Update on New Chimerix JE Vaccine

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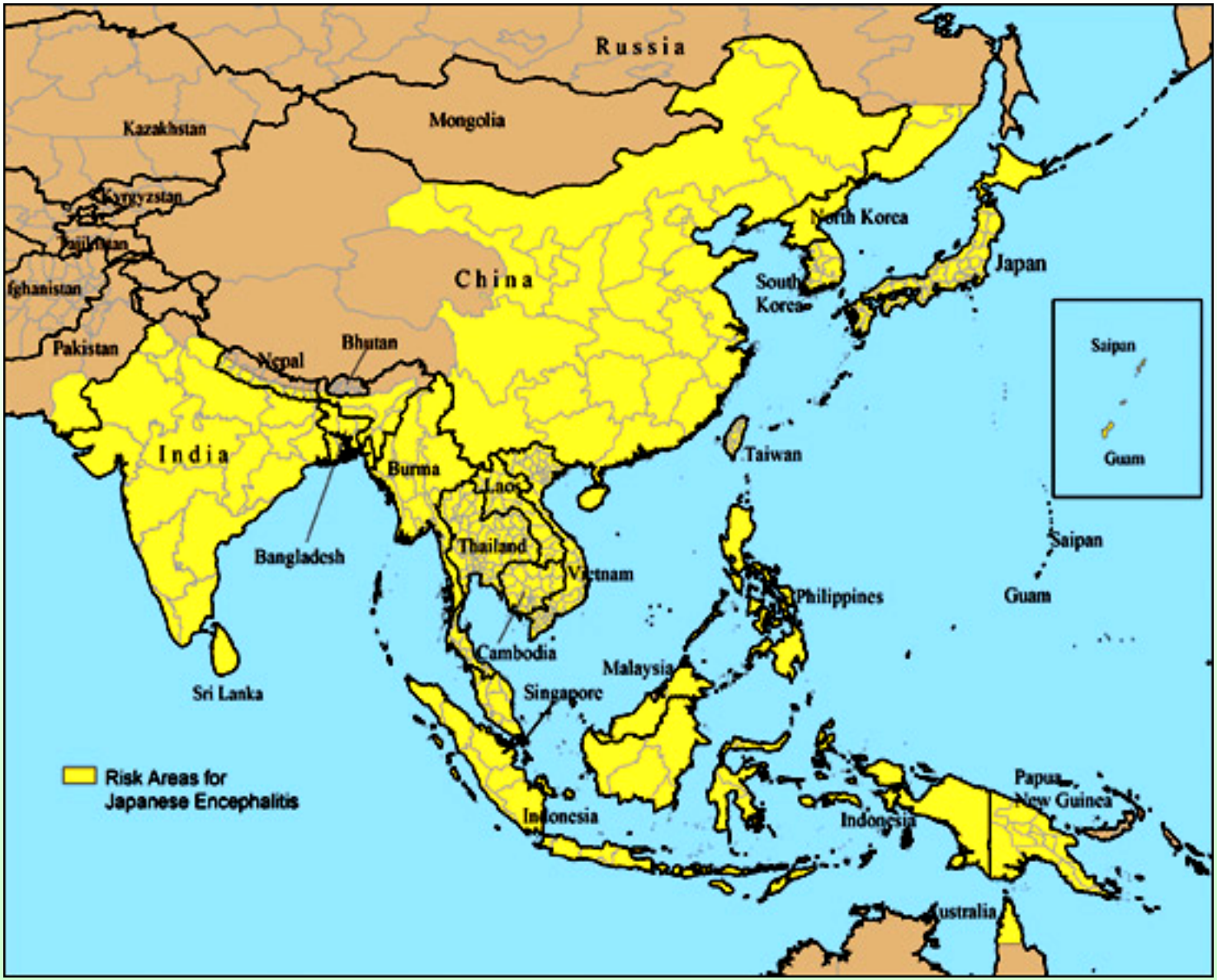
Conflict of Interest

- An investigator of a clinical trial of ChimeriVax™ in children (JE01) at Siriraj Hospital, Bangkok, Thailand

Geographic Distribution of Japanese Encephalitis



3 billion people live in JE endemic area

Culex spp.

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

Vaccines In Use for Large Scale

- **Mouse brain-derived killed vaccine (the most widely used in this region)**
  - Efficacy 91% *(Hoke CH 1988)*
  - Safety concern: urticaria, angioedema, (18-64/10,000 doses) and ADEM (1:100,000)
  - Require 3 doses for 1ry series and booster doses
- **Live Attenuated SA 14-14-2 (CD.JEVAX™)**
  - Produced on primary hamster kidney cells
  - Efficacy 95-100% *(Vaccine 2000;18:1-25, Lancet 2001;358:791-5, Lancet 2005;366:1375-8)*
  - Safe *(JID 1997;176:1366-9)*
  - Require 2 doses (3-12 months apart)

The New JE Vaccine in The Horizon

- **Chimeric attenuated Vaccine (ChimeriVax-JE™, JE-CV)**
  - Premembrane (prM) and envelope (E) protein gene of attenuated SA 14-14-2 replace the corresponding sequences in 17D yellow fever vaccine virus
  - Single dose administration

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)*
- JE-CV is a live-attenuated vaccine based on :

Structural proteins of JE live-attenuated SA14-14-2 virus	+	Replication engine (NS proteins) of the Yellow Fever 17D strain

The prototype vaccine is ChimeriVax-JE *(developed by Acambis and St Louis University in 1997)*

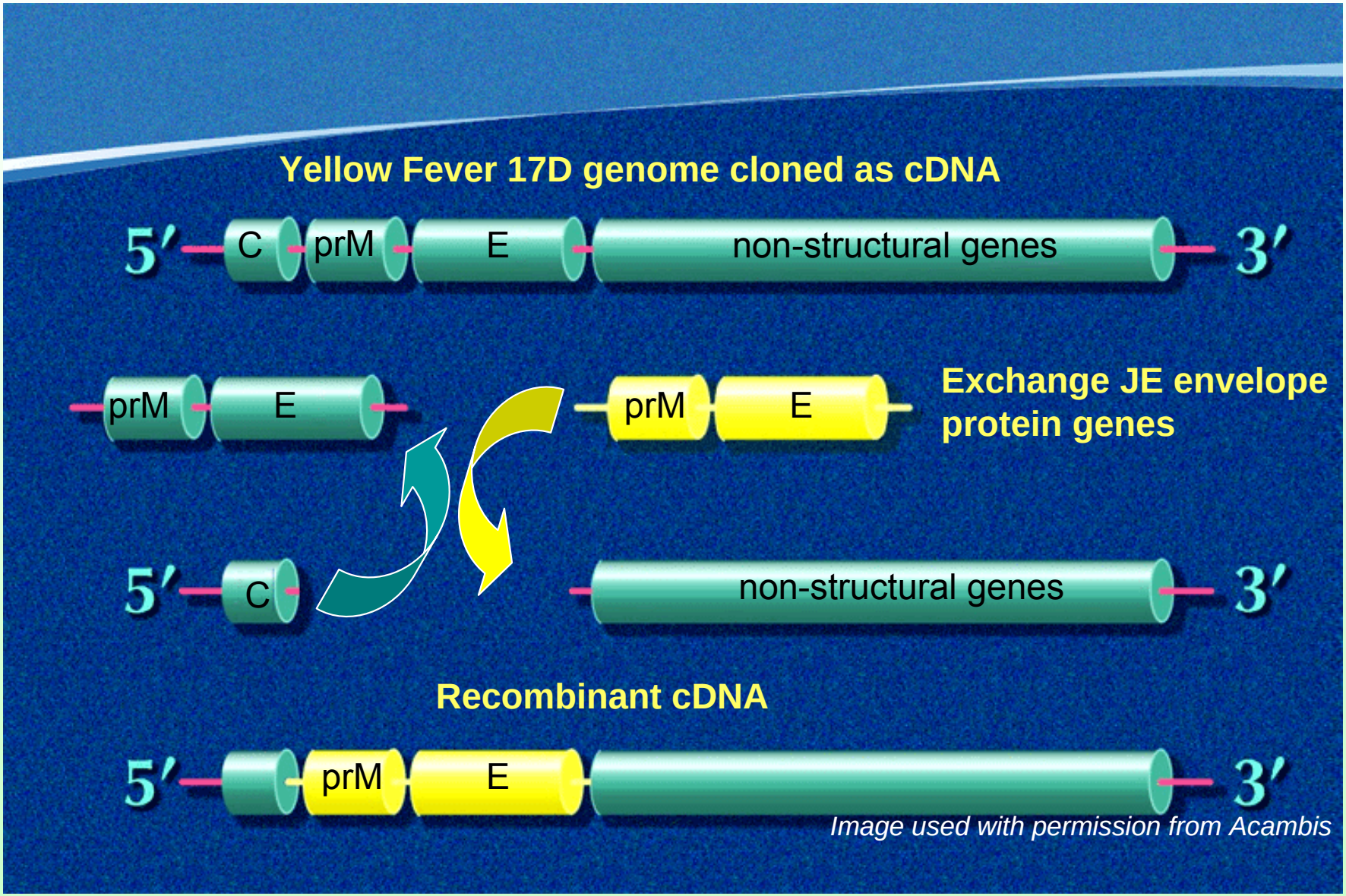
http://www.who.int/vaccine_research/documents/Vector_Borne_Viral_Infections.pdf

