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# Japanese encephalitis incidence and its association with the length of stay and long-term outcome in 2015, Bali-Indonesia



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## ABSTRACT

**Background:** Japanese Encephalitis (JE) had high fatality rate and gave permanent sequelae in more than quarter children affected. Since 1975, JE surveillance in animals found that JE infection had spread throughout the Indonesia regions. Bali is endemic for JE infection, with well enhanced surveillance, and recruited as pilot project area for JE vaccination in Indonesia.

**Objectives:** to assess JE incidence and to investigate JE association with the burden of the disease, the length of stay and severe neurological outcome in Bali province.

**Methods:** We applied clinical case definition of acute encephalitis syndrome (AES) and performed laboratory diagnostic criteria using serum IgM capture ELISA.

**Results:** During the surveillance period, 282 cases were met the AES case definition, 50 (17.7%) were positive for JE infection, resulting

in an annual incidence of 1.2/100 000 population. As many as 46 (92%) were under 15 years old. One (0.02%) subject died, while 18 (36%) survivors had a permanent disability due to brain atrophy or degeneration. Most subjects were admitted during the rainy season, but cases were reported throughout the year. The median length of illness was 10 days for subjects with non-JE encephalitis, while median length of illness 19 days for subjects with JE. The majority (88%) of JE patients were found to live far from a pigsty and mostly living in town. None of them had a history of JE vaccination.

**Conclusions:** The majority of JE cases in Bali was children under 15 years old, and not living in an area near a pigsty. This pattern similar with the previous study, since there is no immunization program available present. Consideration should be given to JE vaccination policy in the near future.

**Keywords:** Incidence, Japanese Encephalitis, Children

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## INTRODUCTION

Japanese encephalitis (JE) is an infection of JE virus on the central nervous system (CNS). JE remains as an important disease in all Asia region, found in East Asia such Japan and Korea, South Asia, such as India and Srilanka, and South East Asia, such the islands of Indonesia, and it reaches the Northern Territory of Australia.<sup>1-4</sup> *Japanese encephalitis* is an arthropod-borne viral disease and transmitted mosquito. The vector is commonly found around a human living area in Indonesia, especially *Culex tritaeniorhynchus* and *Culex quinquefasciatus*. A pig is one of JE virus reservoir. The main reason for high JE infection incidence in Bali is the presence of a large pigsty area on the island. This issue has been discussed nationally, and Bali is chosen as JE infection project investigation area. JE infection in human gives a varying clinical spectrum. It can be asymptomatic with positive antibody sero-conversion, sub-clinical symptoms with only fever as the only symptom, or gives a severe acute meningomyeloencephalitis symptoms.<sup>1-3</sup> In Indonesia, the

incidence was reported highest among rural areas and it increased during the rainy season. The JE incidences in Indonesia was the highest for children between 5-9 years old since there had not been a vaccination program until mid-2016.<sup>4</sup>

In February 2015, The World Health Organization (WHO) made a new statement against JE, that JE virus was still the number one cause of viral encephalitis in Asia. The WHO also stated that in 2015, it was estimated that 3 billion people living in 24 countries around South-East Asia and Western Pacific regions were considered vulnerable to JE infection. The annual incidences of JE were varying among countries, and among age groups. In endemic countries, the annual incidence was 5.4/100,000 in the age group of 0-14 years, and 0.6/100,000 in those older than 15 years. China reported a higher incidence, with 12.6/100 000 in children under 15 years.<sup>1,5</sup> JE surveillance remains a challenge, while the true extent and the prevalence of the virus, and the burden of disease are not well understood. It is estimated that in the world, 67,900

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clinical cases of JE occur annually, with approximately 13,600 to 20,400 deaths, with high rate of residual disability.<sup>6,7</sup>

The objective of this study was to assess the incidence of JE encephalitis and investigate the JE encephalitis association with the burden of the disease, the length of stay and severe neurological outcome in our province.

## METHODS

During 2015, subjects were recruited during a case-based surveillance from all hospitals which treating an acute encephalitis syndrome in Bali province, Indonesia. This study was a part of the Health Ministry of Indonesia and Bali province surveillance of acute encephalitis syndrome (AES) that focused on surveillance standards for JE according to the WHO guidelines.

