

Viral vaccines for travellers

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Travel immunisations

Recommended vaccines:

- **Hepatitis A** is the commonest vaccine-preventable disease in travellers
Vaccine recommended for all non-immune travellers to countries where sanitation and hygiene are suboptimal
- **Yellow fever vaccine:** the only WHO-required vaccine for international travel to certain parts of Africa or South America
- **Influenza** is among the commonest vaccine-preventable diseases in travellers
Strongly considered vaccination for travel coinciding with the influenza season
- **Rabies, Japanese encephalitis, BCG** vaccines are generally reserved for travellers with specific (eg occupational or recreational) or prolonged exposures
- **Hepatitis B**
- **MMR**



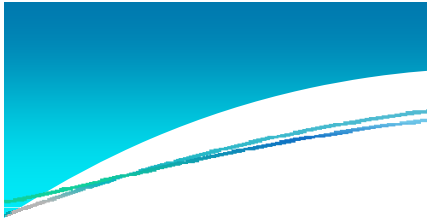
Yellow fever

- Acute viral disease spread by mosquito bites and causing hepatitis and encephalitis
- Endemic in tropical South America and Africa
 - 1985-2004: 28,264 cases & 7,880 deaths (WHO)
 - Africa: 24,684 cases
- two types of transmission cycle:
 - urban cycle – epidemic disease transmitted from infected to susceptible persons by the *Aedes aegypti* mosquito
 - jungle cycle – enzootic disease transmitted among non-human primate hosts by a variety of mosquito vectors, which may also bite and infect humans
- Both transmission cycles occur in Africa, while jungle transmission predominates in South America



Yellow fever

- The risks of illness and death due to yellow fever in an unvaccinated traveller
 - Africa
 - 1:1000 per month and 1:5000 per month respectively during a non-epidemic period
 - increases to 1: 15 per month during an epidemic
 - South America
 - risk of illness and death is probably 10 times lower than in rural West Africa, e.g., 1:10,000 illness, 1:50,000 per month
- Vaccination indicated for all travellers to endemic countries
- Safe and effective, single dose confers 10 years immunity







Yellow fever vaccine

- Vaccine consists of a heat stable, lyophilized live attenuated virus (strains 17D and 17DD)
- vaccine should be stored at 2-8°C and not frozen
- Once reconstituted the vaccine can be kept at room temperature, protected from light and used within 1 hour
- Dose: 0.5 ml by deep subcutaneous injection
- induces neutralizing antibodies in 90% within 10 days and in 99% within 30 days
- Booster dose: one 0.5 ml dose every 10 years



Simultaneous administration of other vaccines and immune globulin

- administration of MMR, varicella and smallpox should be concurrent with yellow fever vaccine
 - If not, they should be given 4 weeks apart
- Immune globulin does not affect the immune response to yellow fever vaccine and may be given concomitantly



Simultaneous administration of other vaccines

- The antibody response to yellow fever vaccine is not inhibited by simultaneous immunisation with:
 - BCG
 - cholera – oral
 - measles
 - diphtheria-pertussis-tetanus
 - meningococcal vaccine
 - Poliomyelitis (IPV)
 - hepatitis A
 - hepatitis B
 - tetanus
 - typhoid vaccine – oral and parenteral



Simultaneous administration of other vaccines

- no data on possible interference between yellow fever and plague, rabies or inactivated Japanese encephalitis vaccines
- No interference between YF vaccine and Chimerivax-JE (JE-CV)



Yellow fever vaccine

- Reactions rare unless person is severely allergic to eggs
- 2-5% have mild headache, myalgia, low-grade fever 5-10 days after vaccination (usually on 6th or 7th day)
- Immediate hypersensitivity reactions (rash, urticaria and/or asthma) are rare (incidence < 1:1 000 000)



Yellow fever vaccine

- Contraindicated in those with
 - severe egg allergy
 - cellular immunodeficiency; appears safe in HIV and recommended if high risk and CD4 over 200
 - Pregnancy (except after 6 months if high risk)

Yellow fever vaccine

- Not used in infants less than 9 months because of risk of encephalitis (6 months if high risk travel)
- Administered in approved Yellow fever vaccination centers
- Given a minimum of 10 days before entry into a risk area

Yellow fever vaccine

- Post vaccination encephalitis (neurotropic disease)
 - Only 25 reports in literature to date from 400 million administered doses since vaccine introduction in 1945
 - occurred in infants 7 months of age or younger, predominantly in infants 4 months of age or less
- 9 cases of encephalitis have been reported among adults, with onset 4–23 days after immunisation
 - Recovery has generally been rapid and complete
 -
- One case of fatal meningoencephalitis reported in an immunocompromised HIV-infected man

Yellow fever vaccine

- Post vaccination encephalitis (neurotropic disease)
- incidence of vaccine-associated neurotropic disease
 - 0.5 to 4 per 1000 in infants under 9 months
 - 1 per 8 million in infants over 9 months



Yellow fever vaccine: Viscerotropic disease

- YF VTD presents within 2-5 days of vaccination
 - fever, myalgia gastrointestinal symptoms
 - rapid progression to hypotension, liver, renal and respiratory failure, encephalopathy, lymphocytopenia, thrombocytopenia, DIC
 - at PM virus isolated from liver, heart, spleen, skin, blood
 - Liver histopathology: midzonal necrosis, microvesicular fatty change, eosinophilic degeneration of hepatocytes-Councilman bodies (as seen in wild type YF)

Reporting Rates Ratio (RRR) for systemic adverse events

Age (yrs)	No.SyAE/10 ⁵ doses	RRR	No. serious SyAE/10 ⁵ doses	RRR
15-24	1.58	1.0	1.05	3.7
25-44	1.57		0.29	
45-64	2.71	1.7	1.13	4.0
65-74	5.8	3.7	3.48	12.3
>75	18.11	11.6	9.06	32
total	2.42		0.96	

Yellow fever vaccine

Four (17%) of the 23 vaccinees with VTD had a history of thymus disease

- thymectomy
- thymic tumor

Thymic dysfunction is an independent risk factor

Yellow fever vaccine

1. Crude estimates of the reported frequency of YF VTD
 - 0.9 to 2.5 per 1 000 000 doses distributed
2. The risk is highest in individuals over the age of 65 years
3. In those over the age of 75 the risk is 12 times higher than young adults
4. VTD has not been reported in individuals receiving booster doses of the vaccine



Recommendations

For protection

For people living or travelling in endemic areas, the vaccine is recommended for those aged ≥ 9 months who are:

- living or travelling in areas of active transmission (i.e. infected areas)
- travelling outside urban areas in countries within yellow fever endemic zones

Travellers to coastal Brazil or Peru, Cuzco and Machu Picchu do not need vaccination but a letter of exemption that is stamped with an official yellow fever license number should be provided