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 14-14-2**
- **The SA 14-14-2 strain was neuro-attenuated and was immunogenic**
- **The SA 14-14-2 is also used for the live attenuated vaccine**

JE-CV Construction*

Chimerix vaccine comprises the prM and E coding sequences of JEV SA-14-14-2 strain inserted into the 17D YFV strain genome



Chimerivax™ technology, Acambis

Recovery of JE-CV Virus

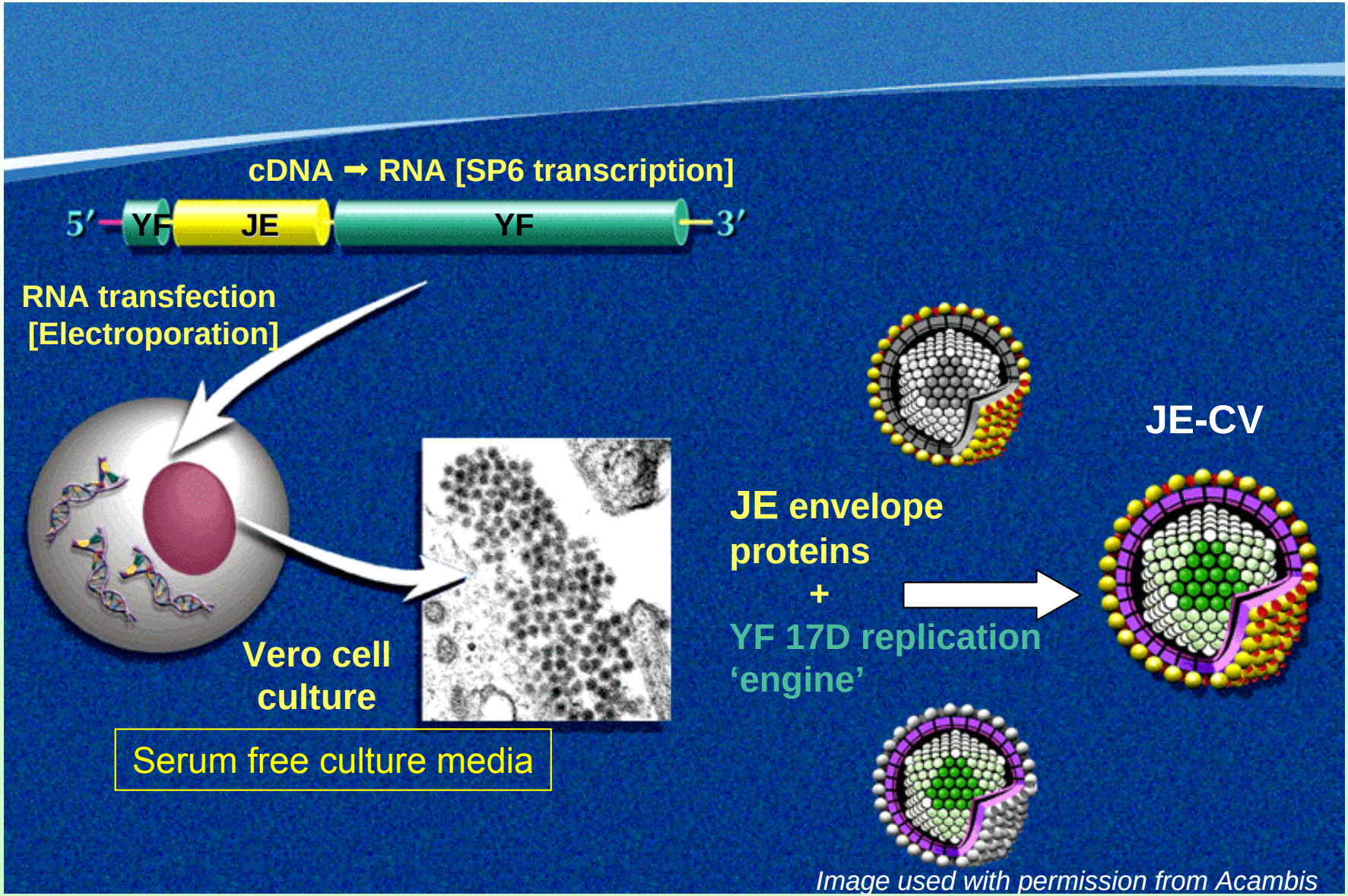


Image used with permission from Acambis

Worrisome for Serious Adverse Events Following Yellow Fever Vaccination

- Yellow fever vaccine is live attenuated based on 17D strain developed since 1937
- Very serious AE may occur around 1/25 million doses
  - 27 cases of neurotropic disease (post vaccination encephalitis) reported from 1945
  - 12 cases viscerotropic disease (multiple organ system failure) reported from 1996
- Onset: 1-6 days for viscerotropic, 4-23 days for neurotropic disease
- Most likely from aberrant host response

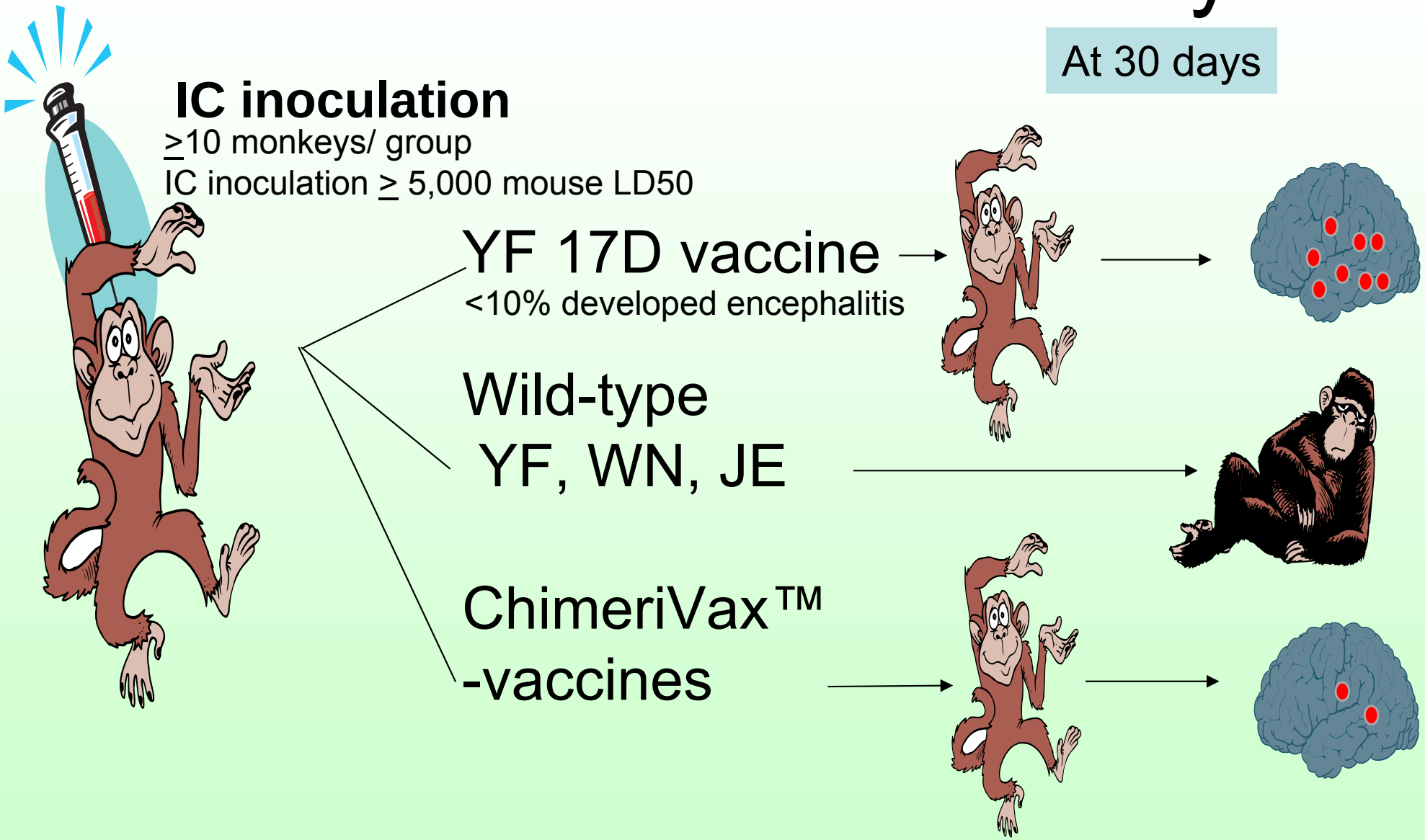
MMWR 2002; 51:989-993; WHO. Wkly Epidemiol Rec 2001;76:217-224

