New Japanese Encephalitis Vaccines

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History

- 1870's: Japan
  - "Summer encephalitis" epidemics
- 1924: Great epidemic in Japan
  - 6,125 human cases; 3,797 deaths
- 1935: First isolated
  - From a fatal human encephalitis case
- 1938: Isolated from *Culex tritaeniorhynchus*
- 1940-1978
  - Disease spread with epidemics in China, Korea and India

(Center for food Security and Public Health Iowa State University – 2004)

Japanese Encephalitis Virus

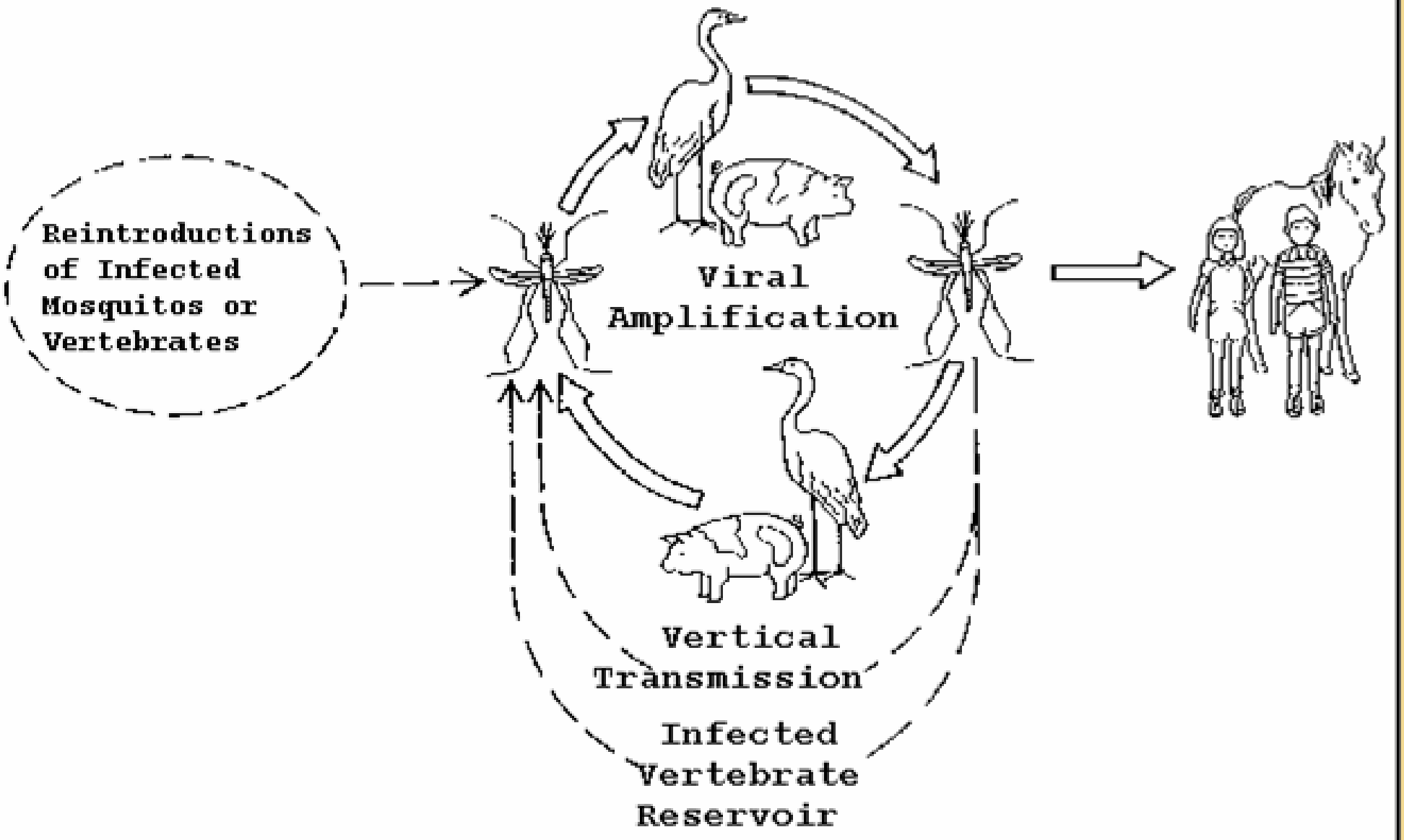
- A mosquito-borne virus (Culex, especially *Culex tritaeniorhynchus*
- Family Flaviviridae, genus Flavivirus, together with YFV and DV
  - Enveloped virus
  - Single stranded RNA
  - Comprises of:

