

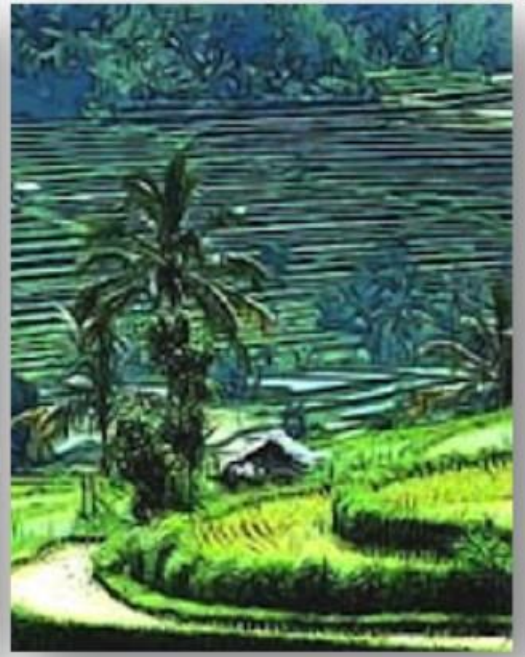

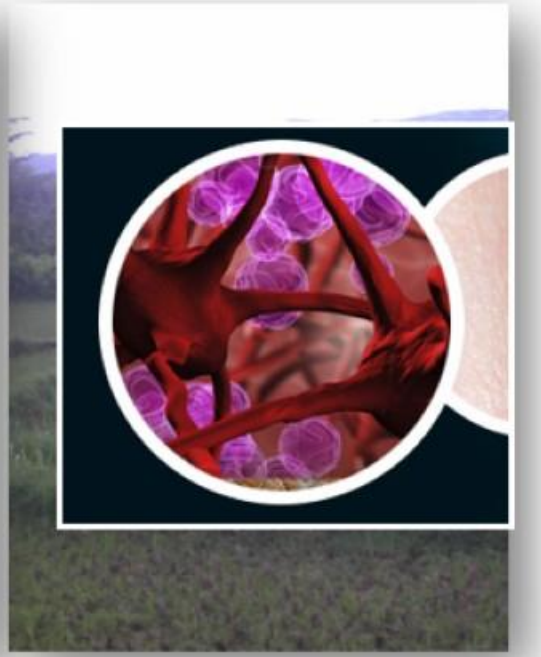

An update on the Epidemiology of Japanese encephalitis in Indonesia

Triwibowo Ambar Garjito

Vector-borne and zoonotic disease research group, Research Center of Public Health and Nutrition,
National Research and Innovation Agency Indonesia

Background

Enzootic cycle of JE

- Japanese encephalitis (JE) (Fam : Flaviviridae) is the main cause of viral encephalitis in the Asian region
- > 3 billion people in 27 countries in the Asia Pacific region are at risk of being infected with JE
- At least 50,000 clinical cases are reported annually, mainly in children <15 years (especially in Asia)
- the case-fatality rate among symptomatic JE cases with encephalitis can be as high as 30%. Permanent neurologic or psychiatric sequelae can occur in 30%–50% of those with encephalitis
- Estimated global impact of JE --> 709,000 disability-adjusted life years (DALY) in 2002

Mulvey, et al., 2021; Tom Solomon, *et al.*, 2000; Turle & Solomon, 2018; MoH Indonesia, 2017; Suwarba, et al., 2015; WHO, 2018

Japanese encephalitis situation in Indonesia from 1960 to 2018

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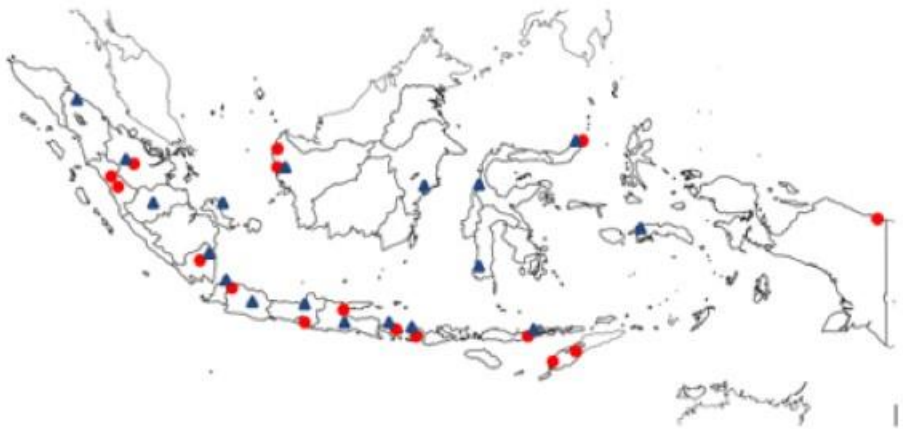
Japanese encephalitis in Indonesia: An update on epidemiology and transmission ecology