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

Neurovirulence for Monkeys

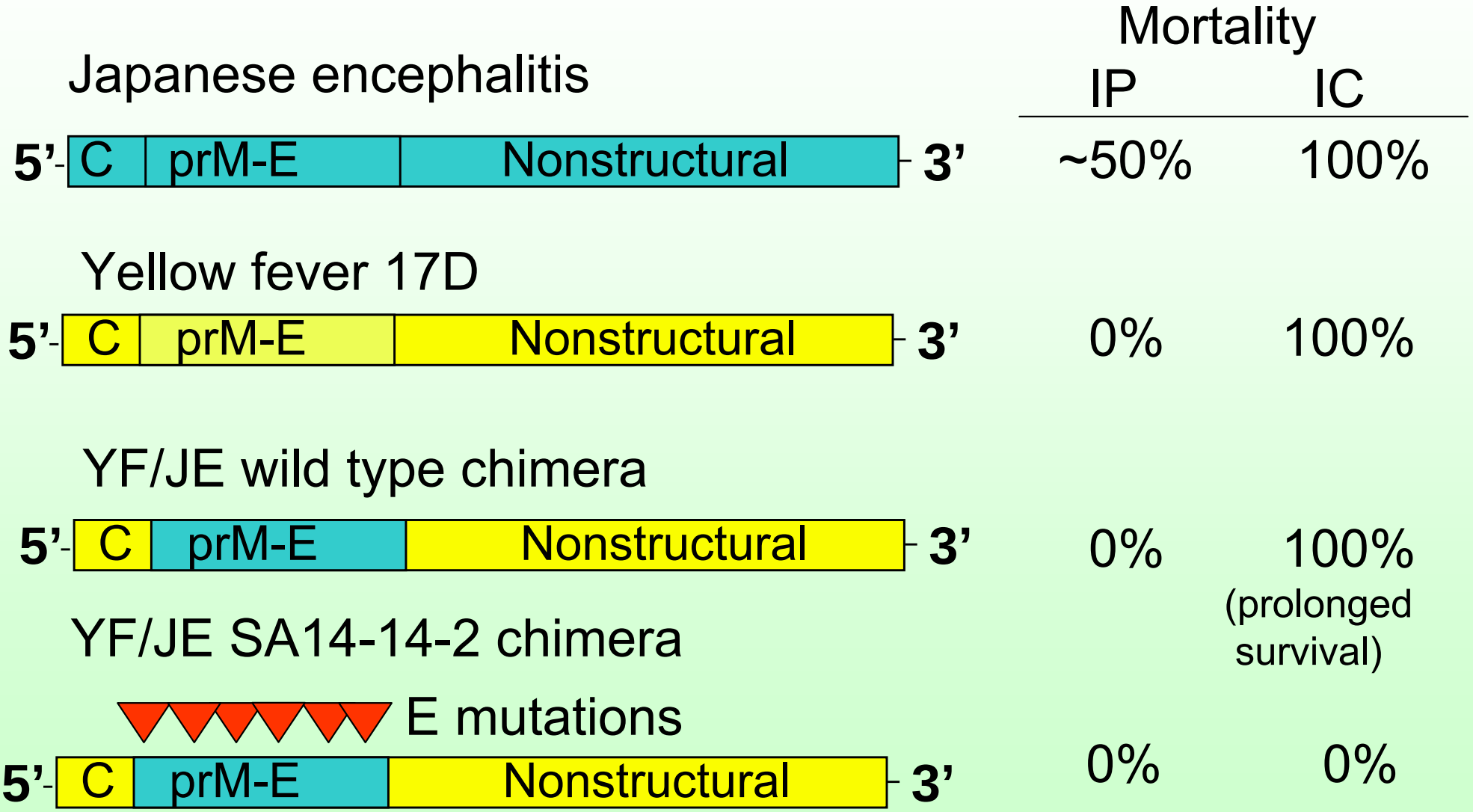


Mouse Neurovirulence Test*

- **Mouse NV test cannot be used for evaluation of YF vaccines because this vaccine is lethal for adult mice inoculated the IC route with as low as 1.6 logs PFU/LD_{50}**
- **The chimeric viruses are not pathogenic for young adult mice**
  - Infant mice become resistance with age. Infant mice can discriminate single amino acid substitutions in chimeric viruses which have minor effects on virulence

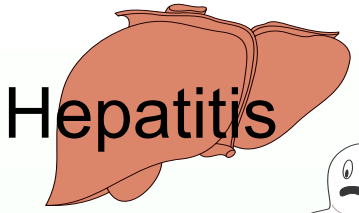
*: Guirakhoo et al, Virology 1999; Monath et al., Biological, 2005

Molecular Control of Neurovirulence (JE)*: Mouse Neurovirulence test



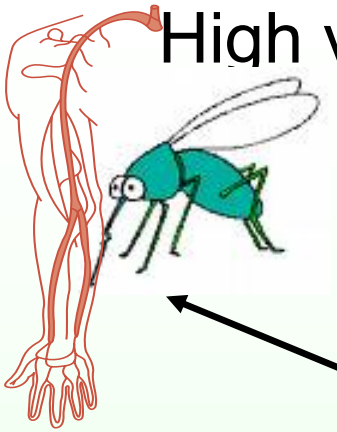
*: Chambers et al, JVI 1999, Arroyo et al JVI 2001

Human, monkey



Hepatitis

20% CFR

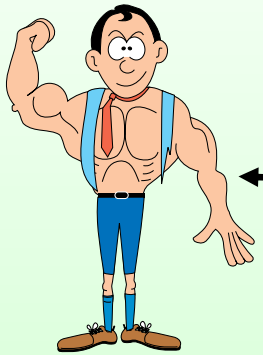


High viremia

Mouse

Yellow fever virus

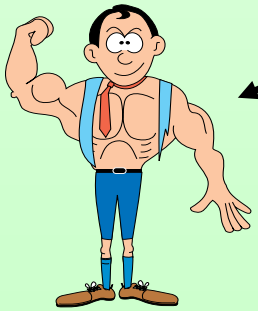
235+ passages
31 (0.9%) amino
acid changes



YF 17D vaccine

Immunity

JE-CV vaccine



Immunity

Why Chimerix JE Vaccine Is Less Virulent

- Attenuation of ChimeriVax depends on multiple factors
  - **Redundant envelope mutations:**
    - Envelope is derived from highly attenuated SA14-14-2 JE vaccine
    - Multiple envelope mutations (10 residues difference between JE-CV and JE Nakayama envelope)
    - No single reversion can restore neurovirulence of JE-CV vaccine
    - No case of postvaccination encephalitis has been reported with JE SA14-14-2 vaccine
  - **Chimerization process add additional attenuation:**
    - Even if all 10 attenuation residues are reverted, the phenotype of the virus resembled parental YF Vaccine virus rather than wild-type JE virus

JE-CV Vaccine

- Virus grown in a well characterized cell line (Vero) using serum-free culture medium
- Freeze-dried formulation
- No preservative or adjuvant
- Single dose for primary immunization
  - **0.5 mL per injection**

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

Phase III Clinical Trials in Adults

- Placebo-Controlled Safety Study
- Immunogenicity and Safety Study

The Study Group Placebo-Controlled Safety Study

AUSTRALIA

– **Andrew Ebringer**, Queensland
  - **Michael Woodward**, Victoria
  - **Damon Eisen**, Victoria
  - **Debbie Marriott**, New South Wales
  - **Jeff Karrasch**, Queensland
  - **Michael Chia**, South Australia

USA

- **Ivor Emanuel**, California
- **Brandon Essink**, Nebraska
- **Gregory Gray**, Iowa
- **Larry Gilderman**, Florida
- **James Hedrick**, Kentucky
- **Steven Hull**, Kansas
- **Thomas Marbury**, Florida
- **Dennis Morrison**, Missouri
- **Serena Mraz**, California
- **Keith Pierce**, Michigan
- **Peter Rogge**, California
- **Robert Rosen**, North Carolina
- **William Seger**, Texas
- **Eric Sheldon,** Florida

Theresa Sligh, California

Kenneth Kim, California

Placebo-controlled Safety Study

Randomized, Double Blind, Multicentre, Placebo Controlled Phase III Study of the Safety and Tolerability Following Administration Of Live Attenuated JE Vaccine

Group	N	Vaccine D0 ↓
1	**1601**	**JE-CV (0.5 ml)**
2	**403**	**0.9% saline (0.5 ml)**

