Japanese Encephalitis: Prevention Through Vaccination

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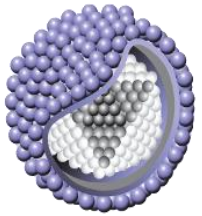
Outline

- Introduction: Epidemiology, Disease and Sequelae
- Prevention: Role of Vaccination
- Vaccines against JE; SP Chimeric Vaccine
- Conclusions

Japanese encephalitis



- Leading cause of viral encephalitis in Asia
- Transmitted mainly by the mosquito *Culex tritaeniorhynchus*
- Around 60,000 cases are estimated to occur each year resulting in at least 15,000 deaths
- 3 billion people (including 700,000 children) live in JE areas.

Geographic Distribution of JE, 2012

MMWR / August 23, 2013 / Vol. 62 / No. 33

Clinical Features

- Less than 1% of people infected develop clinical illness.
- incubation period is typically 5-15 days.
- Symptoms: fever, headache, and vomiting. mental status changes, neurologic symptoms, weakness, and movement disorders
- Seizures are common, especially among children.
- No specific treatments have been found to benefit patients with JE, but hospitalization for supportive care and close observation is generally required.

US CDC

Prognosis and Long-term Sequelae

1–20 per 1,000 of infected individuals [1, 2]
Develop encephalitis

of these…

20–30%	**70–80%**
Will die	**Survive**

of survivors…

50%	**50%**
Escape serious disability	**Left with severe disability**

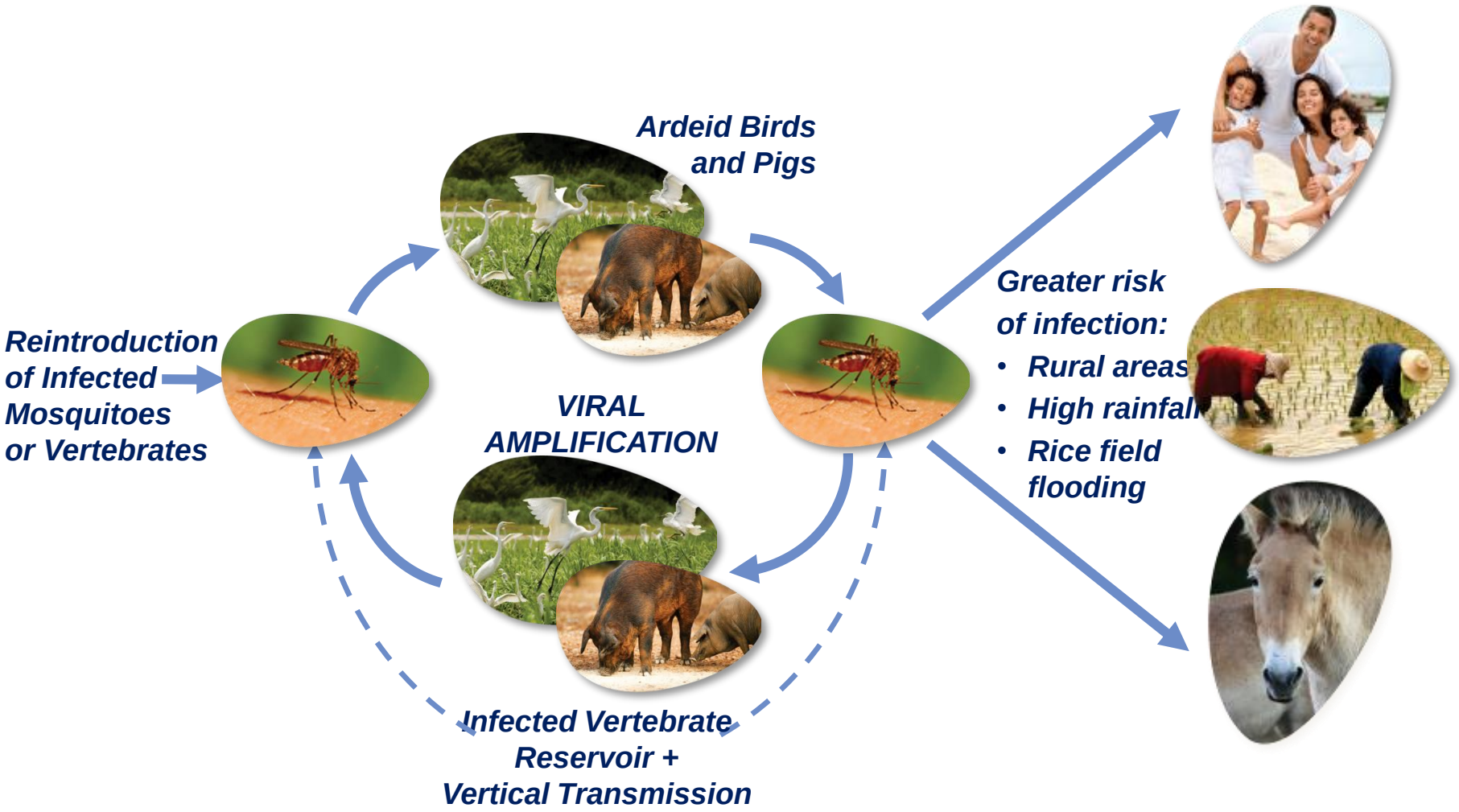
30% Develop significant motor deficits
20% Have convulsions
20% Suffer severe cognitive/language problems

of those escaping serious disability…

50% Develop learning difficulties, behavioral problems and more subtle neurological signs

