

Japanese encephalitis virus

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Topics

- JE epidemiology in Japan
- JE vaccines
- JEV genotype V (JEV GV)
 - Genotype shifting issue
 - Characteristics of JEV GV

JEV

- Belongs to the flavivirus genus of Flaviviridae family
- Causes encephalitis (CNS infection)
- JE is endemic to Asia
- Infects humans through *Culex tritaeniorhynchus* mosquitoes
- Is maintained in nature in a life cycle between birds, mammals such as pigs and mosquitoes

Japanese encephalitis, countries or areas at risk*

* Based on 2012 data



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization/CDC
Map Production: Public Health Information
and Geographic Information Systems (GIS)
World Health Organization



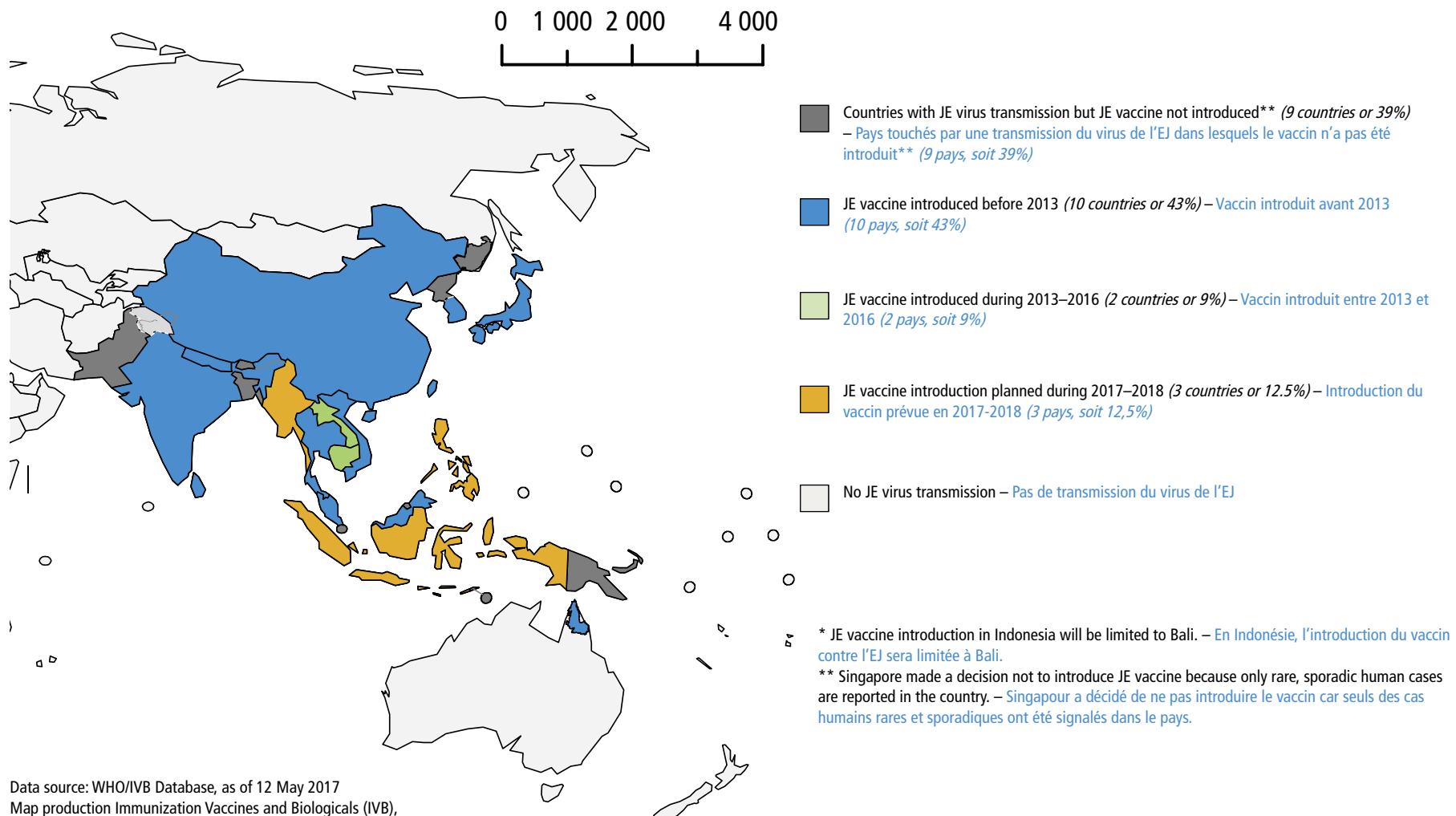
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JE vaccines



- ~~Mouse brain derived inactivated JE vaccine~~
- Vero cell culture derived inactivated JE vaccine
- Attenuated JE vaccine SA 14-14-2
- Chimeric YF vaccine-based JE vaccine