Visit Day 0 (vaccination), 7, 14, 30, phone at 6 M

Subject Disposition

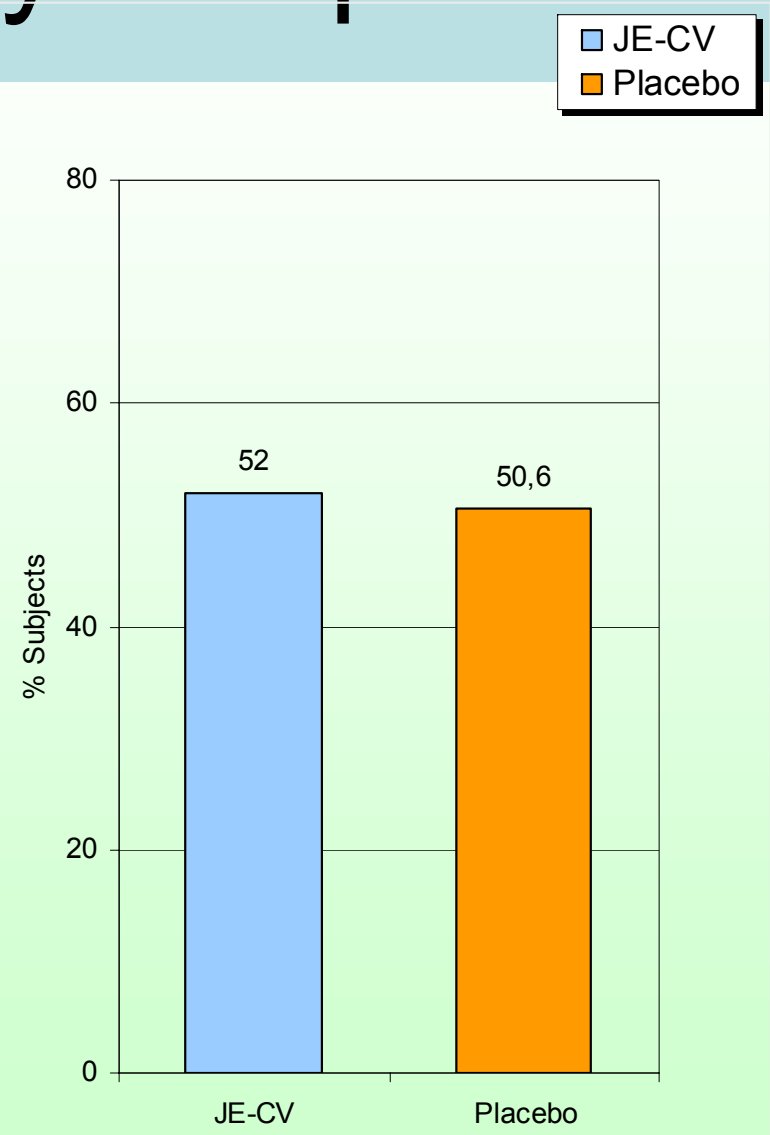
- 2004 subjects enrolled - 22 centres in Australia (6 sites) and USA (16 sites)

Number of Subjects	Group 1 (JE-CV) n (%)	Group 2 (Placebo) n (%)	All n (%)
Randomized	1600	404	2004
Safety Population*	1601 (100.1)	403 (99.8)	2004 (100.0)
Completed up to D30	1583 (98.9)	395 (97.8)	1978 (98.7)
Withdrew up to D30	**18 (1.1)**	**8 (2.0)**	**26 (1.3)**
Reason for Withdrawal			
Lost-to-follow-up	*13 (0.8)*	*3 (0.7)*	*16 (0.8)*
Voluntary	*5 (0.3)*	*3 (0.7)*	*8 (0.4)*
Adverse event	***0 (0)***	***1 (0.2)***	***1 (0.0)***
Physician decision	***0 (0)***	***1 (0.2)***	***1 (0.0)***

* One subject randomized to receive placebo was administered JE-CV, the safety population is based on actual treatment received.

Primary Safety Endpoint

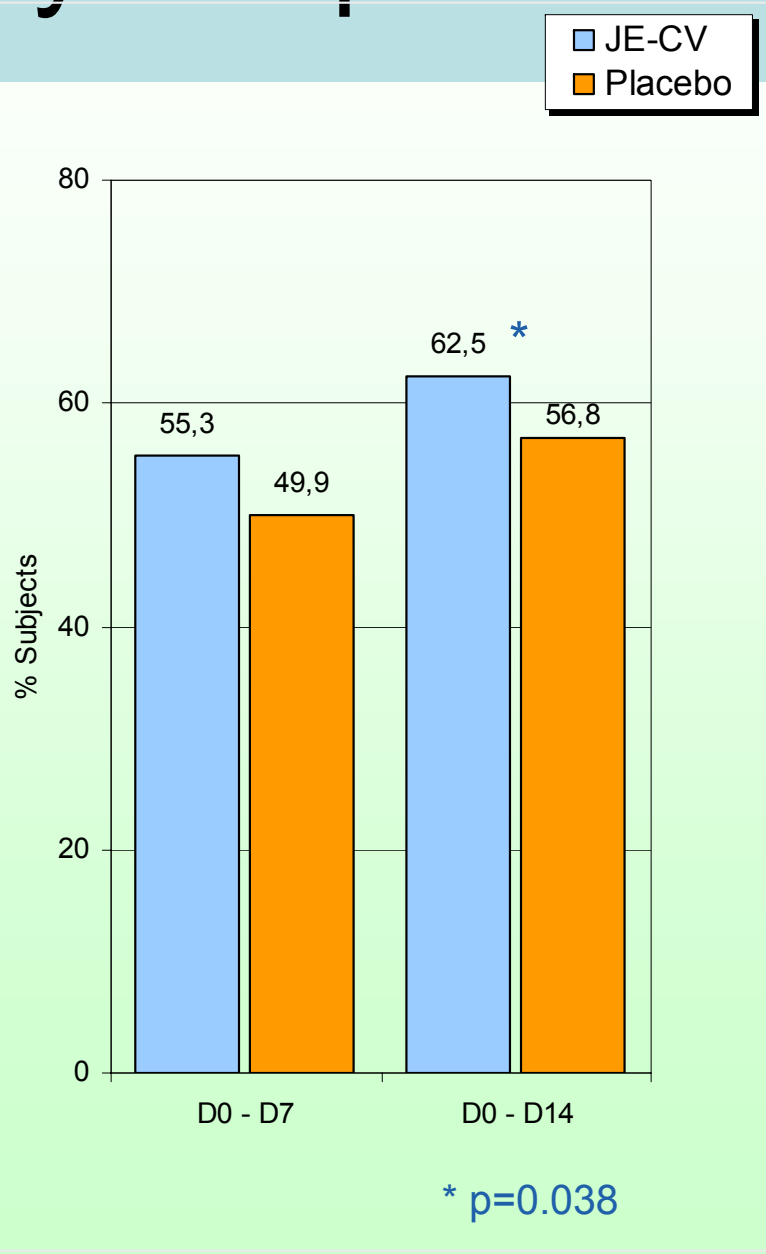
- Similar overall incidence of % of subjects with treatment-related* AEs, D0 - D30
  - p=0.203



* All events considered to be possibly, probably or definitely related to study treatments

Secondary Safety Endpoints

- More treatment-emergent AEs in JE-CV Group D0 - D14



Secondary Safety Endpoints

Most common treatment-related* AEs by SOC, D0-D30

	JE-CV	Placebo
General	**39.4%**	**35.7%**
Nervous system	**27.0%**	**25.6%**
Musculoskeletal	**19.2%**	**14.9%**
Gastrointestinal	**15.6%**	**13.4%**

Similar distribution across SOCs between treatment groups

- **More *feeling hot*, *chills*, *myalgia* and *arthralgia* in JE-CV group**
- **more treatment-related *nasopharyngitis* in placebo group**

* All events considered to be possibly, probably or definitely related to study treatments

Secondary Safety Endpoints

Most commonly reported systemic reactions D0-D30

	JE-CV	Placebo
Headache	**37.3%**	**30.8%**
Fatigue	29.9%	27.8%
Malaise	23.9%	22.8%
Myalgia	**22.0%**	**16.6%**
Arthralgia	**11.2%**	**6.9%**

Systemic reactions

- **– *Headache* (p=0.015), *myalgia* (p=0.02) and *arthralgia* (p=0.013) significantly higher in the JE-CV group**
- **– No statistically significant difference in SI* score > comparable severity of systemic reactions**

Durations for most commonly reported AEs were similar

- **– 0–3 days**
- **– *Injection site pain* of longer duration in JE-CV group; *Arthralgia* and *nausea* slightly longer duration in placebo group.**

*SI=severity Index

Secondary Safety Endpoints

- Injection Site Reactions D0-D30
  - **More in CV-JE but non-significant**

	JE-CV	Placebo
Pain	**12.4%**	**8.9%**
Erythema	**4.6%**	**3.7%**
Pruritus	**4.1%**	**3.0%**
Haemorrhage	**1.3%**	**1.0%**
Swelling	**1.1%**	**1.0%**

