

Transfusion transmission of vector-borne flaviviruses

Japanese Encephalitis Virus

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Disclosures

- Received speaker's honoraria from Sanofi-Pasteur for the JE expert exchange meeting 2018, Hong Kong

Outline

- Japanese encephalitis (JE) background
- Transfusion transmitted JE incident in Hong Kong
- Implications for transfusion safety in Asia
- Prevention of transfusion-transmitted JE

Japanese encephalitis virus

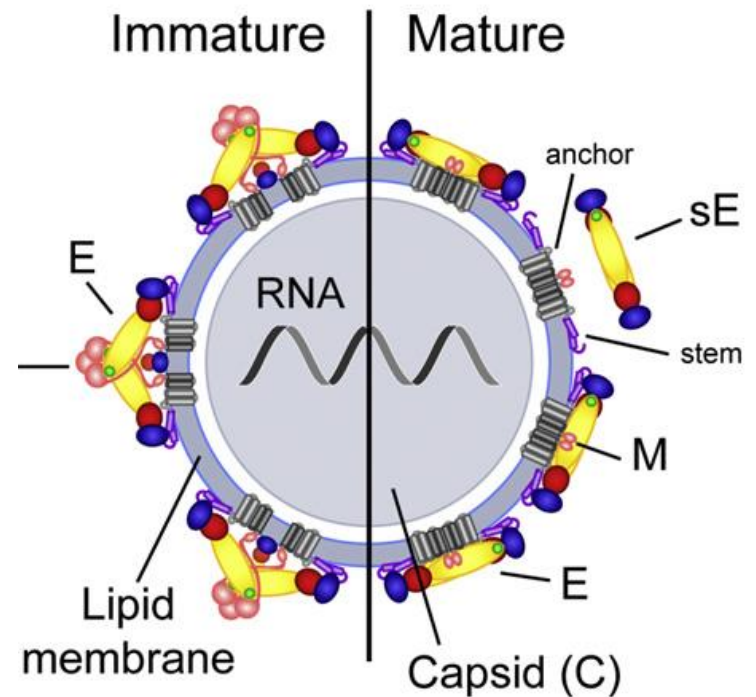
Genus: *Flavivirus*

Enveloped ssRNA virus

Antigenically related to:

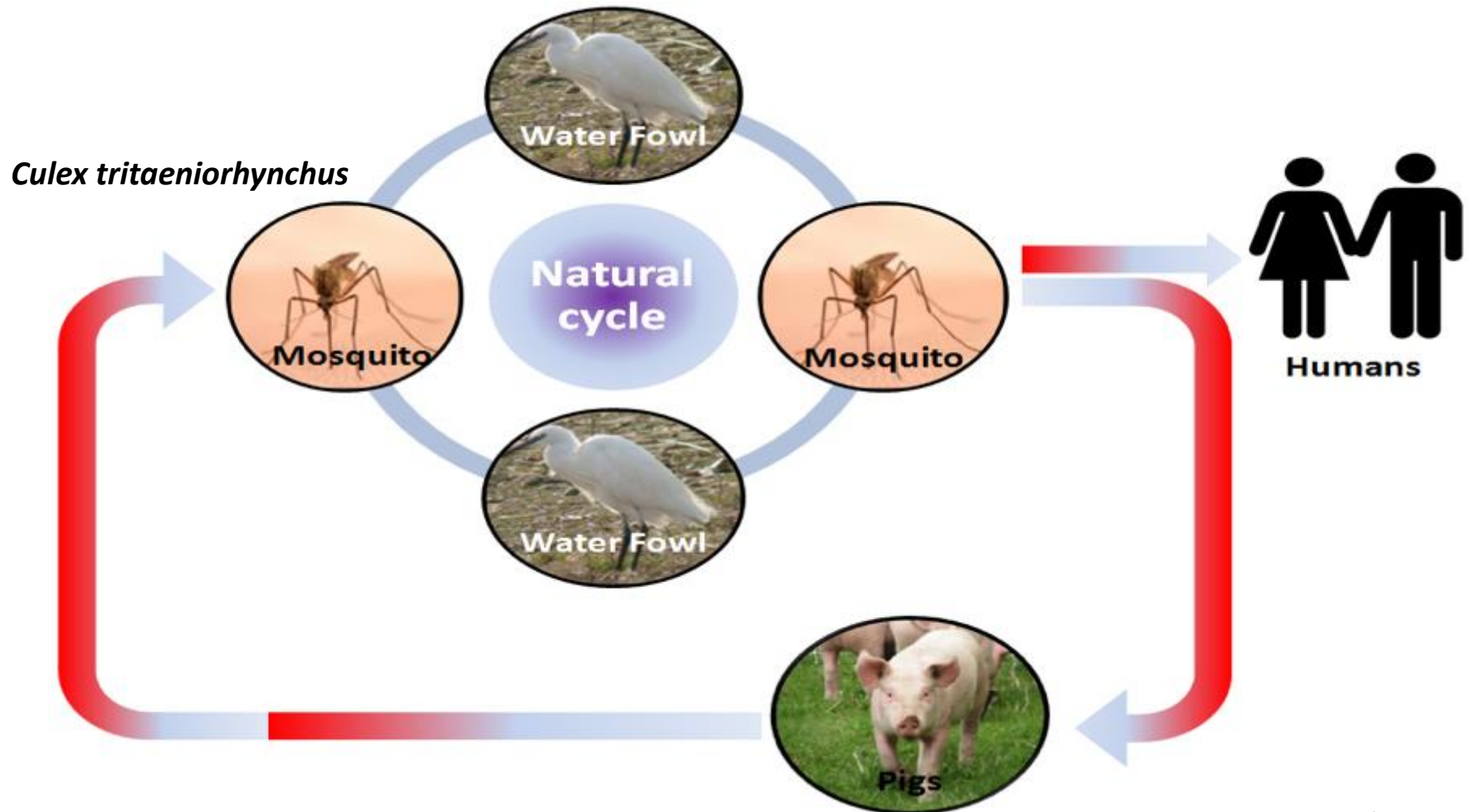
- West Nile virus (WNV)
- Usutu virus
- Murray Valley encephalitis virus
- St. Louis encephalitis virus

