fatality rate, however, can be as high as 30% and permanent neurologic or psychiatric sequelae can be found in 30-50% of those with encephalitis.[1-3]

Globally, it has been estimated that approximately 68,000 cases of JE occur annually. In Asia and the Western Pacific, endemic JEV transmission can be observed in 24 countries, including Myanmar, with over three billion people exposed to risk of infection.[5] In Myanmar, the first confirmed outbreak of JE occurred in eastern Shan State in 1974. By 1979, 198 cases, with 98 deaths (CFR 49.5%), were reported in 11 townships in six states and regions. A JE outbreak was also detected in 1977 among 13 horses and one donkey in the animal breeding center in southern Shan State.[6,7] In 2016, JE outbreaks were reported from Rakhine State.[8,9]

JE primarily affects children and people living in rural areas.[6] Since approximately 70% of the population residing in the rural areas and 28.6% of total population are children 0-14 years, a high risk of JEV transmission exists in Myanmar.[10-11]

Myanmar is divided administratively into Nay Pyi Taw Council Territory, seven states and seven regions.[10] Hospital based AES surveillance has been initiated in limited places since 2007. The Central Epidemiology Unit (CEU) is the responsible unit for the surveillance of JE and AES. In 2016, the CEU developed national guideline on AES surveillance and modified the case definition of JE. Laboratory facilities for AES surveillance are only available at the National Health Laboratory (NHL) where a sample of serum and/or cerebrospinal fluid of an AES case should be tested for JE. Training of volunteers for vector control is implemented by the vector-borne diseases control (VBDC) program. The expanded programme on immunization (EPI), Myanmar, also provides technical advice and training to the health workers.[6]

Analysis of trends and distribution would be useful for implementation of prevention and control activities in high risk geographical areas. Hence, this study aimed to describe the morbidity and mortality trends of JE infected cases, determine the epidemiological characteristics of JE among AES cases, and identify the potential risk factors for JE infection.

Methods

Descriptive Study

A descriptive study was performed by reviewing the AES surveillance data in the CEU. The information from case investigation forms reported during 2014-2016 in the NHL was retrieved. Descriptive characteristics in the case investigation forms included age, gender, residence, clinical features, JE vaccination, and dates of onset and specimen collection. In addition, geographical distributions of JE among AES cases in 2014-2016 were presented. Seasonal patterns during 2014-2016 were described by onset.

An AES case in this study was defined as a person with acute onset of fever (Temperature >100.4°F or 38°C), change in mental status (confusion, disorientation, coma, or inability to talk), with or without new onset of seizures (excluding simple febrile seizure), and tested for JE virus immunoglobulin M (IgM) in NHL in 2014-2016. A JE case was defined as an AES case confirmed to have JEV IgM in serum or CSF by enzyme-linked immunosorbent assay (ELISA).[6]

Analytical Study

We used Epi Info version 7.2.1.0[12] to analyze and identify the potential risk factors using the information from the case investigation forms. The chi-square test was used to compare proportions. Multiple logistic regression analysis was used to identify factors associated with JE among AES cases and all variables were controlled at the same time in the final model. All factors from the univariate analysis with p-value equal to or less than 0.2 were included in final model. Adjusted odds ratio (OR) and their 95% confidence intervals (CI) were calculated to indicate the strength of association.

Results

JE among AES cases in 2014-2016

The annually reported AES cases started to increase from 252 in 2014 to 1,911 in 2016 and JE cases increased from 57 in 2014 to 424 in 2016. The proportion of JE among AES cases was approximately 22.2-22.6% in 2014-2016. JE proportions among AES cases were found to be the highest during and after the rainy season, i.e. June to August, throughout 2014-2016 (Figure 1).

JE cases were identified among AES cases in two states and five regions, with the highest in Mandalay Region and Kachin State in 2014. However, in 2015, JE cases were reported from six states and six regions. In 2016, 13 out of total 15 states and regions, except Kachin and Kayah States, reported JE cases, with the highest in Rakhine State (Figure 2).