Triwibowo Ambar Garjito[a,b,c,*], Widiarti[a], Yusnita Mirna Anggraeni[a], Sitti Alfiah[a], Tri Baskoro Tunggul Satoto[d], Achmad Farchanny[e], Gina Samaan[f], Aneta Afelt[g], Sylvie Manguin[b], Roger Frutos[c,h], Tjandra Yoga Aditama[i]

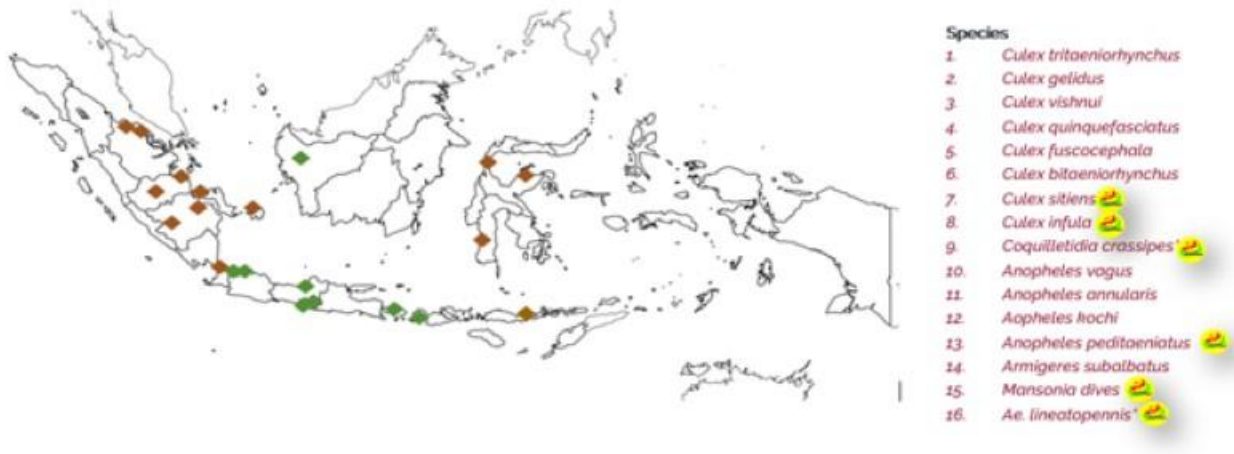
The distribution of JE cases in humans and livestock in Indonesia



Distribution map of confirmed cases of Japanese encephalitis from human serum samples (red dots) and livestock serum (pigs, cows, goats, poultry) (blue triangle) in the period 1960-2016 in Indonesia