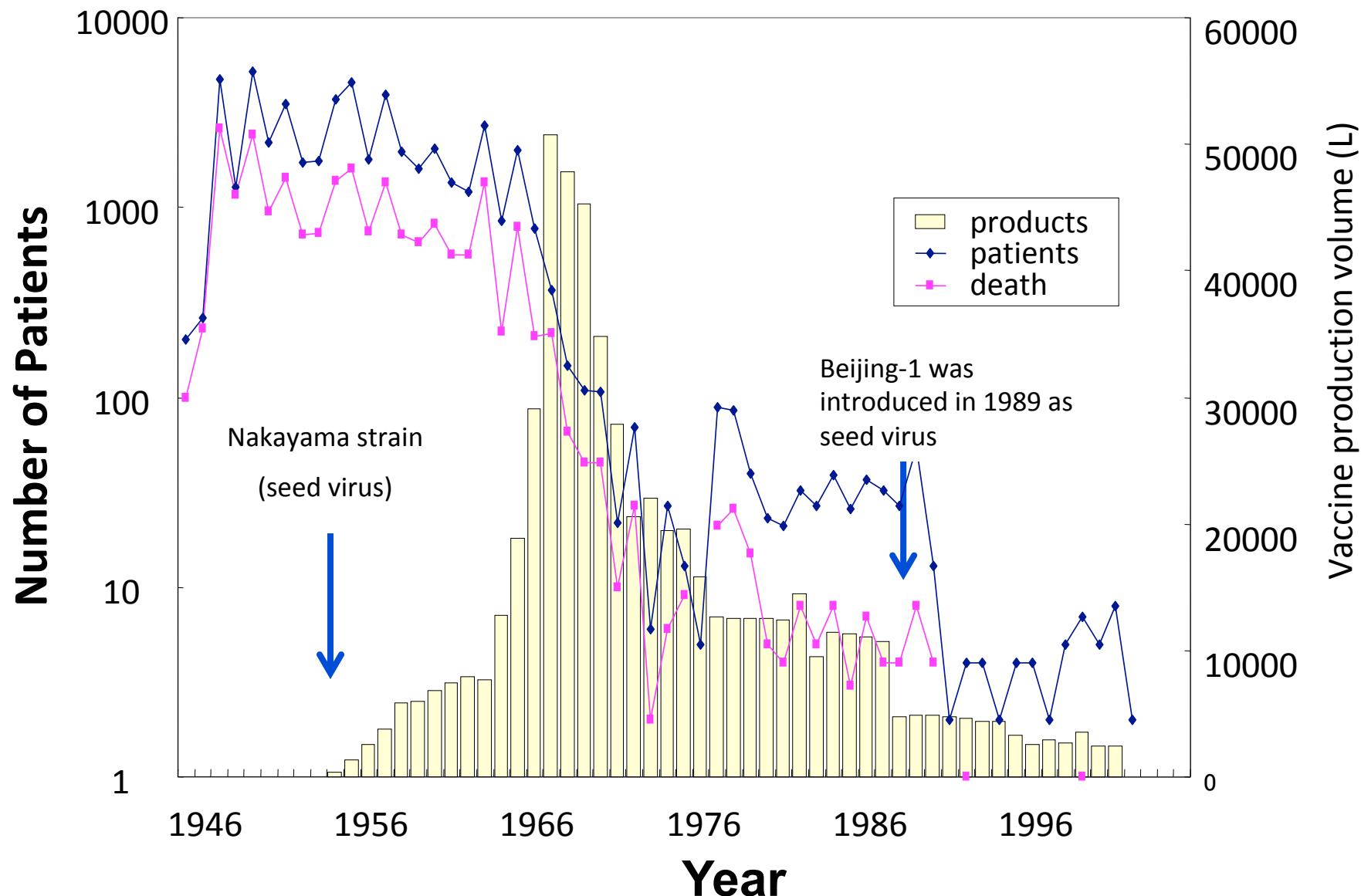
Map 1 Areas with risk of Japanese encephalitis (JE) virus transmission and JE vaccine introduction, 2016*
 Carte 1 Zones à risque de transmission du virus de l'encéphalite japonaise (EJ) et situation au regard de l'introduction du vaccin, 2016*



Data source: WHO/IVB Database, as of 12 May 2017
 Map production Immunization Vaccines and Biologicals (IVB),
 World Health Organization – Source des données: Base de données OMS/IVB, au 12 mai 2017
 Production de la carte: Département Vaccination, vaccins et produits biologiques (IVB), Organisation mondiale de la Santé

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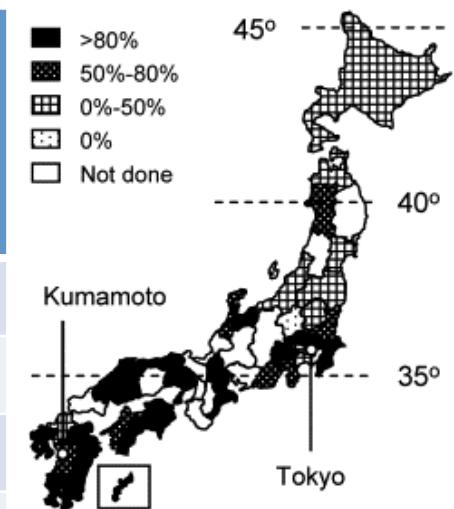
Correlation between vaccine production and number of JE patient