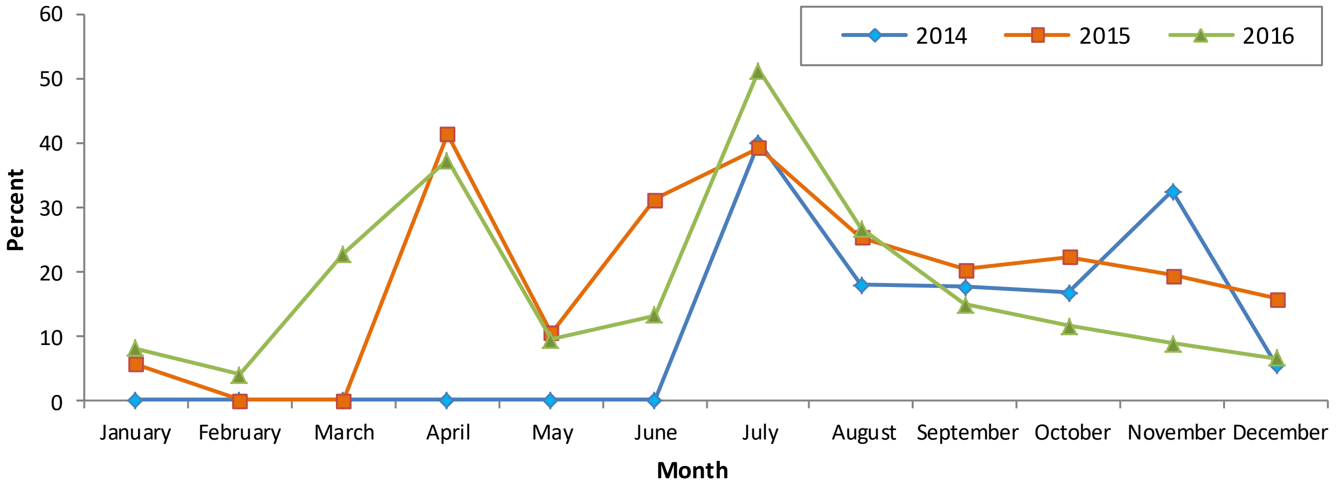

Figure 1. Distribution of Japanese encephalitis among acute encephalitis syndrome cases by months in Myanmar, 2014-2016