    * Structural proteins: *C (capsid), prM (precursor to membrane protein M) and E (envelope)*

    * Nonstructural proteins: NS1-NS5 which are involved in genome replication and viral protein processing

www.who.int/vaccine_research/disease/vector/en/index1.htm.
htpp://en.wikipedia.org/wiki/Japanese_encephalitis

Transmission Cycle of Japanese Encephalitis Virus



Geographic Distribution of Japanese Encephalitis

3 billion people live in JE endemic area and 70 million children were born each year

http://wwwn.cdc.gov/travel/yellowBookCh4-JapaneseEncephalitis.aspx

Epidemiology

- Annual incidence ranges from 6-10 cases per 100,000 inhabitants
- 30,000-50,000 cases of severe CNS infection are reported annually in Asia and Australia, with 10,000 death.
- 30-35% are fatal
- 50% result in permanent neuropsychiatric sequelae
- In Thailand, after EPI included JE vaccine, JE still found in 10-15% of all encephalitis (around 400 cases/yr) *Chokephaibulkit K, et al. PIDJ 2001;20:216-8, TUC study*

Vector-borne viral infections, WHO/IVB/05.XX

Only 1 in 250-1,000 infections are symptomatic

Clinical Features

- Incubation period: 5 to 15 days
- Three importance signs are high fever, headache and altered consciousness
- Three stages of Encephalitis signs
  - *Prodomal stage* (1-6 days): high fever, severe headache, nausea, vomiting
  - *Acute encephalitic stage*: prolong high fever, stiff neck, decrease in consciousness, convulsion, decrease in heart rate, mask like face, speech disorder, aseptic meningitis or a polio-like flaccid paralysis
  - *Late stage and sequele*: fever is decreased, neurological signs may be persisted, psychiatric and intellectual disorders, paralysis

Treatment

- No specific treatment
  - Supportive care
- There is no transmission from person to person
  - No need for isolation

http://en.wikipedia.org/wiki/Japanese_encephalitis

Prevention and Control

Prevention

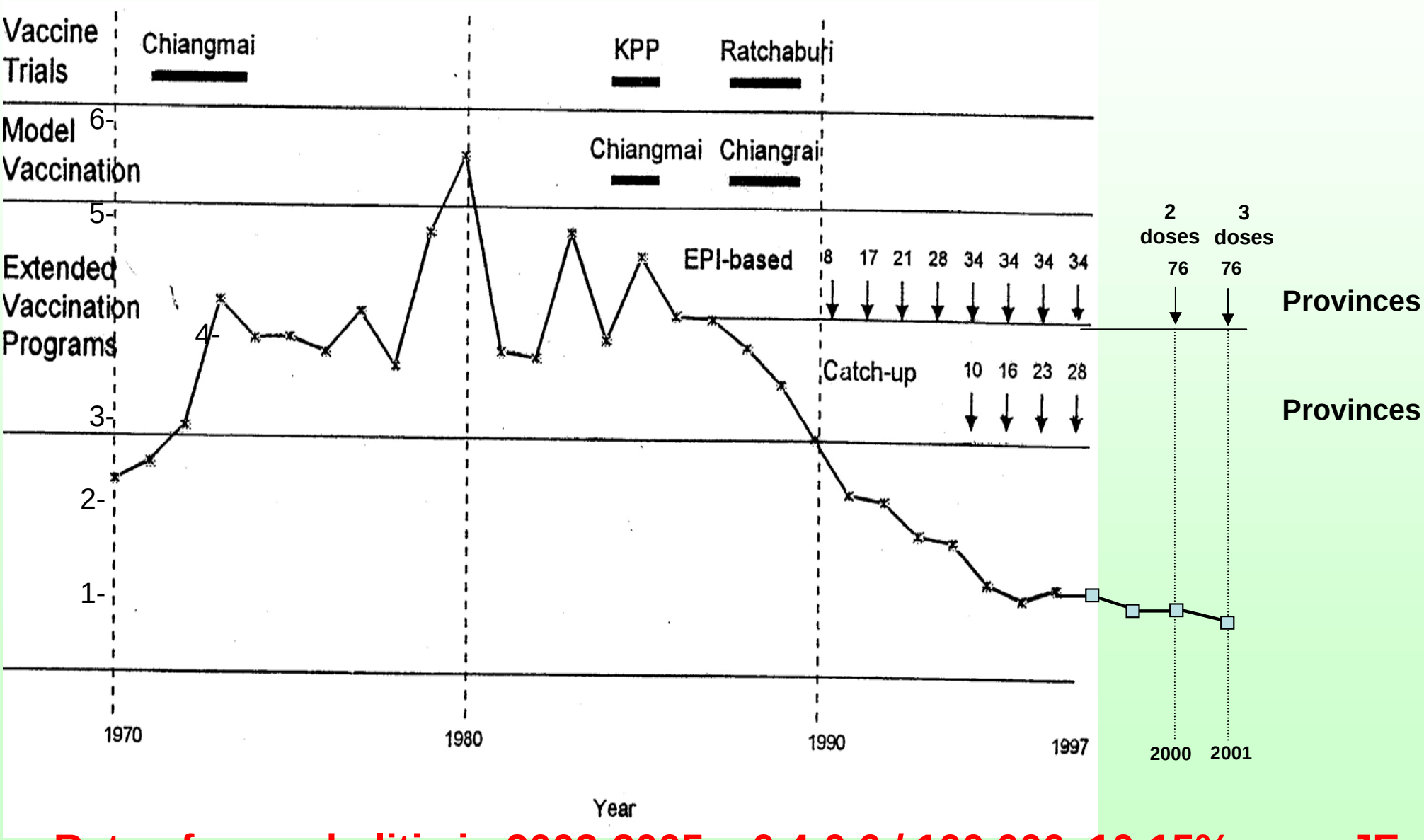
- Vector control
  - Eliminate mosquito breeding areas
  - Adult and larval control
- Vaccination
  - Humans and animals
- Personal protective measures
  - Avoid prime mosquito hours
  - Use of repellants