Secondary Safety Endpoints

- **68 treatment-emergent AEs rated as *severe* reported by 51 subjects**
  - 9 *related*: 3 *probably related* and 6 *possibly related* to study medication
  - JE-CV more than placebo 2.7% v 2.0%
- **7 Serious AEs D0 - D30**
  - JE-CV 5 events
  - Placebo 2 events
  - 6 considered *definitely not related* to study medication
  - 1 (pyrexia) considered to be *probably related* to JE-CV – resolved after 7 days
- **9 Serious AEs reported from D31 to Month 6**
  - All *definitely not related* SAEs

Placebo-controlled Safety Study Conclusions

- JE-CV was safe
- AE incidence 30 days post-vaccination not statistically different between JE-CV and placebo
- AE profile consistent with previous studies

The Study Group : Immunogenicity and Safety

- **AUSTRALIA**
  - **Jim Buttery**, Victoria
  - **Joseph Torresi**, Victoria
  - **Sepehr Shakib**, South Australia
  - **Malcolm Handel**, New South Wales
  - **Peter Nasveld**, Queensland
- **USA**
  - **Luis Angles**, Kansas
  - **Jeffrey Geohas**, Illinois
  - **William Lumry**, Texas
  - **Royce Morrison**, Washington
  - **George Risi**, Montana

- **Development**
  - Acambis
    - **Thomas Monath**

Immunogenicity, Safety and Tolerability Study vs JE-VAX®

A multicentre, randomized, double-blind, phase III study of the comparative immunogenicity, safety and tolerability of two Japanese encephalitis vaccines

Group	N	Vaccine D0 Left ↓ Arm	Vaccine D7 Right ↓ Arm	Vaccine D30 Left ↓ Arm	Vaccine D30 Right ↓ Arm
1	**408**	**Saline (1ml)**	**Saline (1ml)**	**Saline (1ml)**	JE-CV **(1ml)**
2	**408**	JE-VAX® **(1ml)**	JE-VAX®**(1ml)**	JE-VAX® **(1ml)**	**Saline (1ml)**

Visit on Day 0, 7, 14, 30, 44, 60 (serology), phone at 7M

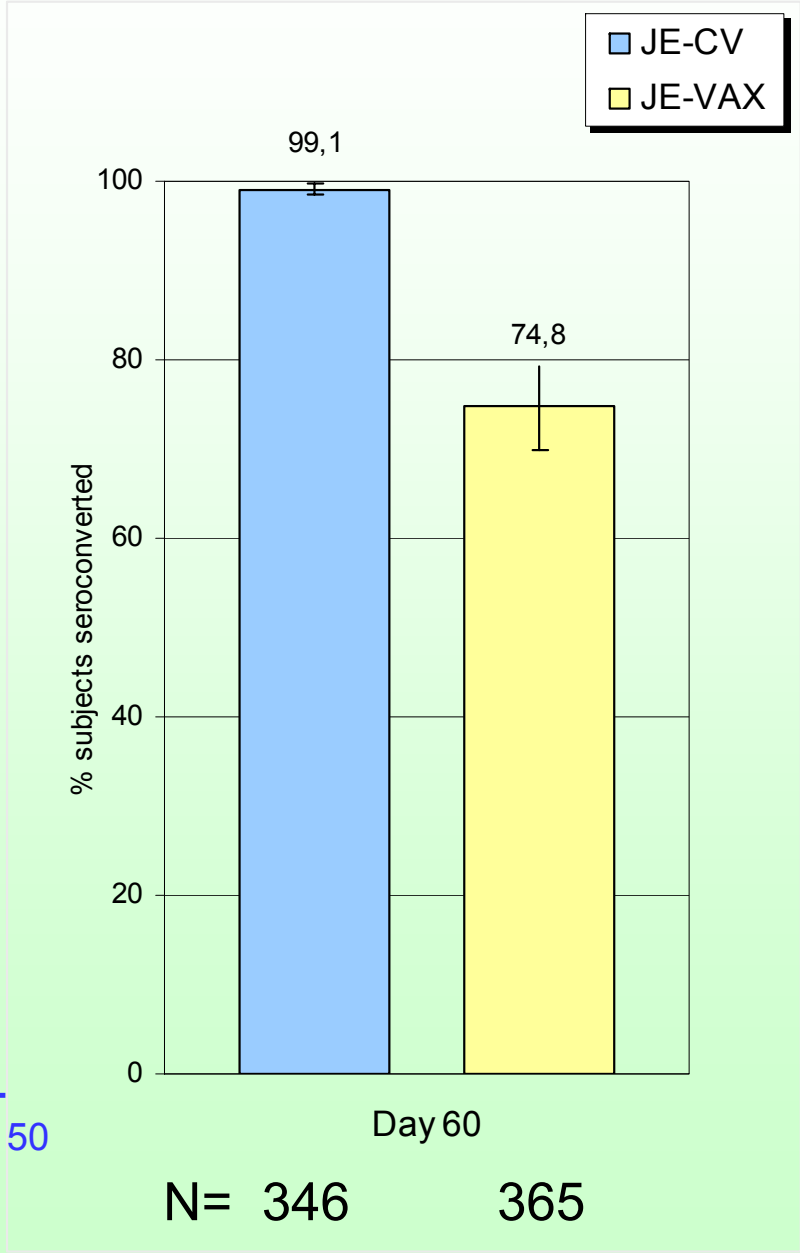
Subject Disposition

- 820 subjects enrolled across 10 centres (5 in USA and 5 in Australia)

Number of Subjects	Group 1 (JE-CV) n (%)	Group 2 (JE-VAX®) n (%)	All n (%)
Randomized	410	410	820
Completed up to D60	381(92.9)	389 (94.9)	770 (93.9)
Withdrew up to D60	**29 (7.1)**	**21 (5.1)**	**50 (6.1)**
Reason for Withdrawal			
Voluntary	*10 (2.4)*	*8 (2.0)*	*18 (2.2)*
Lost-to-follow-up	*12 (2.9)*	*5 (1.2)*	*17 (2.1)*
Physician decision	***4 (1.0)***	***3 (0.7)***	***7 (0.9)***
Adverse event	***3 (0.7)***	***0 (0.0)***	***3 (0.4)***
Protocol violation	***0 (0.0)***	***3 (0.7)***	***3 (0.4)***
Sponsor decision	***0 (0.0)***	***2 (0.5)***	***2 (0.2)***

Primary Immunogenicity Endpoint

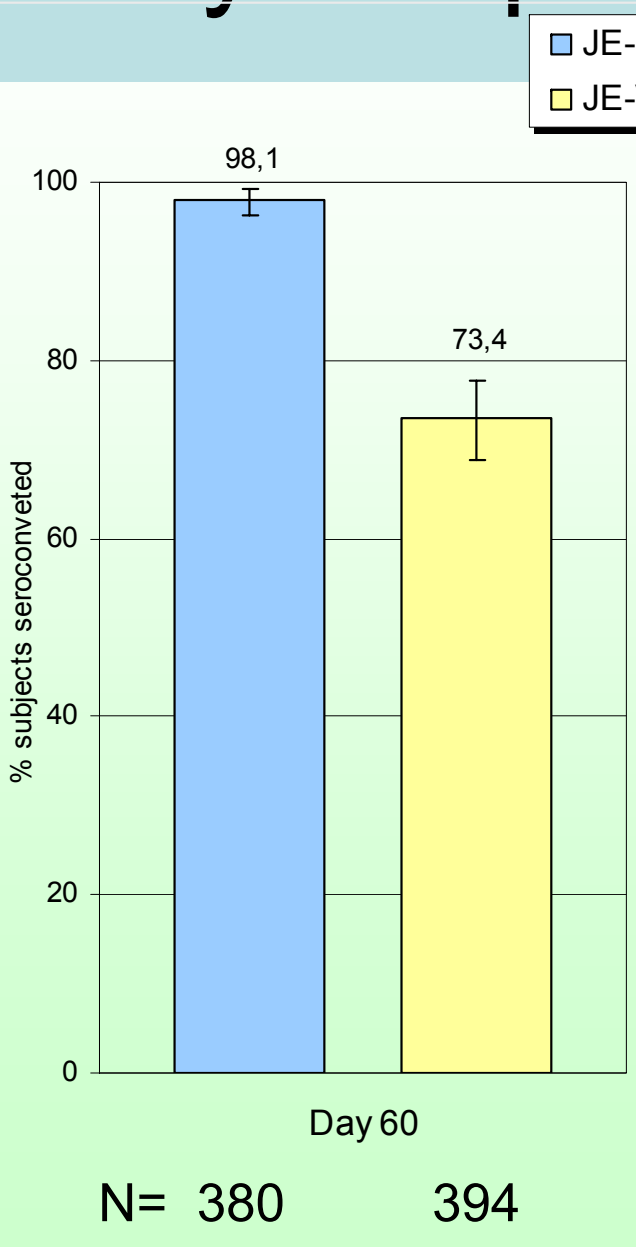
- Proportion of seronegative subjects who seroconverted* to homologous JE vaccine strain, 30 days after primary immunisation schedule (D60)