Recommendations

For legal requirement

The vaccine is recommended for those overseas travellers who:

- visit **nations that require a certificate of vaccination** from all travellers who enter the country
- visit yellow fever infected countries and proceed to countries with an immunisation requirement



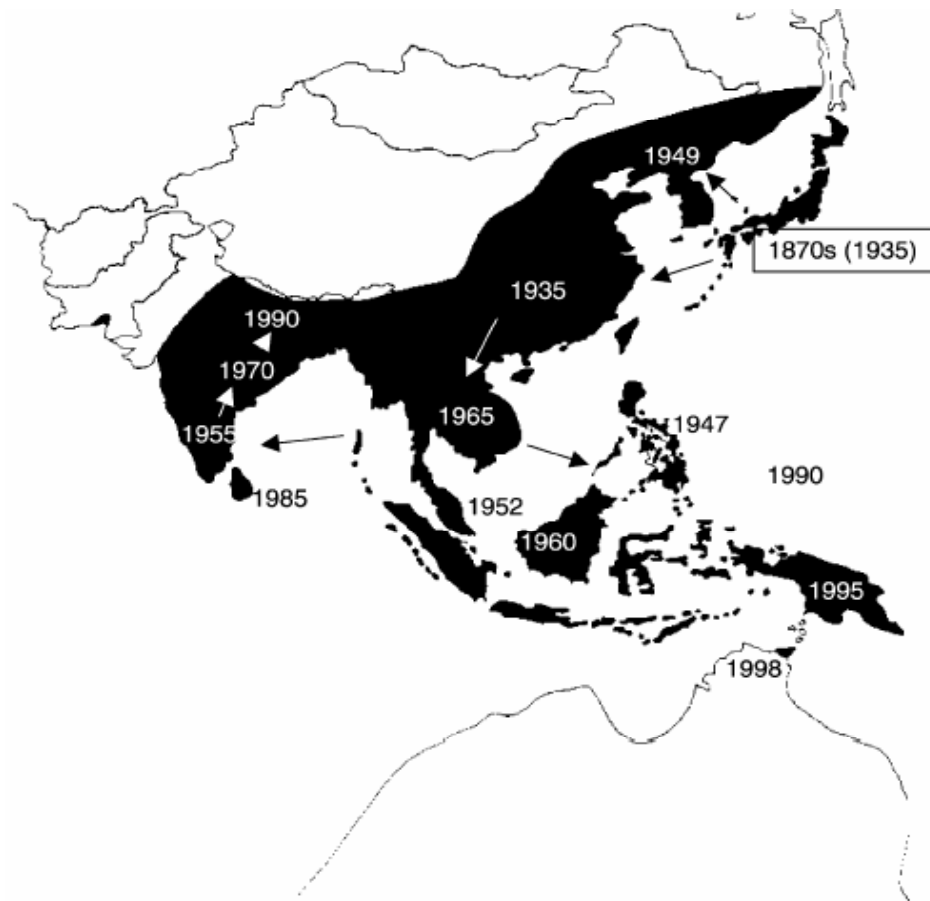
Japanese Encephalitis: ***New Generation Vaccines***



Japanese Encephalitis (JE)

- JE is a *flavivirus* infection transmitted by Culicine mosquito
- JE is transmitted throughout Asia, a region supporting more than 3 billion people—60% of the world's population
- 35,000 cases; 10,000 deaths annually; 50 % permanent neuropsychiatric sequelae
- Australasia: Torres Strait 1995, PNG 1997, Australia 1998

Japanese Encephalitis





Japanese encephalitis

Travellers and expatriates

- The risk of reported JE for the average tourist to endemic areas is $<1:1000,000$
- In non-immunized intensely exposed soldiers in Asia,
 - -rates of 0.005 to 2.1 per 10 000 per week
 - -rates of 0.1 to 1 per 10 000 per week for children in hyperendemic areas
- Accepting the higher estimate and allowing for transmission in most areas being limited to 5 months of the year
 - the risk can be estimated as 1 per 200 000 per week.



JE Vaccine Issues

- JE Vax: Nakayama strain (discontinued)

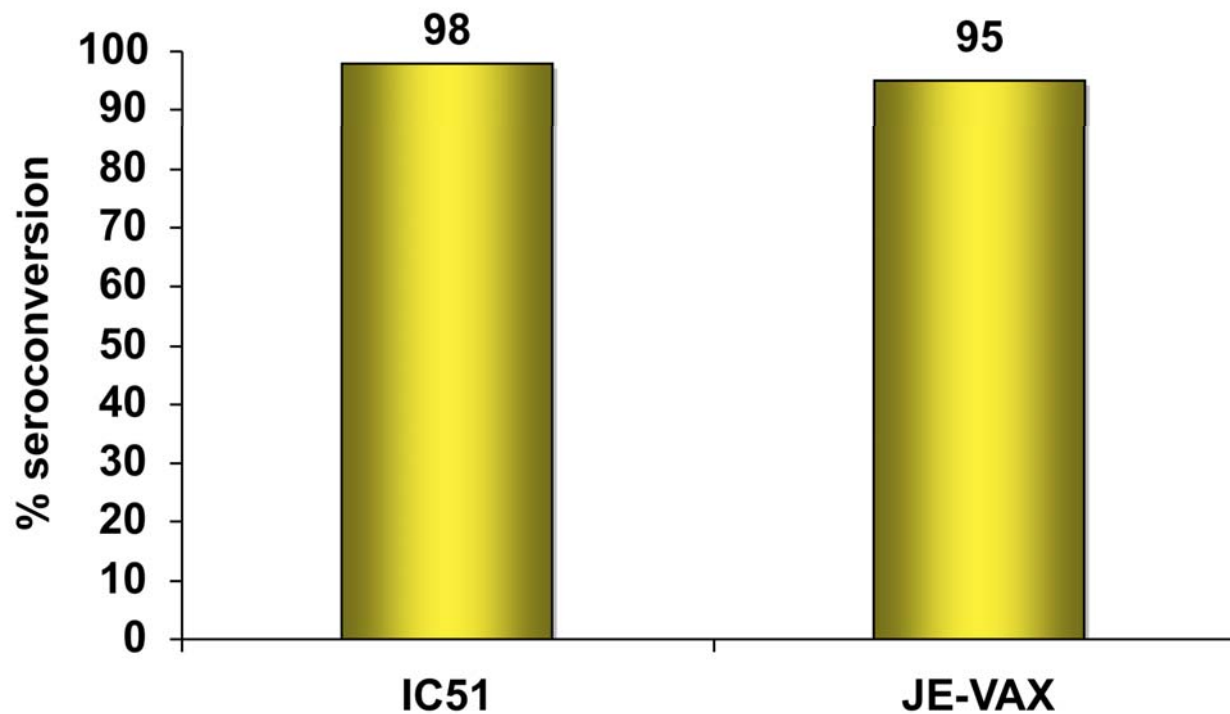
SA14-14-2

- genetically stable, neuro-attenuated JE virus
 - CD-JEVAX (Chengdu biologicals): live attenuated
 - JESPECT® (Intercell / Novartis) : IC51
 - IMOJEV™ (Sanofi-Pasteur): JE-CV