Garjito et al., 2018; Rikhus Vektora, 2015-2018

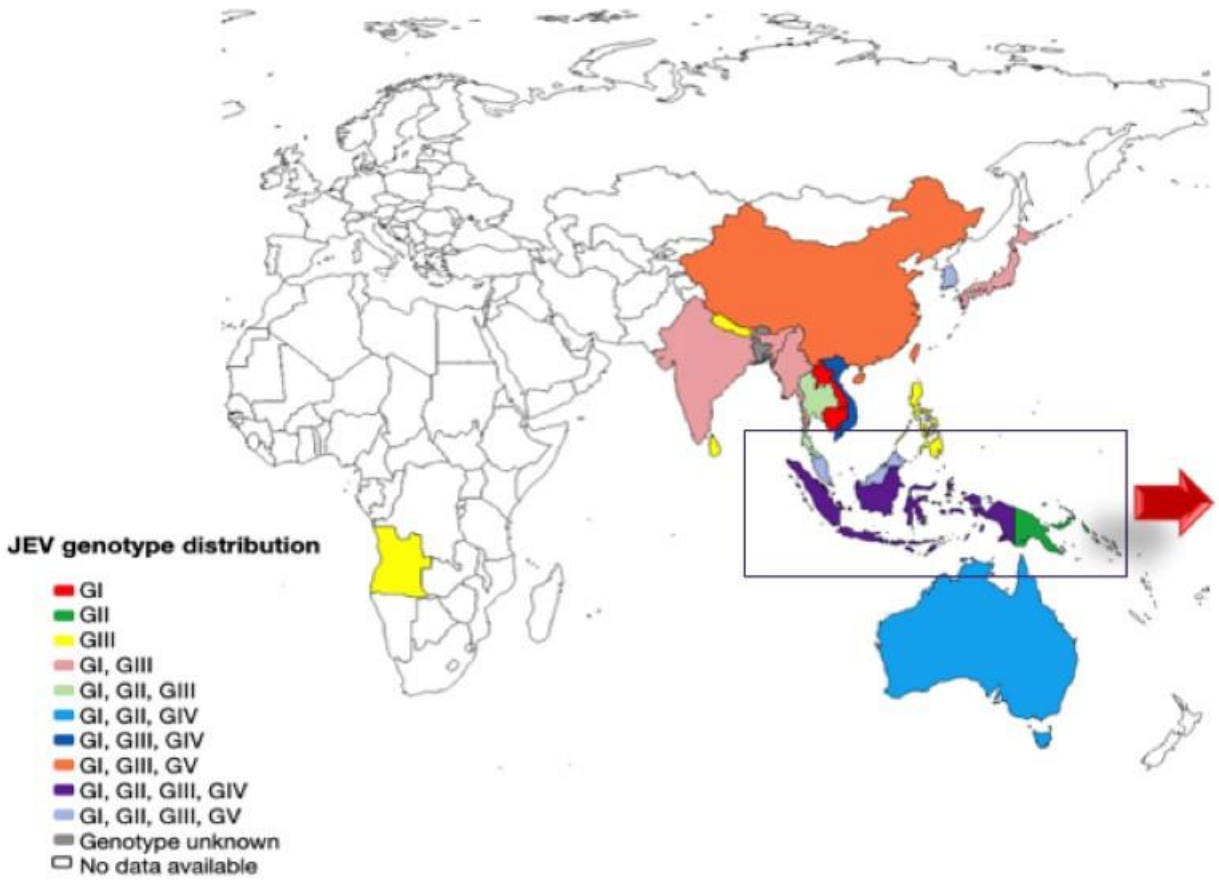
The distribution of the JE vectors in Indonesia



Map of the distribution of the incrimination and confirmation of JE vector in Indonesia; green diamonds: JE vector confirmation results in 1970-2016, brown diamonds: JE vector confirmation results in 2015-2018 (rikhus vektora-MoH Indonesia)

Rikhus Vektora, 2015-2018; Garjito et al., 2018

Recent updates of variation and global distribution of **Japanese Encephalitis virus genotypes**



Genetic diversity of JEV in Indonesia

Xia et al., 2023; Solomon & Winter, 2004; Schuh et al., 2013

JE cases among travelers in Indonesia

Number of JE cases associated with travel to endemic countries from 1973 - 2008

Country	Travel-associated cases (n = 55) No. (%)
Thailand	19 (35)
Indonesia	8 (15)
China	7 (13)
Philippines	5 (9)
Japan	4 (7)
Vietnam	3 (5)
Hong Kong (now China)	1 (2)
Malaysia	1 (2)
Myanmar	1 (2)
Papua New Guinea	1 (2)
Singapore	1 (2)
Not available	4 (7)

Umur pederita :

Risk factors for tourist cases confirmed positive for JE in Indonesia:

- No details
- Lived in the Balinese jungle
- In small islands around Flores in two weeks prior to the onset
- Hotel on Java and Bali with day trips to the islands
- Coastal hotel on Bali with a few day trips to rural areas

Hills, Griggs, Fisher, 2010

Cases of tourists confirmed with JE infection in the last few years after visiting Indonesia

- **2020**
  - Male, 45 years old, to Bali 10 days in Jan 2020 (rainy season)
  - Stayed in Seminyak, Canggu, & Ubud
  - Early symptoms → 1 day after returning to Australia
  - JEV IgM → detectable --> after 5 days of onset, but PCR negative (examined from CSF sample)
  - After 3 weeks of treatment -> recovered, but a loss of memory & concentration