* Subjects seronegative at baseline (<1:10) required a serum dilution $PRNT_{50}$ titre of ≥ 1:10

Primary Immunogenicity Endpoint

- Proportion of subjects who seroconverted* to respective homologous JE vaccine strain, 30 days after completion of the primary immunisation schedule (D60)



*Subjects seronegative at baseline (<1:10) required a serum dilution $PRNT_{50}$ titre of ≥ 1:10; Subjects with pre-existing neutralising antibody at D0 seroconverted ≥four-fold in neutralising antibody titre between D0 and D60 samples

Secondary Immunogenicity Endpoints (1)

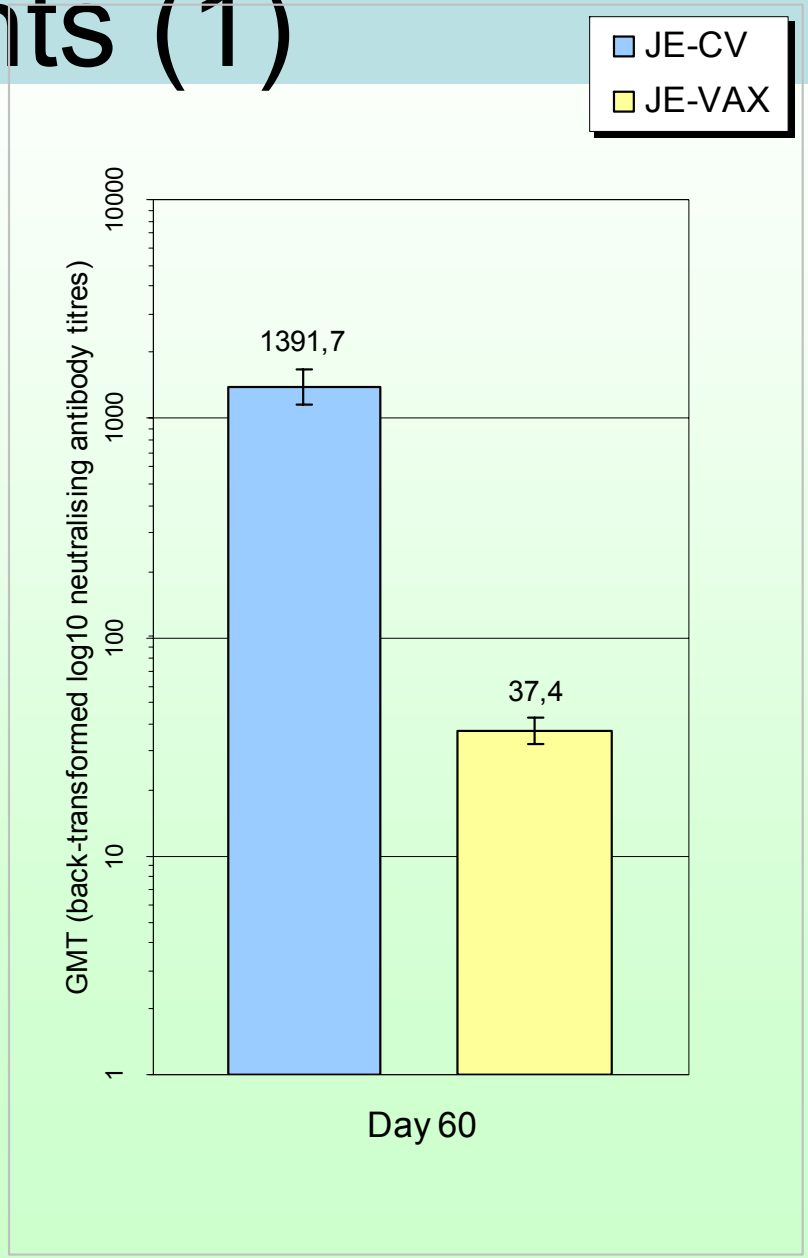
Neutralising antibody

GMTs at D60

- GMT Ratio (JE-CV/JE-Vax) D60 = 37.4

  (95% CI: 29.7, 47.0)

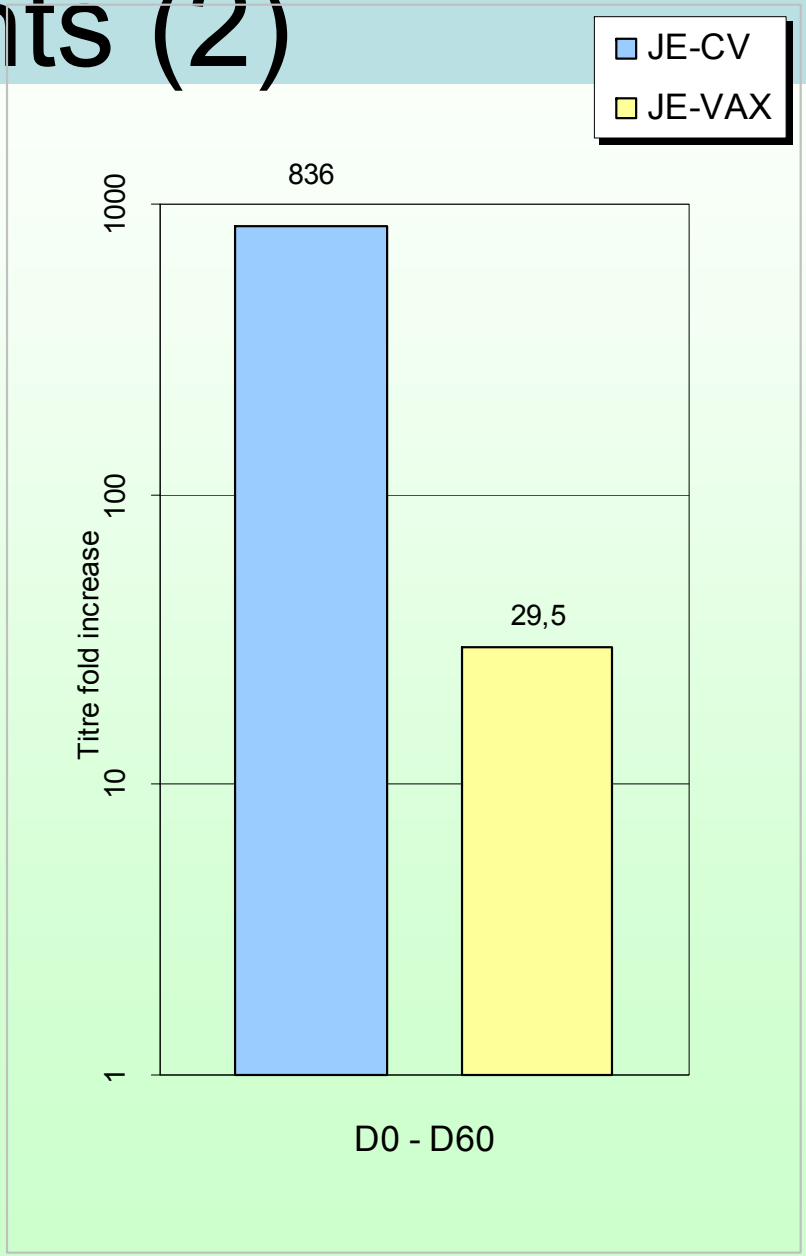
  ➔ **statistical non-inferiority of JE-CV to JE-VAX®**



Secondary Immunogenicity Endpoints (2)