Vaccines Use in Large Scale

- **Mouse brain-derived killed vaccine (the most widely used in this region)**
  - **Nakayama**
  - **Beijing (induce stronger & broader Ab in preclinical study, and give higher yield)**
- **Cell culture-derived inactivated JE (Beijing P-3 strain): used only in China, now being replaced**
- **Cell culture-derived (PHK) live attenuated vaccine (SA 14-14-2 strain)**

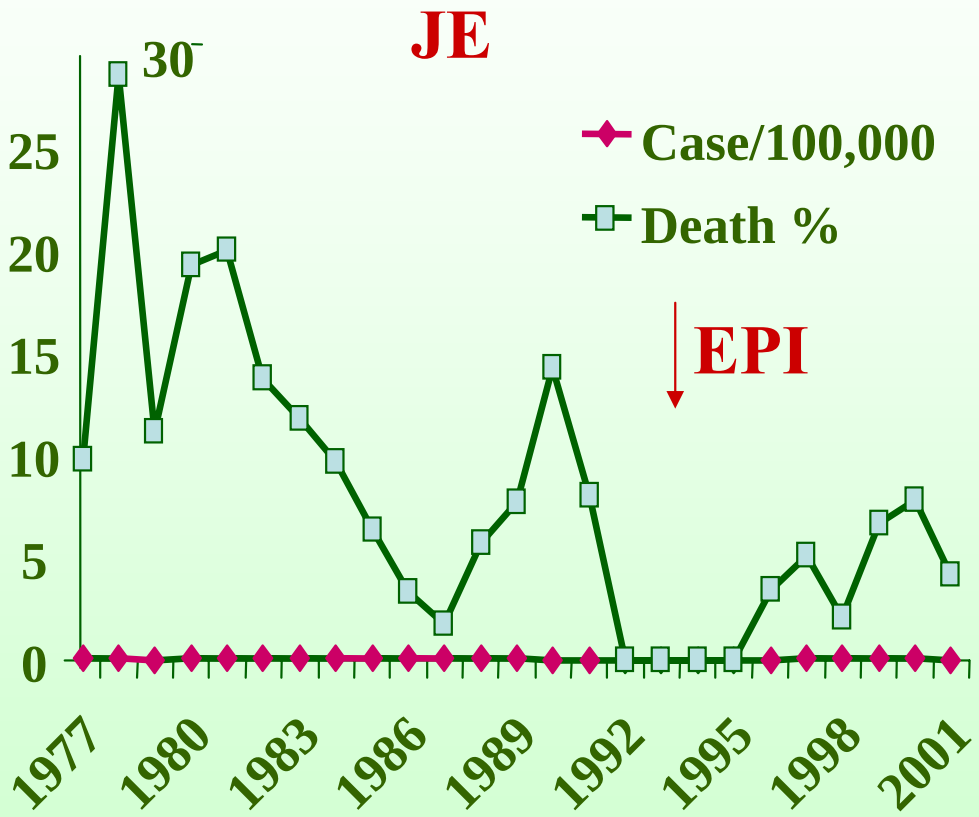
JE Vaccination History in Thailand

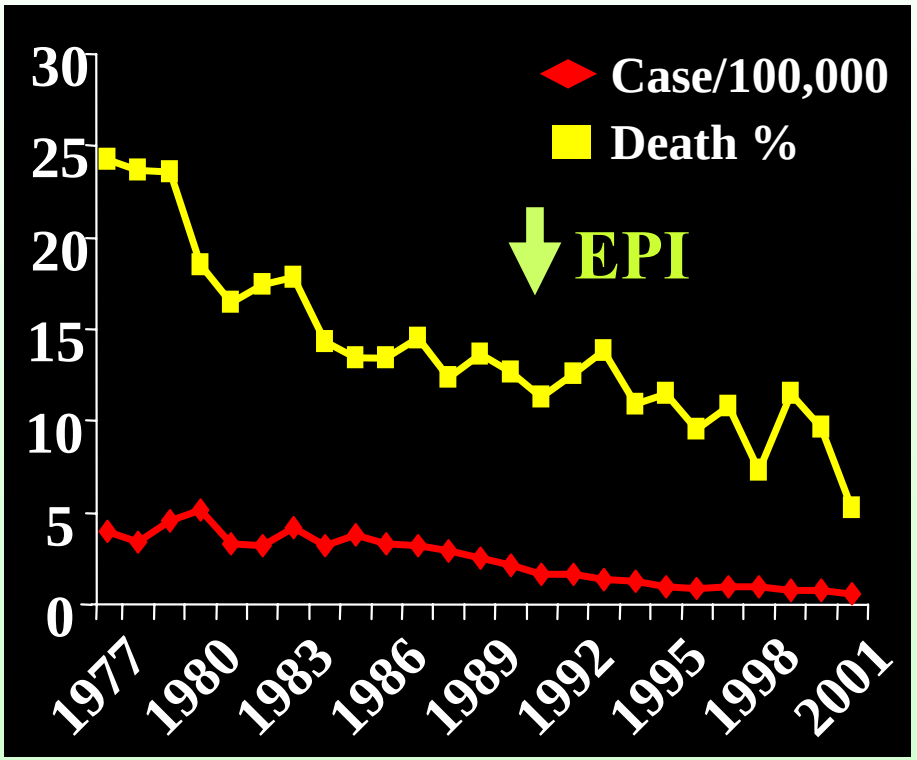
Mouse brain derived vaccine



Rate of encephalitis in 2003-2005 = 0.4-0.6 / 100,000. 10-15% were JE

Surveillance report