Van et al, 2020

- **2019**
  - Male, 59 years old, not yet vaccinated against JE
  - Stayed in Bali for 3 months,
  - Early symptoms → 6 days after returning to Australia -> hospitalized
  - JEV IgM was detected from CSF and serum samples were taken 1 day after being admitted to the hospital
  - The sample was also detected positive for JE infection by RT-PCR
  - Genotype-IV JEV was identified from patient samples
  - The patient died

Pyke et al, 2020

Hospital-based surveillance of JE cases in Indonesia

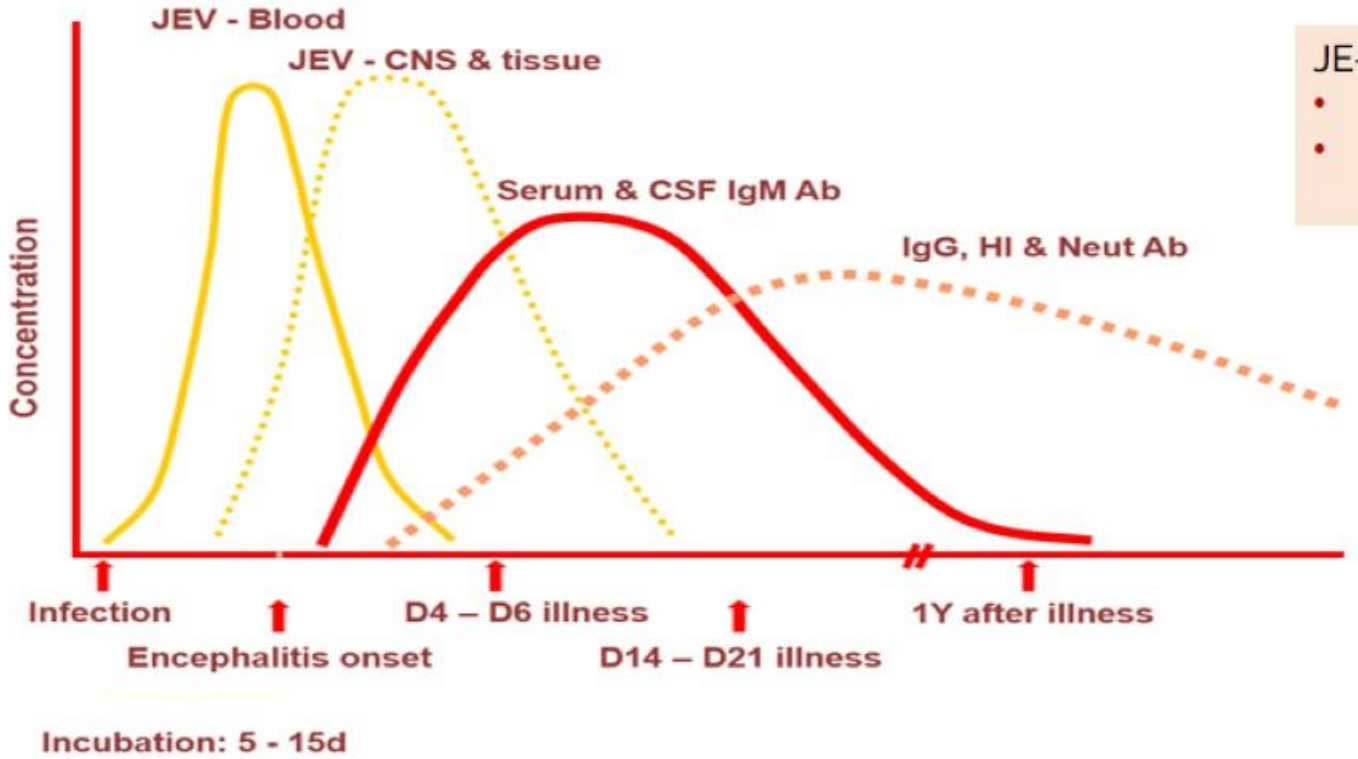
- Hospital-based case surveillance in 12 sentinel provinces (a collaboration between the Indonesian Ministry of Health (MoH) and WHO)
- All cases of Acute encephalitis syndrome (AES) leading to JEV infection were diagnosed using IgM capture ELISA according to WHO recommendations