1. Misra (2010) 6. Diagana (2007), 2 Solomon (2000)

Disease Transmission



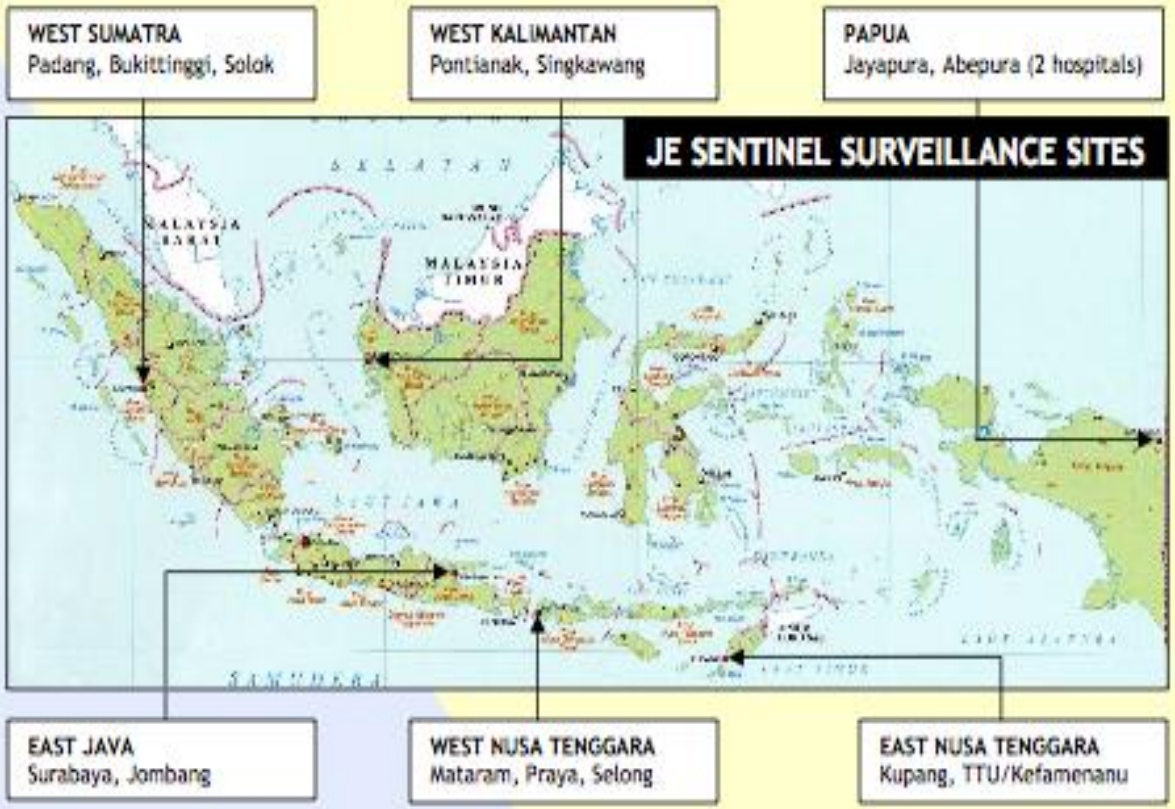
Adapted from ref 3: Misra U & Kalita. J. (2010)

Burden of Disease Often Underestimated

- Laboratory methods of detection not readily available in many Asian settings
- Wherever and whenever it is looked for, JE eventually is recognized as the leading cause of viral encephalitis in Asian countries with varying age-specific estimates [1, 2]
- ~ 67 900 JE cases typically occur annually in the 24 JE-endemic countries, for an incidence of 1.8 per 100 000 overall. ~51 000 (75%) of these cases occur in children aged 0–14 years, which gives an estimated overall annual incidence of 5.4 per 100000 in this age group. [3]

1. Olsen S, et al. Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 21, No. 2, February 2015 2. Komang Kari et al. *BMC Medicine* 2006, **4**:8 3. Campbell G et al. Bull World Health Organ 2011;89:766–774E

Japanese Encephalitis (JE) Surveillance in Indonesia:
Project Activities and Results (February 2007)



Cases of confirmed JE* (2005 -2006)

Province	Confirmed JE cases
West Sumatra[1]	2
West Kalimantan[3]	31
East Java[1]	8
West Nusa Tenggara - Lombok[2]	26
East Nusa Tenggara - West Timor[3]	11
Papua[2]	4
Total	82

** Only 50% cases had a convalescent specimen, so some J positive cases are likely to have been missed.*
[1]Low risk [2]Moderate or mixed risk [3]High risk.

Geographic distribution of reported JE cases in the Philippines

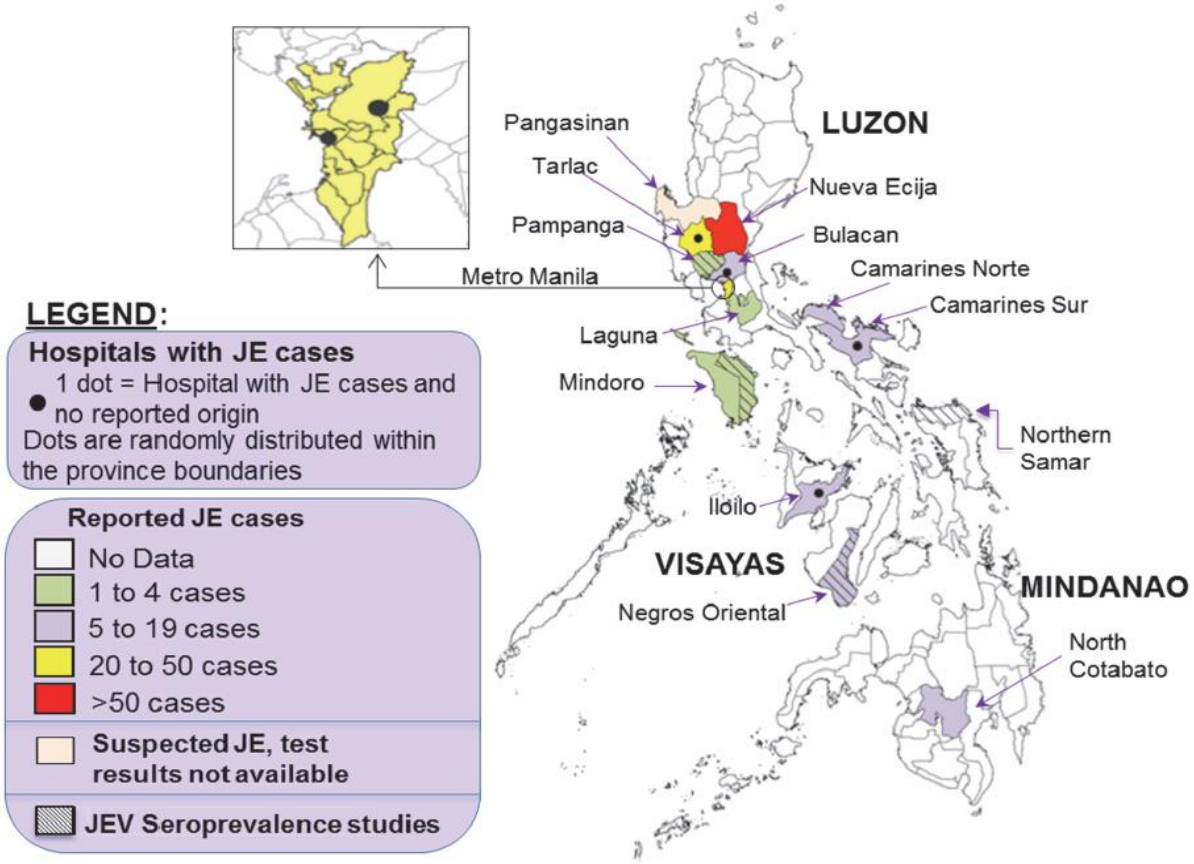


Fig 2. Geographic distribution of reported JE cases, suspected JE cases and seroprevalence surveys in the Philippines, by province. Data from published reports and presentations, 1958–2013. Some reports did not specify origin of cases; in these cases, location of the hospital was mapped (black dots). The number of reported JE cases may have been biased by factors other than the incidence of JE. The preference for certain study sites and duration of studies may have unduly increased the number of cases in some provinces. There were additional cases with no detailed residence information: 28 cases in Luzon and 7 cases in Visayas. A seroprevalence survey was also conducted in Manila, but obscured by overlapping black dot for hospital.