Communicable Diseases Division
Ministry of Public Health





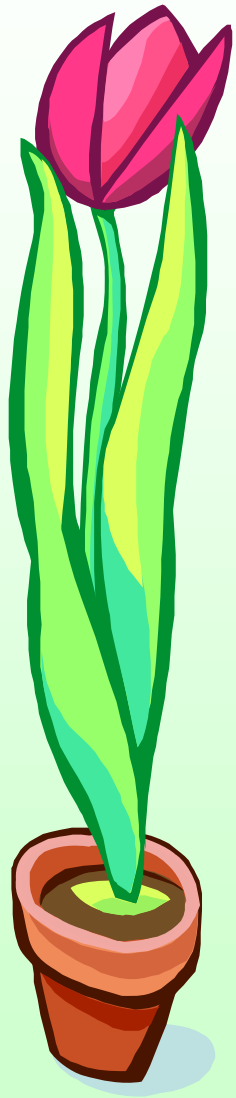
Cum # of cases (1971-2003)		40,413 (7,050 deaths)
Annual case rate :	1980	2,413 cases (447 deaths)
	2002	345 cases (30 deaths)

Rate of encephalitis in 2003-5 = 0.4-0.6 / 100,000

Viral etiologies in 40 Thai children with encephalitis

1996-1998 Siriraj Hospital (after selective JE-EPI)

Viral Etiologies	*No. of Patients (%)*
Dengue	8(20)
Japanese encephalitis	6(15)
Herpes simplex	4(10)
Human herpes virus type 6	3(7.5)
Mumps	2(5)
Enterovirus	1(2.5)
Varicella-zoster	1(2.5)
Rabies	1(2.5)
Unknown	14(35)
Total	40(100)

