Vaccins encéphalite japonaise

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Conflits d'intérêt

I have or had within the past few years financial relationships (grants for research or to attend meetings, paid lectures, advisory boards) relevant to my presentation with:

Vaccines	***Drugs***
Bavarian-Nordic	
Baxter	
Crucell	DrFalk Pharma
GlaxoSmithKline	
GlycoVaxyn	Optimer
Intercell	Roche
Novartis Vaccines and Diagnostics	Santarus
Sanofi Pasteur	Salix

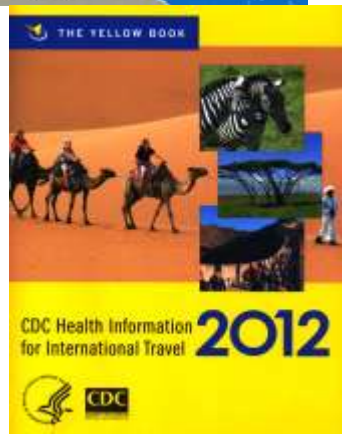
Menu

- Encéphalite japonaise
- Epidémiologie
  - Aspects généraux
  - Risque du voyageur
- Le (les) vaccins
- Conclusions: recommandations et algorithme

Basics on Japanese encephalitis (JE)

- Mosquito-borne flavivirus
- Leading cause of viral neurological infection and disability in Asia[1]
- LMOFF6 6 6 6 estimated among residents of 24 endemic countries[2]
  - 1.8 per 100,000 overall
  - 5.4 per 100,000 in 0-14 y/o children
- Outcome
  - **1/3 fatal**
  - **1/3 with sequelae**
  - 1/3 full recovery

JE endemic areas 2010[3]



1. PATH. 2008. http://www.path.org/projects/JE_in_depth.php
2. Campbell GL et al. Bull WHO 2011;89:766-744.
3. CDC. Health Information for International Travel, 2011, p.207

Clinical features of Japanese encephalitis (JE)

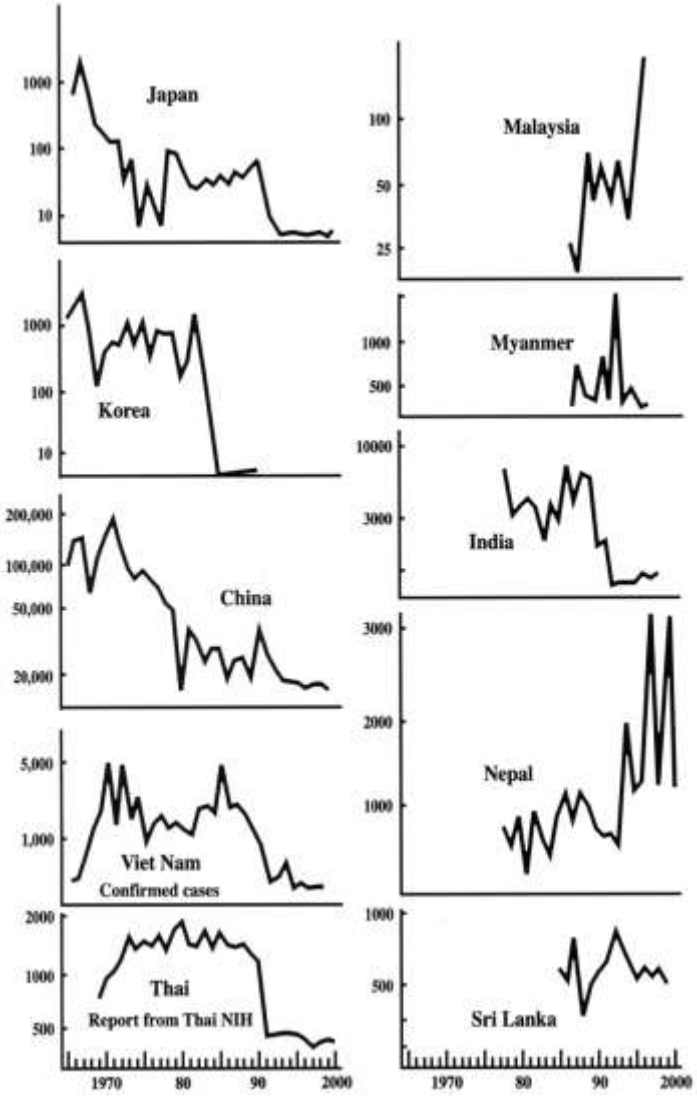
Incubation period:	(4-) 15 days
Symptomatic:	**1 in 200-500 infections** (more with growing age)
Onset:	High fever, headache Less frequent: vomiting, diarrhea, myalgias
From 2nd day:	Nuchal rigidity Rapidly developing encephalitis - Confusion ... coma - muscle spasms - peak about 1 week after onset → recovery or death
Prognosis (WHO):	CFR 30% (0.3 to 60%, CDC) Among survivors: 30% with sequelae

Transmission of Japanese encephalitis (JE)

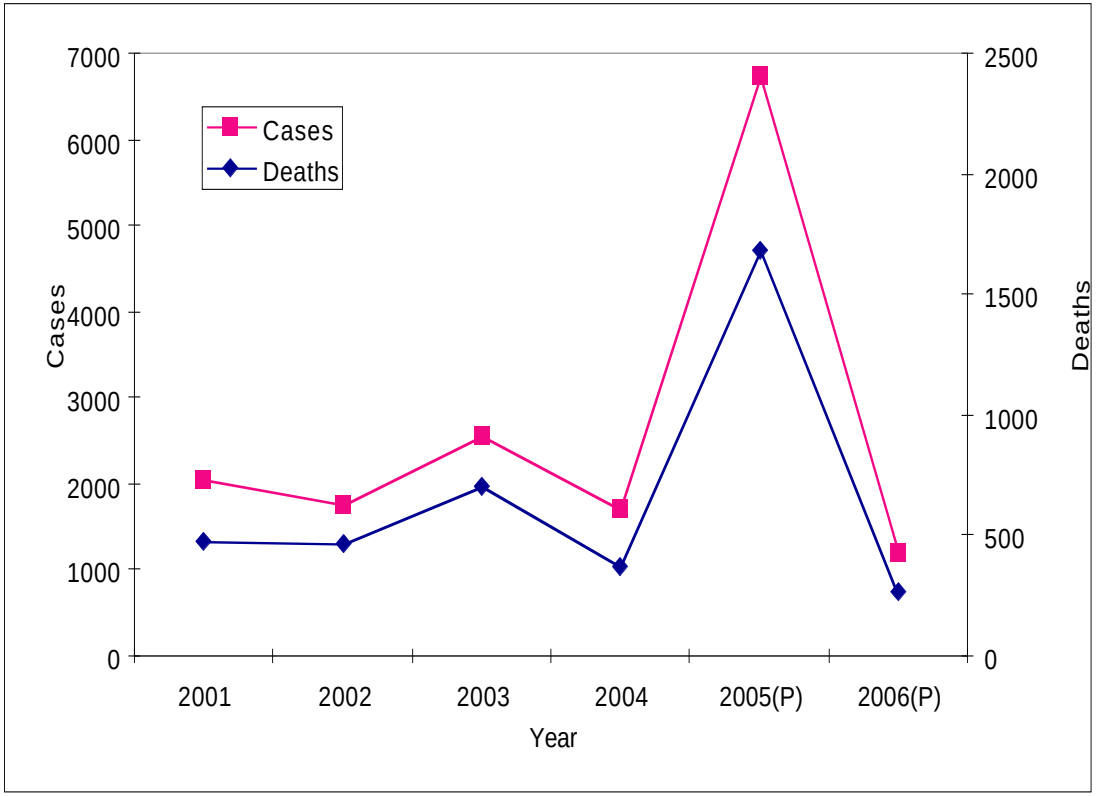
Vector:	mosquitoes (females) belonging to the groups - Culex tritaeniorhynchus - Culex vishnui
Breeding:	particularly **rice-fields**
Biting:	**crepuscular (twilight) periods**
Virus:	Flavivirus
Circulation:	ardeid birds (herons and egrets)
Amplifier:	**Pigs,** birds