Lopez AL. et.al. Epidemiology of Japanese Encephalitis in the Philippines: A Systematic Review. PLOS Neglected Tropical Diseases. DOI:10.1371/journal.pntd.0003630. March 20, 2015

Presence of JEV in the amplifying hosts and circulation of the infected

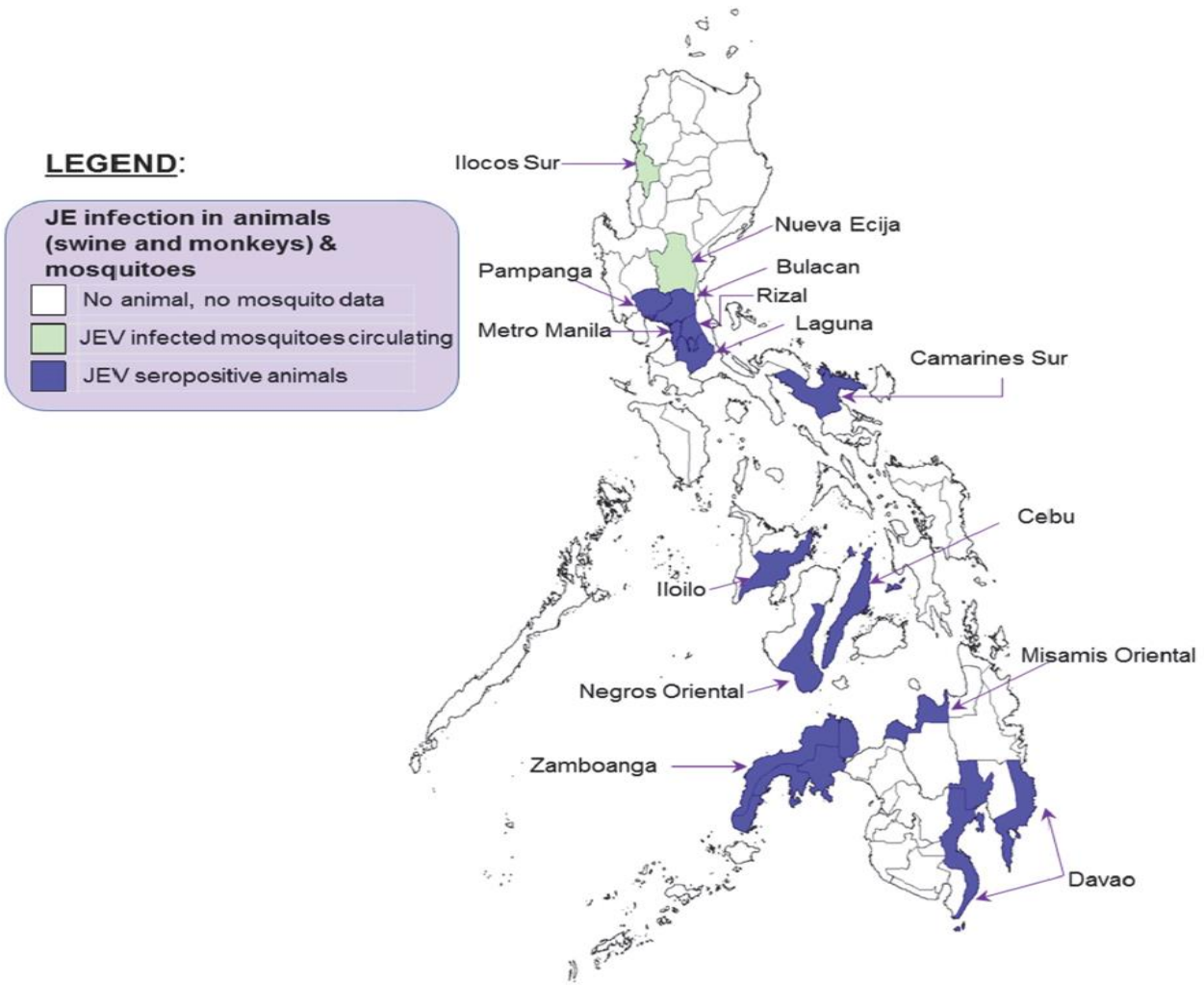


Fig 3. Geographic distribution of animal and mosquito studies in the Philippines, 1958–2012.

Lopez AL. et.al. Epidemiology of Japanese Encephalitis in the Philippines: A Systematic Review. PLOS Neglected Tropical Diseases. DOI:10.1371/journal.pntd.0003630. March 20, 2015

JE is present in all regions of the Phils

Fig 6. Geographic distribution of suspected and confirmed JE cases in the Philippines. Data from surveillance and referral testing, January 2011 to March 2014. There were additionally 21 confirmed JE cases out of 159 cases referred by hospitals in Metro Manila without available data on geographic origin.

Lopez AL. et.al. Epidemiology of Japanese Encephalitis in the Philippines: A Systematic Review. PLOS Neglected Tropical Diseases. DOI:10.1371/journal.pntd.0003630. March 20, 2015