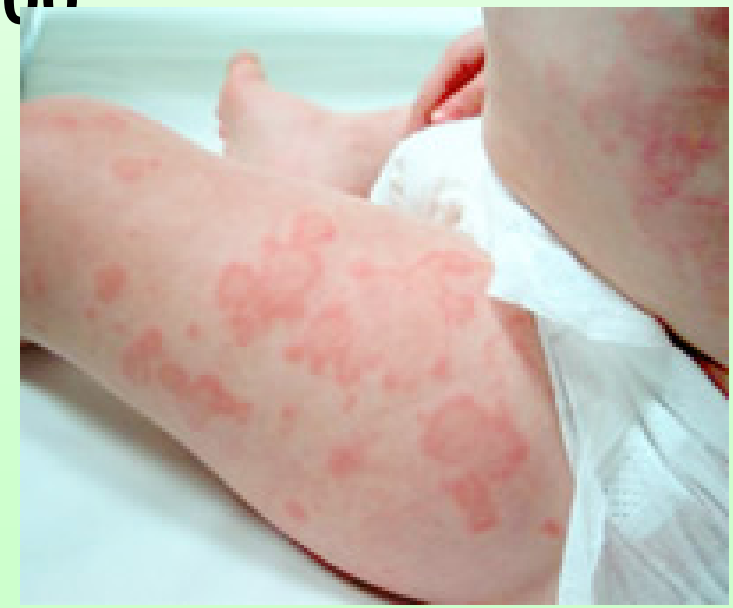


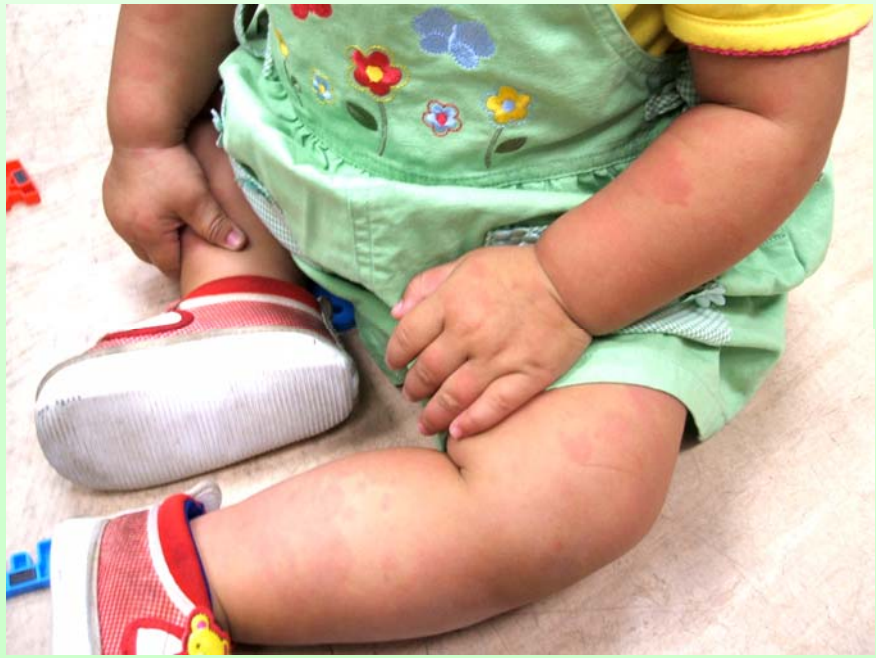
Chokephaibulkit K, et al. PIDJ 2001;20:216-8

Draw Back of Mouse-Brain Vaccine

- **Field efficacy 91%** *(Hoke CH 1988)*, **but short span protection (3-5 yr)**
- **Required multiple doses, 2-3 doses primary series and boosting doses**
- **Adverse events caused by myelin basic protein (now <2 ng/ml); hypersensitivity reaction and ADEM (acute disseminated encephalomyelitis) 1:50,000-100,000**

urticaria and angioedema (incidence 18-64/10,000 doses)





We Need a Better JE Vaccine

- Less shot
- More effective
- Less side effects

Draw back of mouse brain-derived vaccine

- Need > 3 shots >> expensive and inconvenient

- Frequent side effects esp. urticaria / angioedema

- Rare but serious hypersensitivity and neurologic reaction (rate 0.2/100,000)