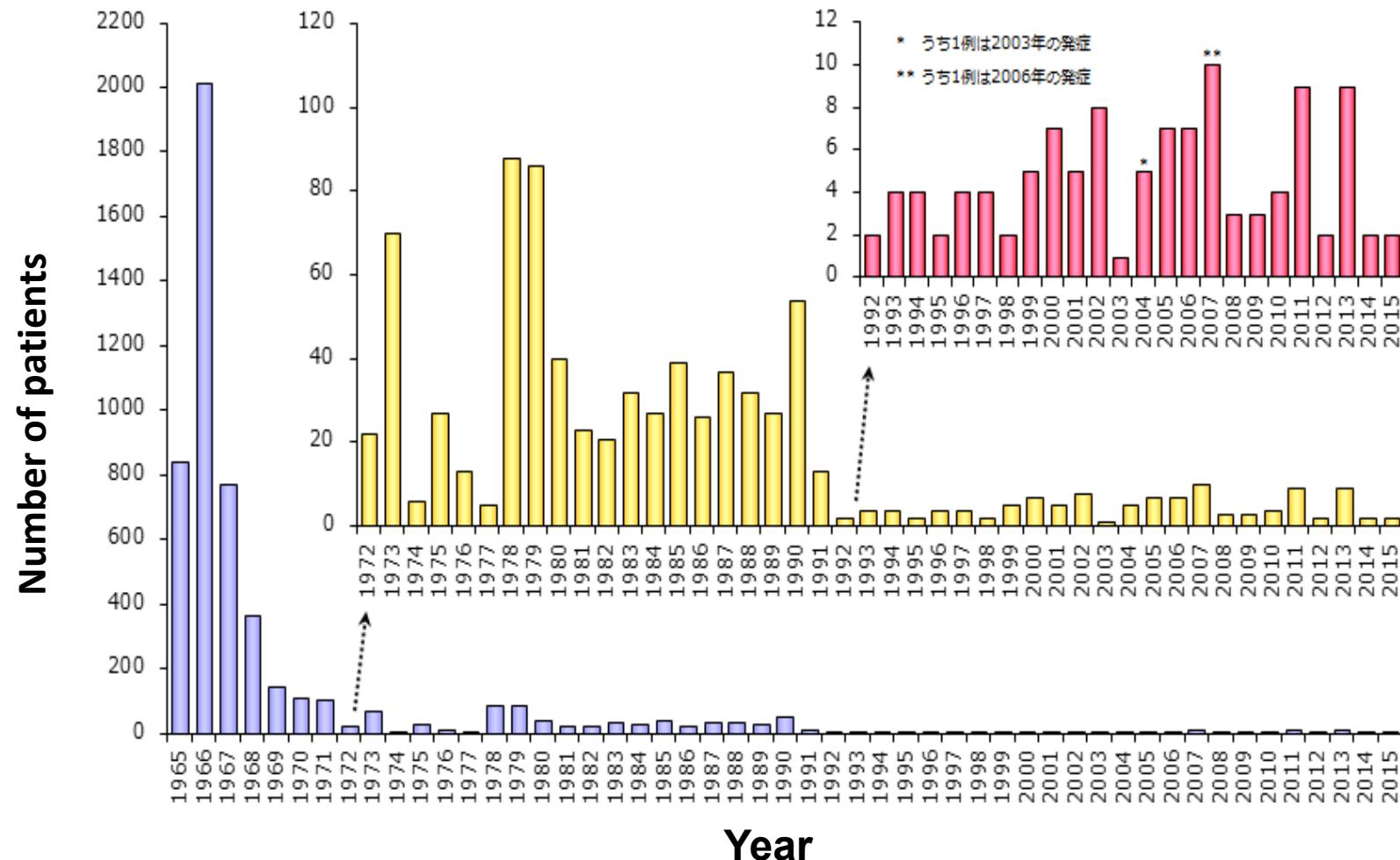
JEV infection in Japan

Annual infection rates in Kumamoto, 2004–2008, and Tokyo, 2004–2006, calculated from the number of unvaccinated children aged 0–9 years with neutralizing antibodies

Area	Gender	Total no.	No. of positive	% positive	Average survival period (year) ^a	Annual infection rate (%) ^b
Kumamoto	Male	80	7	8.8	3.7	2.4
	Female	65	8	12.3	4.3	2.9
	Female	145	15	10.3	4.0	2.6
Tokyo	Male	127	13	10.2	3.2	3.2
	Female	73	3	4.1	2.8	1.5
	Total	200	16	8.0	3.1	2.6



Human Japanese encephalitis cases in Japan, 1965-2015



1954; MB: Nakayama strain

1989; MB: Beijing-1 strain

2009; Vero: Beijing-1 strain

1954-'66;

recommendation

1967-'75;

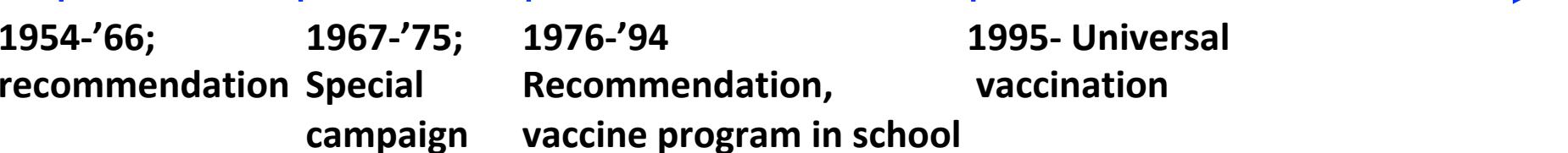
Special
campaign

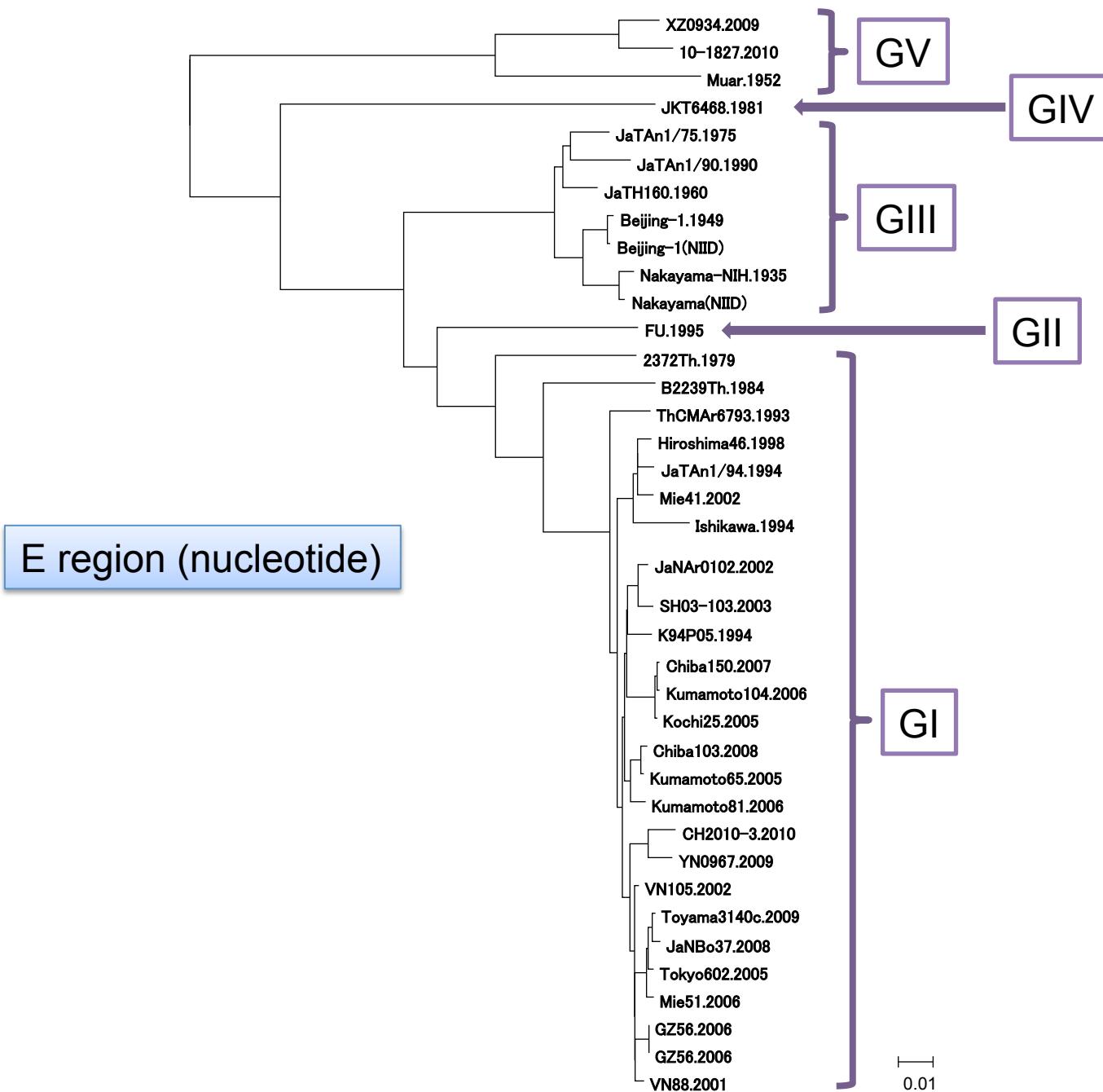
1976-'94

Recommendation,
vaccine program in school

1995- Universal

vaccination





		Difference in amino acid sequence (whole) (%)				
Genotype	Strain	K9P05	FU	Nakaya ma	JKT646 8	Muar
I	K9P05					
II	FU	2.1				
III	Nakayama	3.1	2.2			
IV	JKT6468	6.2	5.3	4.8		
V	Muar	9.9	8.6	8.5	9.2	