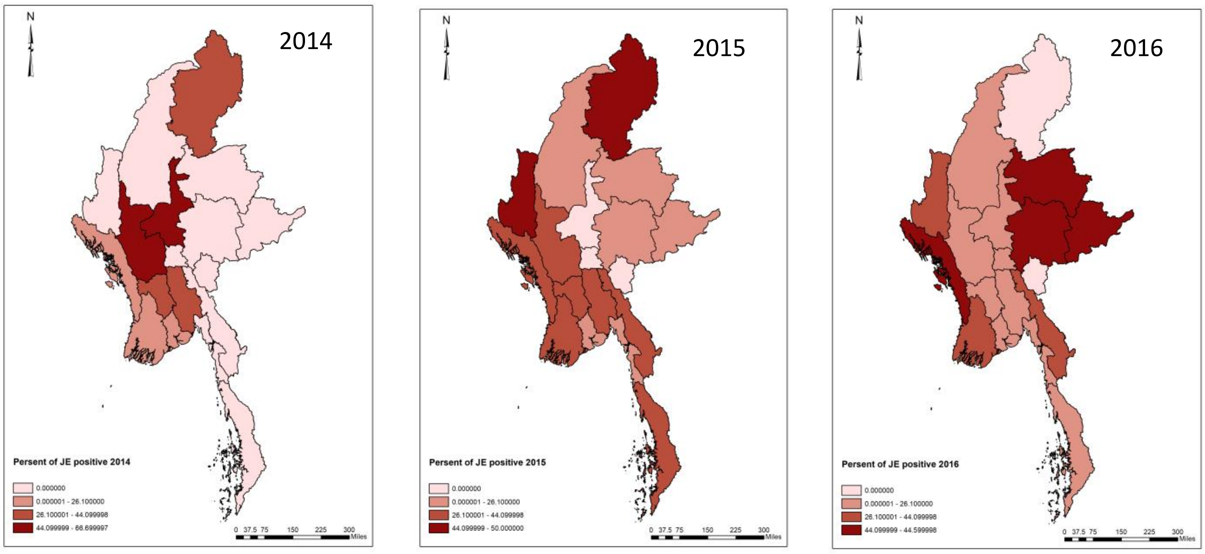

Figure 2. Percent distribution of Japanese encephalitis among acute encephalitis syndrome cases by states and regions of Myanmar, 2014-2016

Proportions of JE among AES cases were high in the rural areas, from 26.8% in 2014, 31.7% in 2015 and 31.5% in 2016 (Table 1). In 2016, high JE proportions among AES cases were in children 1-14 years old (30.9%), particularly in those 5-9 years of age, with 43.1% in 2014, 36.3% in 2015, and 33.8% in 2016. The lowest proportion (2.0%) was seen among under one year of age (Figure 3). Moreover, higher proportion of JE cases was seen in males during 2014-2016. The most common clinical manifestations of JE cases were neck stiffness (35.0%) in 2014 and unconsciousness in 2015-2016 (55.0% and 50.5% respectively) (Figure 4).

Table 1. Distribution of Japanese encephalitis (JE) and acute encephalitis syndrome cases (AES) in rural and urban areas of Myanmar, 2014-2016

Area	2014		2015		2016	
	AES case examined	JE positive case (%)	AES case examined	JE Positive case (%)	AES case examined	JE positive case (%)
Rural	127	34 (26.8)	328	104 (31.7)	1,007	317 (31.5)
Urban	82	10 (12.2)	206	21 (10.2)	688	90 (13.1)
Unknown	43	13 (30.2)	114	21 (18.4)	216	17 (7.9)
Total	252	57 (22.6)	648	146 (22.5)	1,911	424 (22.2)

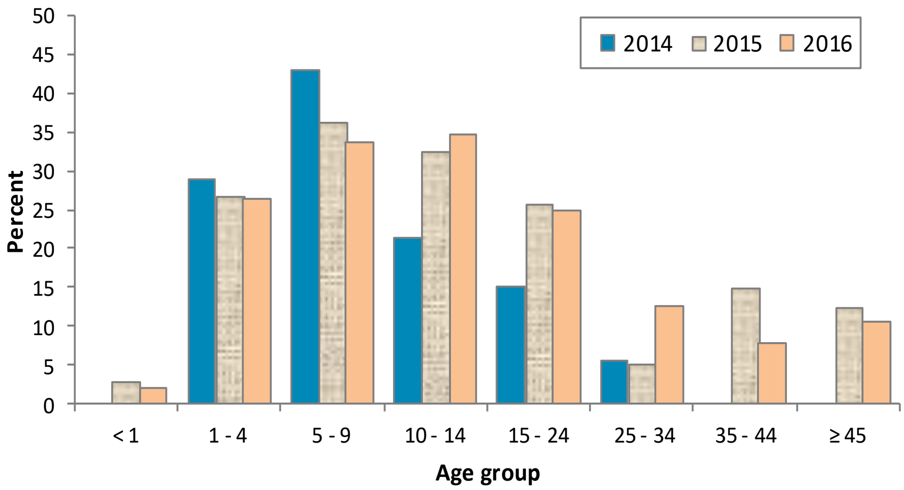

Figure 3. Distribution of Japanese encephalitis among acute encephalitis syndrome cases by age groups in Myanmar, 2014-2016