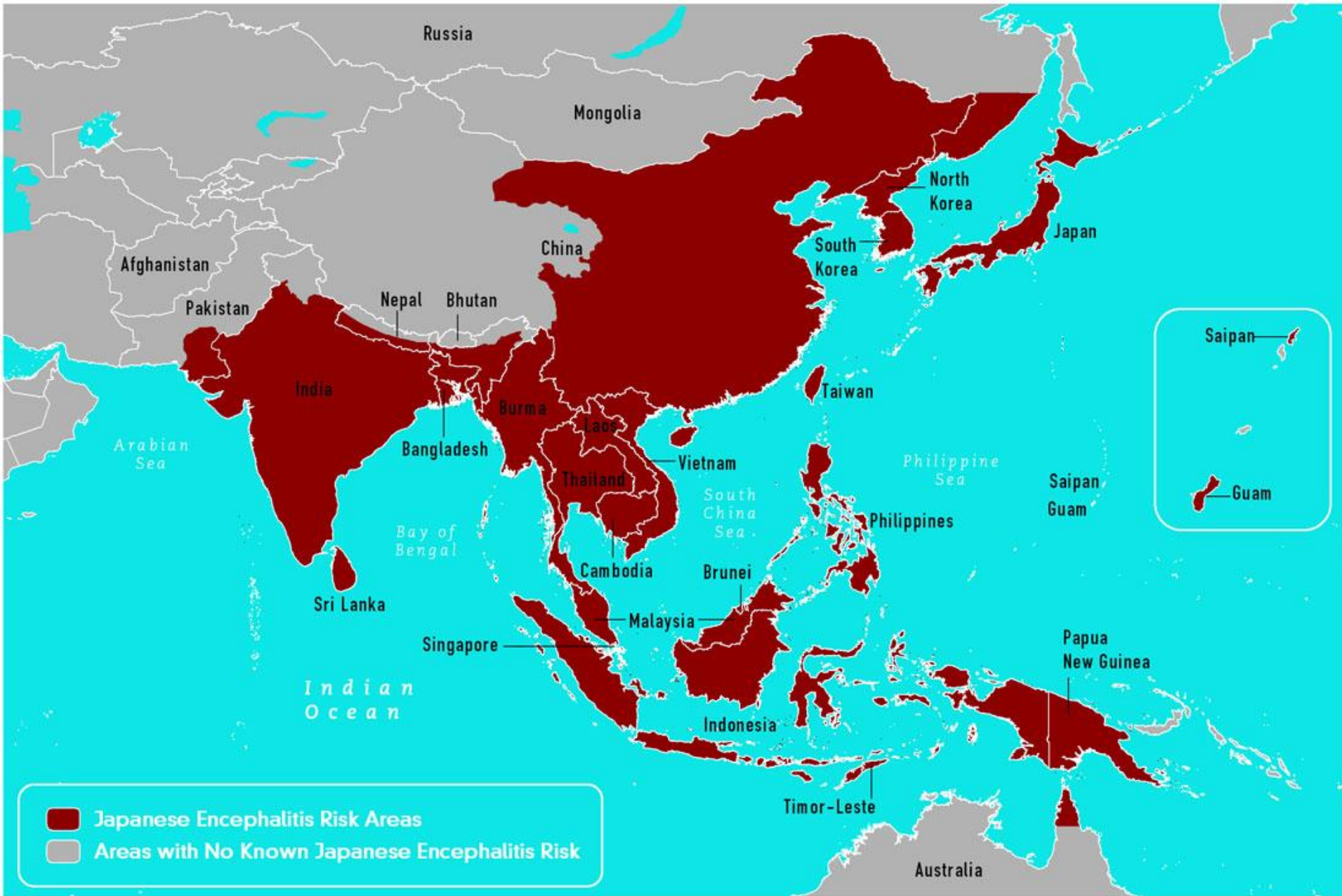
'JE serocomplex'