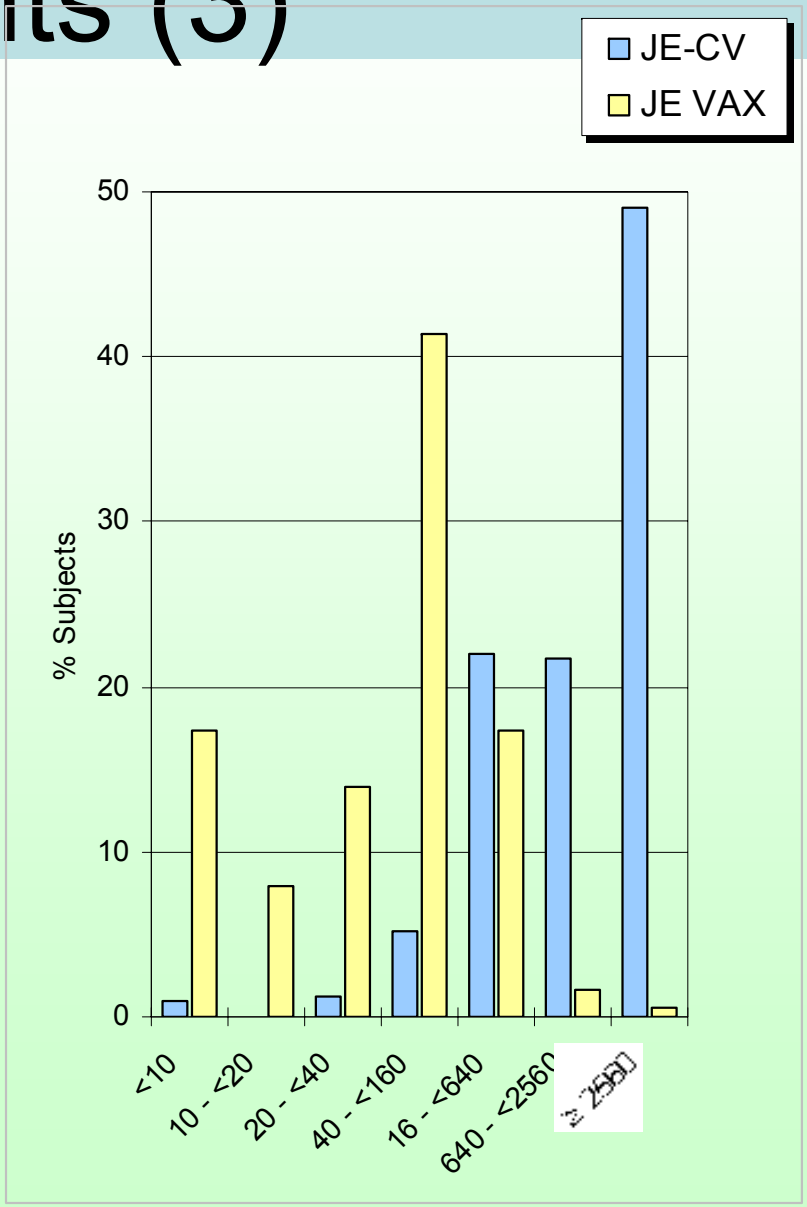
- Titre fold increase in serum dilution PRNT50 between D0 and D60

•Difference in mean fold increases = 807 (95% CI: 689.3, 924.8) in favour of JE-CV



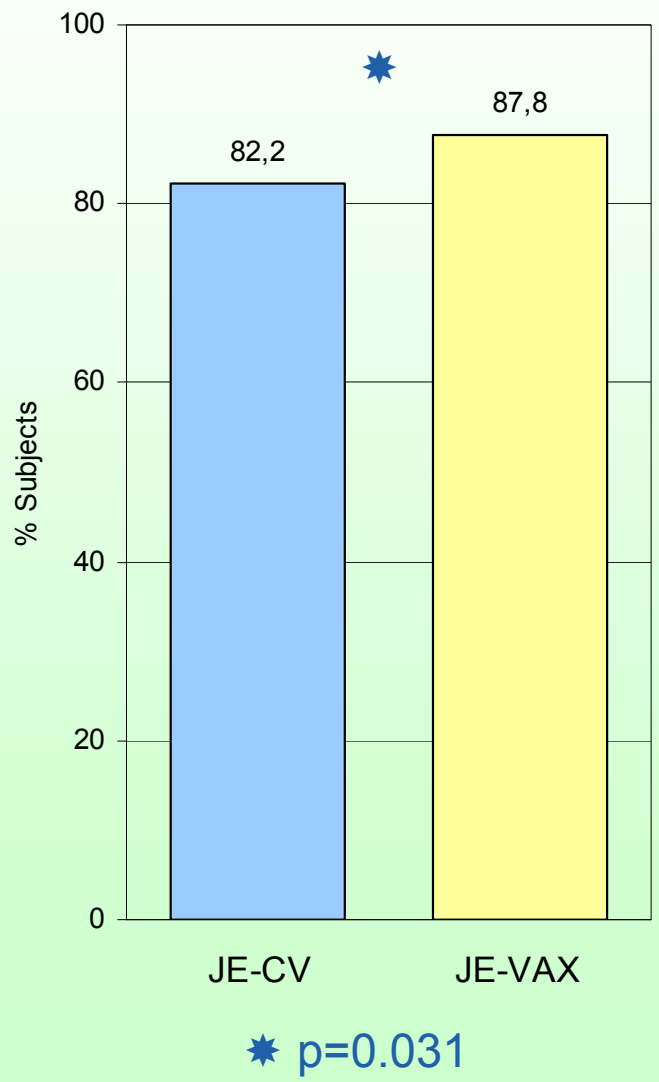
Secondary Immunogenicity Endpoints (3)

- Distribution of neutralising antibody titres at D60
  - **Statistically significant difference between groups (p<0.001)**



Primary Safety Endpoint

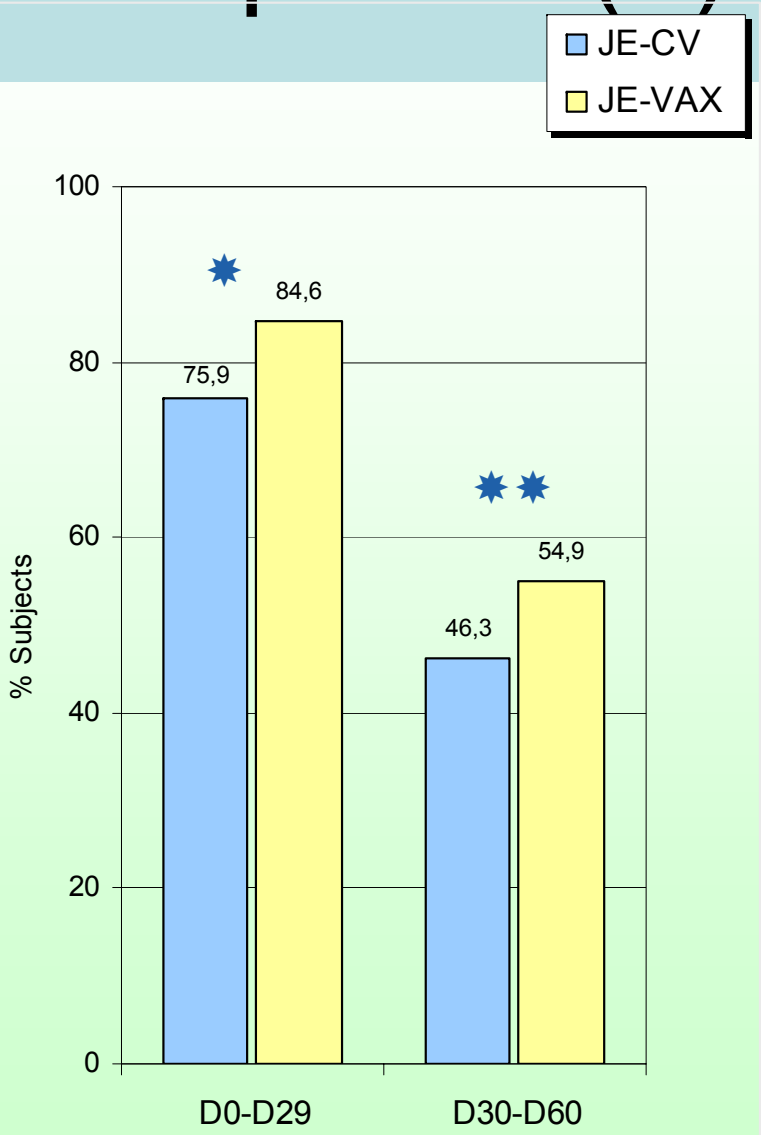
- % of subjects reporting solicited* AEs, D0 - D60
  - **D0 - D60 significantly lower in JE-CV group (p=0.031)**



* All AE reporting in both study periods was “actively solicited” via structured interviews and diary cards

Secondary Safety Endpoints (1)

- More AEs reported D0-D29 than D30-D60
- JE-CV vaccination was at D30
  - **Percentage of subjects in JE-CV group with AEs higher after** placebos **(D0-D29) than after CV-JE** vaccination **(D30-D60)**



Secondary Safety Endpoints (2)

- Most commonly reported SOC for treatment-related* AEs, D0-D60

	JE-CV	JE-VAX®
General†	**55.1%**	**75.9%**
Nervous system	**37.6%**	**38.3%**
Musculoskeletal	**22.9%**	**25.9%**
Gastrointestinal	**22.4%**	**20.7%**

* All events considered to be possibly, probably or definitely related to study treatments

† $p < 0.001$

Secondary Safety Endpoints (3)

- Most commonly reported treatment-emergent systemic reactions, D0-D60

	JE-CV	JE-VAX®
Headache	**47.1%**	**46.3%**
Fatigue	**37.1%**	**32.0%**
Malaise	**27.6%**	**27.6%**
Myalgia	**25.6%**	**26.1%**

Secondary Safety Endpoints (4)

- Injection site AEs, D0-D60

	JE-CV	JE-VAX®
Pain	**25.6%**	**63.9%**
Erythema	**6.6%**	**30.0%**
Pruritus	**7.1%**	**26.1%**
Swelling	**3.7%**	**20.7%**

Secondary Safety Endpoints (6)