From January to December 2015, all Bali hospitals were required to report all cases suspected of CNS infection in all age groups. All of the reported cases were included in our study. The inclusion criteria were patients in all age group suspected for AES and complex febrile seizure. A patient was diagnosed with AES if the person had a fever when admitted or had a history of fever, accompanied by a seizure or symptoms of a decreased consciousness. A complex febrile seizure was defined as a seizure during a fever (axillary temperature over 38°C), with an extra-cranial process as its underlying cause, and the seizure lasted more than 15 minutes, or the frequency of the seizure more than once in 24 hours or a partial/focal seizure.<sup>1,2,4</sup> The exclusion criteria were subjects (1) with a positive malaria rapid test, (2) had clinical features of tetanus, (3) positive for dengue infection, with positive NS1, or IgG and IgM anti-dengue, and (4) children diagnosed with simple febrile seizure. These subjects were included for Health Ministry of Indonesia Bali province surveillance of AES.<sup>1,4</sup>

All patient serum was tested for IgM and IgG antibodies against JE and dengue since Bali also had a high prevalence of dengue infection (flavivirus). We used IgM-capture ELISA per WHO recommendation<sup>1</sup> JE infection was distinguished from dengue with higher titers, and the primary infection was differentiated from secondary infections based on IgM and IgG ratio. The serum was obtained on the fifth (5<sup>th</sup>) day of fever or after because a sero-conversion was usually found during those times.

The patient's guardian was asked whether the family has a pig in their living environment. The patient immunization status was checked by asking the guardian whether the patient had ever received a JE vaccination, and by checking the immunization

**Table 1** Subjects Characteristics

Variables	Non-JE (n=262) f (%)	JE (n=50) f (%)
Sex, male	178 (67.9)	38 (76.0)
<b>Age</b>		
<15 year	246 (93.9)	46 (92.0)
≥ 15 years	16 (6.1)	4 (8.0)
Pigsty environment	28 (10.7)	6 (12.0)
Vaccination history	None	none

**Table 2** JE and Non-JE Encephalitis Comparison With The Neurological Outcome

	Severe n (%)	Non-Severe n (%)	p
JE			
Yes	23 (10.8)	189 (89.2)	0.001
No	18 (36)	32 (64)	
Total	41 (15.6)	221 (84)	

record, usually kept by the patient's guardian. The patient age and sex data were based on what were written in the medical record.

## RESULT

A total of 312 subjects were reported with a diagnosis of acute encephalitis syndrome (AES) and complex febrile seizure. Only 282 met the diagnosis definition. JE infection was positive in 50 subjects (17.7%), resulting an annual incidence of 1.2/100,000 population in 2015. Children under 15 years old were 46 of them (92%). One (0.02%) subject died, while 18 (37%) survivors had a permanent disability due to brain atrophy or degeneration. Most subjects were admitted during the rainy season, but cases were reported throughout the year. The median length of illness was 10 days for non-JE, while for the JE was 19 days. The characteristics of the patients were reported in Table 1.

Bivariate analysis was performed using the chi-square test to analyze JE infection association with severe neurological outcome (Table 2). Mortality was found only in one patient with JE, while the severe neurological outcome was significantly higher in JE group ( $p < 0.05$ ).

## DISCUSSION

Our study showed that Bali province was endemic for JE infection. The annual incidence high according to the WHO annual incidence among

countries.<sup>1-3</sup> In many parts of tropical Asia, it was typical that the JE incidence highest in children under 15 years old, and the peak was in the rainy season (from October to March). The incidence in children under 15 years was high due to JE natural tendency in an area with no vaccination program. Our result was similar to research in other countries that did not have a large vaccination program. There was a change of JE infection pattern, mostly in urban area nowadays. This may be due to other animals can be its reservoir, such as birds. Our study showed that the occurrence was highest in children, while in other countries with large immunization program showed a changing tendency to older age group.<sup>8,9</sup>

JE infection in Bali was not related to pigsty environment. We found the majority of the patients were living in a town without a pigsty, only 12% of patients had a pigsty. This should be taken into account in planning a vaccination program, where the children living in a non-pigsty environment are also in need of a JE vaccination.

We also found that the median length of stay of JE patients was longer compared to non-JE encephalitis patients (19 vs 10 days respectively). The severe neurological outcome was significantly higher in JE compared to non-JE encephalitis patients, with CT-scan revealed a brain atrophy and degeneration.

JE is a vaccine-preventable disease. Our findings showed the necessity of a mass vaccination program and vector control. JE vaccination should be integrated into the national immunization schedule.<sup>10-12</sup> Adjunctive intervention such as mosquito control should not replace JE childhood vaccination. Because JE vaccination does not induce a herd immunity, a high coverage and the sustenance of the vaccination must be reached. Reports from countries with wide JE vaccination program showed a decrease in incidence and a shift in age group affected to elderly after a few decades.<sup>1,11</sup>

## CONCLUSION

In Indonesia, JE remains a serious cause of encephalitis that gives significant sequelae, especially in children. Since JE is a preventable disease, a mass vaccination program in children must be a priority to reduce the incidence.

## STUDY LIMITATIONS

The WHO recommended a serum collection during admission and an additional sample after a few days from the first if it was negative. A first negative sample with a positive on the second one is a proof of JE infection in a highly endemic area, where there are many asymptomatic JE infection.<sup>1,2</sup> We only collected the serum once. In addition, we chose to perform serum examination because a cerebrospinal fluid is not stable, and a brain autopsy (for viral isolation) is against the population culture and religion.

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