Immunizing travelers against neurological infections – New opportunities, new challenges

Robert Steffen

Conflicts of interest

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**
- Bavarian-Nordic
- **Baxter**
- Crucell / Johnson & Johnson
- GlaxoSmithKline
- Intercell
- **Novartis Vaccines & Diagnostics**
- **Sanofi Pasteur**
- SBL Vaccin

Drugs

DrFalk Pharma
Optimer
Roche
Santarus
Salix

McDonald‘s
Swiss International Air Lines

Spectrum of Disease and Relation to Place of Exposure among Ill Returned Travelers

David O. Freedman, M.D., Leisa H. Weld, Ph.D., Phyllis E. Kozarsky, M.D., Tamara Fisk, M.D.,* Rachel Robins, M.D., Frank von Sonnenburg, M.D., Jay S. Keystone, M.D., Prativa Pandey, M.D., and Martin S. Cetron, M.D., for the GeoSentinel Surveillance Network†

Table 2. **Diagnosis According to Syndrome Group and Travel Region among Ill Travelers Returning from the Developing World.***

Diagnosis	All Regions (N=17,353)	Caribbean (N=1115)	Central America (N=1326)	South America (N=1675)	Sub-Saharan Africa (N=4524)	South Central Asia (N=2403)	Southeast Asia (N=2793)	Other or Multiple Regions (N=3517)†
				number of cases per 1000 patients				
Systemic febrile illness‡	226	166	153	143	371	171	248	145
Neurologic disorder‡	15	23	24	16	10	15	10	16

‡ P<0.01 for the comparison among regions.

Rare: 1% of patients

N Engl J Med 2006;354:119-30

Travel-related diseases of the nervous system: Non-infectious: more frequent!

- **Adverse events** (neuropsychiatric)
  - Mefloquine and other antimalarials, vaccines (e.g. YF)
  - Repellents, insecticides (infants)
  - Recreational drugs
- Nutritional poisoning, e.g. Ciguatera
- Environmental
  - **Acute mountain sickness** → cerebral edema
  - Diving → decompression sickness
- **Motion sickness**
- Pressure palsies (post-flight)
- **Jet-lag** exacebates tension headache
- Sleep deprivation, jet-lag → seizure

Hill DR. J Travel Med 2000;7:259-66
Potasman I et al. J Travel Med 2000;7:5-9
Toovey S. Travel Med Infect Dis 2009;7:2-6
Wilder-Smith EP & Wilder-Smith A in Tropical Diseases in Travelers, Schwartz E. ed., Wiley-Blackwell, 2009

Epidemiology of viral travel-related infectious diseases of the nervous system

Vaccine preventable

- **Rabies**
- **Japanese encephalitis**
- Tick-borne encephalitis
- Poliomyelitis
- (Measles)
- (Influenza)

Other

- West Nile Virus (WNV) infections
- Rift Valley Fever (RVF)
- Toscana Virus infections
- Dengue fever
- **Etc., etc.**

Rabies in Belfast, Northern Ireland

Telegraph.co.uk

A woman who contracted rabies while working in an African animal sanctuary has become the first Briton to die from the virus for four years.

By Lucy Cockcroft

Last Updated: 7:51AM GMT 07 Jan 2009

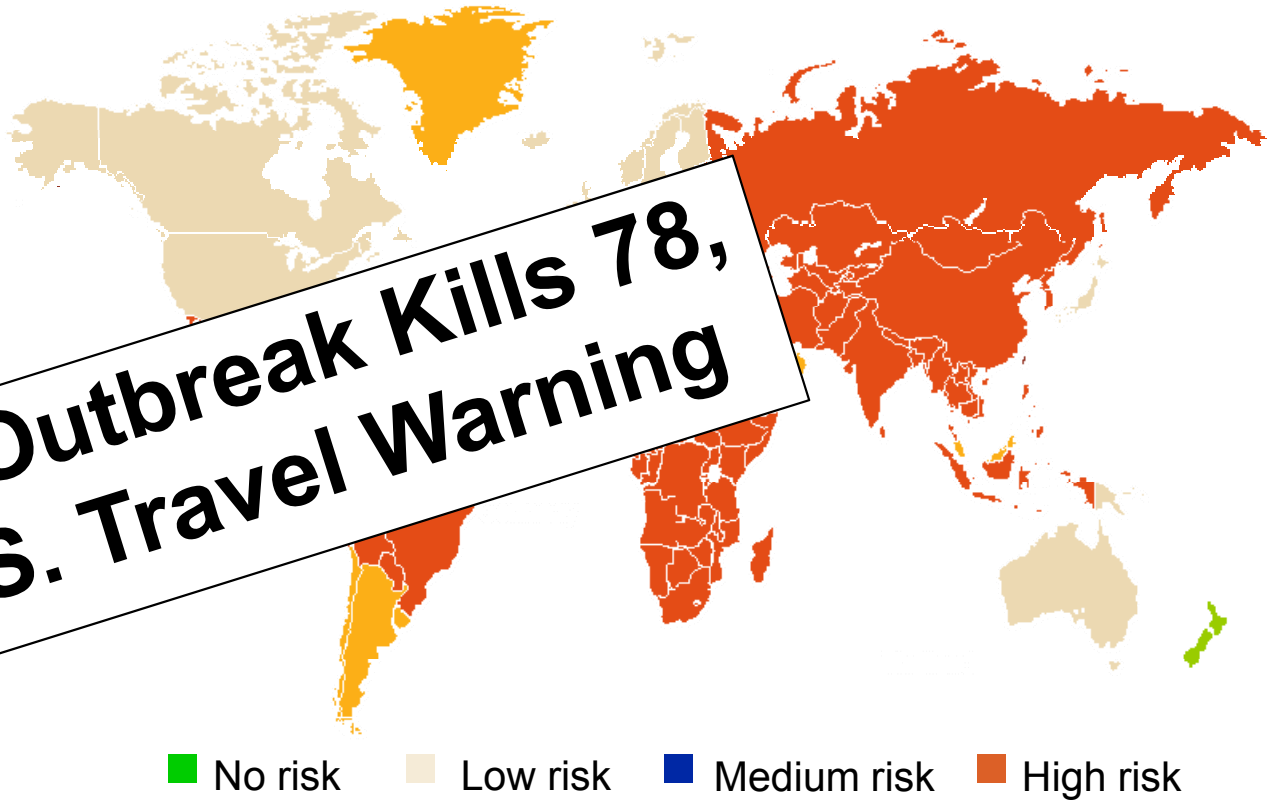
Rabies victim Lisa McMurray, who is thought to have contracted the disease from a dog
Photo: PA