Heinz et al, 2012

Japanese encephalitis: epidemiology





WHO estimate: ~ 70000 cases per year

US CDC



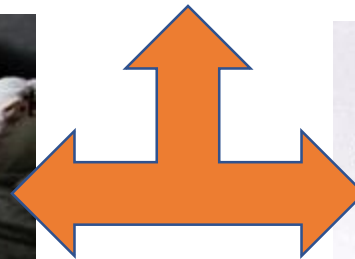


Mai Po marshes

- 90,000 migratory birds
- 380 bird species



43 pig farms



Culex mosquitos

- Low level endemicity (0 – 6 cases/year)
- Sporadic cases concentrated in residential areas close to pig farms
- Universal vaccination not recommended

Clinical Manifestations

- Most infections are asymptomatic (> 99%)
- In endemic areas without universal childhood vaccination, affects children < 15 years

Kari K et al, BMC Med, 2006

- Trend to involve unvaccinated adults in areas with childhood vaccination

Hsu LC et al, PLoS Negl Trop Dis, 2014

Chang YK et al, Am J Trop Med Hyg, 2017

Sunwoo JS et al, Emerg Infect Dis, 2016

- Incubation period: 4-14 days after mosquito bite
- Neuroinvasive with breaching of BBB

Clinical Features

Prodrome (~ 7 days):
fever, myalgia,
headache, anorexia

- Pneumonia
- Stasis ulcers
- UTIs

Encephalitis

- Altered mental status (drowsiness → stupor)
- Personality changes
- Mutism and slurred speech
- Seizures
- Extrapyrimal features
- Autonomic dysfunction (hyperpnea)
- Muscle weakness