Japanese Encephalitis Vaccines

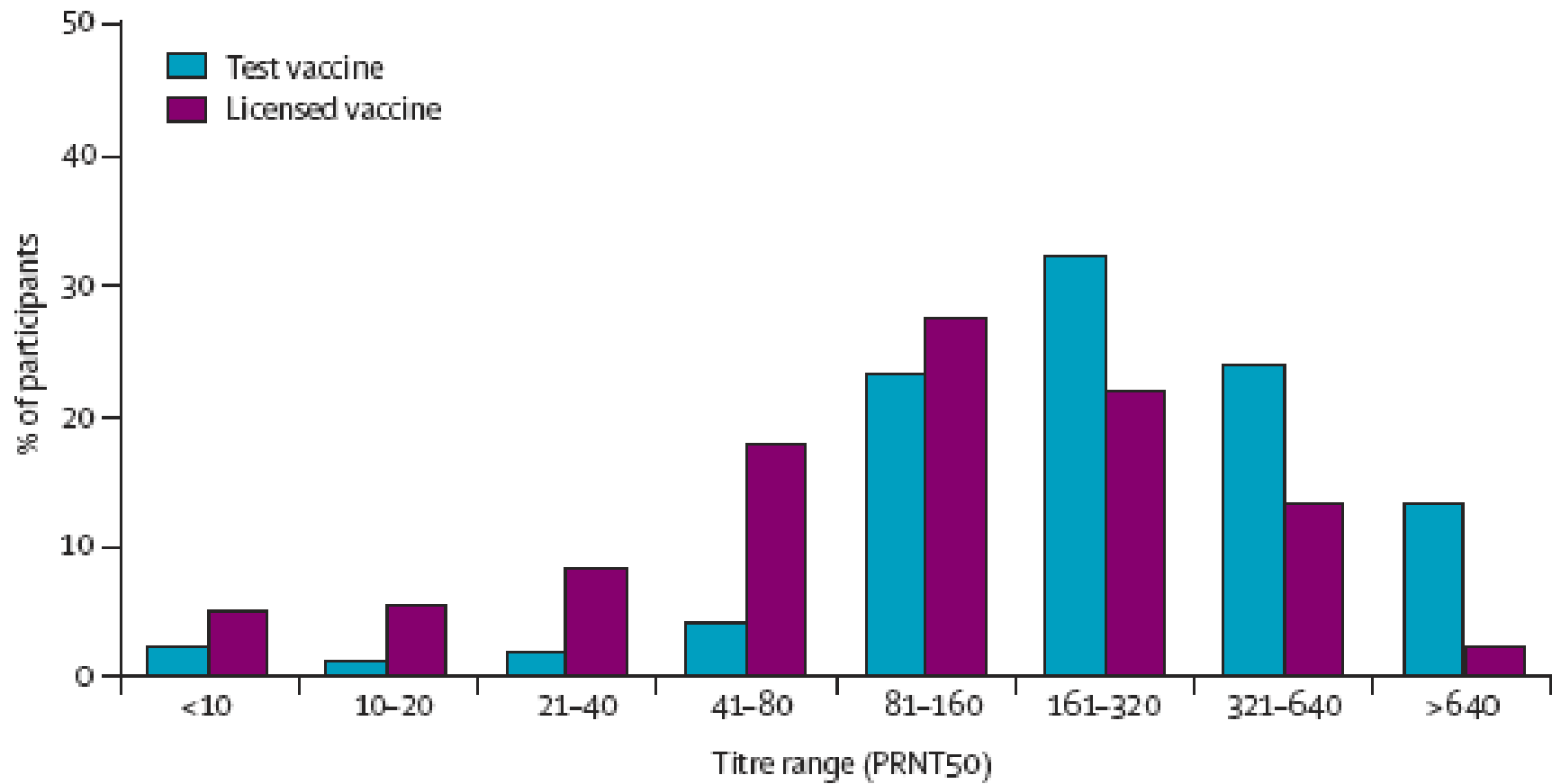
	JE-VAX (stopped)	IXIARO® (Intercell / Novartis)	CD-JEVAX (Chengdu biologicals)	IMOJEV™
Virus Strain	Nakayama	SA 14-14-2	SA 14-14-2	SA 14-14-2
Vaccine	Formalin Inactivated Lyophilized	Formalin Inactivated Liquid	Live attenuated Lyophilized	Live attenuated Lyophilized
Cell growth	Mouse brains	Vero cells	Primary hamster kidney	Vero cells
Adjuvant/ Preservative	Thiomersol	Aluminium hydroxide	-	None
Dose	3 doses of 1.0ml D0, 7, 28 + booster	2 doses of 0.5 ml D0, D28	Single dose 0.5 ml, booster after 3m-1y	Single dose, 0.5ml
Seroconversion rate (%)	74%-95%	98%	99%	99%
Geometric mean titre (range)	38 (32 - 43)	244 (5 to 19783)	188 (130-261)	1392 (1156 - 1674)
Long-term	74% at 6 mths	83% at 12 mths	95% at 5 years	95% at 12 mths