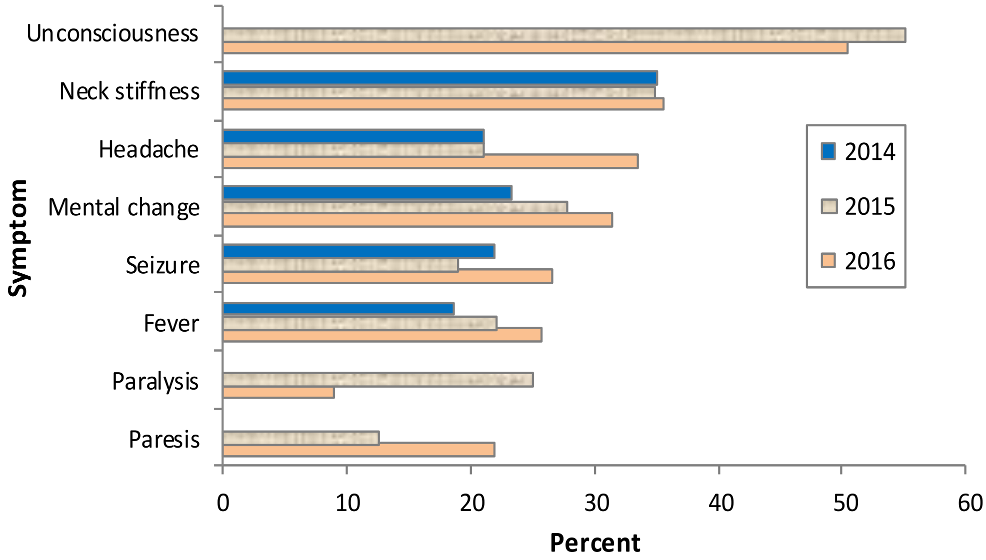

Figure 4. Clinical manifestations of Japanese encephalitis cases in Myanmar, 2014-2016

Description on JE among AES cases in 2016

Most of the AES cases (1,431/1,911, 74.9%) were initially diagnosed as viral encephalitis/meningitis or fever with central nervous system (CNS) symptoms while about 22.2% of all the AES cases were confirmed as JE cases. The highest proportion of JE was found in the cases with diagnosis of viral encephalitis/meningitis or fever with CNS symptoms (25.8%). Bacterial encephalitis or meningitis were the initial diagnosis in 113 of AES cases, of whom 26 (23.0%) were confirmed by laboratory testing. None of the AES cases had previous JE vaccination history before their onset of AES.

Among total 1,503 serum samples tested, 388 (25.8%) were positive for JE. Of the JE positive cases, 207 (53.4%) had a specimen obtained 3-7 days after onset of illness. Another 75 (19.3%) cases had all specimens collected between 8-14 days of illness onset. Only 57 (14.7%) cases were collected within two days of disease onset. Out of 784 CSF tested samples, 151 (19.3%) had positive JE results. Although 71 (47.0%) of the positive cases had a specimen obtained 3-7 days after onset of illness, only 18 (11.9%) cases were collected within two days of illness onset.

Analytical Study

From the univariate analysis, the characteristics significantly associated with JE were age, residence, distance between rice field and home, and having pigs, chickens and/or ducks, sheep and/or goats in/nearby the house (Table 2). The highest proportion of JE was in children 5-14 years old (34.2%), followed by those 1-4 years old (26.5%). The proportion decreased with increasing age in adults and was very low in children under one year old. Those living in rural areas and near the rice fields less than one kilometer away from the home had the highest proportion of JE. Clinical manifestations significantly associated with JE were presence of fever, seizure, mental change, headache, neck stiffness and unconsciousness (Table 3).

From the multivariate analysis, the factors significantly associated with JE were age groups: 1-4 years old (Adjusted OR = 40.7, 95% CI = 12.7-130.5), 5-14 years old (Adjusted OR = 52.0, 95% CI = 16.4-165.5), 15-24 years old (Adjusted OR = 31.1, 95% CI = 9.1-106.1) and 25 years old and above (Adjusted OR = 14.7, 95% CI = 4.3-50.2), living in rural areas (Adjusted OR = 2.9, 95% CI = 2.2-4.0) and having chickens and/or ducks in/nearby the house (Adjusted OR = 1.4, 95% CI = 1.0-1.9) (Table 4).