Age distribution of suspected and confirmed JE cases, Philippines

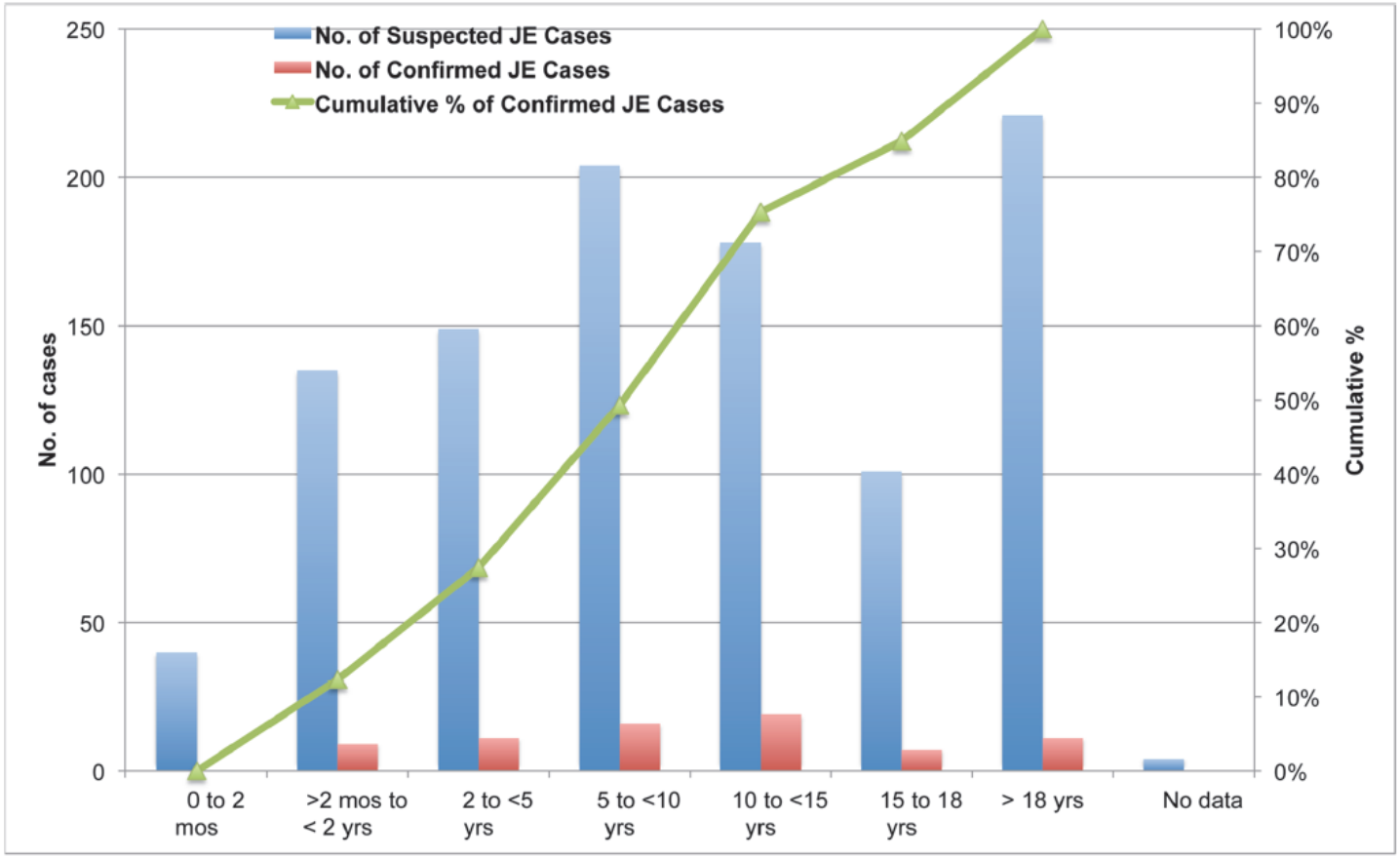


Fig 5. Age distribution of suspected (n = 1032) and confirmed (n = 73) JE cases and cumulative percentage of confirmed JE cases, January 2011 to March 2014. Suspected JE cases include simple line listing of AES cases without laboratory confirmation, case-based sentinel surveillance for JE with laboratory confirmation and clinician referred specimens for testing to RITM.

Lopez AL. et.al. Epidemiology of Japanese Encephalitis in the Philippines: A Systematic Review. PLOS Neglected Tropical Diseases. DOI:10.1371/journal.pntd.0003630. March 20, 2015

Conclusions on the Epidemiology of Japanese Encephalitis in the Philippines: A Systematic Review

- Japanese encephalitis constitutes a **significant public health burden in all regions of the Philippines**, and
- Supports the **inclusion of JE vaccine in the national immunization program**
- The lack of reported AES cases as well as JE cases in some provinces suggests a weakness in disease surveillance rather than the absence of disease

Control of JE: Possible Mechanisms

- Farm management (intermittent irrigation, pig farming practices
- Economic development (health care provision, housing location)
- Enzootic life cycle management (mosquito avoidance, pig vaccination, human vaccination)

… control is only achievable through multiple strategies; among them, human vaccination is the most practical and effective method of control *

Erlanger (2009).

*WHO (2006).

Public Health Consideration

The WHO encourages the use of JE vaccine as the single most effective preventive measure.

•Vaccination must be maintained to preserve a low level of incidence

•According to the WHO, JE vaccination should be extended to all areas where JE is a demonstrated public health problem

•The WHO consider the use of attenuated vaccine as an attractive method

•Guidelines recommend JE vaccination for travelers to endemic areas

•Geographical Japanese Encephalitis spread is a phenomenon that can’t be ignored

Impact of JE Vaccines in Japan and Korea

Country	JE Incidence rate/100,000 (1955-1966)	JE Incidence rate/100,000 (1990-2000)	Per cent reduction
Japan	2.5	0.01	99.6
Korea	7.3	<0.01	99.9

http://www.path.org/vaccineresources/files/JE_Reduction_and_Control_by_2015

Recent rates of JE in selected countries with presumed controlled JE

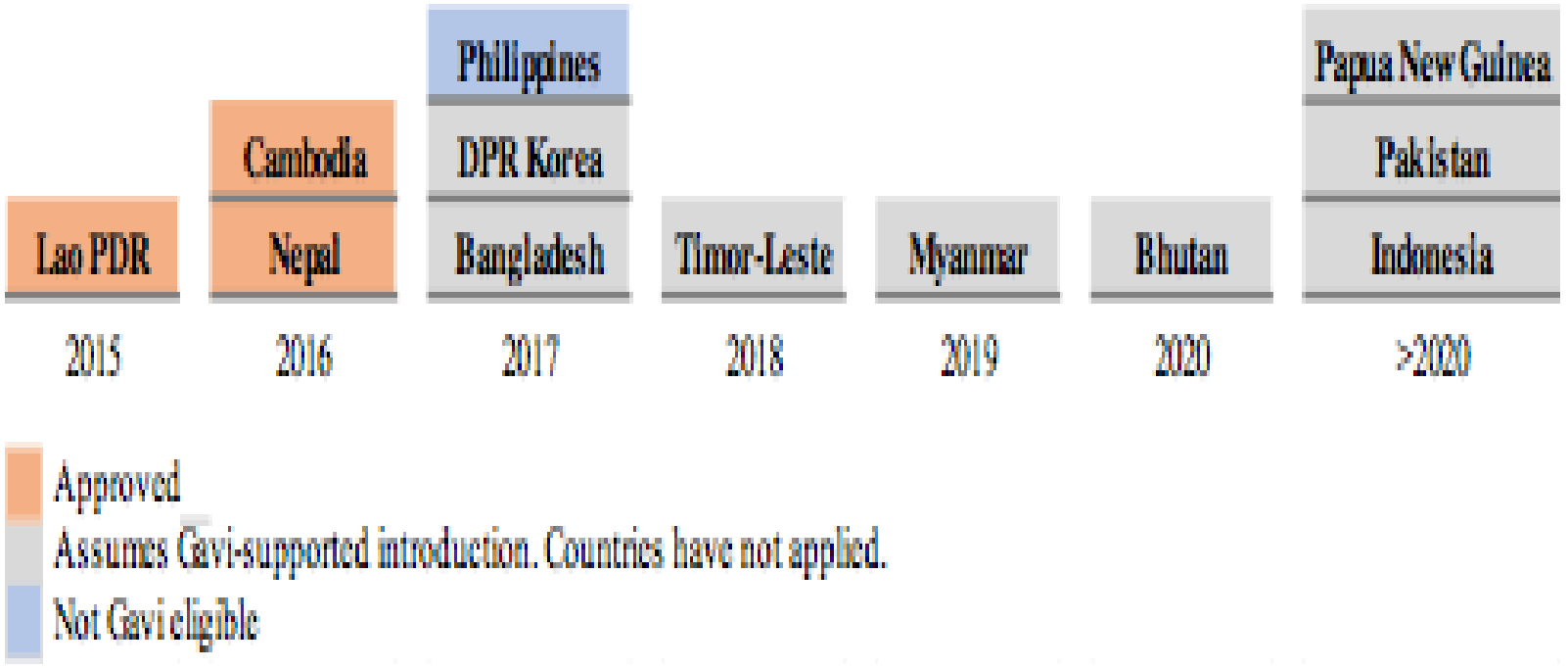
Country	No. of cases (years)	Rate in total population/100,000
Australia/Torres Strait Islands	0 (2001-2006)	0
Japan	5.5. average (range 1-7/yr) (2000-2005)	0.004
Republic of Korea	2.3 average (range 0-6/yr) (2001-2006)	0.005
Chinese Taipei	29 (2006)	0.12
Sri Lanka	28 average (range 18-39/yr) (2006-2008)	0.14
Thailand	43 (2007)	0.07