JESPECT®



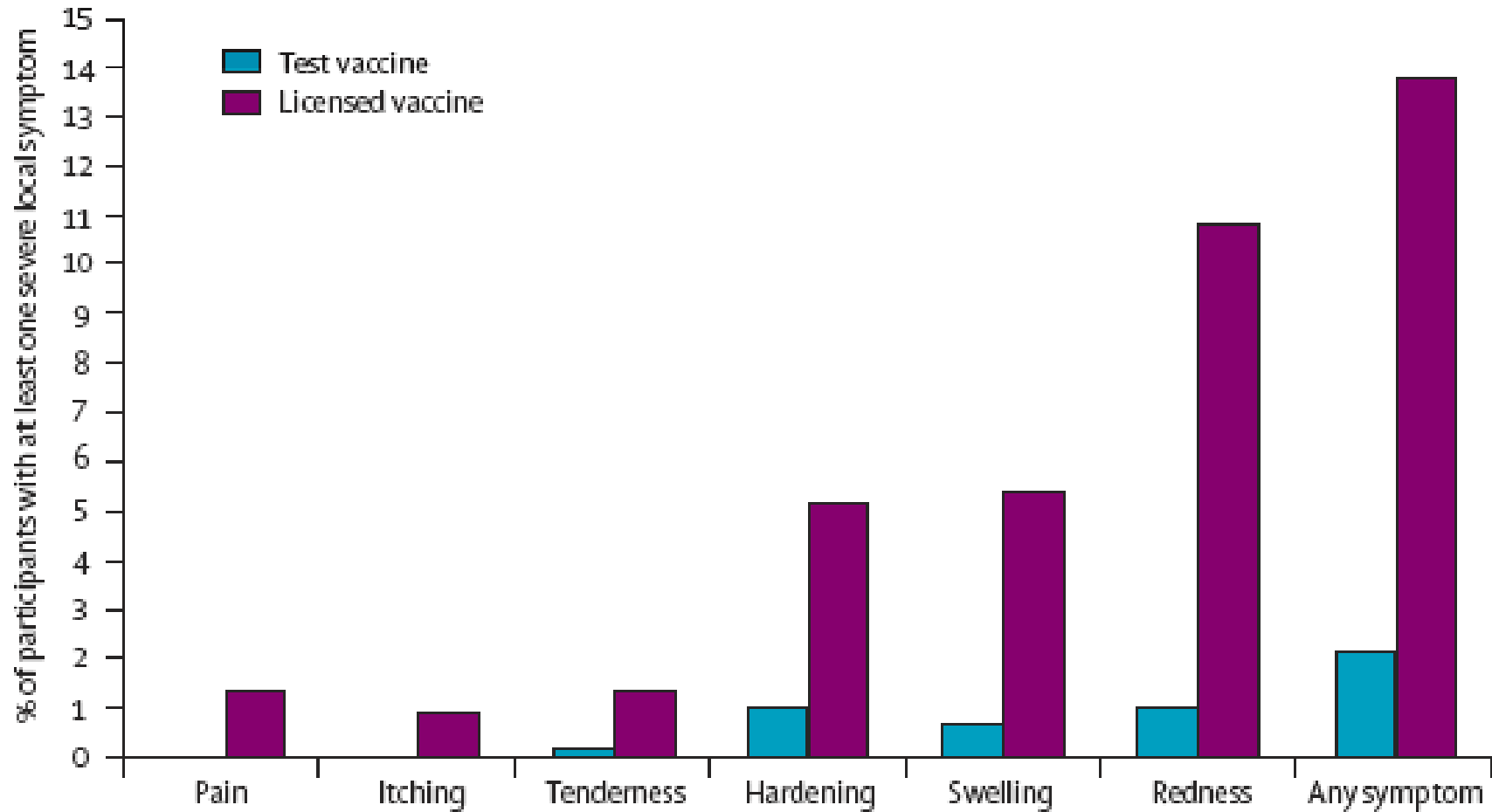
	IC51	JE-Vax	Risk difference (95% CI)
Geometric mean titre (range)	244 (5 to 19783)	102 (5 to 1864)	2.3 (1.97 to 2.75)

JESPECT[®]



Tauber et al., Lancet 2007; 370: 1847–53

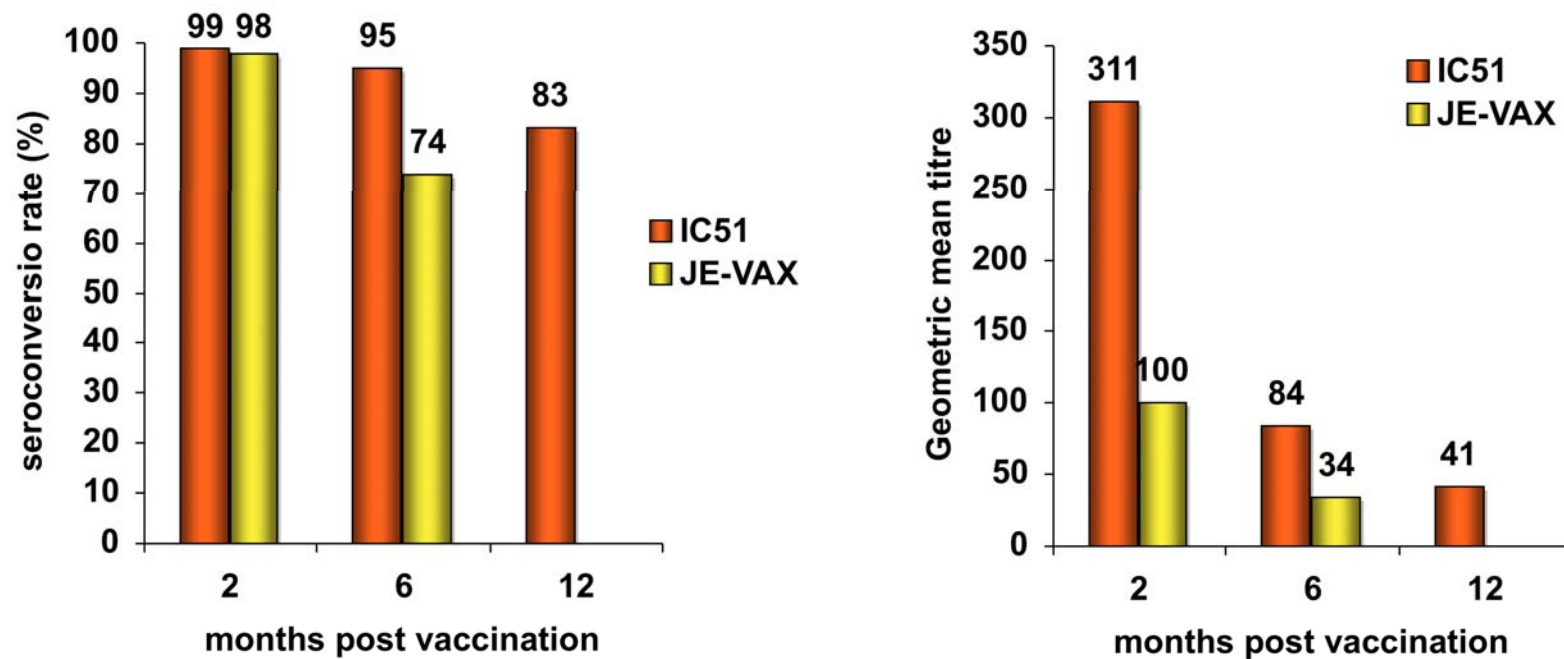
JESPECT®



Tauber et al., Lancet 2007; 370: 1847–53

Tauber et al J Infectious Diseases 2008; 198:493–9

JESPECT®



Booster every 1yr for high risk travel otherwise every 2 yrs

Schuller et al., Vaccine 26 (2008) 4382–4386



IMOJEV™

- Joint development between sanofi pasteur and Acambis
- JE-CV is a live-attenuated vaccine based on :
 - **Structural proteins of JE live-attenuated SA14-14-2 virus**
 - +
 - **Replication engine from the Yellow Fever (YF) 17D**
- 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. JID, in press