Culex mosquito laying eggs (CDC)

Outbreaks of JE — often a surprise



India — recent years



Oya A & Kurane I. J Travel Med 2007;14:259-68
www.namp.gov.in/je.html

Current JE incidence trends – INCREASE

- Countries **without** public health programs
  - NO surveillance system
  - NO specific diagnostic tests
  - NO vaccination program

  E.g.: Bangladesh, Cambodia, India, Laos
- Population growth
- Irrigation for rice production
- Pigs rearing in many family farms

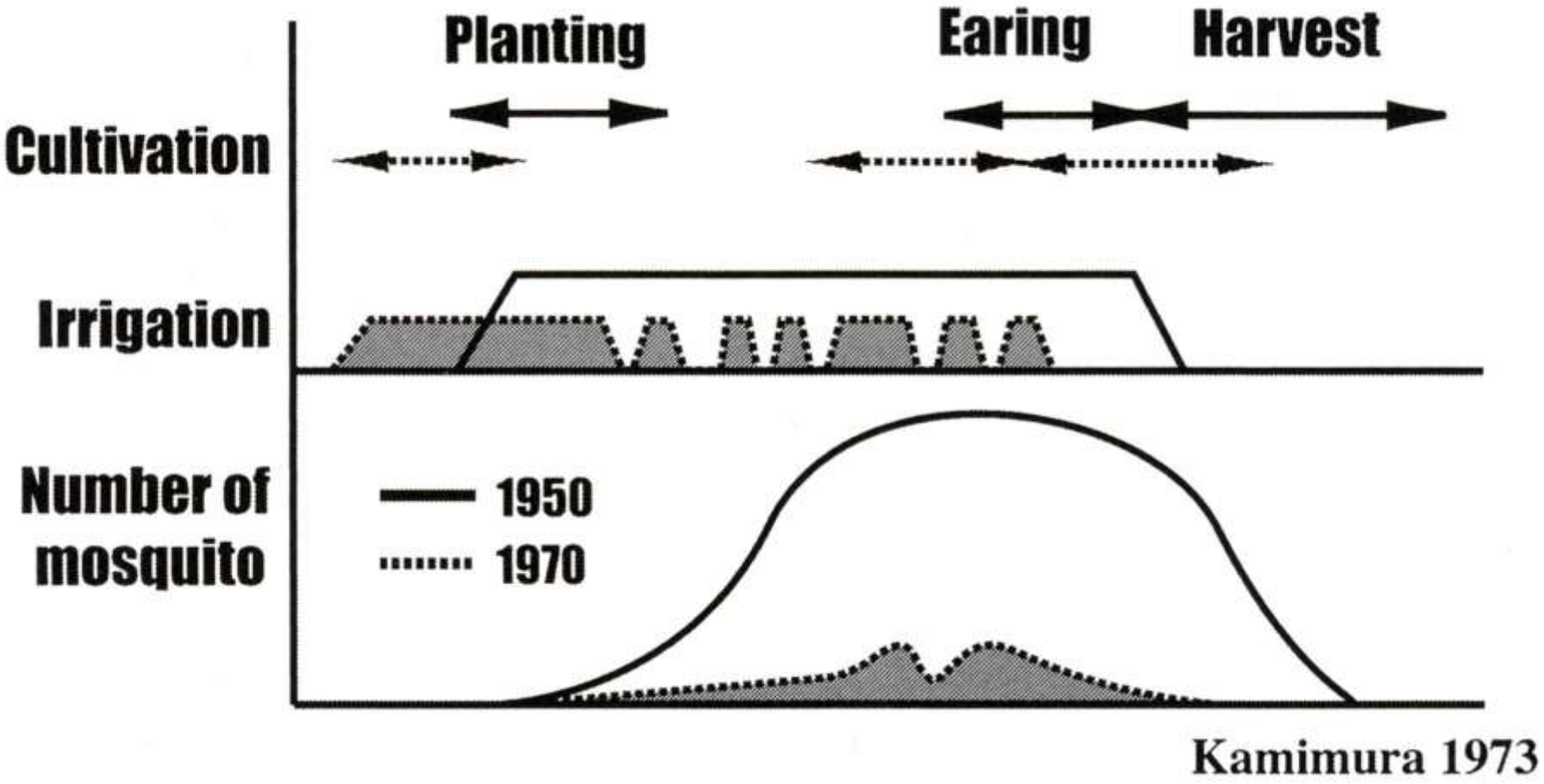
Erlanger TE et al. Emerg Infect Dis 2009;15:1-7
Oya A & Kurane I. J Travel Med 2007;14:259-68

Current JE incidence trends – DECREASE

- Countries **WITH** public health programs
  - Surveillance system
  - Specific diagnostic tests
  - Vaccination program