http://www.path.org/vaccineresources/files/JE_Reduction_ontrol_by_2015

Characteristics of JE immunization programs

Country	JE immunization program	Strategy	Scheduled age to begin routine immunization	Vaccine used
Australia*	Targeted risk areas†	Routine	12 mos	MB§
Bangladesh	None	—	—	—
Bhutan	None	—	—	—
Brunei Darussalam	None	—	—	—
Burma (Myanmar)	None	—	—	—
Cambodia	Subnational¶	Routine	10 mos	LAV
China	National**	Routine	8 mos	LAV, VC
Taiwan	All areas	Routine	15 mos	MB
India	Risk areas††	Routine	16–24 mos	LAV
Indonesia	None	—	—	—
Japan	National	Routine	36 mos	VC
Laos	None	—	—	—
Malaysia	Subnational	Routine and outbreak response§§	9 mos	MB
Nepal	Subnational***	Routine	12 mos	LAV
North Korea	N/A¶¶	N/A	N/A	N/A
Pakistan	None	—	—	—
Papua New Guinea	None	—	—	—
Philippines	None	—	—	—
Russia*	None	—	—	—
Singapore	None	—	—	—
South Korea	National	Routine	12–24 mos	MB
Sri Lanka	National	Routine	9 mos	LAV
Thailand	National	Routine	18 mos	MB
Timor-Leste	None	—	—	—
Vietnam	Subnational†††	Annual campaign	12 mos	MB

GAVI Estimate: Unconstrained JE Vaccine Introductions 2015-2020



Source: Gavi SDF v10.

2015 Childhood Immunization Schedule

VACCINES FOR SPECIAL GROUPS

Vaccines for Special Groups include:
- Japanese Encephalitis Vaccine (JE Vaccine)
- Cholera Vaccine
- Meningococcal Vaccines(MCV4/MPSV4)
- Typhoid Vaccine
- Rabies Vaccine
- Pneumococcal Vaccine (PCV/PPV)

JAPANESE ENCEPHALITIS VACCINE (JE VACCINE)
Given subcutaneously (SC)
Given at a minimum age of 12 months
Indicated for populations residing in or travelling to geographic risk areas as defined by health authorities
The minimum age is 12 months
Children 1-17 years of age should receive 1 primary dose followed by a booster dose after 12-24 months
Individuals 18 years and older should receive a single dose

CHOLERA VACCINE
Given per orem (PO)
Given at a minimum age of 12 months as a 2 dose series 2 weeks apart.
Recommended for outbreak situations and natural disasters as declared by health authorities

MENINGOCOCCAL VACCINES (MCV4/MPSV4)
Given intramuscularly (IM) or subcutaneously (SC).
Tetravalent meningococcal (ACYW-135) conjugate vaccine MCV4-D, MCV4-TT and MCV4-CRM given intramuscularly (IM).
Tetravalent meningococcal polysaccharide vaccine (MPSV4) given SC/IM.
Dosing schedule:
- MCV4-D, minimum age is 9 months. For children 9-23 months, give 2 doses, 3 months apart. For children 2 years and above give 1 dose.
- MCV4-TT given to children 12 months and above as a single dose.
- MCV4-CRM given to children 2 years and above as a single dose.
- Revaccinate with an MCV4 vaccine every 5 years as long as the person remains at increased risk of infection
- MPSV4 given to children 2 years and above as a single dose. If MPSV4 is used for high risk individuals as the first dose, a 2nd dose using MCV4 should be given 2 months later.
- Booster doses of MPSV4 are not recommended.

Indicated for those at high risk from invasive disease: persistent complement deficiencies, anatomic/ functional asplenia, HIV, travelers to or residents of areas where meningococcal disease is hyperendemic or epidemic; or belonging to a defined risk group during a community or institutional meningococcal outbreak.

TYPHOID VACCINE
Given intramuscularly (IM)
Given at a minimum age of 2 years old with revaccination every 2-3 years
Recommended for travellers to areas where there is risk of exposure and for outbreak situations as declared by public health authorities

RABIES VACCINE
Given intramuscularly or intradermally (IM/ID)
Recommended regimens for Pre-exposure Prophylaxis:
- Intramuscular regimen: PVRV 0.5 ml or PCECV 1 ml given on days 0, 7, 21 or 28.
- Intradermal regimen: PVRV or PCECV 0.1 ml given on days 0, 7, 21 or 28.

A repeat dose should be given if the vaccine is inadvertently given subcutaneously.
Rabies vaccine should never be given in the gluteal area since absorption is unpredictable.
Periodic booster doses in the absence of exposure are not recommended for the general population.
In the event of subsequent exposures, those who have completed 3 doses of pre-exposure prophylaxis regardless of interval between exposure and last dose of the vaccine, will require only booster doses on day 0 and 3. Booster doses may be given IM (0.5 ml PVRV or 1 ml PCECV) or ID (0.1 ml PVRV or PCECV). There is no need to give rabies immune globulin.

PNEUMOCOCCAL VACCINES (PCV/PPV)
Given intramuscularly (IM)
For children >2 years with high risk conditions*:
- Without any pneumococcal vaccination: administer 1 dose of PCV13 followed by a dose of PPV at least 8 weeks later
- With previous PCV, without PPV vaccination: give 1 dose of PPV at least 8 weeks after the most recent dose of PCV
- With previous PPV, without PCV: give 1 dose of PCV13 at least 8 weeks after the most recent dose of PPV

A single revaccination with PPV should be administered 5 years after the first dose to children with high risk medical conditions*.