IMOJEV™ (JE-CV)

- 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

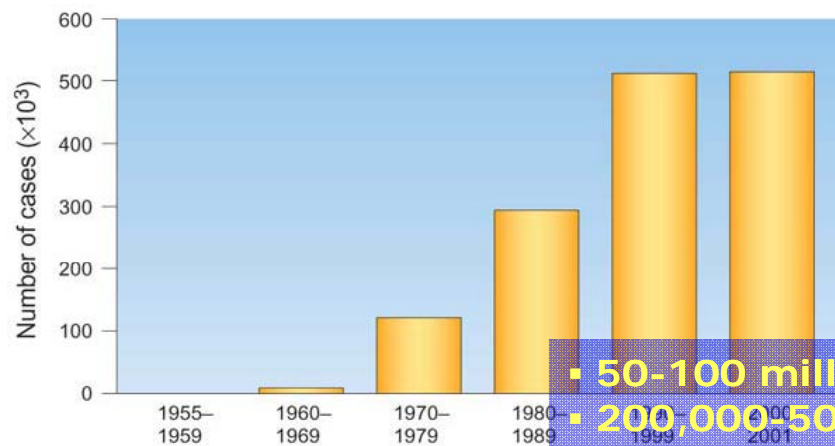


IMOJEV™ (JE-CV)

- High Efficacy
 - **Seroconversion at D60 - 99.1% JE-CV vs. 95% 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)

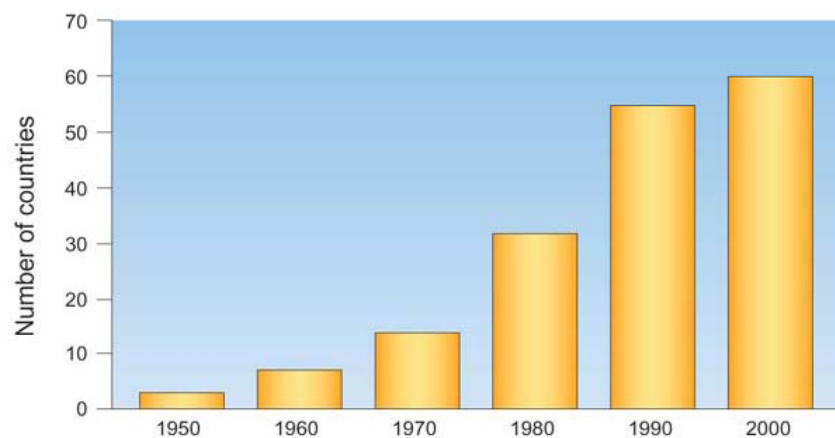
Dengue fever

a Dengue/dengue hemorrhagic fever, average annual number of cases reported to WHO, 1955–2001

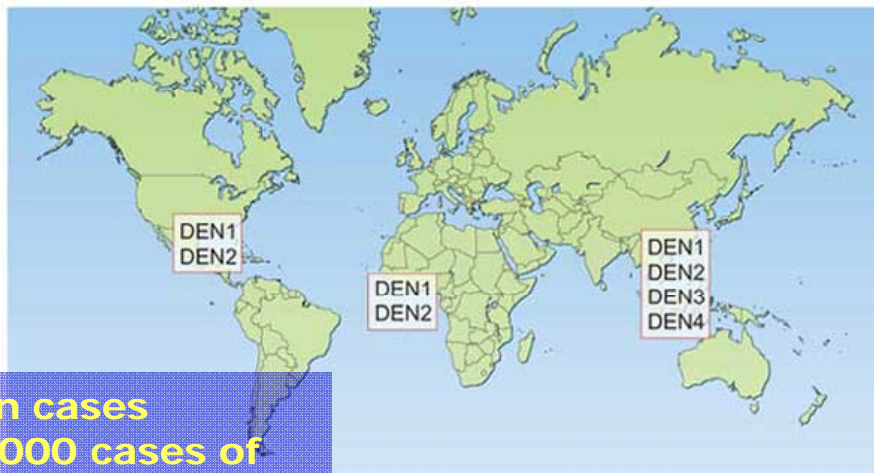


- 50–100 million cases
- 200,000–500,000 cases of DHF
- > 20,000 deaths/year

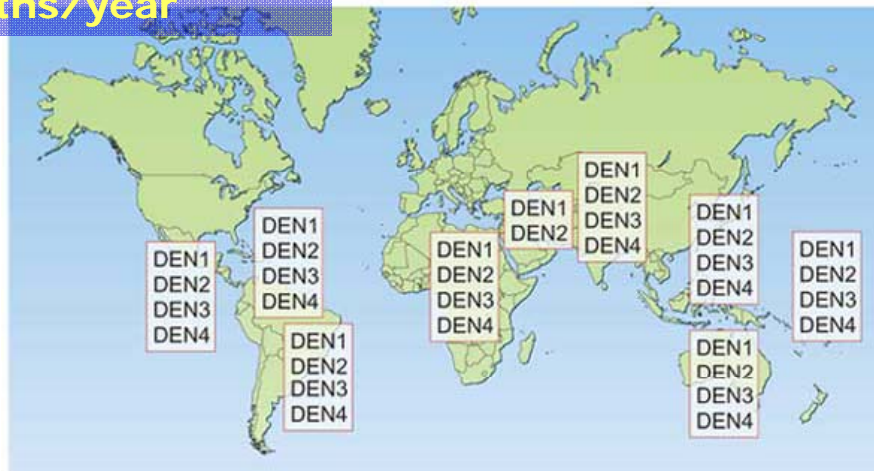
b Countries in the world reporting DHF cases, 1950–2000 (cumulative)*



Global distribution of dengue virus serotypes, 1970



Global distribution of dengue virus serotypes, 2004



Dengue fever

- Serological evidence of dengue fever
6 to 45% of travellers with fever after returning from endemic areas

Doherty, et al 1995; Schwartz, et al 1996; Jelinek et al, 2000

- retrospective study of Swiss travellers, serological evidence of DF in 8% of symptomatic patients