Characteristics of JEV GV Muar
strain, which was isolated from CNS
of fatal JE patient in Malaysia in
1952

In China

Genotype V Japanese encephalitis virus is emerging

Li et al. Virology J. 8:449, 2011

In Korea

Emergence of Japanese encephalitis virus genotype V in the Republic of Korea

Takhampunya et al. Virology J. 8:449, 2011

Detection of Japanese encephalitis virus genotype V in *Culex orientalis* and *Culex pipiens* (Diptera: Culicidae) in Korea

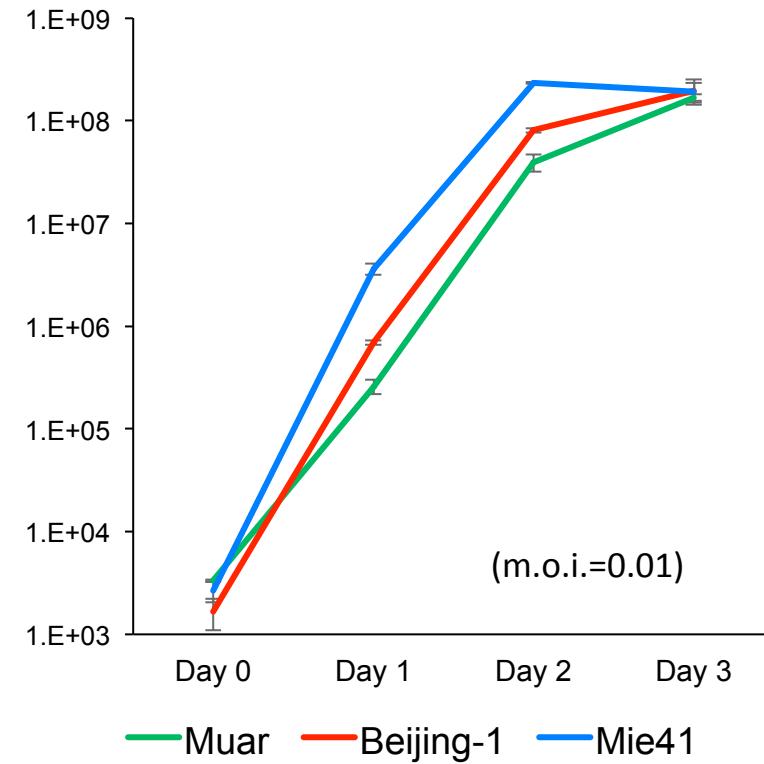
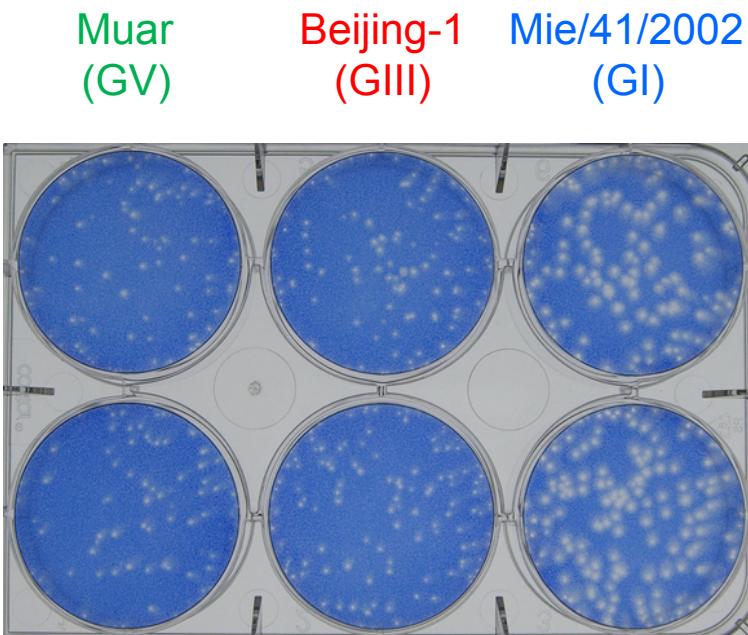
Kim et al. PLoS ONE (DOI:10.1371/journal.pone.0116547)