*High risk medical conditions include chronic heart disease (cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy); diabetes mellitus; cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; HIV infection; chronic renal failure; nephrotic syndrome; treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin's disease; solid organ transplantation; or congenital immunodeficiency.

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JE vaccines

Platform	Strain used	Type	Considerations
Mouse brain culture	Beijing-1 Nakayama	Inactivated	Limited duration of protection; multiple doses; higher reactogenicity
Primary hamster kidney	SA-14-14-2	Live attenuated	Longer duration of protection; fewer doses
Vero cell culture	Beijing-1 P-3 Kolar (JEV821564-XY) SA-14-14-2	Inactivated	Duration of protection in endemic areas unknown; multiple doses
Vero cell culture	SA-14-14-2/YF17D	Live recombinant	Longer duration of protection expected; fewer doses

Source: WHO

Chimeric Vaccine Technology

Live Attenuated Recombinant Vaccine

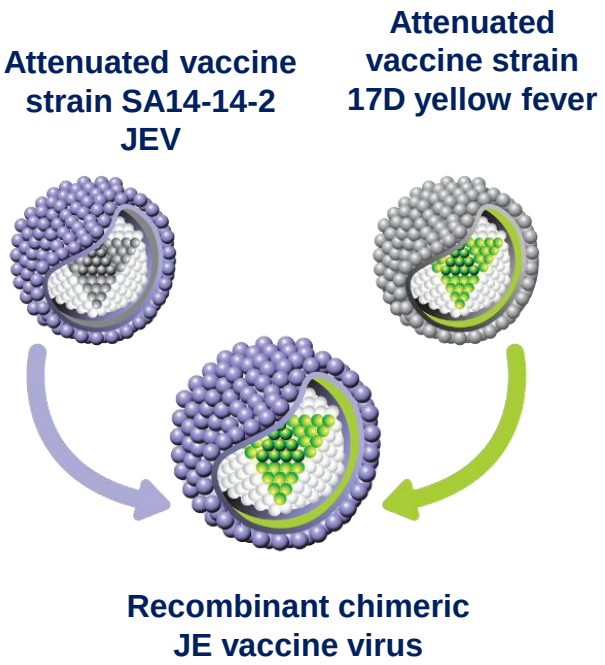
Live Attenuated

Provides most effective and long-lasting humoral and cellular immunity

Recombinant Technology

This enables the generation of a new vaccine virus from two different attenuated viruses, whose characteristics are appropriate for vaccine production.

Recombinant Vaccine Technology



Vero Cell Technology

Advantages

- Reliability, consistency and avoid risk of contamination
- Tested and shown to be free from adventitious agents
- Higher yield and greater vaccine purity
- Avoids the continued use of animals
- Most widely accepted cell lines by regulatory authorities
- Have been used for over 30 years for polio and rabies vaccine.

Japanese encephalitis Recombinant Vaccine (live attenuated) Main Characteristics

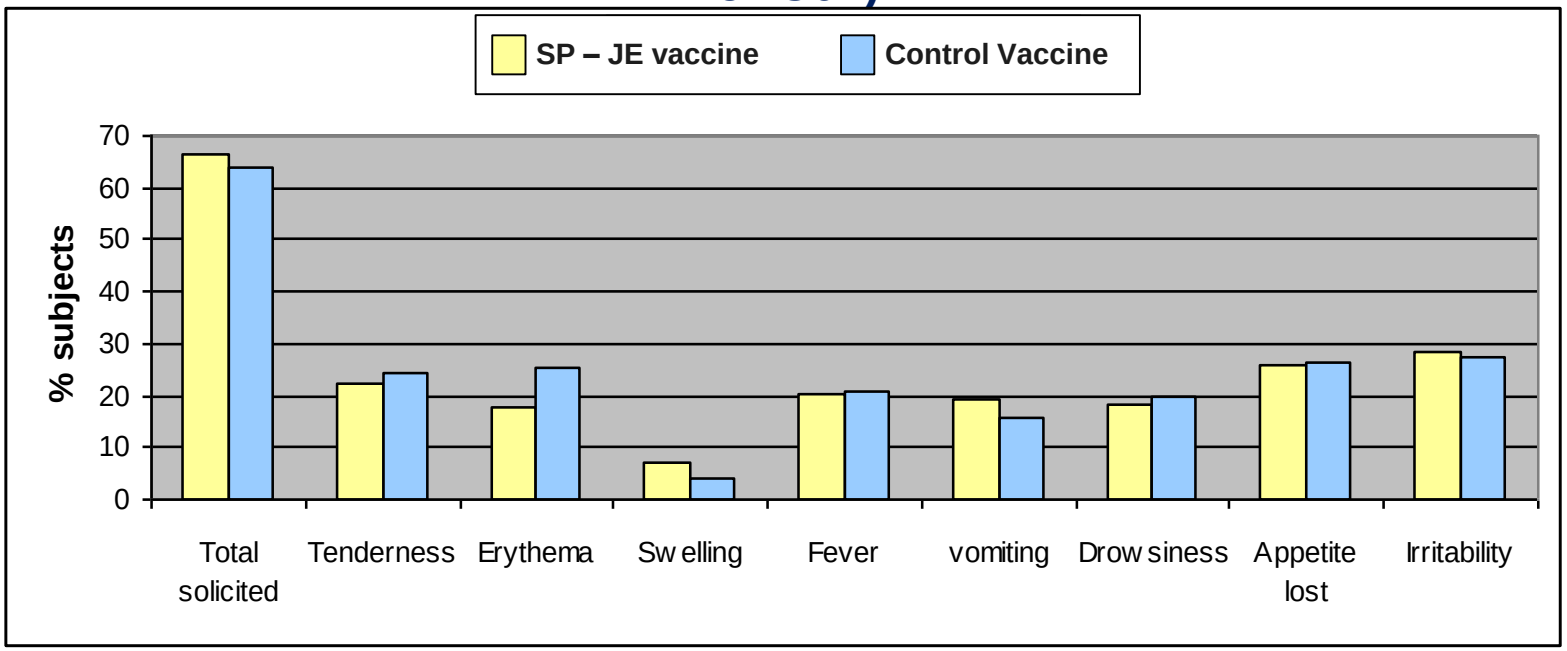
- **General description:**
  - Freeze-dried vaccine for the prophylaxis of Japanese Encephalitis for subcutaneous administration
  - Virus grown in a well characterized cell line (Vero) using serum-free culture medium
- **Presentation:**
  - Unidose (1D): Freeze-dried vaccine in glass vial + diluent in vial (0.5ml) + syringe + 2 needles
- **Indications**: Children and adults 12 months and over
- **Recommended vaccination schedules:**

Age Indication	Primary dose	Booster dose
Children (1 to 17 years old)	1 dose	1 dose : 12-24 months after the primary dose
Adults (18 years and above)	1 dose	No booster dose