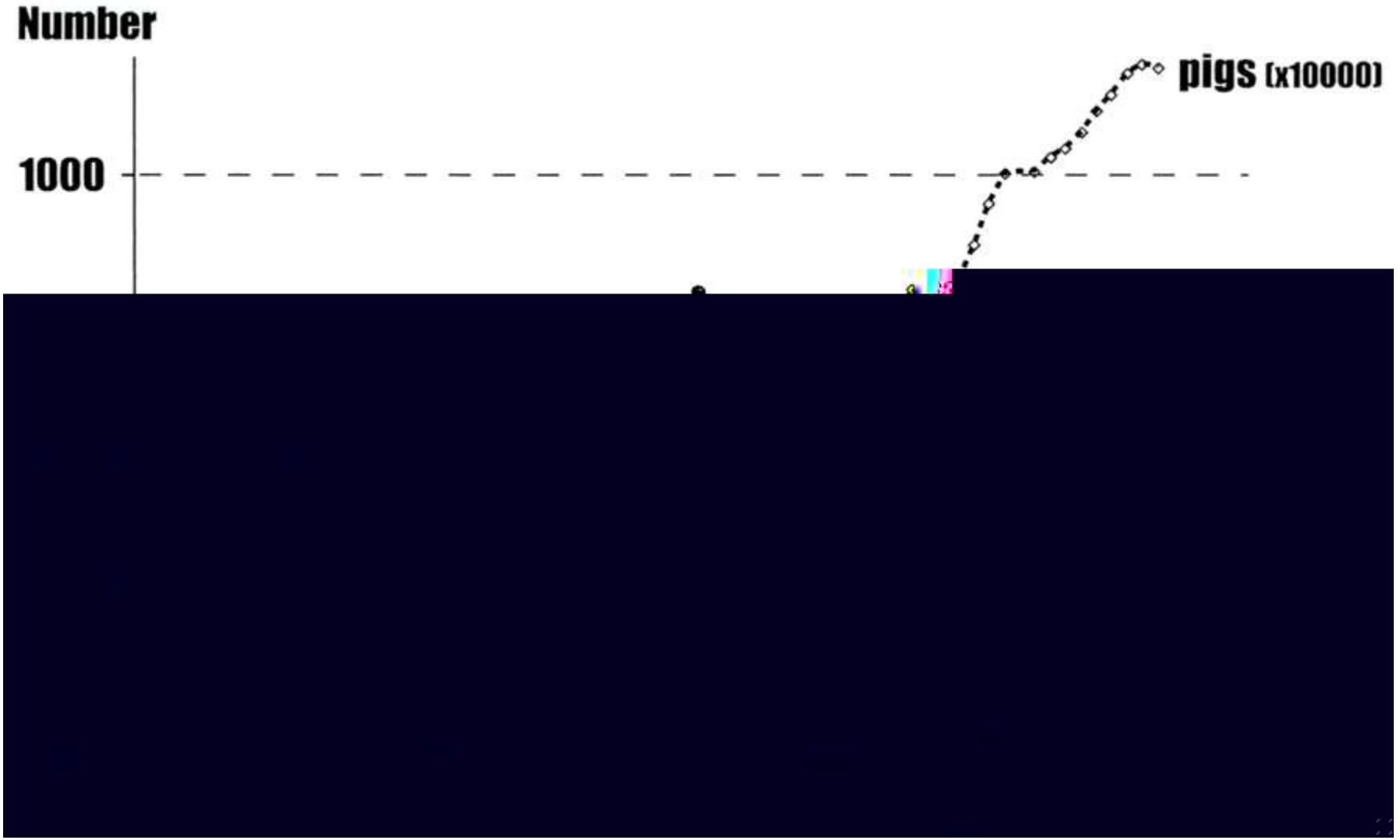
  E.g.: China, Japan, Nepal, South Korea, Sri Lanka, Thailand
- Intermittent irrigation in rice fields
- Collective pigsties far from population centers
- Use of pesticides

Burchard GD et al. J Travel Med 2009;16:204-16
Erlanger TE et al. Emerg Infect Dis 2009;15:1-7
Jelinek T. Expert Rev Vaccines 2008;7:689-93
Oya A & Kurane I. J Travel Med 2007;14:259-68
WHO position paper. Wkly epidem Rec 2006;81:331-40



Changes of rice cultivation procedures and decrease in mosquito numbers between 1950 and 1970. Irrigation in the rice pads has been occasionally stopped during rice cultivation since 1970.

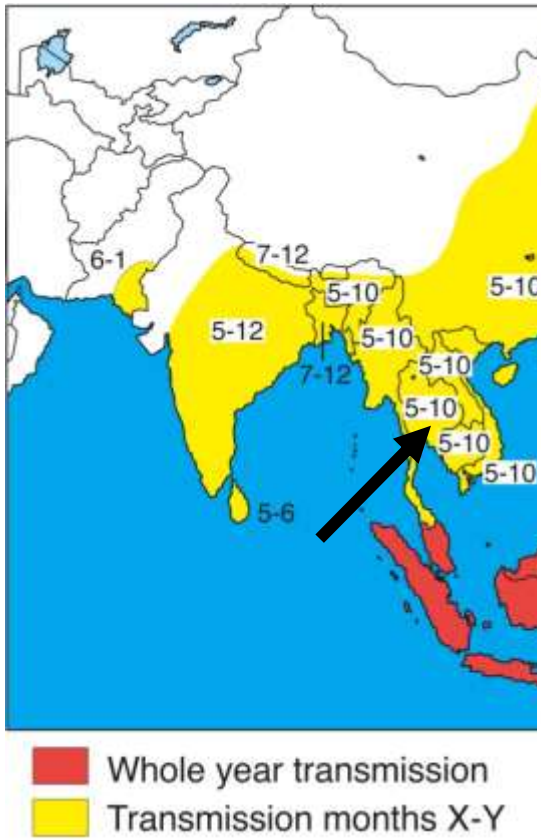
Oya A., Kurane I. J Travel Med 2007;259-68

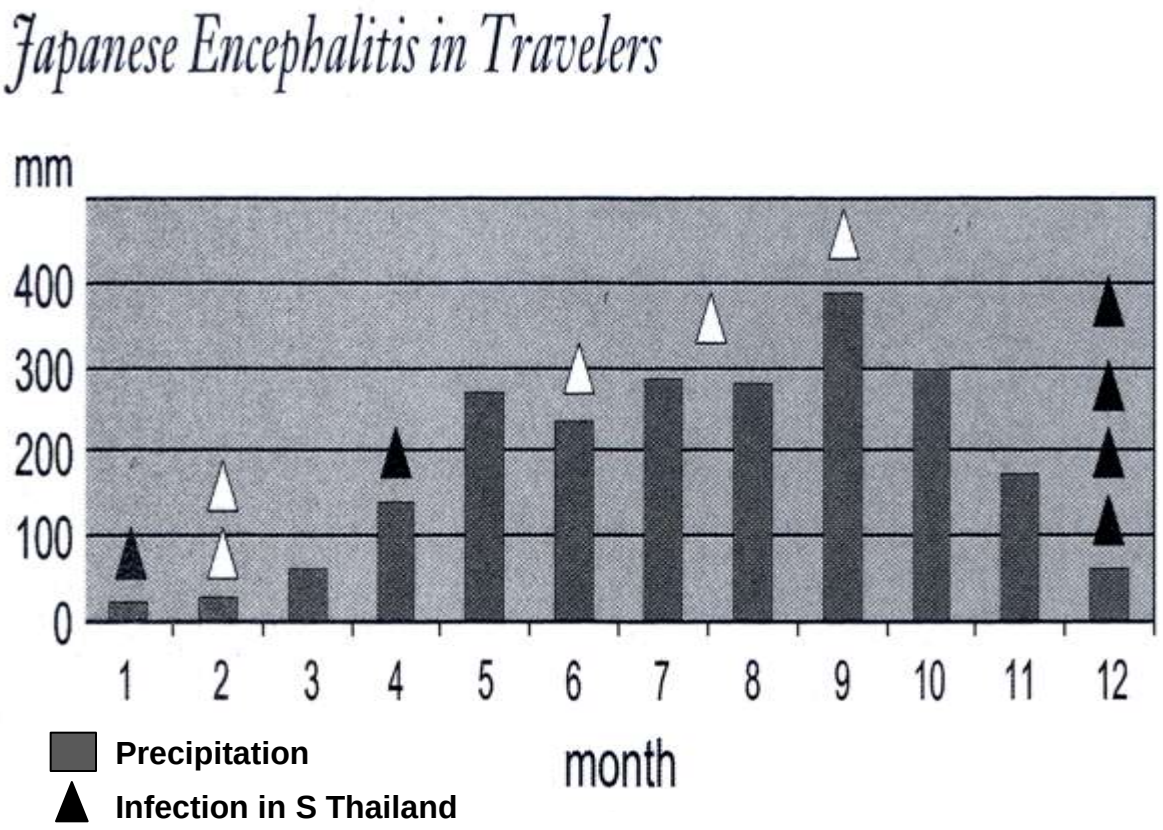


Converse relationship between the numbers of pigs and patients with Japanese encephalitis in Japan

Oya A., Kurane I. J Travel Med 2007;259-68

Is there reliable evidence on the to season of transmission?