10-35% mortality

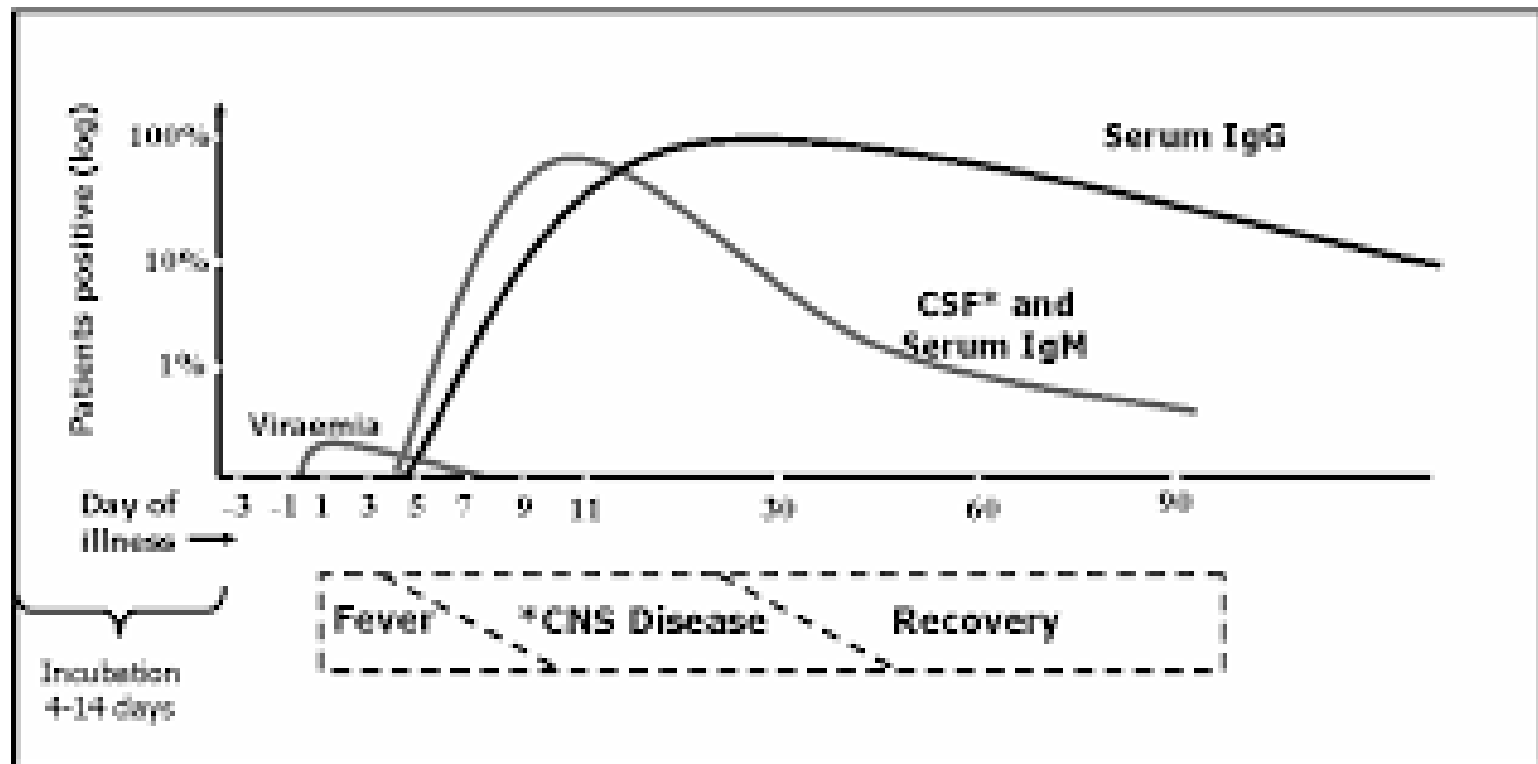
Post-encephalitis

- Movement disorder
- Seizures (EEG abnormalities)
- Behavioral disorders
- Motor weakness/ ataxia
- Blindness

30-50%

Rare cases of clinical
relapse after recovery

Diagnosis



JE Vaccines

S.K. Unni et al. / Microbes and Infection 13 (2011) 312–321

Table 1
List of vaccines against JEV.

S.No.	Vaccine	Company
1	JE-VAX, inactivated mouse brain-derived Nakayama virus	Biken
2	IC-51 (IXIARO), inactivated vero cell-grown SA14–14–2 strain	Intercell
3	Inactivated Vero cell-grown Beijing strain	Biken
4	Live-attenuated PHK cell-grown SA-14-14-2	Chengdu Institute of Biological Sciences
5	ChimeriVax-JE, Live, chimeric SA14 -14-2/Yellow Fever vaccine	Acambis

IXIARO/ JESPECT

- SA-14-4-2 strain grown in Vero cell lines
- Formalin inactivated; aluminum hydroxide adjuvant
- High seroconversion rates (~ 95%)
- 2 doses, 28 days apart
- Also licensed for children > 2 months old

ChimeriVax – JE / IMOJEV

- Live attenuated (Vero)
- YFV 17D strain backbone + SA-14-4-2 derived JEV prM and E genes
- Seroconversion rates > 95%
- Licensed in Australia and Thailand (IMOJEV, THAIJEV)

Hong Kong tackles world's first case of patient contracting Japanese encephalitis through blood transfusion

Globally unprecedented case puts focus on the city's blood donation policy

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COMMENTS:

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RESEARCH

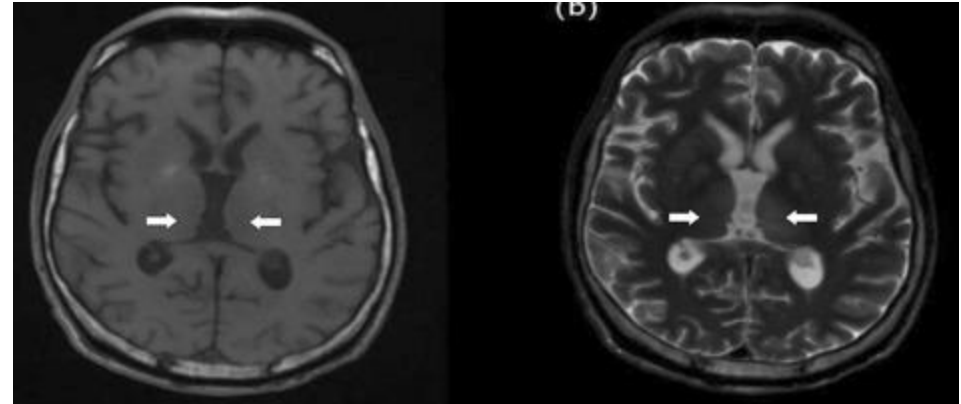
Japanese Encephalitis Virus Transmitted Via Blood Transfusion, Hong Kong, China

Vincent C.C. Cheng,¹ Siddharth Sridhar,¹ Shuk-Ching Wong, Sally C.Y. Wong, Jasper F.W. Chan, Cyril C.Y. Yip, Chi-Hung Chau, Timmy W.K. Au, Yu-Yan Hwang, Carol S.W. Yau, Janice Y.C. Lo, Cheuk-Kwong Lee, Kwok-Yung Yuen

¹These authors contributed equally to this article.

The patient

- 52 year old man with severe chronic obstructive pulmonary disease
- Underwent **lung transplantation** on May 10, 2017
- Post-operatively complicated by pneumonia requiring continuous hospitalization
- Taking tacrolimus, prednisolone and mycophenolate mofetil
- Developed fever, rash and decreased consciousness on July 6, 2017
- Progression to confusion and myoclonus