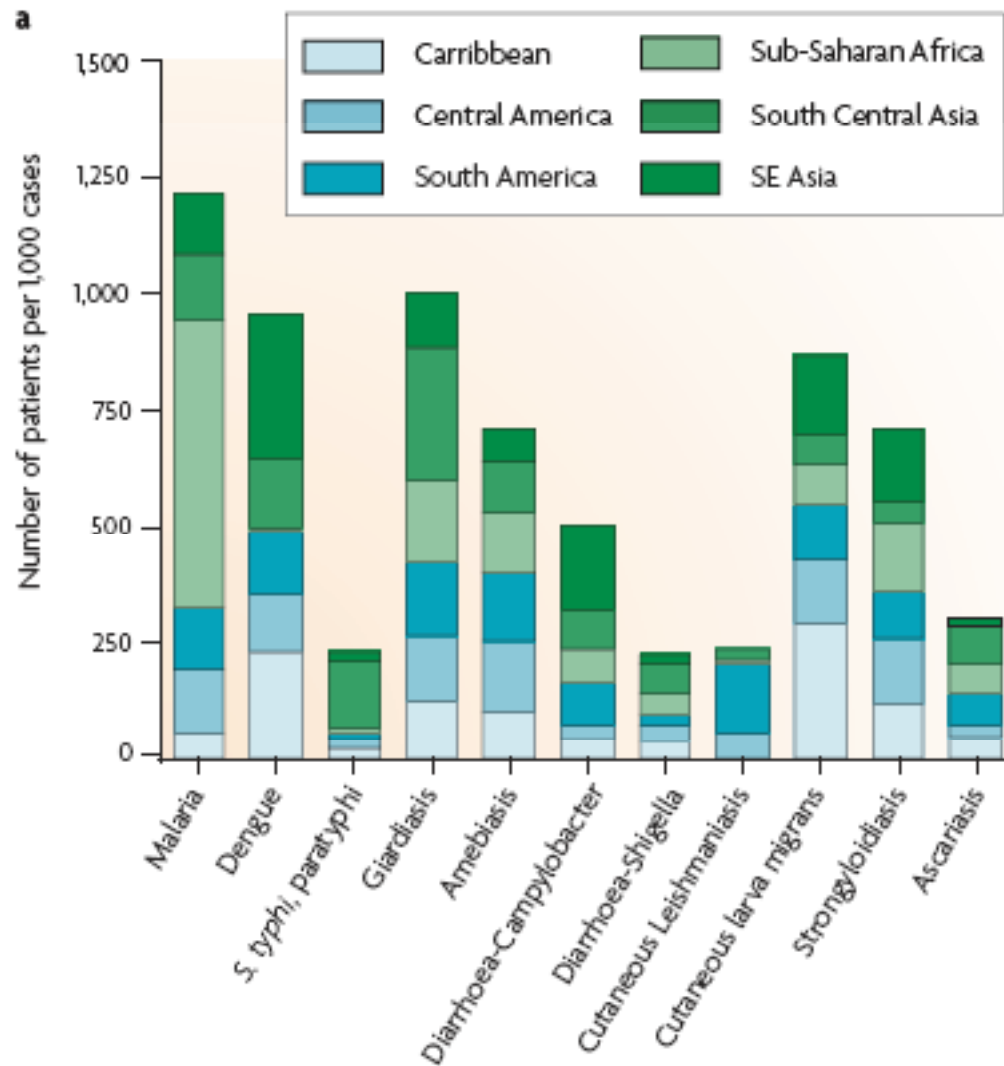
Jelinek et al, 2000

- 8% of febrile returned travellers in Australia have DF

O'Brien et al 2001

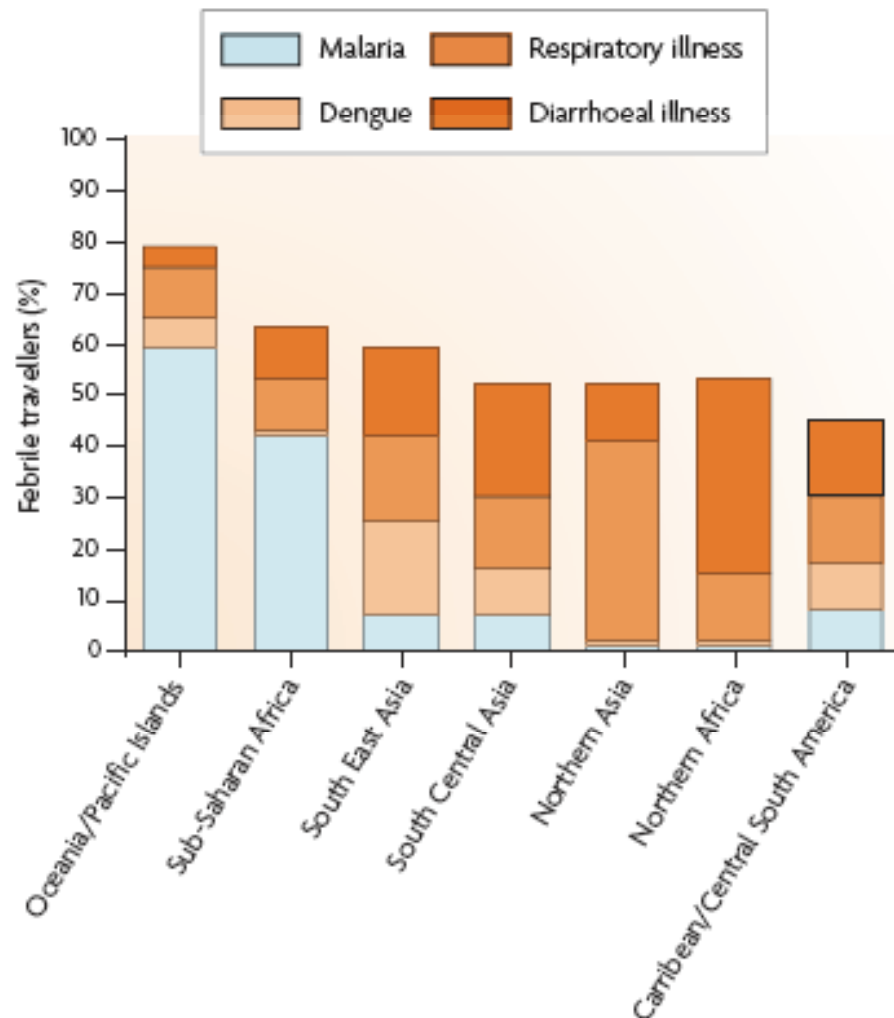
- DHF occurs in small proportion (0.9%) of travellers