Buhl M.R. et al, J Travel Med 2009;16:217-19

Risk of JE transmission

FOREIGN POPULATION	RATE
Finnish / Swedish travellers	**1 case / 300,000**
Travellers from any nationality	1 case/million **trips**
Travellers, rural areas (CDC 1993)	2-10 / 1000 / year
US soldiers, Thailand	4,3 / 1000 / year
COMPARISON	
Immunologically naïve locals	<0.1 >1/1000/y

Hills SL et al. Am J Trop Med Hyg 2010;82:930-6.
Buhl M & Lindquist L. J Travel Med 2009;16:217-9.
Shlim DR & Solomon T. Clin Infect Dis 2002;35;183-8.
WHO position paper. Wkly epidem Rec 2006;81:331-40.
Werlinrud AM et al. J Travel Med 2011; 18:411-13.

Assessment of JE cases in travelers

- 1973 - 2008: total of 55 cases record
  - 18% case fatality rate /
- BUT
  - xpatriates, 11% soldiers
  - **nan 1 month** stay abroad
  - Some just **beach vacation** with excursion(s)
  - **Thailand (n=19), Indonesia** (8), China (7), etc.

France — 2 cas:

1996, F 59 ans, touriste en Thaïlande (Bernard P, 1998)
2000, M 22 ans, touriste en Indonésie (Monnet FP, 2003)

Hills SL et al. Am J Trop Med Hyg 2010;82:930-6.

JE among travelers to Thailand

Patient		Stay	Type	Outcome	Reference
y/o	Resident of	Chronology			
21 F	England	9 wk THA/MAL/1992	Beach + 3d Trek	N/A	1
25 M	**Norway**	**2 wk Krabi/1997**	**Beach**	**N/A**	MSIS rapport
60 M	Finland	2 wk, S. Thailand	Beach + Nat. Park	Sequelae	N/A
22 F	U.S.A.	1 month Thailand	Student, Chiang Mai	N/A	2
30 F	Netherlands	N/A, Thailand	N/A	Slow recovery	3
60 M	**Finland**	2 wk Phuket, Khao Lak	Beach, 2 excursions	**Sequelae**	3
91 M	**Italy**	**3 mo. Phuket/2008**	**Room Kata Beach**	**Died**	Thitiphuree p.c.

1 Burdon JT. J Infect 1994;28:175-9
2 CDC. MMWR 2005;54:123-5
3 Lehtinen V. J Clin Virol 2008;43:93-5

JE among visitors to Bali

Patient		Stay	Type	Outcome	Ref
y/o	Resident of	Chronology			
10 F	**Australia**	**14d / 1988**	**Beach hotel***	**Died**	1
60 F	**Swedish**	**10d / 1994**	**Beach hotel***	**Recovered**	2
51 M	**Danish**	**12d / 1994**	**Beach hotel***	**Died**	3
80 M	Swedish	3 wk /	Bali (+ Java)	Sequelae	4

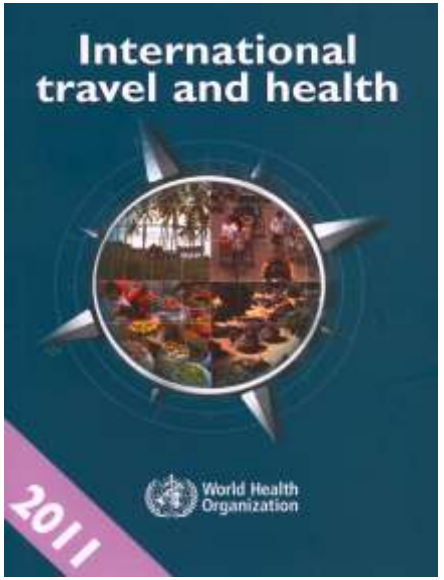
* one / few single day excursions

1 Macdonald WBG et al. Med J Aust 1989;150:334-9
2 Wittesjö B et al. Lancet 1995;345:856
3 Buhl M et al. Scand J Infect Dis 1996;26:189
4 Ostlund MR et al. Scand J Infect Dis 2004;36:512-3

Risque pour les voyageurs (OMS)

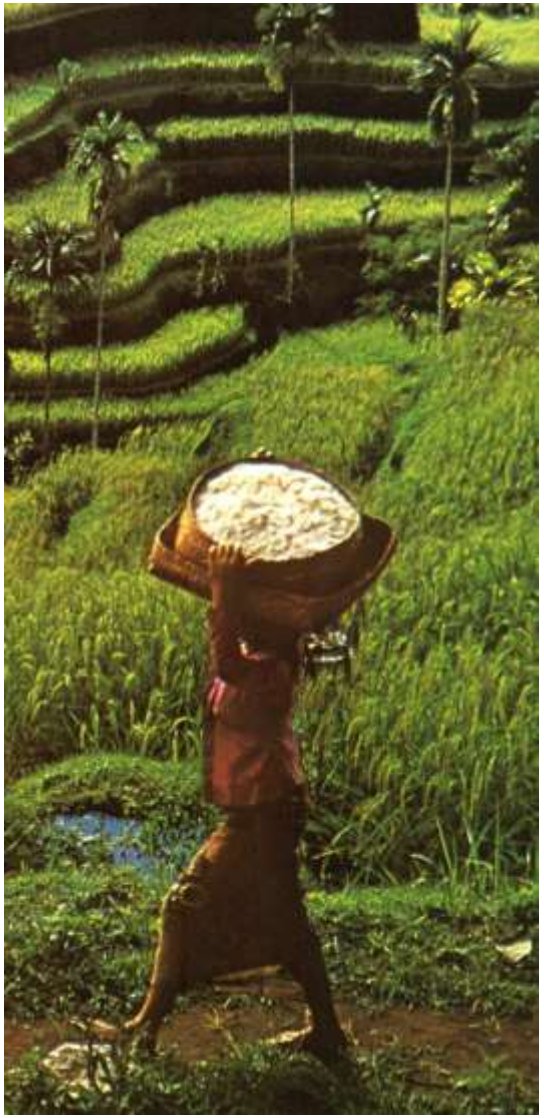
b 6 6 est très faible pour la plupart des voyageurs qui se rendent en Asie,

- surtout pour ceux qui effectuent un court séjour en milieu urbain,
- mais il varie
  - suivant la saison,
  - la destination,
  - la durée du voyage et les
  - 6 D



OMS: Voyages internationaux et santé 2011, p.103.