- **Route of administration:** Subcutaneous

Reactogenicity in pediatric population

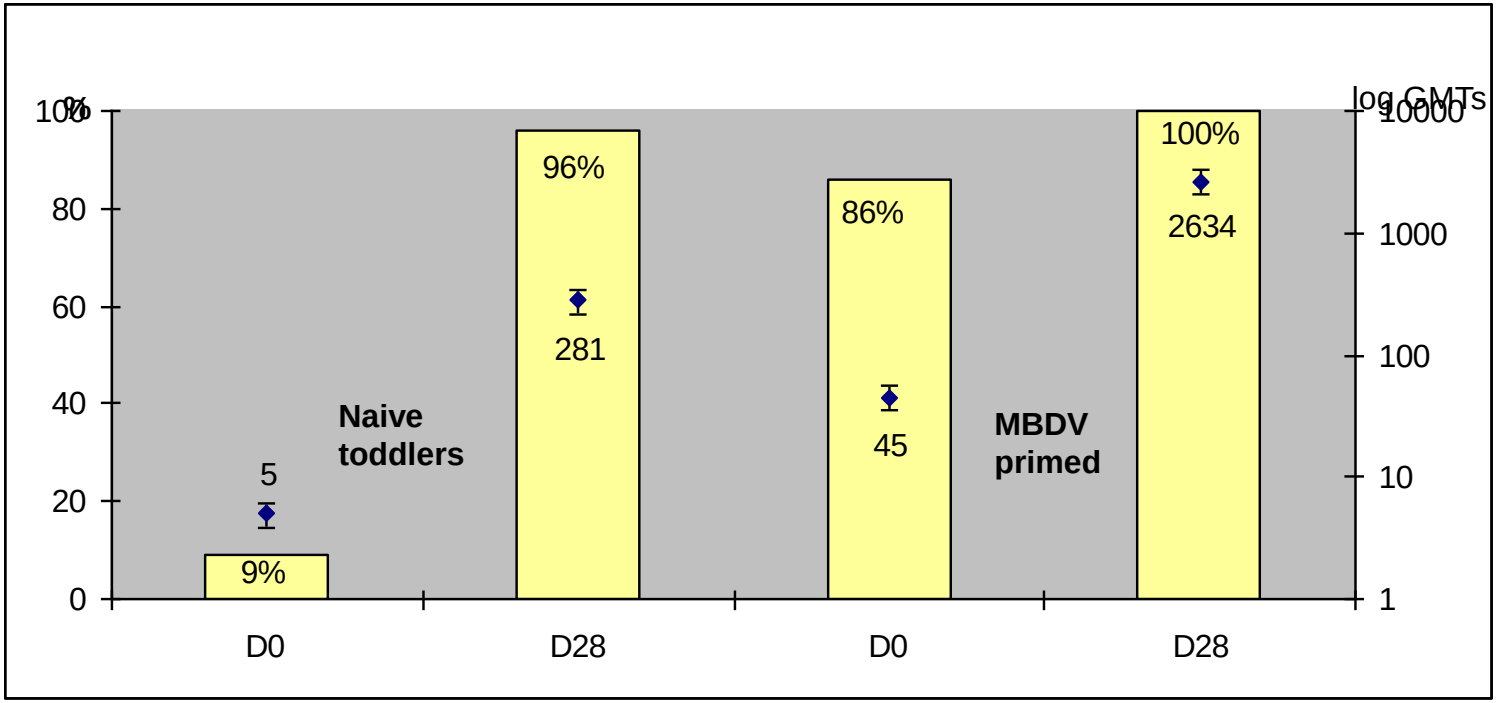
Solicited injection site and systemic reactions in all Japanese encephalitis Recombinant Vaccine (live attenuated) subjects (n= 1097) versus control vaccine: Hepatitis A Vaccine (n = 102) (study code JEC02)



Unsolicited adverse reactions occurred in 1.2% and 1.0% respectively in Japanese encephalitis Recombinant Vaccine (live attenuated) and control vaccine, most reactions lasted 3 days or less

Feroldi E. et al Human vaccines 2012, in press

Short-term Immunogenicity in pediatric population.



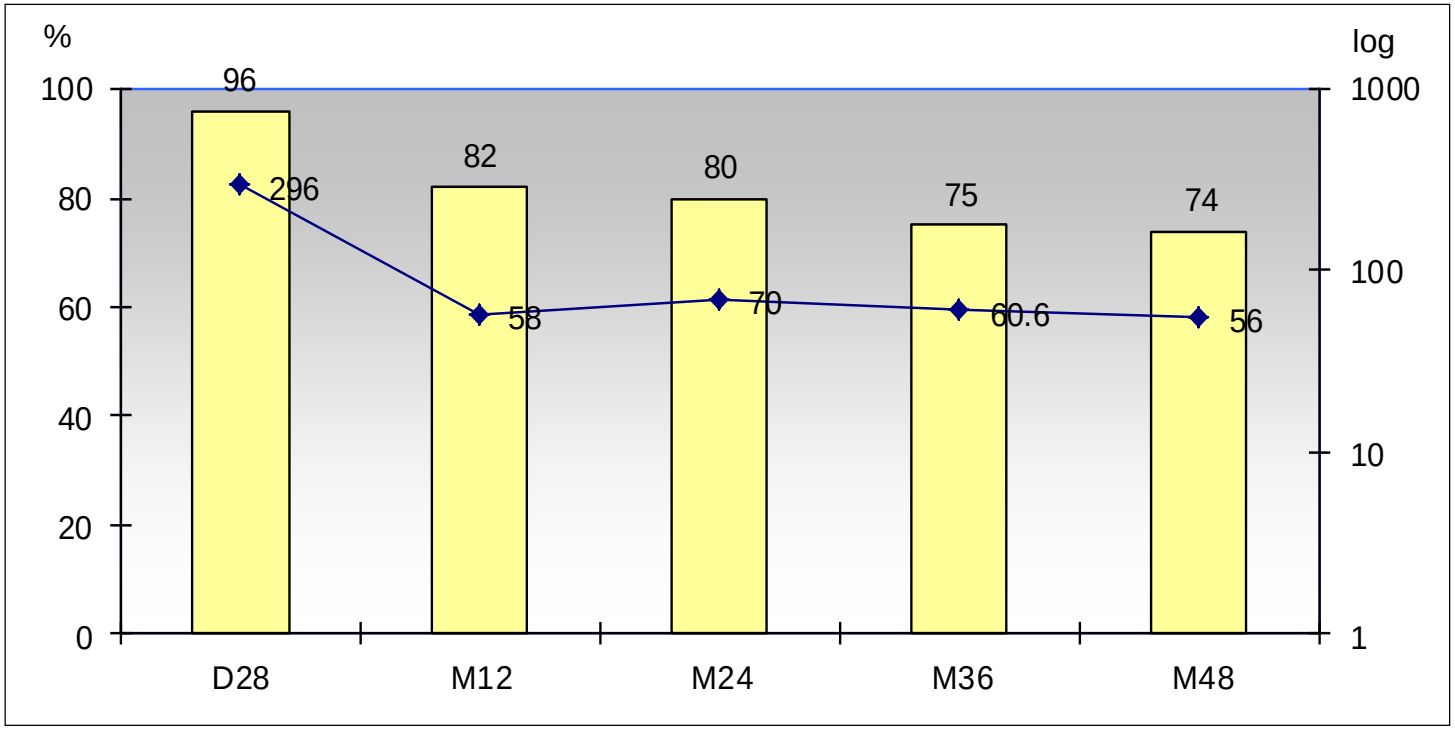
- Naive toddlers 12-24 months of age
- n=200
- GMTs D28: 281 (219-362)