New (Better) JE Vaccine In The Horizon

- **Live Attenuated SA 14-14-2**
  - Produced on primary hamster kidney cells
- **Chimeric attenuated JE (ChimeriVax-JE): phase 2-3**
  - Premembrane (prM) and envelope (E) protein gene of attenuated SA 14-14-2 replace the corresponding sequences in 17D yellow fever vaccine virus
- **Vero-cell derives inactivated vaccines: phase 1- 2**
  - Beijing strain grow in ATCC vero cell, then formalin inactivated
  - SA14-14-2 PDK strain in vero cell

Origin & Passage History of SA-14-14-2

- **SA 14, wild-type parent virus, was isolated from a pool of *Culex pipiens* larvae by 11 passages cultivation in mouse brain**
- **Further passages in mice and plaque purifications led to the 14-14-**
- **The SA 14-14-2 demonstrated a fine balance of safety through stable neuroattenuation and immunogenicity**

Live Attenuated Virus SA-14-14-2 JE Vaccine

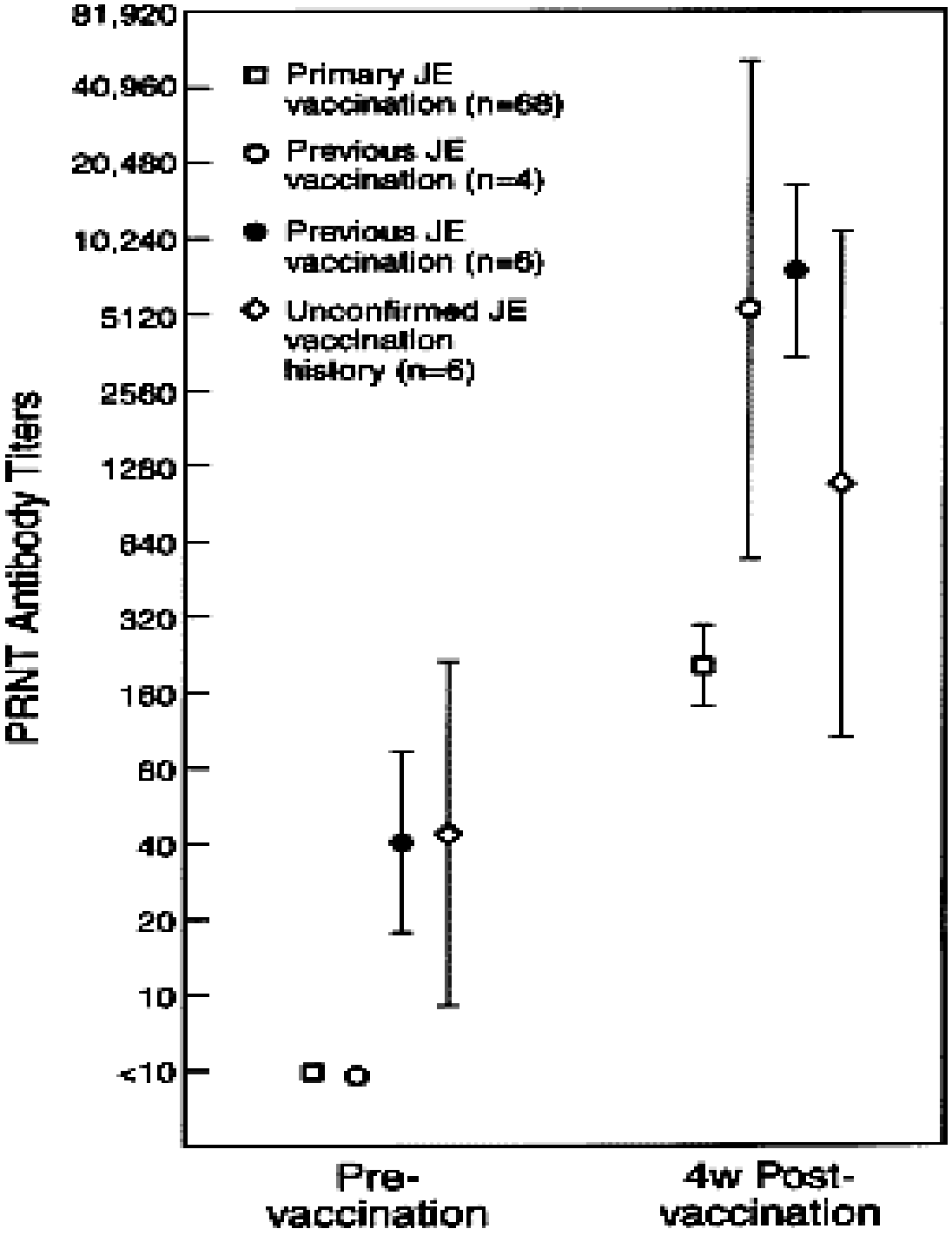
- **Registered in China (1989), Korea, Nepal, India, Sri Lanka, and Thailand**
- **Large scale use in china show efficacy reduced JE in china 2.5/100,000 in 1990 to <0.5/100,000 in 2004**
- **No serious A/E reported in 30 days in 13,266 children, rate of A/E 4.1/10,000 after first dose** *(JID 1997;176:1366-9)*
- **Efficacy in 5 studies using 2 doses, 1 year apart (N>500,0000) = 95-100%** *(Vaccine 2000;18:1-25)*
- **A study in Nepal showed an efficacy of 99.3% after a single dose in that year, and 98.5% in the following year** *(Bista MB. Lancet 2001;358:791-5, Ohrr H. Lancet 2005;366:1375-8)*
- **The study of 150 Thai children 9-15 month-old revealed 95% seroconversion after 1 dose, and can be boosted with mouse brain vaccine** *(Chotpityasunondh T. JITMM 2007, pg 56)*