Lessons learned from recent reports



JE transmission NOT limited to „rice fields“ — may also occur in:

Beach hotel tourists (Bali, Thailand, Vietnam)

Tourists in cities (Angkor, Beijing, Hongkong)

VFRs (and refugees)

Werlinrud AM et al. J Travel Med 2011; 18:411-13.
Jeurissen A, Strauven T. Acta Neurol Belg 2011;111:143-5.
CDC. MMWR 2010;60:276-8.
Hills SL et al. Am J Trop Med Hyg 2010;82:930-6.

Four Seasons

Le(s) vaccins contre l'encéphalite japonaise

- Vaccin dévelopé par Intercell (IC-51)

  IXIARO® (Novartis Vaccins Europe, etc.)

  JESPECT® (CSL Australie, etc.)

- JE-VAX (Biken: Nakayama, cerveau de souris) historique
- JE-VC (Biken: cellules Vero) Japon (Février 2009)
- JE (Green Cross Vaccine Corporation: ± JE-VAX) Corée du Sud
- JenceVac (Shanta Biotech / GCVC-Corée, cerveau de souris)
- Vaccin vivant atténué SA 14-14-2 Chine, etc. (1988)
- Chimerivax-JE (Sanofi-Pasteur en évaluation)

Comparison of IXIARO and mouse-brain-derived vaccines

Characteristics	Mouse-brain-derived vaccines	**IXIARO**
Live/inactivated	Inactivated	Inactivated
Virus substrate	Mouse brain	Vero cells
Adjuvant	None	Aluminum hydroxide
Stabilizers	Porcine gelatin	None
Preservative	Thimerosal	None
Format	Lyophilized	Liquid, pre-filled syringe
Dosing schedule	3 doses (days 0, 7, 28)	2 doses (days 0, 28)

Tauber E et al. Lancet 2007; 370: 1847-1853.

IXIARO® — Composition

- Vaccin **inactivé**
- Contient 6 mcg de protéine purifié de JEV
- Souche atténuée SA14-14-2
- Produit dans des cellules Vero
- W 6 6 6 hydroxide d aluminium (0.25mg)

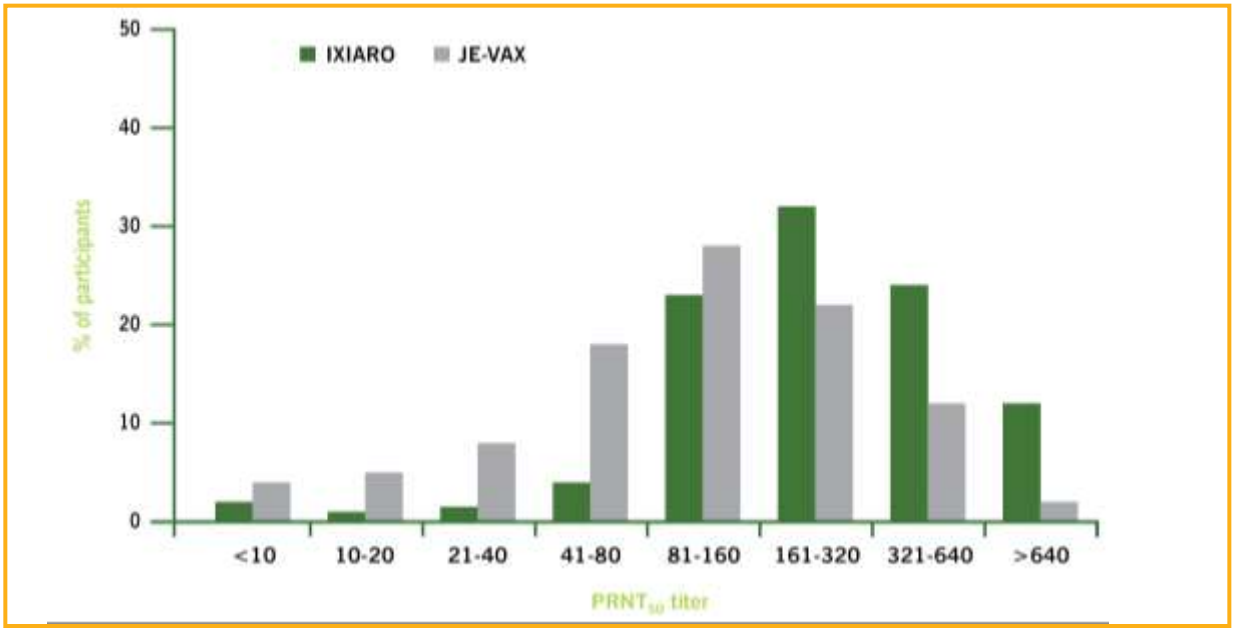
EXCIPIENTS

- Chlorure de sodium, phosphate monopotassique, phosphate disodique
- Traces de formaldéhyde et de sulfate de protamine suite au processus de fabrication

Immunogenicity: IXIARO / JESPECT vs. JE-VAX

- IXIARO / JESPECT provided protective antibodies* in **up to 98% of subjects**
- **Two doses** of IXIARO / JESPECT were non-inferior to three doses of JE-VAX
- Geometric Mean Titer (GMT): 244 for IXIARO / JESPECT and 102 for JE-VAX

JEV neutralizing antibody levels at day 56



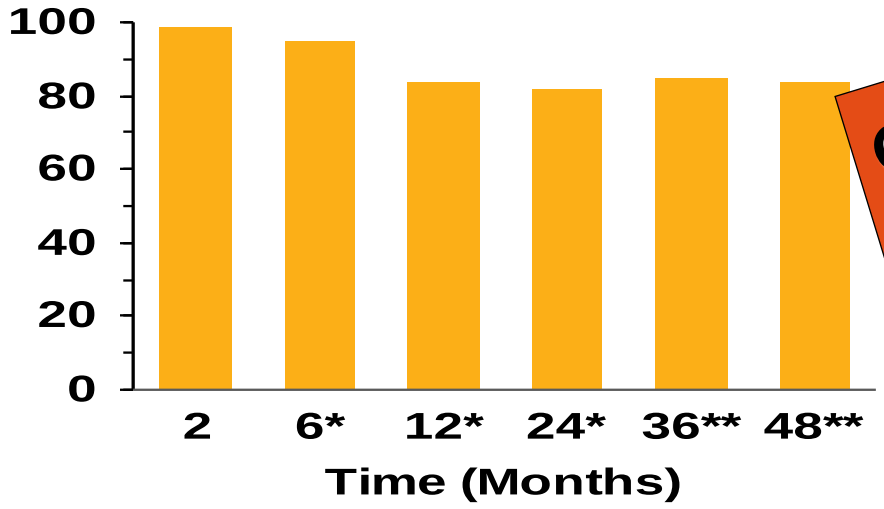
*A sero-protective threshold is defined as a PRNT titer of greater than 1:10.

Tauber E et al. Lancet 2007; 370: 1847-1853.
Hombach J et al. Vaccine 2005; 23: 5205-5211.