- Children 2-5 years, previously primed with MBDV (12 months before)
- n=100
- GMTs D28: 2634 (1928-3600)

Chokephaibulkit K; PIDJ vol29, N°12, 2010

Last results from long-term follow-up
Naive toddlers single dose

- Naive toddlers aged 12-24 months; n=200
- Sensitivity analysis
- GMT in protective range at M 24: 70.3 (54.3 - 91.1)

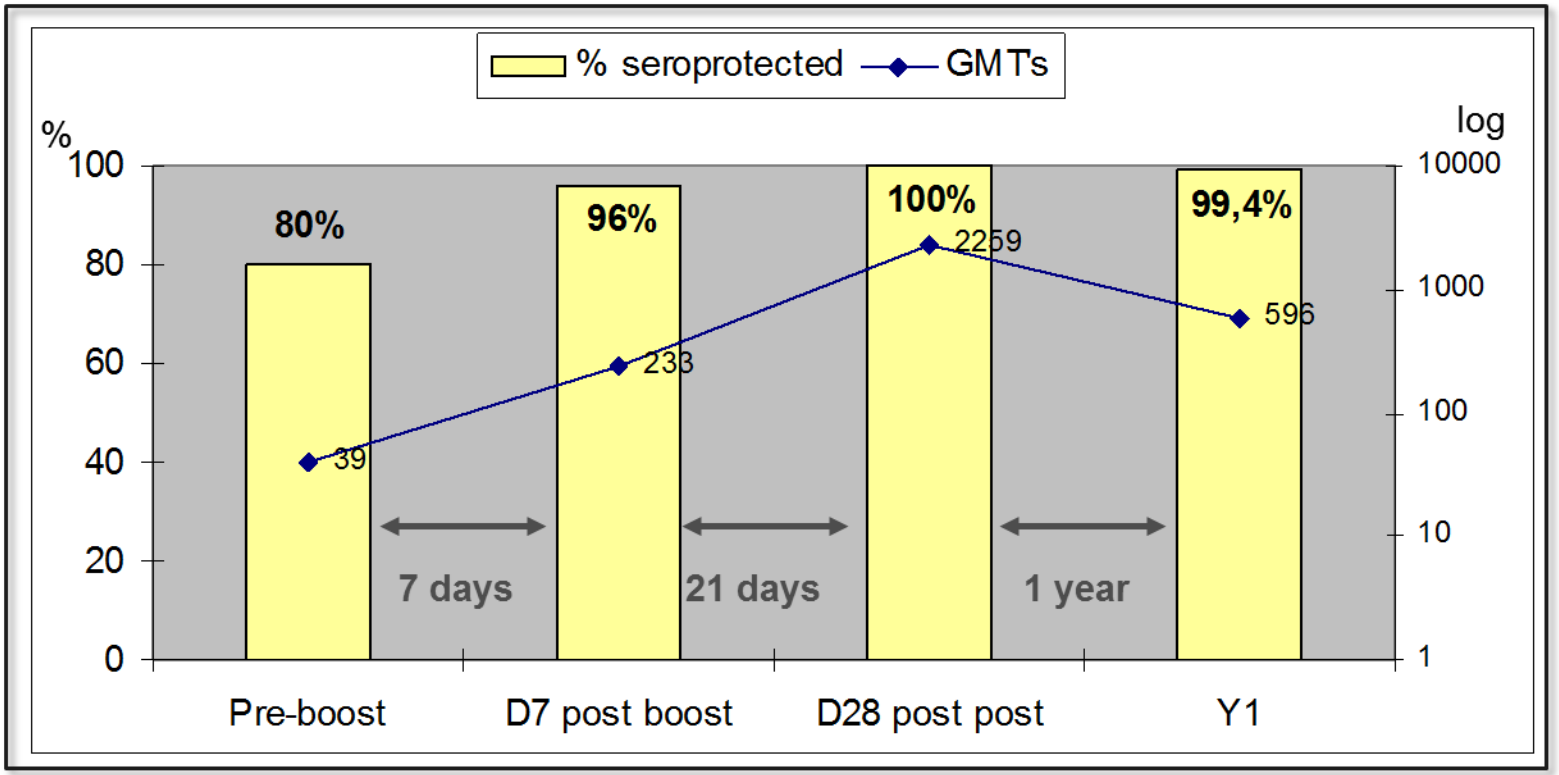


Initial decline (mainly first 6 months) is followed by a decrease at a much slower rate.

Data up to M12: Chokephaibulkit et al Pediatr Infect Dis J 2010 Dec;29(12):1111-7

Booster administration (JEC15) When given 24 months post primary SP-JE vaccination

JEC15; N = 349 subjects, The Philippines



- A strong booster effect (GMTs x57) is evidenced when Japanese encephalitis Recombinant Vaccine (live attenuated) vaccine booster dose is administered.
- With regards to slow decrease after Y1 (see previous slides), long-term protection is anticipated until end of childhood. Modeling (as done for adults will be performed in 2013)

Feroldi E et al. ACPID 2012 presentation Abstract A-477-0020-00212

Clinical profile:
Pediatric population Summa

- One primary immunization dose of Japanese encephalitis Recombinant Vaccine (live attenuated) ensures more than 95% seroprotection in naive children 28 days post-vaccination
- A booster dose given 12 to 24 months post primary immunization ensures long lasting protection
- Japanese encephalitis Recombinant Vaccine (live attenuated) has a good safety profile
- Japanese encephalitis Recombinant Vaccine (live attenuated) induce 100% protection when used as a booster of Japanese encephalitis Recombinant Vaccine (live attenuated) or inactivated JE vaccines

Conclusions

- JE is the leading cause of viral encephalitis in Asia and causes significant morbidity and mortality, especially in the pediatric population.
- It is under-recognized by health practitioners and the public, and a lot of challenges remain in terms of surveillance and control.
- It is vaccine-preventable.
- To achieve greater success in reducing burden of disease, measures to improve awareness, technical help from donors and agencies, and commitment to vaccination must be enhanced.

Thank You