http://www.who.int/vaccine_research/documents/Vector_Borne_Viral_Infections.pdf

Frequency of Adverse Events of Inactivated Mouse Brain Derived VS Live Attenuated SA 14-14-2 JE Vaccines

Reaction type	Frequency of reported adverse events	
	Inactivated mouse brain derived	Live attenuated PHK (SA 14-14-2)
Local reactions – tenderness, redness, swelling	20%	<1%
Mild systemic – headache, myalgia, GI symptoms, low-grade fever	10-30%	Fever < 0.5% Total 21%
Hypersensitivity (delayed onset common)	1-64:10,000	None reported
Acute encephalitis	1:50-75,000 to 1:million	None reported

Report of the Bi-Regional Meeting on Japanese Encephalitis, WHO 2005



Anamnestic responses (NT Ab) using SA14-14-2 live attenuated JE vaccine

Post-vaccination GMT were significantly higher in children previously immunized with inactivated JE vaccine than in primary vaccinees ($p<0.001$).

Y. Mo Sohn et al. Vaccine 1999;17:2259-64.

Chimeric live-attenuated vaccine

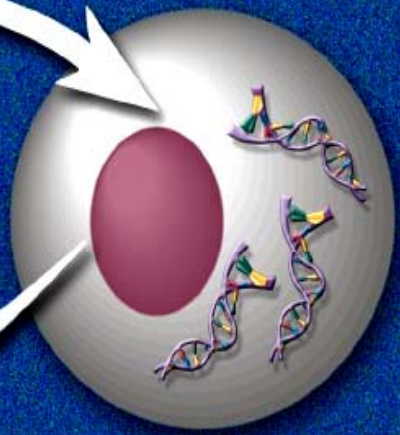
- Combining genes from different flaviviruses has been shown to further increase the attenuation of the donor sequences* *Pugachev et al (2007) Vaccine 25:6661-6671; McGee et al (2007) JID, in press*
- Chimerix vaccine comprises the prM and E coding sequences of JEV SA-14-14-2 strain inserted in phase into the 17D YFV strain genome
- Virus grown in a well characterized cell line (Vero) using serum-free culture medium
- The vaccine virus has structural proteins like JE but non-structural proteins like Yellow Fever virus
- The prototype vaccine is ChimeriVax-JE *(developed by Acambis and St Louis University in 1997)*

http://www.who.int/vaccine_research/documents/Vector_Borne_Viral_Infections.pdf

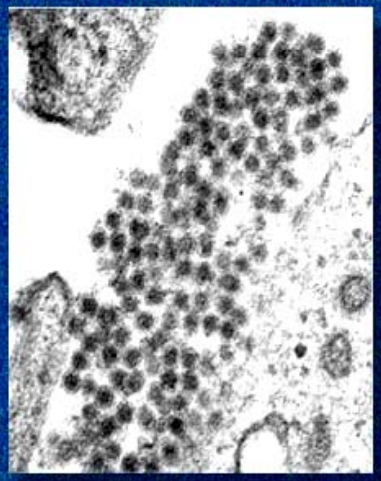
Construction of Chimeric Virus

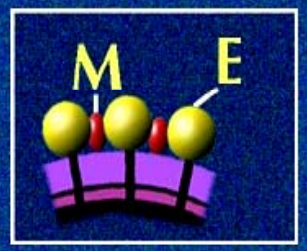
Full length cDNA → SP6 transcribe to RNA