Discussion

In Myanmar, the annual reported AES and JE cases was found to be increasing over a three-year period from 2014-2016. This increasing trend could reflect the heightened awareness of the clinicians to send samples for laboratory diagnosis, the increase utilization of health facilities by patients and the development of national guidelines in 2016. However, the incidence of JE among AES cases has remained unchanged, from 2014-2016. Additional risk factors include children aged 1-14 years, people those living in rural areas and having chickens and/or ducks in/nearby the house.

JE cases were reported sporadically throughout the year with peaks from June to August which coincides with the rainy season and potentially an increase in the prevalence of the mosquito vectors. JE incidence declined significantly with the onset of winter.[13] The occurrence of JE cases increased from seven states/regions in 2014 to almost all states/regions of Myanmar in 2016.

Table 2. Distribution of Japanese encephalitis (JE) among acute encephalitis syndrome cases (AES) by demographic characteristics in Myanmar, 2016

Characteristic	Number of AES case examined	Number of JE positive case (%)	P-value
Total	1,911	424 (22.2)	
Age (year)			
<1	343	7 (2.0)	<0.001
1-4	490	130 (26.5)	
5-14	640	219 (34.2)	
15-24	152	38 (25.0)	
≥25	275	29 (10.5)	
Gender			
Male	1,052	246 (23.4)	0.163
Female	859	178 (20.7)	
Residence			
Rural	1,007	317 (31.5)	<0.001
Urban	688	90 (13.1)	
Environmental factors			
Distance between rice field and home (km)			
< 1	327	98 (30.0)	0.019
1-5	119	27 (22.7)	
> 5	1,041	229 (22.0)	
Pig in/nearby the house	408	138 (33.8)	<0.001*
Chicken and/or duck in/nearby the house	468	156 (33.3)	<0.001*
Sheep and/or goat in/nearby the house	33	13 (39.4)	0.040*
Cattle and/or buffalo in/nearby the house	232	68 (29.3)	0.051*

* Comparison between those reporting: yes and no

Table 3. Distribution and univariate analysis of Japanese encephalitis (JE) among acute encephalitis syndrome (AES) cases by clinical manifestation in Myanmar, 2016

Clinical manifestation	Number of AES case examined	Number of JE positive case (%)	P-value
Total	1,911	424 (22.2)	
Fever	1,432	369 (25.8)	<0.001*
Seizure	878	234 (26.7)	0.014*
Mental change	483	152 (31.5)	<0.001*
Headache	402	135 (33.6)	<0.001*
Neck stiffness	227	81 (35.7)	<0.001*
Unconsciousness	99	50 (50.5)	<0.001*
Paresis	50	11 (22.0)	0.707*
Paralysis	11	1 (9.1)	0.477*

* Comparison between those reporting yes and no

Table 4. Multiple logistic regression analysis on possible risk factors for Japanese encephalitis infection among acute encephalitis syndrome cases in Myanmar, 2016 (n=1,911)

Characteristic	Adjusted odds ratio	95% CI
Personal factors		
Age under 1 year	Reference	
Age 1-4 years	40.7	12.7-130.5
Age 5-14 years	52.0	16.4-165.5
Age 15-24 years	31.1	9.1-106.1
Age ≥25 years	14.7	4.3-50.2
Gender (male/female)	1.1	0.8-1.4
Environmental factors		
Residence (rural/urban)	2.9	2.2-4.0
Distance between rice field and home (km)		
No field	Reference	
Distance (<1)	0.9	0.6-1.4
Distance (1-5)	0.7	0.4-1.2
Pig in/nearby the house	1.0	0.7-1.4
Chicken and/or duck in/nearby the house	1.4	1.0-1.9
Sheep and/or goat in/nearby the house	1.4	0.6-3.3
Cattle and/or buffalo in/nearby the house	0.9	0.6-1.3