JE/AES cases in Indonesia 2014-2019

NO	PROVINSI	2014		2015		2016		2017		2018		2019		JUMLAH	
		SAMPEL	POSITIF IgM JE	SAMPEL	POSITIF IgM JE	SAMPEL	POSITIF IgM JE	SAMPEL	POSITIF IgM JE	SAMPEL	POSITIF IgM JE	SAMPEL	POSITIF IgM JE	SAMPEL	POSITIF IgM JE
1	BALI	55	6	208	22	244	17		4	95	1	56	1	658	51
2	KALBAR	5	1	13	3	15	8	7	0	14	5	40	9	94	26
3	SULUT	7	1	13	4	25	2		0	18	0	18		81	7
4	NTT	0	0	13	3	13	8	7	1	4	0	6		43	12
5	DKI JAKARTA	0	0	20	2	4	1	12	0	21	0	26		83	3
6	JABAR	0	0	13	0	NA	NA	14	0	8	0	38		73	0
7	DI YOGYAKARTA	0	0	14	6	35	6	29	0	31	0	76		185	12
8	JATENG	4	0			2	0	11	1	27		21		65	1
9	SUMUT	2	0			0	NA		NA			10		12	0
10	MALUKU	NA	NA												0
11	NTB	0	0			5	0	3	0	9	0	14		31	0
12	BATAM					1	1	2	0	4	0	6		13	1
	TOTAL	73	8	294	40	344	43	85	6	231	6	311	10	1338	113

Problems in the JE diagnostic in Indonesia

- Non-specific clinical symptoms → make it difficult to specifically differentiate encephalitis and viral meningitis
- More than 100 viruses can cause acute encephalitis
- High potential cross-reactivity with other flaviviruses
  → So far 7 flaviviruses have been identified serologically to infect humans in Indonesia



JE-specific IgM capture ELISA
- **Advantages:** simple, good IgM detection sensitivity
- **Disadvantages:** cross-reactivity occurs with other flaviviruses

WHO recommended method for routine surveillance

Overview of several cases of Japanese encephalitis

Diagnosis : **JE**
IgM anti JE positive

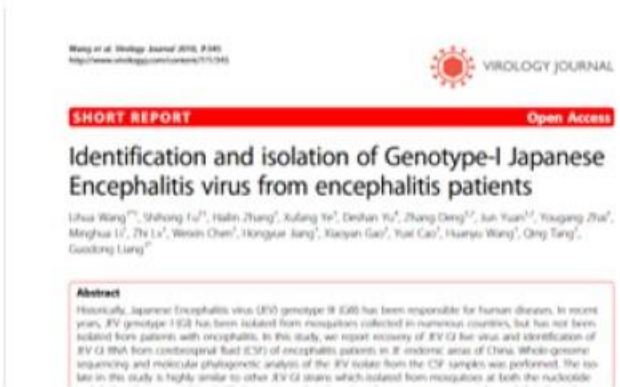
Diagnosis: **JE**
IgM anti JE positive

Diagnosis : **encephalitis** → **JE**??
IgM anti JE negative

Courtesy from Prof. Tom Solomon,MD, PhD; and Dr. dr. I Gusti Ngurah Made Swarba, SpA(K) (2020)

The implications and challenges of the existence of JEV Genotype-1 in Indonesia

- The detection method currently used in routine JE surveillance in humans in Indonesia (IgM capture ELISA) is feared to be inadequate for detecting JEV genotype-1.



VIROLOGY JOURNAL

SHORT REPORT Open Access

Identification and isolation of Genotype-I Japanese Encephalitis virus from encephalitis patients

Abstract

Historically, Japanese Encephalitis virus (JEV) genotype III (GIII) has been responsible for human diseases. In recent years, JEV genotype I (GI) has been isolated from mosquitoes collected in numerous countries, but has not been isolated from patients with encephalitis. In this study, we report recovery of JEV GI live virus and identification of JEV GI RNA from cerebrospinal fluid (CSF) of encephalitis patients in JE endemic areas of China. Whole-genome sequencing and molecular phylogenetic analysis of the JEV isolate from the CSF samples was performed. The isolate in this study is highly similar to other JEV GI strains which isolated from mosquitoes at both the nucleotide

Wang et al. (2010) reported in a study conducted on several cases that were clinically diagnosed as JE cases but were not confirmed as JE patients using JEV-specific IgM capture ELISA on serum and cerebrospinal fluid (CSF) samples.