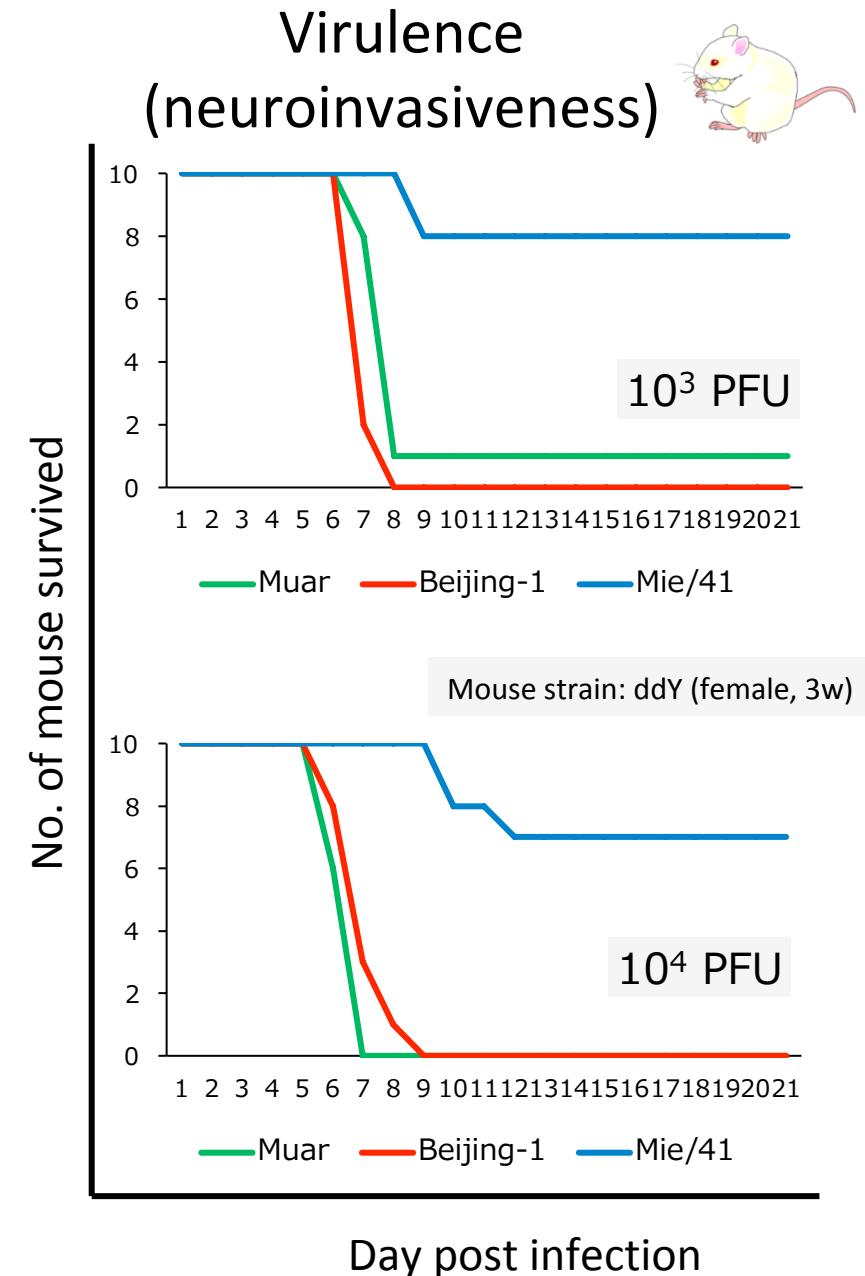
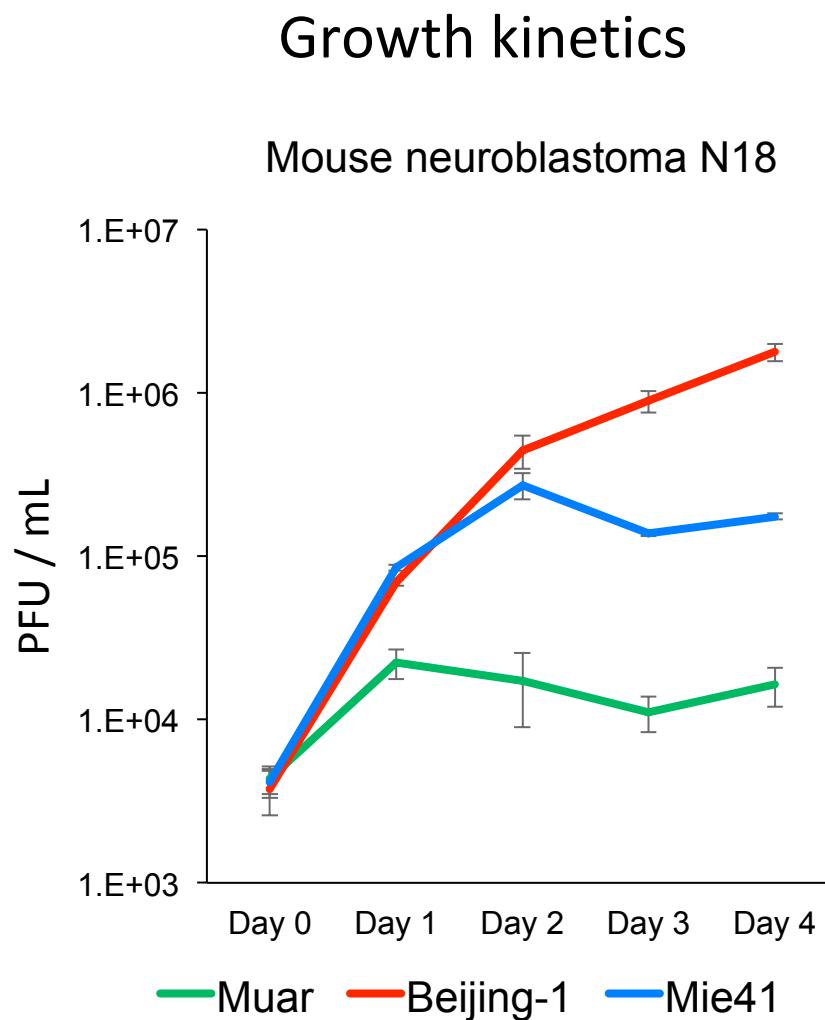


We need to..

- ✓ pay more attention to the dynamics of circulating JEV
- ✓ understand the nature of GV JEV