Despite that, JE and AES cases might still be under reported if hospitals from remote areas were unable to send specimens of suspected AES cases for laboratory confirmation of JEV IgM due to laboratory facilities for AES surveillance being only available at the NHL.[6] Among the AES cases, majority of JE positive cases were found in those living in rural areas, one-third were those living near rice fields of less than one kilometer where the main case occupation was farming and about one-third were those having domestic animals in/nearby the house. This finding was similar to the findings of a study in India which postulated that this may be due to an expansion of irrigated rice production systems which increase mosquito vector density.[13]

JEV infection could be detected in chickens, ducks and pigs.[4,14,15] One study in Indonesia found that 25 (20.6%) out of 121 sera samples of ducks, 72 (36.7%) out of 196 sera samples of chickens and 65 (32.2%) out of 202 sera samples of pigs were JEV antibodies positive by ELISA.[4]

In our study, a high proportion of JE case was found in children with AES cases aged 1-14 years, in 2014-2016. This finding is similar to what was found in a similar study in China by Zundong Yin et al in 2010, where 45-77% of JE cases were found in children under 15 years of age.[16] This could reflect that the children under 15 years were more susceptible to JE infection than adults for a lack of immunity and may have been exposed to mosquito vectors due to frequent visits to the rice fields with their parents. Those with clinical symptoms of fever, seizure, mental change, headache, neck stiffness and unconsciousness were found in a higher percentage of JE positive cases than among AES cases.

Although most of the JE positive cases had an initial clinical diagnosis such as viral encephalitis/meningitis, other encephalitis or other diagnosis, 74.9% of AES cases were initially diagnosed as viral encephalitis/meningitis or fever with CNS symptoms. In other studies, of the 2,815 AES cases identified at sentinel hospitals, 1,194 (42%) were initially diagnosed as viral encephalitis/meningitis.[17] This difference might be due to a local physician preference to assign a diagnosis of viral encephalitis or other encephalitis rather than JE if there were no supporting laboratory results. A significant proportion of cases found to be positive for JE were also detected among those who were initially diagnosed as bacterial meningitis/ encephalitis (23.0%).

Confirmed JE cases were found in 53.4% of serum specimens and 47.0% of CSF specimens, which were obtained 3-7 days after illness onset. Besides, 11-14% of the specimens were collected within two days of illness. There might have been false-negative results because about 75% of samples would be JEV IgM positive at four days after onset of illness.[6] Had we obtained follow-up specimens, additional JE cases might have been identified from AES cases. Moreover, there may have been incorrect information about date of illness onset provided by health care providers.

In multivariate analysis, the proportion of JE among AES cases was significantly higher among people aged between 1-80 years old. The persons who lived in rural area and who had the family or neighbor own domestic animals such as chicken and/or duck were significantly associated with JE positive. This is consistent with another study in Vietnam which found the proportion of JE positivity among AES cases was significantly higher among children aged 6-15 years compared with aged five years or less and adults over 15 years of age (p-value <0.01).[17]

There were some limitations with this study. We found that there was missing information in AES case investigation forms and therefore the residual neurological sequelae and outcomes were not studied because of incomplete clinical notes in these surveillance forms.

We recommended that all suspected AES cases undergo laboratory testing for JEV and monitoring of disease situation should be pursued by public health authorities. Responsible persons for AES surveillance should complete case investigation forms starting from township hospital following the national guideline. JEV immunization campaigns should prioritize those aged 1-14 years, especially people living in rural areas, family members of confirmed cases and those who own or are neighbors to those who own domestic animals such as chickens and/or ducks.

The reported annual incidence of JE among AES has increased over a three-year period from 2014-2016 and poses an important public health threat in Myanmar. An immunization campaign should be initiated to target the most affected areas including rural areas and those aged 1-14 years given the increase in risk revealed by this study.

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