- The sample was declared positive after an examination of the cerebrospinal fluid (SCF) was carried out and detected using RT-PCR.
- The results of this study stated that all samples were detected positive for JEV only from CSF samples using RT-PCR
- All samples were identified as Genotype-I JE virus

Table 1 Results of IgM, RT-PCR and virus isolation to detect evidence of JEV in 1 clinical samples from encephalitis patients

Patient	Age(y)	Sex	Onset time	Clinical diagnosis	Interval between onset and sampling(d)	Sample type	Laboratory diagnosis		Genotype
							IgM	RT-PCR	
GZ56*	0.5	F	11/08/2006	JE	1	S	-	-	GI
					1	C	-	+	
GZ1	13	M	24/08/2006	JE	1	S	-	-	GI
					1	C	-	+	
GS105	12	F	10/05/2006	JE	2	S	-	-	GI
					2	C	-	+	
YN114	28	M	01/07/2008	JE	3	S	-	-	GI
					3	C	-	+	
YN135	37	M	12/07/2008	JE	3	S	-	-	GI
					3	C	-	+	

Abbreviations: C, cerebrospinal fluid; S, serum; F, female; M, male; GZ, Guizhou province; GS, Gansu province; YN, Yunnan province; "+", positive; "-", negative.
* Virus strain GZ56 was obtained from patient GZ56.

Wang et al. (2010)

JEV Vaccination Program in Indonesia

- The JE vaccination program has started in Indonesia.
- Currently, no less than 890,050 children in Bali aged 9 months to 15 years are targeted for vaccination.
- The vaccine used is the single dose Chengdu SA14-14-2 vaccine (live-attenuated JE vaccine) carried out in 2 phases
- The JE vaccine has been included in the routine immunization program in Bali

Age	Type of immunization
<24 hour	*Birth dose* Hepatitis B
1 month	BCG, OPV
2 month	DPT-HB-Hib 1, OPV 2
3 month	DPT-HB-Hib 2, OPV 3
4 month	DPT-HB-Hib 3, OPV 4 & IPV
9 month	Measles / Measles Rubella (MR)
10 month	Japanese encephalitis
18 month	MR, DPT-HB-Hib 4
7th years old	MR, DT
8th years old	Td
11th years old	Td, *HPV 1*
12th yeras old	*HPV 2***

Type of vaccine	trademark	JEV strains	Efficacy
Inactivated mouse brain-derived	JE-VAX (Biken, Sanofi Pasteur GCC (Berna, Biotech, AdImmune Corp)	Nakayama Beijing	87-95% 94%
Live-attenuated	CD JEVAX (Chengdu)	SA 14-14-2	90%
Inactivated, vero cell-derived	IXIARO (Intercell Novartis) JESPECT (Intercell, Valneva)	SA 14-14-2 SA 14-14-2	94-96% 89-98%
Live-attenuated recombinant (chimeric)	IMOJEV (Sanofi Pasteur)	SA 14-14-2	>95%

Suarba, 2020; Dit P2PTVZ, 2021

The existence and distribution of confirmed cases of JE in Bali before and after the JEV vaccination program implementation

2014

AES samples: 55; positive: 6 (11%)

2015

AES samples: 208; positive : 22 (10,6%)

2016

AES samples: 243; positive : 17 (6,9%)

2017

AES samples : NA ; positif : 11 (NA%)

2018

JEV vaccination program was started in 2018

AES samples : 197; positive : 5 (2,5%)

2019

AES samples : 173; positive : 4 (2,3%)

2020

AES samples : 68 ; positive : 6 (8,8%)

- Why is it that after the successful and comprehensive JE vaccination, confirmed cases are still being found?

Dinkes Prov Bali, 2020

Lessons learned from China and Korea

- Low levels of neutralizing antibodies induced by JE-based G-III vaccines have now been identified against the emergence of G-V JEV in China and Korea.