GeoSentinel Surveillance Network



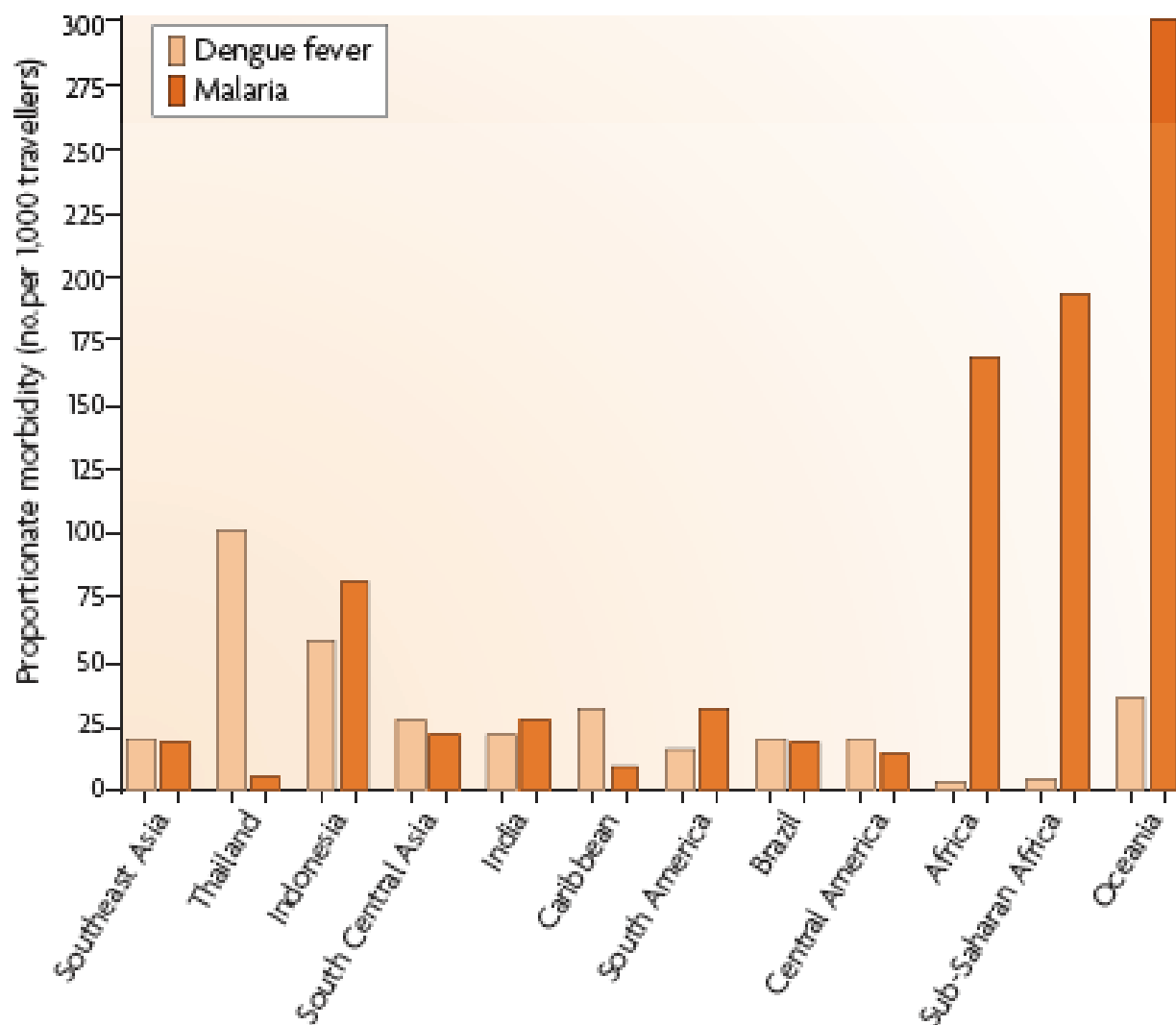
Torresi and Leder. Nature Reviews Microbiology. Dec 2009.

GeoSentinel Surveillance Network



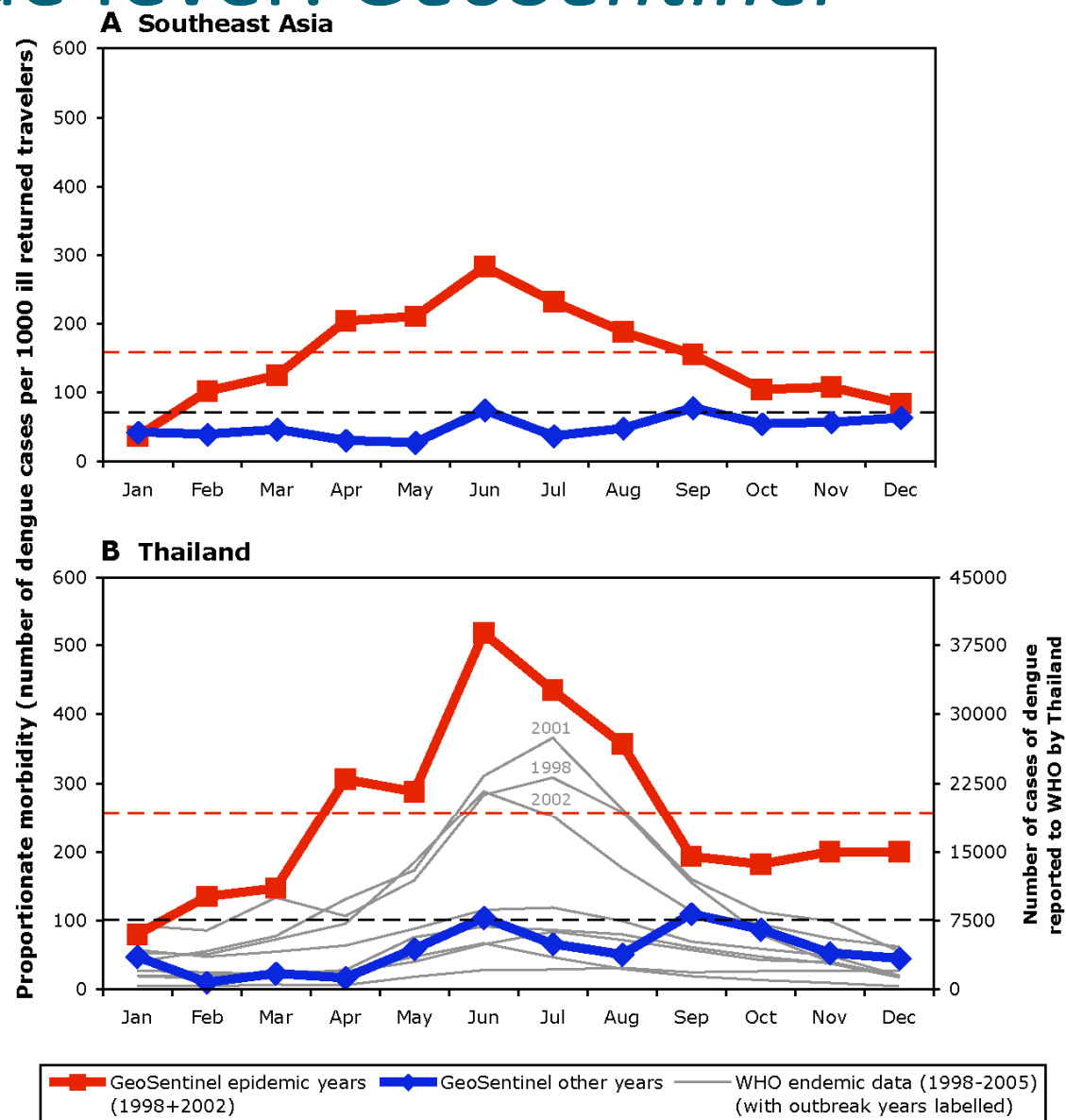
Torresi & Leder. *Nature Rev Micro.* Dec 2009
Wilson et al., *Clin In Dis* 2008

GeoSentinel Surveillance Network



Torresi and Leder. Nature Reviews Microbiology. Dec 2009.