Plaque morphology and growth in Vero cells

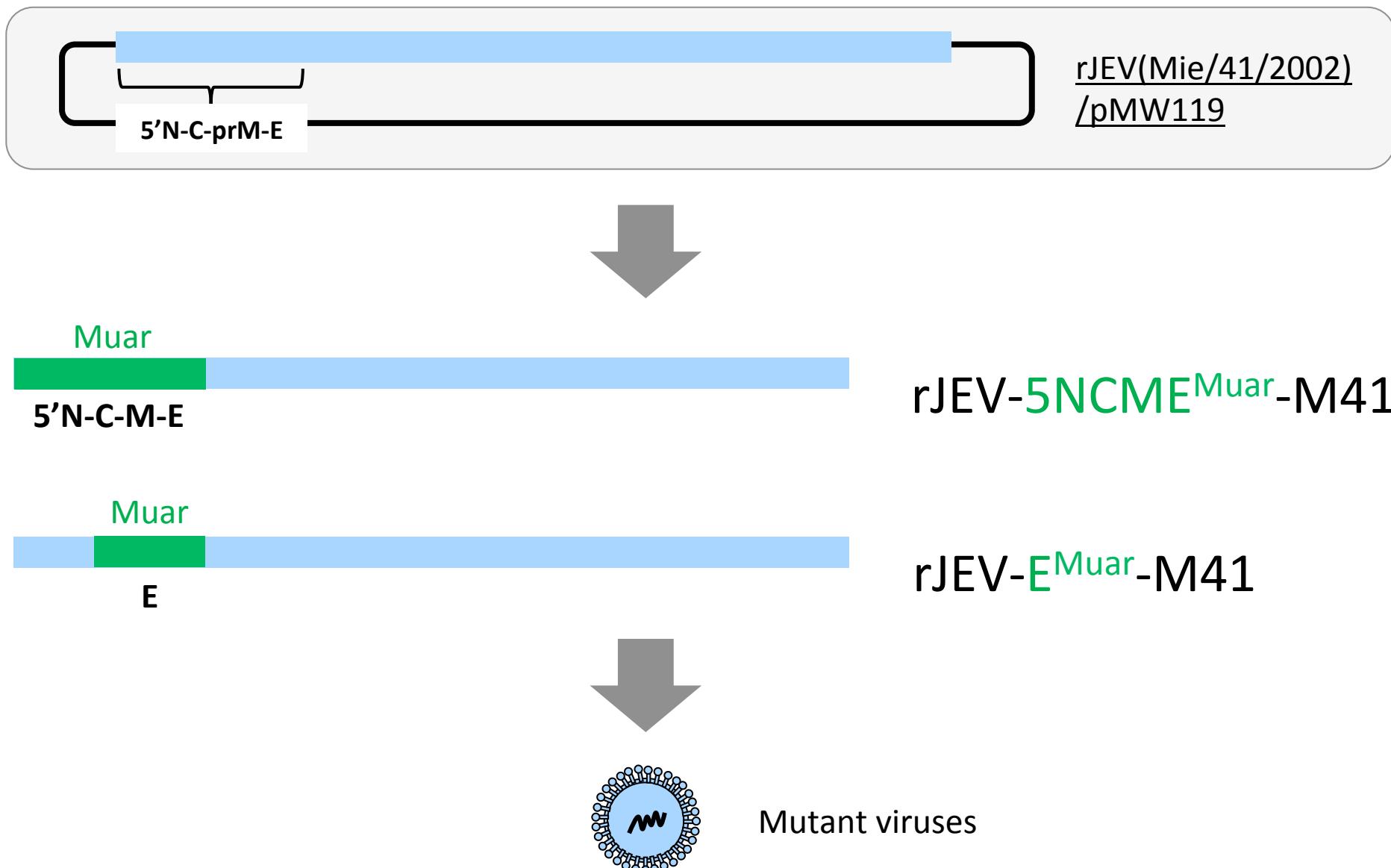




Summary of in vitro growth and virulence in mice

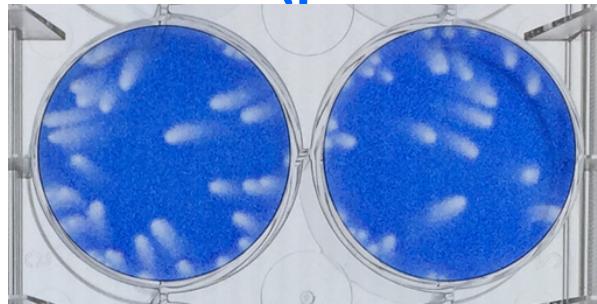
Strain	In vitro growth		Virulence in mice
	Vero	N18	
GV Muar	+	±	+++
GIII Beijing-1	+	+++	+++
GI Mie/41/2002	++	++	+

Production of mutant JEVs

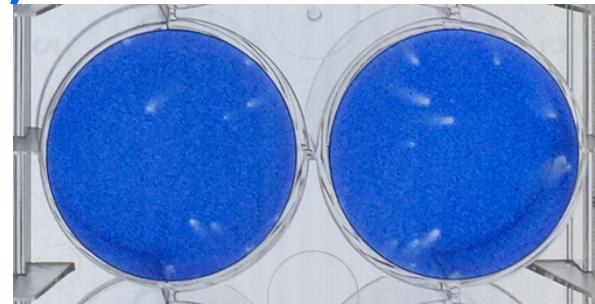


Plaque morphology in Vero cells

Mie41 (parental virus)