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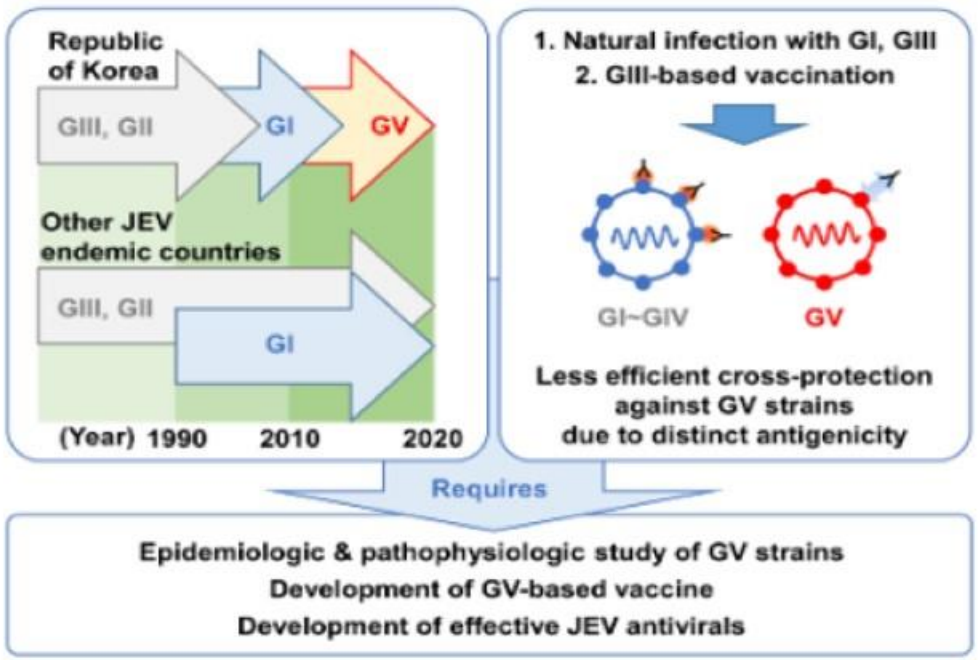
Minireview

Emerging Japanese Encephalitis Virus Genotype V in Republic of Korea

Ah-Ra Lee[1†], Jae Min Song[2†], and Sang-Uk Seo[1*]

[1]Department of Biomedicine and Health Sciences, Department of Microbiology, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea
[2]School of Biopharmaceutical and Medical Sciences, Sungshin Women's University, Seoul 01133, Republic of Korea



PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Low Protective Efficacy of the Current Japanese Encephalitis Vaccine against the Emerging Genotype 5 Japanese Encephalitis Virus

Lei Cao[1,2,3☯], Shihong Fu[1,2☯], Xiaoyan Gao[1,2], Minghua Li[1,2], Shiheng Cui[1,2], Xiaolong Li[1,2], Yuxi Cao[1,2], Wenwen Lei[1,2], Zhi Lu[1,2], Ying He[1,2], Huanyu Wang[1,2], Jinghua Yan[3], George Fu Gao[3]*, Guodong Liang[1,2]*

1 State Key Laboratory of Infectious Disease Prevention and Control, National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, People's Republic of China, 2 Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Hangzhou, People's Republic of China, 3 CAS Key Laboratory of Pathogenic Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences, Beijing, People's Republic of China

☯ These authors contributed equally to this work.
* gaof@im.ac.cn (GFG); gdliang@hotmail.com (GL)

This study revealed the current JE vaccine derived from the G3 JE virus(JEV) does not provide adequate levels of protection against the emerging G5JEV genotype.

Lee, et al., 2022

Follow up to do/propose for the 13th e-ASIA Call for Proposals :

Molecular and epidemiological study of Japanese encephalitis in Indonesia is needed due to :

1. The complexity of the JEV genotype in Indonesia (G-I to G-IV) may have an impact on the difficulties of the JE diagnosis in human cases.
2. The hospital-based JEV surveillance in Indonesia in the last decade showed that only 8.44% of AES samples collected from 12 JE sentinel hospitals in Indonesia were confirmed positive for JE through IgM ELISA capture.
3. Not all hospitals are willing and able to carry out routine cerebrospinal fluid (CSF) collection for patients with Acute encephalitis syndrome (AES)
4. Routine JE surveillance in Indonesia is only limited to human surveillance and is not carried out routinely on vectors and disease reservoirs

The objectives :

1. To determine the updated JEV genotype circulating in Indonesia
2. To determine the ongoing dynamic transmission of JEV in Indonesia
3. To strengthen routine JE surveillance in humans, vectors, and its disease reservoirs
4. To develop more adequate JE detection methods in humans in Indonesia
5. To strengthen case management in humans.

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5. Tim publikasi paper 2
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