Dengue fever: *GeoSentinel*



Dengue fever: GeoSentinel

Region or Country of Exposure	Number of ill-returned travelers with dengue	Number of ill-returned travelers with malaria	Total number of ill-returned travelers	Dengue proportionate morbidity (per 1,000 ill-returned travelers)	Malaria proportionate morbidity (per 1,000 ill-returned travelers)
Southeast Asia	264	103	3694	71	28
<i>Thailand</i>	154	9	1523	101	5
<i>Indonesia</i>	38	53	652	58	81
South Central Asia	90	70	3303	27	21
<i>India</i>	66	57	2119	31	27
Caribbean	47	14	1470	32	9
South America	40	49	2427	16	20
<i>Brazil</i>	22	12	685	32	18
Central America	37	27	1867	20	14
Africa	25	1216	7231	3	168
<i>Sub-Saharan Africa</i>	23	1201	6201	4	194
Oceania	11	91	303	36	300
Other or multiple	7	23	4443	2	5
Country Missing	1	12	182	5	66
Total	522	1605	24920	21	64

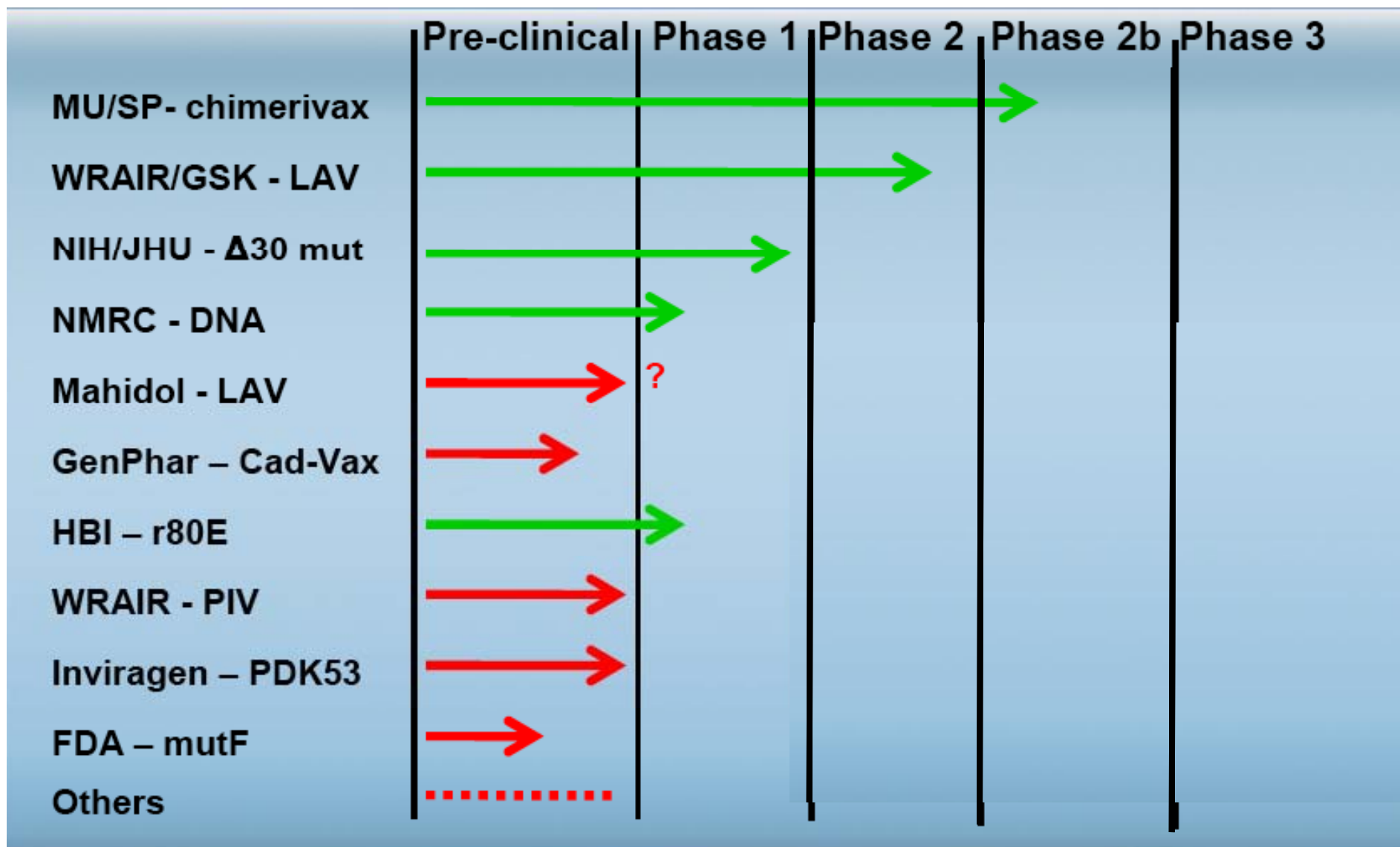
Epidemic
Yrs

Epidemic
Yrs
(Jun-Jul)

250

500

Dengue Vaccines





Chimeric YF-dengue vaccine: CYD1-4

- Description
 - Tetravalent, live attenuated vaccine
- Route of administration
 - Subcutaneous
- Vaccine schedule
 - 3 injections, 0, 6, 12 months



Safety Data

• Based on safety database from Phase I trials: 431 subjects who have received ≥ 1 dose (220 adults, 71 Adolescents, 140 children)

- No SAE related to vaccination
- No mild dengue-like syndrome as previously observed with whole virion live-attenuated candidate dengue vaccines
- Reactogenicity profile (clinical & biological) comparable to control vaccines
- No increase in reactogenicity
 - in FV immune subjects in comparison to FV naive subjects
 - in younger subjects (youngest group 2-11 years)
 - after a 2nd or a 3rd dose



Conclusions on Immunogenicity

- Humoral immune response
 - In Non-endemic Populations
 - **Balanced immune response against all 4 serotypes after 3 doses of tetravalent dengue vaccine with 95 to 100% seroconversion after the third dose.**
 - **Higher immune responses observed in children**
 - **Previous YF vaccination has a priming potential**
 - In Endemic Populations
 - **Booster effect in people previously exposed to flavivirus**

3 dose schedule (0, 6 and 12 months) in future Phase III efficacy trials commencing

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