Proportion with persisting protective antibody levels

- 83% (151/181) of subjects who received IXIARO / JESPECT maintained protective antibody titers 12 months after vaccination §
- A study investigating the ideal booster interval is **ongoing (5th year)**

Protective antibody levels up to 48 months after first vaccination



GMT in protective range:

12 months	41.2
24 months	44.3
36 months	43.8
48 months	46.0

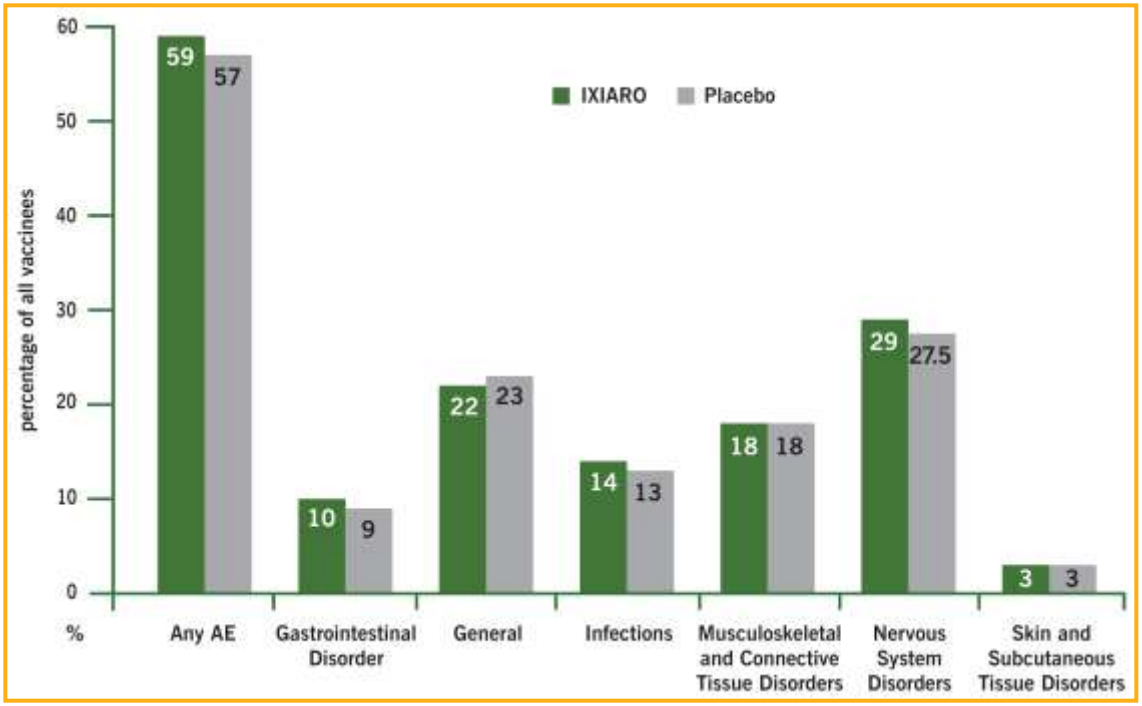
§ Sero-protective threshold is defined as a PRNT titer of greater than 1:10
*** n = 181; ** n = 152**

Schuller E et al. Vaccine 2008; 26: 4382-4386.
Hombach J et al. Vaccine 2005; 23: 5205-5211.

IXIARO / JESPECT: Tolerance profile

- SAEFI occurred in 0.5% (10/1993) of subjects receiving IXIARO and 0.9% (6/657) of subjects receiving placebo (vaccine without antigen)
- Headache noted in 3%; **no allergic reactions were observed**

Common AEs during the total study period



Tauber E et al. J Infect Dis 2008; 198: 493-499.

Utilisation d'IXIARO

- **Série primaire: j0, j28 ± 4 (0.5 ml par dose)**
- **Injection IM** (ou SC en cas de risque de saignement)
- **Début de protection: 1 semaine après 2ème dose**

  NOTE: 1 dose resulte en seroconversion limité
- **Usage concomitant OK avec**

  Havrix

  Twinrix

  Typhim Vi

Contre-indications

- Hypersensibilité
  - Au principe actif
  - W6 6 6 6 6 6
  - W6 6 6 6 6
- Maladie fébrile aiguë grave
- Age < 18 ans (Manque de données)
- (Grossesse: 6 6 6 6 ?
- (Allaitement: 6 6 6 6 ?

Problèmes — incertitudes (1)

- étude en route

(n = 1900 agés 2 mois à 17 ans, Philippines)

CDC / USA:

- Enrol children in pediatric clinical trial (5 sites)
- Administer IXIARO off-label 0.5 ml; age 2 months - 2 y: 0.25 ml
- Refer children to travel clinic in Asia (Asian vaccines)

Suisse: procédures pragmatiques similaires

Kaltenbock A et al. Vaccine 2010;28:834-9.
www.cdc.gov/nci/dod/dvbid/jencephalitis/children.htm

- Régistration pédiatrique: submission 2012 FDA/EMA

Problèmes — incertitudes (2)

- Schéma accéléré: étude en route
- Booster (3ème dose) après IXIARO: 1 à 2 années (?)
- Et en suite?: étude en route
- Booster après JE-Vax: étude en route

- Batch JEV09L37A, utilisé en France: protection?
  (Délivré Juin 2010, périmé Août 2011)

Global availability of IXIARO/JESPECT

- As per Novartis Vaccines, February 2012:

  Europe: A, B, CH, CZ, D, DK, E, F, GB, H, IRE, I, NL, N, PL, P, S, SF

  Asia: Hongkong, Israel, Macau, (Singapore),

  Oceania: Australia, New Zealand

  Americas: Canada, U.S.A.

- International Society of Travel Medicine

  Global Travel Clinic Directory

  Product Availability Listing

  (Member benefit only, Q1/2013)

www.istm.org

JE vaccine recommendations, travellers

Traditional:

- i 6 6 6 6 6 H-4 weeks
- With RURAL overnight stays

Example: Agronomics student preparing Ph. D. thesis, living close to rice fields

NEW (2010): *no more minimal stay*

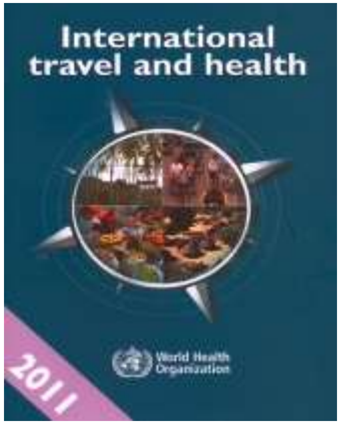
Do we protect all at risk? → NO!

Consider:

- Cumulative exposure
- Request for maximum protection

WHO: International Travel and Health, Geneva 2010, pp 115-7.
CDC: 'Yellow book' 2010,
wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/japanese-encephalitis.aspx

Recommandations pour les voyageurs (OMS)



b 6 6est recommandée aux voyageurs

- qui ont des activités de plein air

  (camping, randonnée, activités professionnelles, etc.)

- pendant la saison de transmission

- dans les pays ou zones à risque,

  notamment dans les endroits où les cultures sont irriguées par inondation.

- Z 6 6 6 6 6 6 B6 6 6 6

  6 6 B6 6 6 6 6 6 6 6 6 D

- Les moyens de prévention sont la protection contre les piqûres de moustiques > 6 ?6 6 6 D

OMS: Voyages internationaux et santé 2011, p.103.