Muar



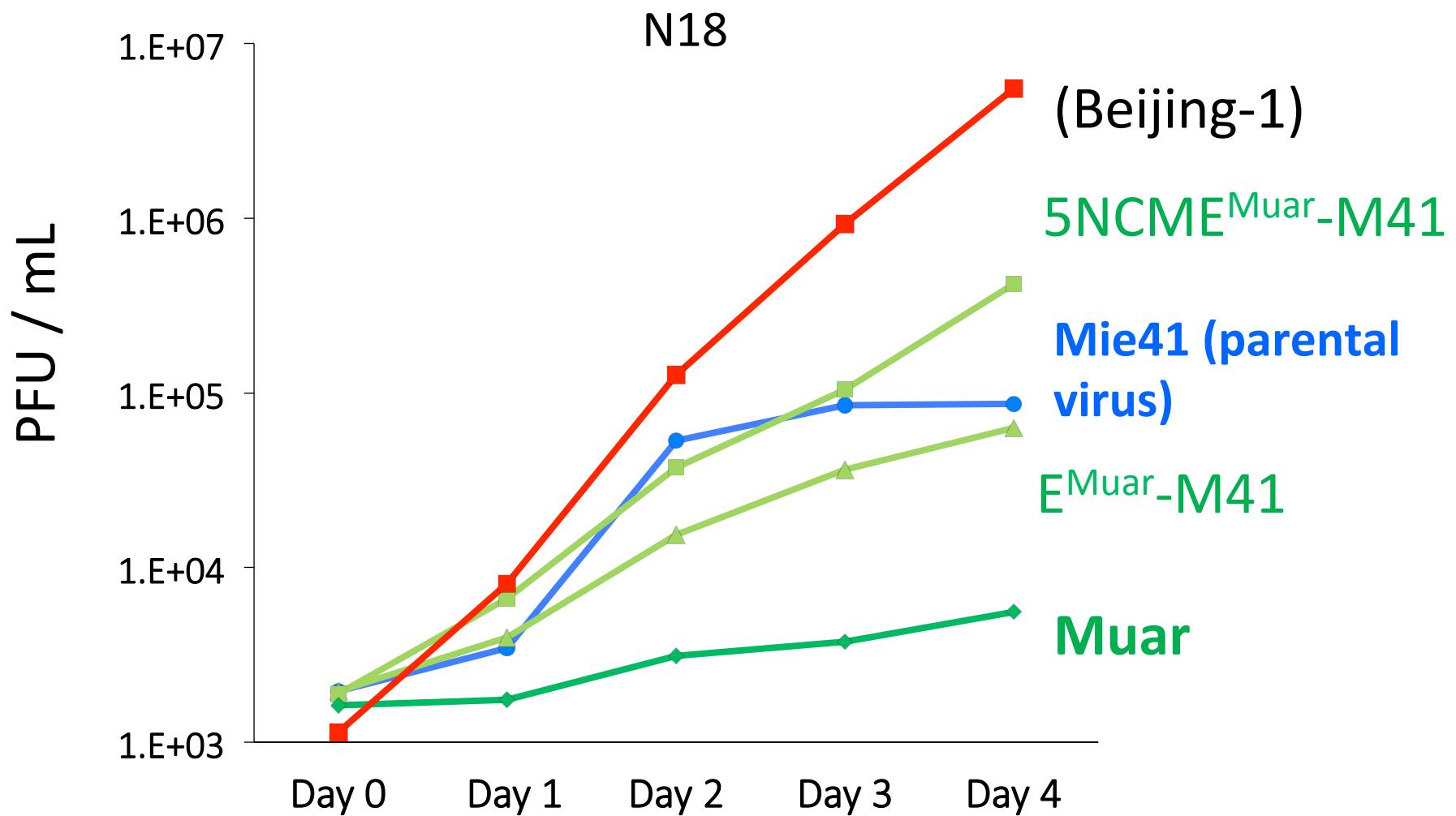
5NCME^{Muar}-M41



E^{Muar}-M41



Growth kinetics



Neutralization potency of the sera from
JE patients in Vietnam against
genotype I and V JEVs

PRNT titers of pooled mouse sera, which were recovered from mice at 14 days after the initial immunization with the inactivated Nakayama and Beijing-1 vaccines, against GI, GIII, GV, and vaccine strains

Genotype	Strain	Nakayama vaccine		Beijing-1 vaccine	
		x2 dilution	x8 dilution	x2 dilution	x8 dilution
Vaccine strain	Nakayama(NIID)	>640	320	320	160
	Beijing-1(NIID)	80	40	320	160
GI	Hiroshima/46/1998	80	40	160	80
	Mie/41/2002	320	80	160	80
	Tokyo602/2005	160	40	80	80
	Kochi/25/2005	160	40	160	40
	Kumamoto/65/2005	80	40	160	40
	Mie/51/2006	160	80	80	80
	Kumamoto/81/2006	80	40	80	40
	Kumamoto/104/2006	80	40	80	40
	Chiba/150/2007	160	40	160	40
	Chiba/103/2008	80	40	80	40
GIII	JaNBo37/2008	160	80	160	80
	GMT of GI viruses	124.4	48.3	116.8	54.8
	JaTH160/1960	80	40	160	80
	JaTAn1/75/1975	160	40	80	80
	JaTAn1/90/1990	160	80	160	160
	GMT of GIII viruses	127.0	50.4	127.0	100.8
GV	Muar/1952	20	<10	20	10

List of JE patients tested in this study

Patient No.	Age (years)	Sex	Date of onset	Date of collection	After onset
5819	40	Male	2014/5/29	2014/6/1	3
5855	22	Male	2014/6/12	2014/6/24	12
5856	6	Female	2014/6/15	2014/6/24	9
5857	5	Female	2014/6/11	2014/6/24	13
5859	2	Male	2014/6/18	2014/6/24	6
5862	8	Male	2014/6/18	2014/6/24	6
5864	16	Male	2014/6/7	2014/6/24	17
5865	10	Male	2014/6/18	2014/6/24	6
5879	32	Female	2014/6/14	2014/6/27	13
5880	2	Male	2014/6/16	2014/6/27	11
5882	2	Female	2014/6/17	2014/6/27	10
5898	2	Female	2014/6/26	2014/7/3	7
5899	19	Female	2014/6/26	2014/7/3	7
5905	19	Male	2014/6/22	2014/7/1	9
5919	10	Female	2014/7/5	2014/7/7	2
5936	34	Male	2014/7/7	2014/7/10	3
5942	25	Male	2014/7/7	2014/7/14	7
5956	11	Female	2014/7/1	2014/7/16	15
5959	6	Female	2014/7/15	2014/7/17	2
6043	26	Female	2014/7/29	2014/8/1	3
6051	21	Male	2014/7/30	2014/8/5	6
6114	20	Female	2014/8/9	2014/8/13	4