Lumbar puncture:-

CSF cell count of $20 \times 10^6/L$

Lymphocyte predominant

CSF protein elevated to 1.61 g/L

HSV, VZV, EV PCR negative

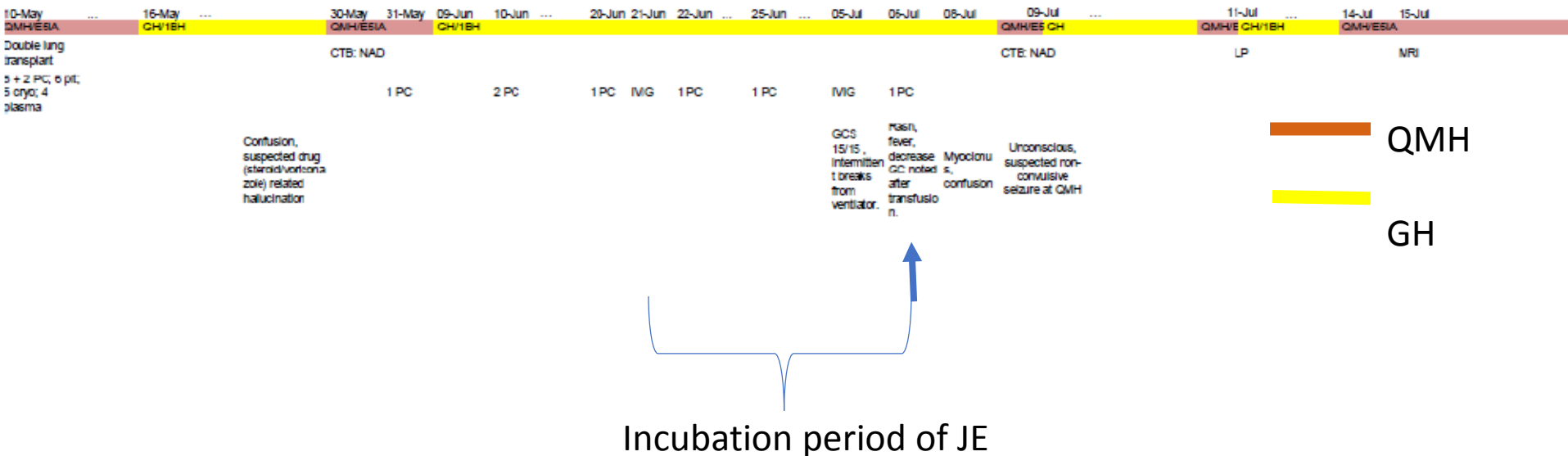
Cryptococcal Ag negative

AFB smear, TB PCR negative

CSF JEV IgM: **POSITIVE**

CSF JEV PCR, Plasma JEV PCR, BAL JEV PCR : **POSITIVE**

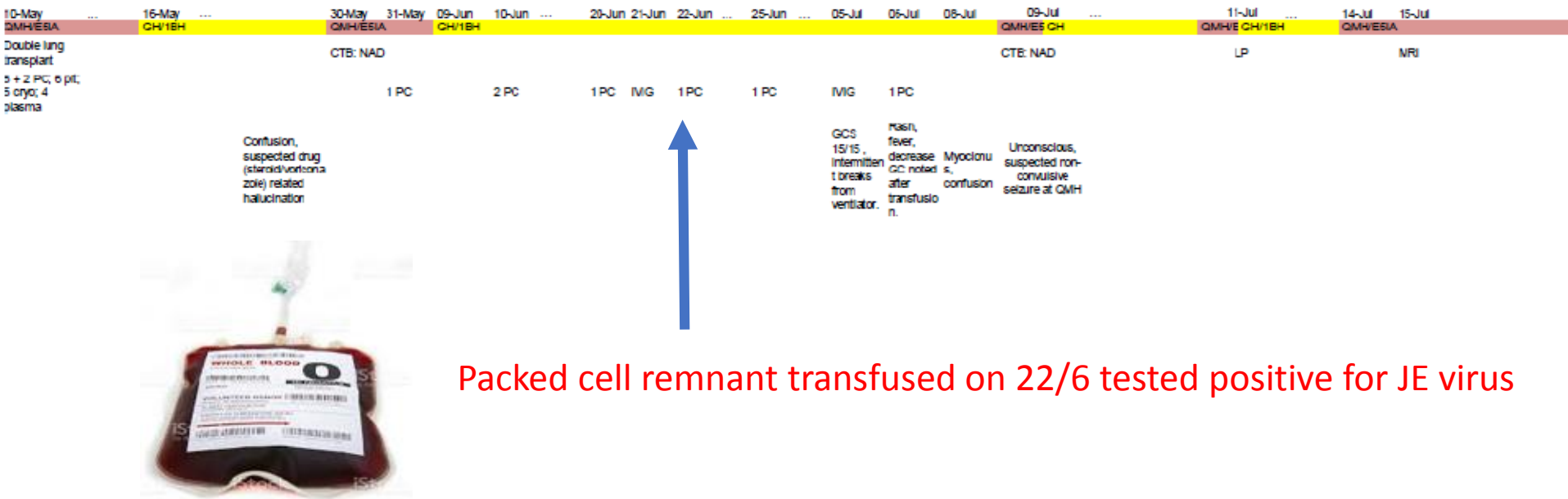
Gantt chart of the index case



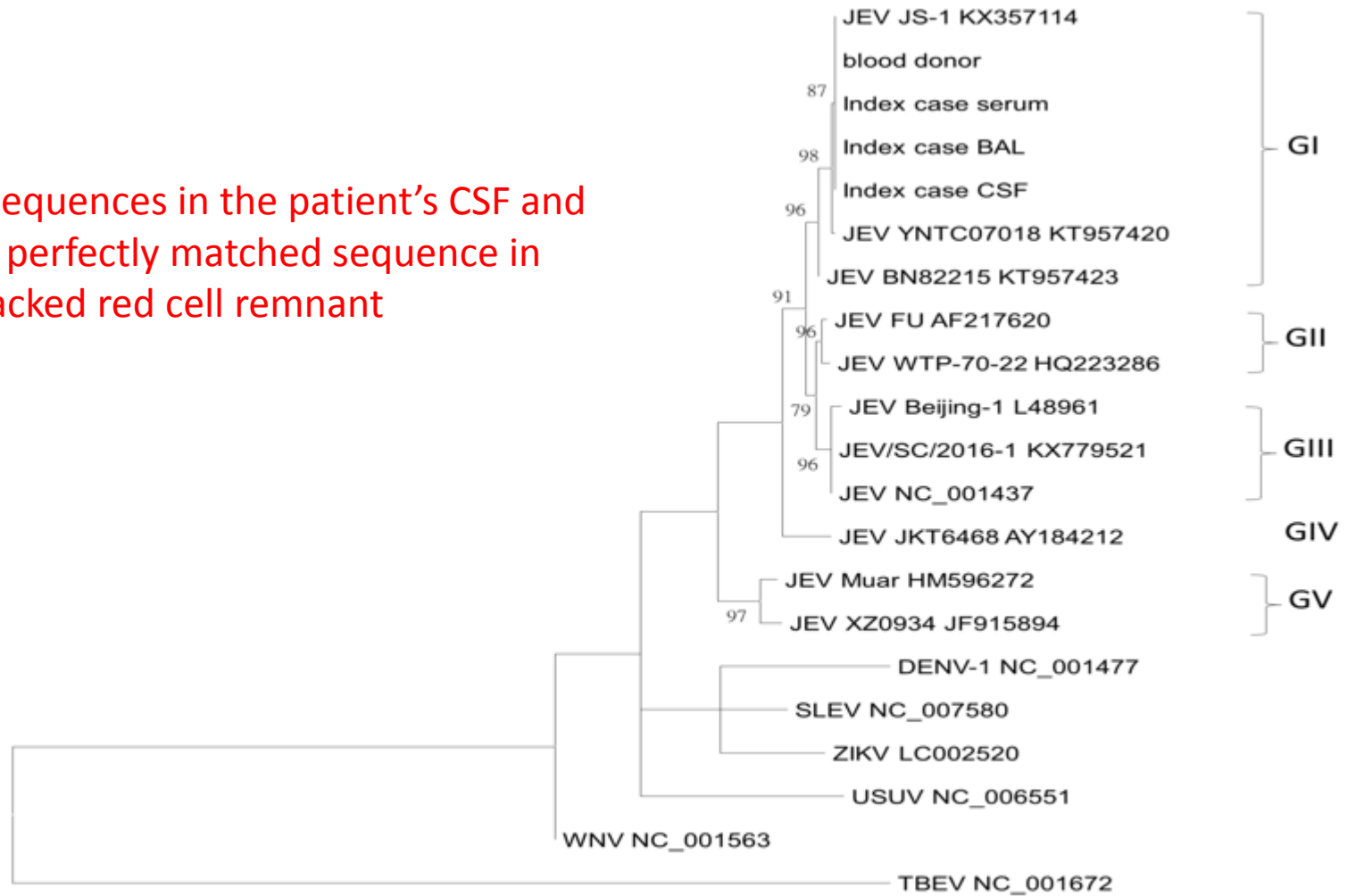
- Mosquitos in hospital wards? Unlikely, because he was nursed in air-conditioned wards all along
- Transmission by organ donation? ~ 2 months since transplantation, other organ recipients healthy
- Transmission by blood products?

? Transmission by blood transfusion

Retrieve residual blood products for testing



Viral sequences in the patient's CSF and blood perfectly matched sequence in the packed red cell remnant



- Blood donor was a 46 year old man
- Living in an area with proximity to pig farms
- Completely asymptomatic

M/46
(blood donation on 29th May 2017)



M/61

Acute myeloid leukemia
Platelet transfusion
on 2nd June 2017

Anti-JEV IgM: -ve
(25th May 2017)

Anti-JEV IgM: +ve
(5th July & 22nd July 2017)

Asymptomatic
seroconversion

M/52

Double lung transplant
recipient
Red cells transfusion
on 22nd June 2017

Anti-JEV IgM: -ve
(31 May 2017)

Anti-JEV IgM: +ve
(15 & 18th July 2017)

Symptomatic infection

M/64

Intracranial hemorrhage
Plasma transfusion
on 20th June 2017

Patient died on 4th July 2017 for
respiratory failure

Infection of JEV:
not confirmed

JE can be transmitted via transfusion of blood products

Follow-up actions

Communication:

- Family of index case patient
- Secondary case patient
- Risk communication to public
- Encouragement to public to keep donating blood

Public health action:

- Active case finding
- Vector control around the donor's area of residence

Blood product safety: conclusion of the HK RC-BTS

- Likely to be a rare and isolated incident
- Continuous surveillance for further cases of JE in HK

How common is transfusion-transmitted JE in Asia?