- 81 treatment-emergent AEs rated as *severe* reported up to D60
  - **7.1% JE-VAX® vs. 4.1% JE-CV**
- 14 AEs rated as *severe* were considered treatment related
  - **12 JE-VAX® vs. 2 JE-CV**
- 7 Serious AEs D0-D60. All *definitely not related* to study treatment
  - **JE-VAX®** 3 **events for** 3 **subjects**
  - **JE-CV** 4 **events for** 2 **subjects**
  - **No treatment-related SAEs reported from D60 to Month 7**
  - **Five unrelated SAEs were reported from D60 to Month 7**

Conclusions

- Higher immunogenicity in JE-CV
  - **Seroconversion at D60- in those with seronegative at baseline: 99.1% JE-CV vs. 74.8% JE-VAX®**
  - **Seroconversion or increased 4-fold at D60 – 98.1% JE-CV vs. 73.4% JE-VAX®**
- Rapid immune response
  - **93.6% seroconverted 14 days after JE-CV vaccination**
- No safety concerns
  - **Profile consistent with previous reports**
- Fewer AEs reported following one dose of JE-CV + placebo (post D30) than two placebo doses (pre D30)

Pediatric Trials

- **Ongoing pediatric studies Acambis Inc. sponsored study**
  - **H-040-004: Phase II comparative study in India**
- **Sanofi Pasteur sponsored studies**
  - **JEC01: Phase II comparative study in Thailand**
  - **JEC02: Phase III comparative study in Thailand and the Philippines**

H-040-004
Phase II comparative study

- Objectives
  - To evaluate the safety, tolerability and immunogenicity of JE-CV vaccine and inactivated mouse brain JE vaccine
- Country: India
- Age-population: 9 mo to 10 yr old
- Sample size: 96
- JE-CV single dose *vs.* MBDV (KasauliInstitute) 2-dose schedule
- Independent Data Monitoring Committee to monitor safety data
- Status
  - Ongoing (9 mo to 2 yr old group to be completed)
- No data analyzed yet

Two Pivotal Studies in Children

JEC01: Phase II comparative study

- **THAILAND**
- Prof. Arunee Sabchareon (Faculty of Tropical Medicine, Bangkok)
- Assoc. Prof. Kulkanya Chokephaibulkit(SirirajHospital, Bangkok)
- Prof. UsaThisyakorn, Assoc. Prof. Chitsanu Pancharoen(ChulalongkornHospital, Bangkok)

JEC02: Phase III comparative study

THAILAND

- Assoc. Prof. Chitsanu Pancharoen(ChulalongkornHospital, Bangkok)
- Assoc. Prof. Pope Kosalaraksa(Srinagarindhospital, KhonKaen)
- Assoc. Prof. Veerachai Watanaveeradej(Phramongkutklaohospital, Bangkok)
- Prof. SuteeYoksan (CVD Mahidol University)

The PHILIPPINES

- Dr. Maria Rosario Capeding, (Research Institute for Tropical Medicine (RITM), MuntinlupaCity)

JE01: Phase II Controlled Study of the Safety and Immunogenicity

Objective

- To describe the safety of a single dose of JE-CV in comparison to Hepatitis A

- To describe the immune response to JE before and after a single dose of JE-CV

JE-CV vs. Hep. A (cross-over)

- STEP 1: 2-5 yrs old children previously vaccinated with mouse-brain derived JE vaccine

- STEP 2: 12-24 mos old Toddlers previously not vaccinated with a JE vaccine

STEP 2 start after the D14 safety data reviewed of STEP 1 by Safety Review Committee

Immune responses to JE virus strains

- Homologous JE-CV strain

- Wild types and genotypes

JE01: A Controlled Study of the Safety and Immunogenicity of ChimeriVax™-Japanese Encephalitis Vaccine in Thai Toddlers and Children

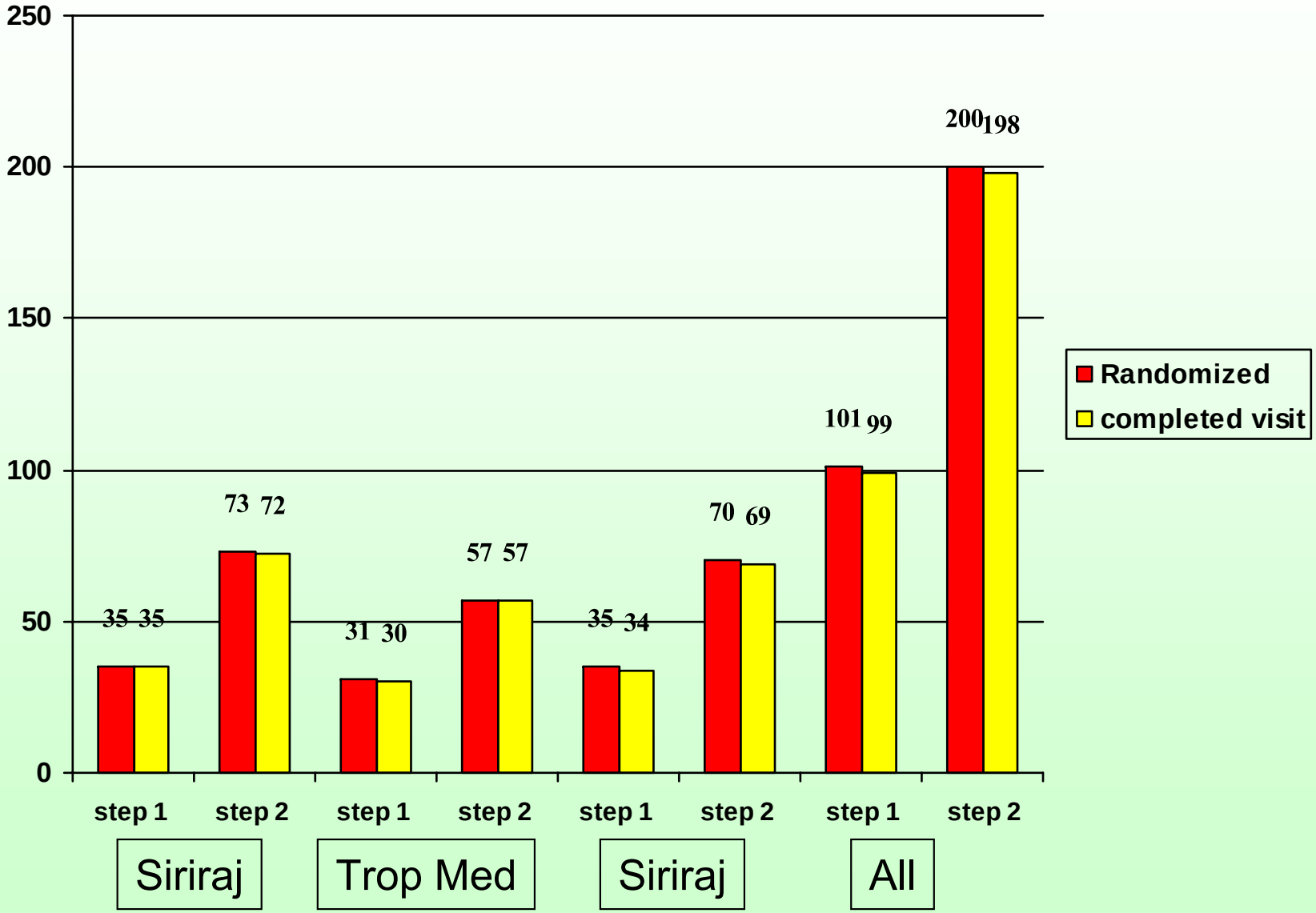
Vaccination	D 0	D 28	D 180
Group 1	JE-CV	HAV1	HAV2
Group 2	HAV	JE-CV	HAV2

Phone D2-7 after vaccination

F/U Visit on Day 0, 4, 15, 43, 56, 180

Check viremia on Day 4 after JE-CV

JE01: Study Enrolment Status, Thailand



JEC01 Investigator's newsletter #4 Aug 2008

Serious Adverse Events Reported Up to Day 56

11 Serious AE reported, all were assessed as not related to the vaccine

Serious AE by organ system		
	JE-CV	HAV
Respiratory	2	6
GI	0	1
Ac febrile ill	0	2

JEC01 Investigator's newsletter #4 Aug 2008

JEC01 Follow-up Study

- A five year long term follow-up for immunogenicity will be implemented in all sites at time of 6 months follow-up visits

JE02: Phase III comparative study

Bridging study between Acambis lot and GPO-MBP lots vs. control group

Objective

- To demonstrate the equivalence of the lot produced by Acambis with the lots produced at GPO-MBP

- To describe the safety

12-18 mos old toddlers previously not vaccinated with a JE vaccine

- Groups 1-3 : GPO-MBP

- Groups 4 : Acambis

- Groups 5 : Hepatitis A

Sample size: 1200

Thailand and The Phillippines

Status: Enrollment completed

What yet to learn

- **Long term protection**

  - need booster dose?

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

Thank You
For Your Attention