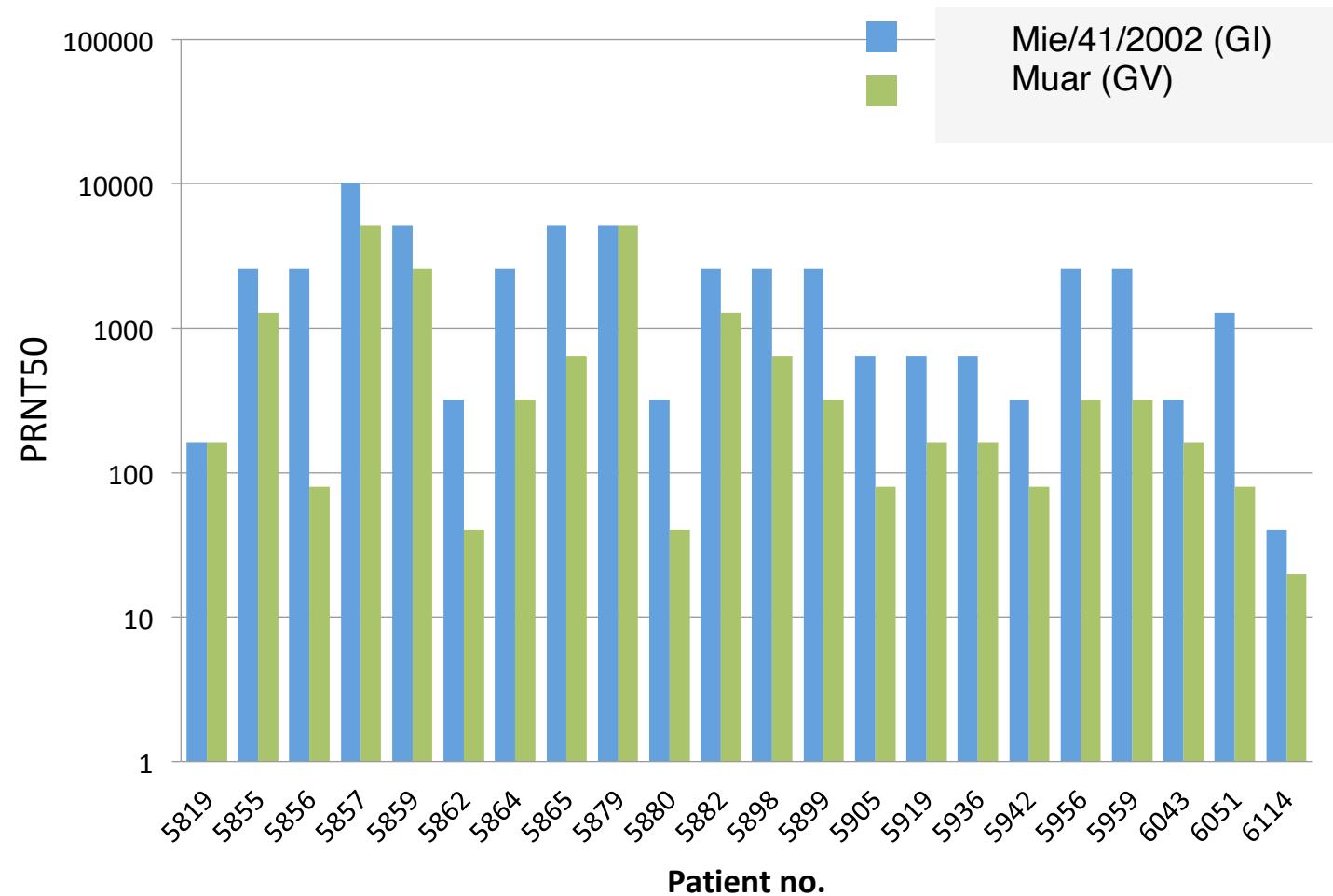
Son La Province



- ✓ Age 2-40 y
- ✓ Anti-JEV IgM ELISA positive (Thuy et al. 2017)
- ✓ Onset date: between May and August, 2014
- ✓ Sample collection: 2-17 days after onset

Nuguen TTT, et al. Jpn J Infect Dis, 2018

PRNT⁵⁰ titer of the sera from JE patients against GI and GV JEVs

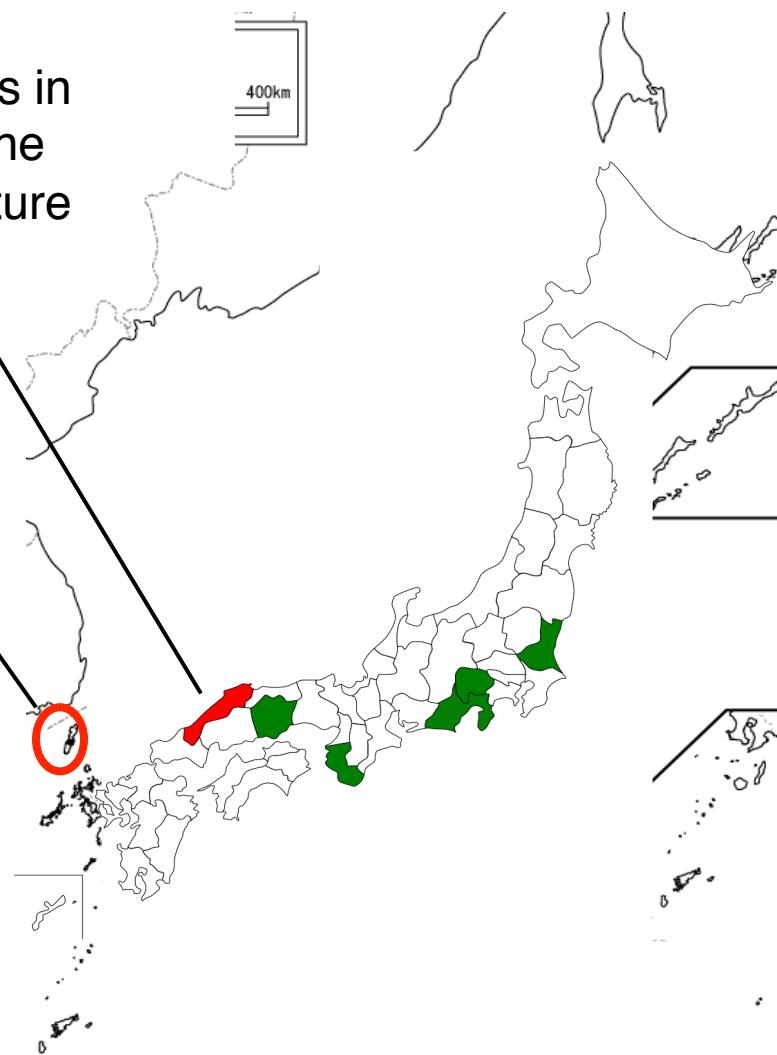


Son La Province

Eleven patients with JE were reported in Japan in 2016

4 cases
Tsushima
Island,
Nagasaki

2 cases in
Shimane
prefecture



The ratio of JEV GV NT titer against those to JEV GI and JEV GIII

Tsushima, Nagasaki

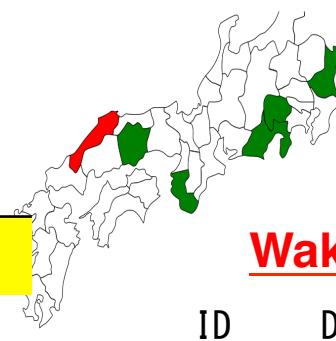
ID	Days from disease onset	Genotype V: Genotype I	Genotype V: Genotype III
1/1s	21	2:1	1:1
2/1s	32	1:2	1:4
3/1s	21	2:1	1:1
4/1s	6	<u>1:16</u>	<u>1:8</u>

Shizuoka, Yamanashi

ID	Days from disease onset	Genotype V:Genotype I	Genotype V:Genotype III
9/1s	10	1:1	1:1
9/2s	74	1:2	1:2
10/1s	7	<u>1:8</u>	<u>1:8</u>

Okayama and Shimane

ID	Days from the disease onset	Genotype V: Genotype I	Genotype V: Genotype III
5/1s	8	<u>1:8</u>	<u>1:8</u>
5/1s	24	1:2	1:4
6/1s	8	<u>1:16</u>	<u>1:16</u>
6/2s	20	<u>1:8</u>	<u>1:8</u>
7/1s	4	1:2	1:2
7/2s	19	1:1	1:1



Wakayama

ID	Days from disease onset	Genotype V:Genotype I	Genotype V:Genotype III
8/1s	2	1:2	1:2
8/3s	17	1:1	1:1

Summary

- JEV is circulating in Asia
 - About 2-3% of Japanese are infected with JEV annually
- JEV can be preventable by JE vaccination, but further strategies are required
- Immune response to JEV GV induced by JE vaccines is significantly lower than those raised to JEV GI and JEV GIII
- JEV genotype V is more virulent in mouse model
 - 5' noncoding region including prM-E region is responsible to the higher virulence
- JEV genotype shift from GI to GV should be closely monitored
 - It is highly possible that JEV GV is circulating in South Korea and China
 - There is no evidence that genotype shifting is occurring in Asia including Viet Nam and Japan

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