High endemicity areas with nascent vaccination programs

- Many acquire immunity by adulthood → blood pool less likely to be contaminated
- Adult recipients have degree of protection against transfusion transmitted disease
- Difficult to differentiate community acquired from transfusion transmitted JE

Lopez AL et al, PLoS Negl Trop Dis, 2015

Lee EJ et al, PLoS One, 2016

Intermediate/ low endemicity areas with established vaccination programs

- Mass vaccination for children in many of these areas; unvaccinated adults at highest risk
- Annual incidence of JE ~ 0.1 / 100,000 → incidence of JEV infection ~ 1/10,000

Zheng Y et al, Rev Med Virol, 2012

Hsu LC et al, PLoS Negl Trop Dis, 2014

- Possibility of donating contaminated blood; lack of protective antibodies among recipients
- Probability of symptomatic JE in recipients ~ 1/million

TABLE 1. Factors that could influence the infectivity of a transfusion

Viral factors

Viral load

Viral genotype/clade

Genome mutations

Ratio of detectable nucleic acid equivalents to infectious particles

Stage of viral infection (acute vs. chronic)

Binding of virus to endogenous neutralizing antibodies

Diminishing viral replicative capacity with component storage

Donor factors

Stage of infection

Presence of antibody to the agent

Transfusion factors

Transfusion of other components with neutralizing antibody

Blood component being transfused (see below)

Product factors

Specific component (eg RBCs or FFP)

Storage duration of RBCs

Patient related factors

Existing immunity through natural infection or vaccination (HBV)

Lack of viral receptors (i.e., resistance to infection)