Recommendations CMVI

1.2.1 Encéphalite japonaise

b 6 6 6 6 6**n'est pas recommandée systématiquement** à tous les voyageurs qui se rendent dans les régions où le virus circule (Avis du Haut Conseil de la santé publique, 2009; cf. carte 1). Seuls sont concernés :

- les adultes, expatriés ou devant **résider plus de 30 jours** dans ces régions ;
- les adultes se rendant dans ces régions,
  - avec une activité extérieure importante,
  - plus particulièrement dans les zones de rizières ou de marécages,
  - pendant la période de transmission du virus, notamment pendant la saison des pluies,
  - **quelle que soit la durée du séjour.**
- Les situations suivantes sont considérées comme à risque :
  - nuit passée à la belle étoile sans moustiquaire,
  - B6 6 6 B6 B6 DDB6
  - 6 6 6 6 6 6 6 6 6 6 D

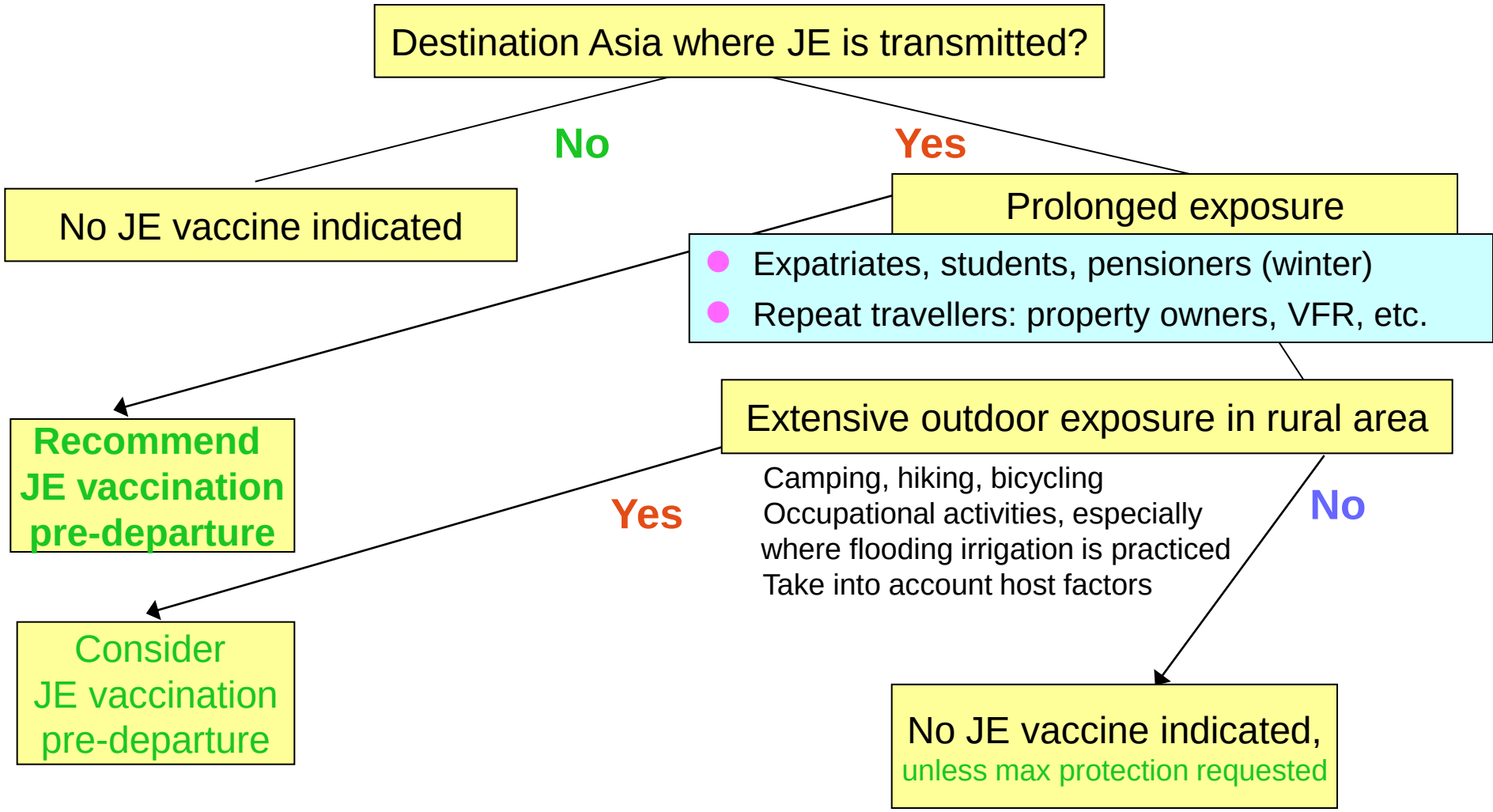
Avis du Haut Conseil de la santé publique. BEH 2011; No 18-19 (17 mai): p 208.

JE immunization recommendations for travellers, 2011/2012

Country/region	World	USA	U.K.	AUS
Criteria: *Experts:*	*WHO*	*CDC*	*NaTHNac*	*NH&MRC*
Plan to **live** in endemic areas	+	+	+	
Long term residents (>3 months)		+	+	+
Visiting **rural** areas:		(endemic)		
>30 nights		+		+
>14 nights		PLUS		
- high risk (also <14 nights)	+ (*, **)	+ (*, **)	+ (***)	+ (**)
During **season** of transmission	+	+	+	(+)

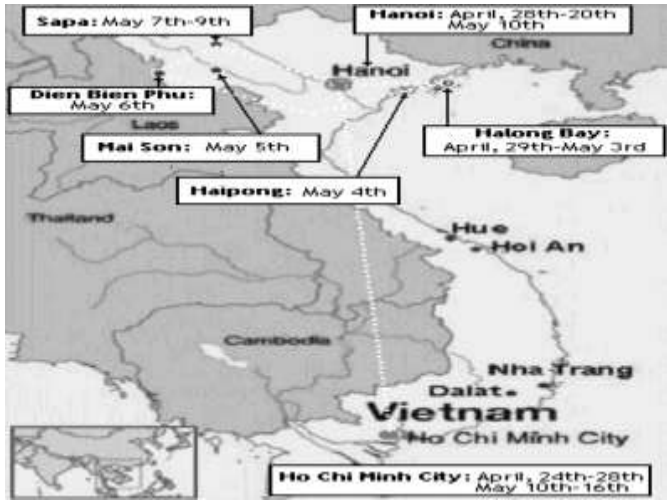
***** **Extensive outdoor, evening and nighttime exposure in rural areas**
****** **High individual risk (farming, camping, no bed nets)**
******* **Itinerary through rice fields and marshland; activities including fieldwork, camping, cycling**
+ **Immunization is recommended**