Transfect RNA (Electroporation)

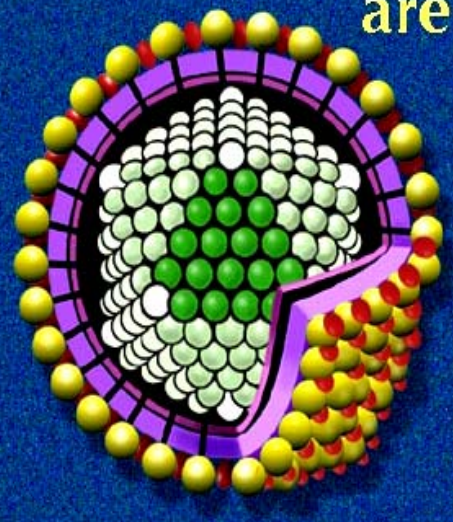


Grow virus in Vero cell culture





Envelope proteins are JE



Replicative 'engine' is YF 17D

JE-CV Pre-Clinical Safety

- Neurovirulence (IC inoculation)
  - Less neurovirulent than YF 17D vaccine virus (mice, monkeys)
- Neuroinvasiveness (IP inoculation)
  - Not neuroinvasive (mice, hamsters, monkeys)
- Viremia
  - Low, transient viremia (monkeys)
- Extraneural pathology
  - No organ dysfunction (monkeys)
  - No histopathological lesions (monkeys)

Monath et al (1999) Vaccine 17:1869; Monath et al (2000) J Virol 74:1742; Guirakhoo et al (1999) Virology 257:363; Arroyo et al (2001) J Virol 75:934; Monath et al (2005) Biologicals 33:131

Clinical Proof of Principle of Chimerix Live Vaccine Incorporate Gene of Heterologous Flavivirus, JE-CV

A randomized, double blind study

	N	%Viremic*	%JE sero conversion	GMT (PRNT)	A/E**
YF non-immune					
5.0 log CV	**6**	**83**	**100**	**254**	**3/6**
4.0 log CV	**6**	**83**	**100**	**128**	**5/6**
5.0 log YF-Vax	**6**	**100**	**0**	**15**	**4/6**
YF immune					
5.0 log CV	**6**	**83**	**100**	**327**	**3/6**
4.0 log CV	**6**	**100**	**100**	**270**	**4/6**
5.0 log YF-Vax	**6**	**0**	**0**	**13**	**4/6**

Viremic peak on day 4-5 (range 1-9), last 1-2 days
** No SAE, most are local and mild systemic

Monath TP. Vaccine 2002;20:1004-18

JE-CV Adult Clinical Development

- Clinical development in adults completed
  - 9 studies carried-out by Acambis
  - Under US IND and/or Australian TGA CTX
- From Phase I/II to Phase III studies, ended with
  - Phase III immunogenicity
  - Phase III safety
- Comparators
  - JE-VAX®, placebo
- More than 2000 adults received a dose of JE-CV

JE-CV Preliminary Phase III Adult Results

- Immunogenicity
  - 99% seroconversion* after single JE-CV dose compared with 74.8% after 3 doses of JE-VAX® 30 days after vaccination
  - 93.6% seroconversion 14 days after single JE-CV immunization
- Safety
  - No vaccine-related serious adverse events observed during observation period
  - Overall incidence of adverse events following vaccination slightly lower than JE-VAX® group
  - The majority of adverse events in those vaccinated with JE-CV were mild or moderate in nature

JE-CV Vaccine

- Virus grown in a well characterized cell line (Vero) using serum-free culture medium
- Bulk liquid vaccine tranferred to Thailand (GPO-MBP, Chachoengsao) from USA for formulation, filling, freeze-drying, QC testing and release
- Freeze-dried vaccine - storage at 2-8◦C
- No preservative or adjuvant
- Single dose for primary immunization
  - 0.5 mL per injection

JE-CV – Centered on Thailand

- Scale-up, formulation, filling, freeze-drying and QC testing by GPO-MBP
  - Thailand will be the country of origin
- Clinical development of the pediatric indication in Thailand
- Filing of a registration dossier in Thailand
- Export from Thailand

What yet to learn about the new vaccines

- Long term protection

  - need booster dose(s)?

- Impact of co-administration with other vaccines
- Immunogenicity and safety in immunocompromised persons

The hope is that a better and affordable vaccine be included in EPI soon!

Thank You
For Your Attention