Degree of immunosuppression

Body weight and/or blood volume

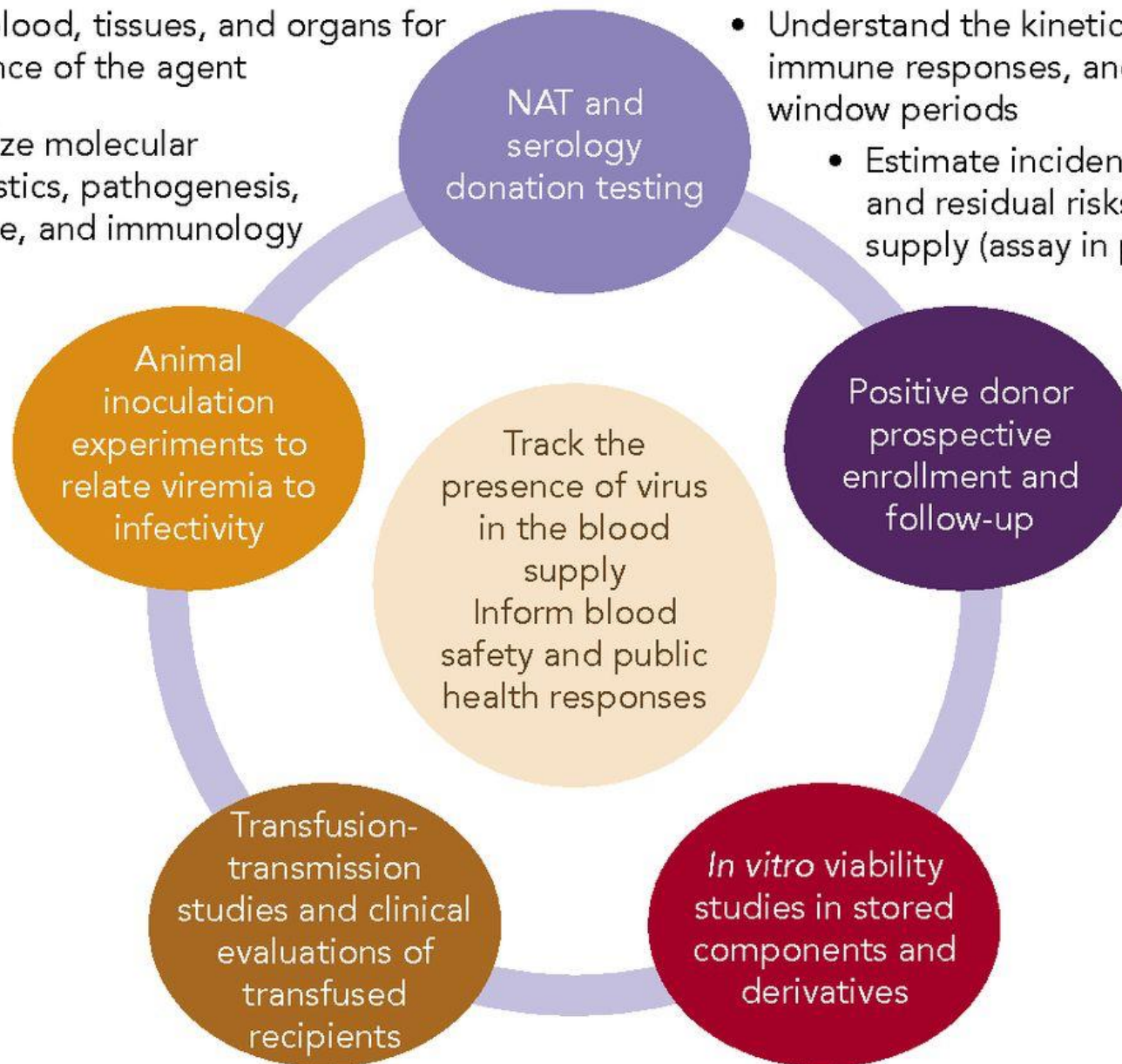
Adapted from Kleinman et al.⁴

FFP = fresh frozen plasma; HBV = hepatitis B virus.

Factors affecting transmission and symptoms

- Prolonged viremia among asymptomatic donors?
- Immunosuppression → ? Higher risk of symptomatic JE
- Transfusion transmitted JE → ? Higher rate of symptomatic infection
- Which product?
 - Both cellular and acellular blood fractions probably infectious
 - JEV capable of hemagglutinating red cells, ? accumulate in the red cell fraction

- Evaluate blood, tissues, and organs for the presence of the agent
- Characterize molecular characteristics, pathogenesis, persistence, and immunology



- Understand the kinetics of viremia, immune responses, and assay-specific window periods
 - Estimate incidence, prevalence, and residual risks for the blood supply (assay in place)

- Build repositories and tools for the wider scientific community
- Evaluate transfusion-transmission rates
- Understand the pathogenesis of the infection and disease outcomes

Possible preventive measures

Measures	Cons
Donor screening questionnaires Post-donation product quarantine	Majority of infections are asymptomatic
Donor exclusion based on residence/ work close to pig farms	Restriction of donor pools
Seasonal restriction of donors from high-risk areas during rainy season	Intermittent year-round rainfall
JEV NAT - IDT - Seasonal IDT - Targeted IDT - MPT	No high-throughput commercial test Challenges with evaluation and EQA
Pathogen reduction	Applicable to plasma and platelets, but not RBC

DONOR INFECTIOUS DISEASE TESTING

Evaluation of a new West Nile virus nucleic acid test for screening of blood donations

TABLE 2. Cultured isolates of WNV flavivirus variants

Sample dilution	% Reactive (reactive/valid replicates tested)			
	JEV	SLEV	MVEV	KUNV
1:1.00E+02	100% (8/8)	100% (4/4)	100% (4/4)	100% (4/4)
1:1.00E+03	100% (8/8)	100% (4/4)	100% (4/4)	100% (4/4)
1:1.00E+04	100% (8/8)	100% (4/4)	100% (4/4)	100% (4/4)
1:1.00E+05	100% (8/8)	100% (4/4)	100% (4/4)	100% (4/4)
1:1.00E+06	100% (8/8)	100% (4/4)	100% (4/4)	100% (4/4)
1:1.00E+07	100% (8/8)	100% (4/4)	100% (4/4)	100% (4/4)

JEV = Japanese encephalitis virus; SLEV = St. Louis encephalitis virus; MVEV = Murray Valley encephalitis virus; KUNV = Kunjin virus; WNV = West Nile virus.

Cobas WNV test for use on the Cobas 6800/8800 system

Stanley J et al, Transfusion, 2019

Moving towards pan-JE serocomplex NAT?

Pathogen removal/ inactivation

Plasma

- Ethanol precipitation
- Solvent/ detergent treatment
- Heat treatment
- Nanofiltration
- Chromatography
- Low pH treatment
- Commercial platforms

Cellular blood products

- Leucodepletion
- UV-C irradiation
- Riboflavin/ UVA
- Amotosalen/ UVA
- Amustaline/ glutathione

Laughunn A et al, Transfusion, 2018

Aubry M et al, Transfusion, 2017

Laughunn A et al, Transfusion, 2017

Summary

- JEV is a newly identified potential threat to transfusion safety in Asia
- Strategies for control:
 - Vaccination campaigns for at-risk groups
 - Ongoing surveillance for transfusion transmitted JE in endemic areas
 - Move towards development of pan-JE serocomplex NAT for blood donation screening
 - Implementation of PRT and evaluation of efficiency of existing platforms for clearing JEV
- Caution with potential blood donors with recent travel to JE endemic regions, especially if:
 - Travel to rural areas in the rainy season
 - No JE vaccination

Thank You