JE vaccination decision algorithm for travelers



Reserved for discussion

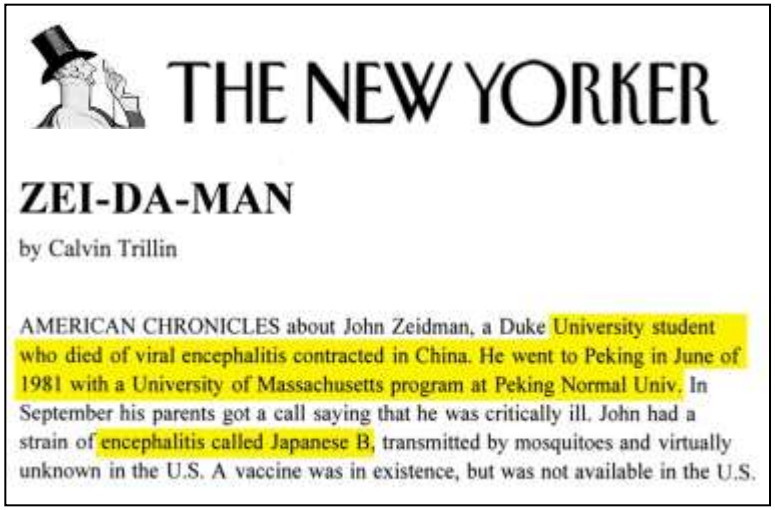
JE among visitors to Vietnam



Patient		Stay	Type	Outcome	Ref
y/o	Resident of	Chronology			
49 M	Italy	3 wk / 2006	Tourist/hotels	Few sequelae	1
9 M	U.S.A.	<4 wk / 2008	VFR	Sequelae	2
37 F	Sweden	8 wk, North	Tourist	? Sequelae	Backhaus p.c.
65 F	Sweden	<1 mo, South	Tourist	Recovered	Vene p.c.
56 M	Sweden	<1 mo, South	Tourist	Sequelae	3
41 M	Sweden	N/A, South	Tourist	Sequelae	Nilsson p.c.

1 Caramello P et al. J Travel Med 2007;14:346-8
2 The Olympian (Seattle) 28.3.2008
3 Widerström M. Smittskydd 2001;9:97

JE among visitors to China



THE NEW YORKER

ZEI-DA-MAN

by Calvin Trillin

AMERICAN CHRONICLES about John Zeidman, a Duke University student who died of viral encephalitis contracted in China. He went to Peking in June of 1981 with a University of Massachusetts program at Peking Normal Univ. In September his parents got a call saying that he was critically ill. John had a strain of encephalitis called Japanese B, transmitted by mosquitoes and virtually unknown in the U.S. A vaccine was in existence, but was not available in the U.S.

Patient		Stay	Type	Outcome	Ref
y/o	Resident of	Chronology			
20 M	U.S.A.	3 mo / 1981	Student/Beijing	Died	1
35 F	U.K.	N/A 1982	Hongkong	Died	2
48 F	New Zealand	3 wk / 2004	Tourist	Sequelae	3
59 F	Germany	2 wk / 2006	Tourist + VFR	Sequelae	4
?? M	Finland	Long term	Beijing	Sequelae	5

1 -Da- -94
2 Rose Mr. J Infect 1983;6:261-5
3 Cutfield NJ. Int Med J 2005;35:497-8
4 Reppel M et al. Clin Neurol Neurosurg 2008;Dec16 (Epub only)
5 Siikamaki H. Suomen Laakarilehti 2002;40:3989-90

JE among travelers to various destinations

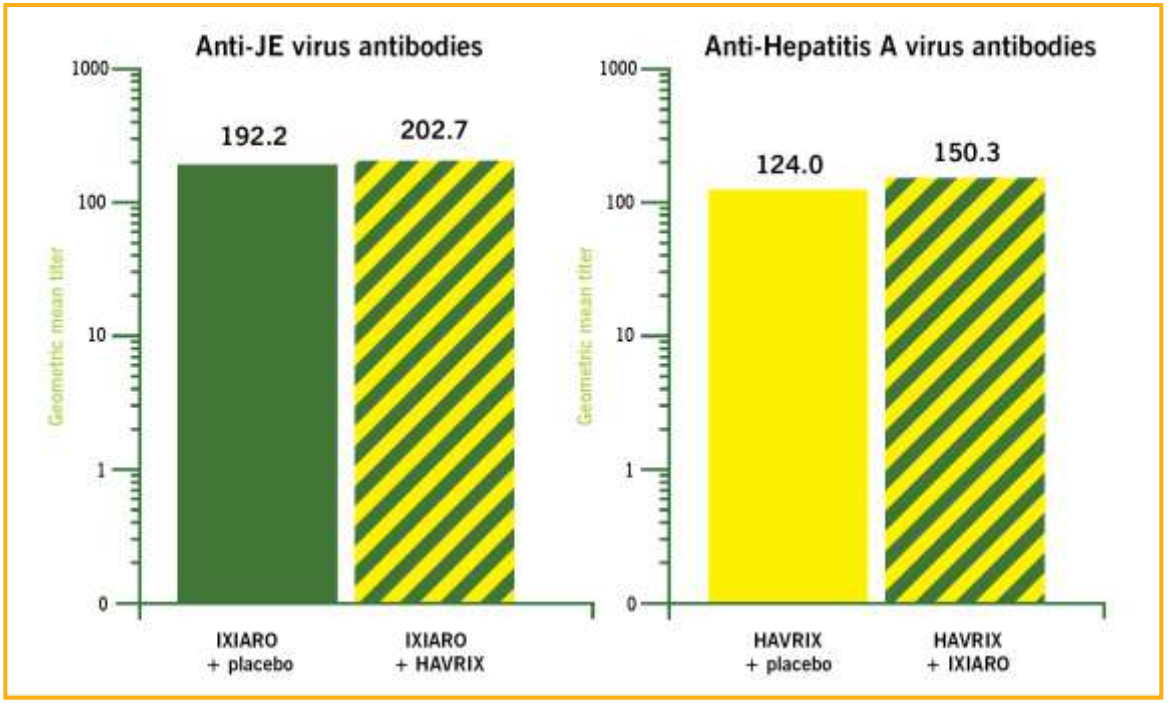
Patient		Stay	Type	Outcome	Ref
58 M	Norway	long, Philippines	Looking for Spouse	Died	Blystad p.c.
65 M	Norway	3 y, Philippines	Looking for Spouse	Died	Blystad p.c.
29 F	Netherlands	N/A, Indonesia	N/A	Slow recovery	1
32 F	Germany	Japan	Researcher	Recovered ?	Jelinek p.c.

1 Delsing CE. Ned Tijdschr Geneeskd 2005;149:2423-7

Immunogenicity: coadministration of IXIARO + Havrix

- Combination of IXIARO and Havrix non-inferior to either vaccine alone

Geometric mean titers for anti-JE virus antibodies and anti-Hepatitis A Virus antibodies



Havrix given with the first IXIARO dose

Steffen R et al. Poster presentation at the XVIIth International Congress for Tropical Medicine and Malaria 2008; Poster 216.
Lehner C et al. Abstracts of the 56th American Society of Tropical Medicine and Hygiene Annual Meeting 2007; Abstract 122.

Basic characteristics of IXIARO (=JESPECT)

- contains 6 mcg of i
  encephali
  f
  14-2)
- Vero cells
- adsorbed on aluminum hydroxide
- 0.5 ml per dose

A new vaccine