Lisa McMurray, from Northern Ireland, had been in a critical condition in the intensive care unit of Belfast's Royal Victoria Hospital since the condition was diagnosed in December. It is thought she was infected with the virus, which is invariably fatal if not treated immediately, after being scratched or bitten by a rabid dog she had been helping to look after.

Rabies

- Transmitted by bites or scratches
  - 55’000 deaths/year
  - **India greatest risk**
  - Most human deaths following a **dog bite**
  - 30 to 60% in **children** aged <15 ye
  - 10
- **100%** non-immunes

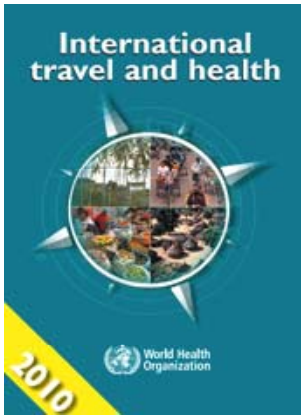
Areas at risk of rabies[1]



Bali Rabies Outbreak Kills 78, Leads to U.S. Travel Warning

WHO Rabnet http://gamapserver.who.int/mapLibrary/Files/Maps/Global_Rabies_ITHRiskMap.png (2010)
WHO Rabnet maphttp://gamapserver.who.int/Library/Files/Maps/human deaths_2003.jpg 3.
WHO International Travel and Health 2010, pp. 119-125

Particular risk for rabies



Destination:

India (15'000-20'000†)

Particularly, travel related:

- **Children***
- **Bicycle*/motorbike** riders
- **Trekkers, hikers*** (e.g. Nepal)
- **Prolonged stay***
- Professionals with exposure*
- Spelunkers*

*** WHO: International Travel and Health, Geneva 2010, Chapter 6, pp 119-25**

Potential rabies exposure in travelers

- U.S. Peace Corps: PEP in 4.4% per year

Bernard K & Fishbein DB. Vaccine 1991;9:833-6

- Swiss expatriates: 1.8% per year

Hatz CF et al. Vaccine 1995;13:811-5

- Nepal: 0.19 (tourists) to 0.57 (expatriates)/year

Pandey P et al. J Travel Med 2002;9:127-31

- Risk perception, French: 6.7%

Altmann M et al. J Travel Med 2009;16:107-11

Rabies in dogs imported from....

- Iraq: ‚animal rescue operation'

CDC. MMWR 2008;57:1076-8

- Morocco: various cases

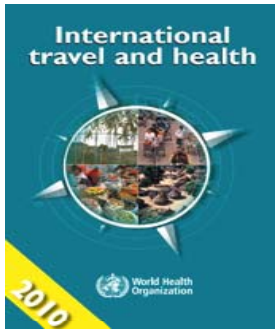
Eurosurveillance 2008;13 (11)
Eurosurveillance 2004;8 (36)

From Times Online

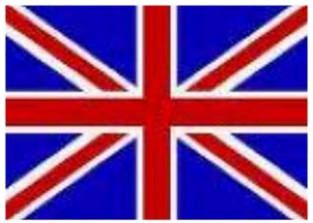
August 30, 2004

EU-wide alert after rabid dog found in France

Rabies immunization recommendations



„Pre-exposure prophylaxis for those planning a visit to rabies endemic country, especially if the visited area is far from urban centres, where...“



„Rabies pre-exposure vaccine should ... to adults and children who are at ... se

- **travelling to remote are...**
- **undertaking bi...**
- **trave... ...ic countries**
- **... ...andlers, and laboratory...“**

Various vaccines available in different countries

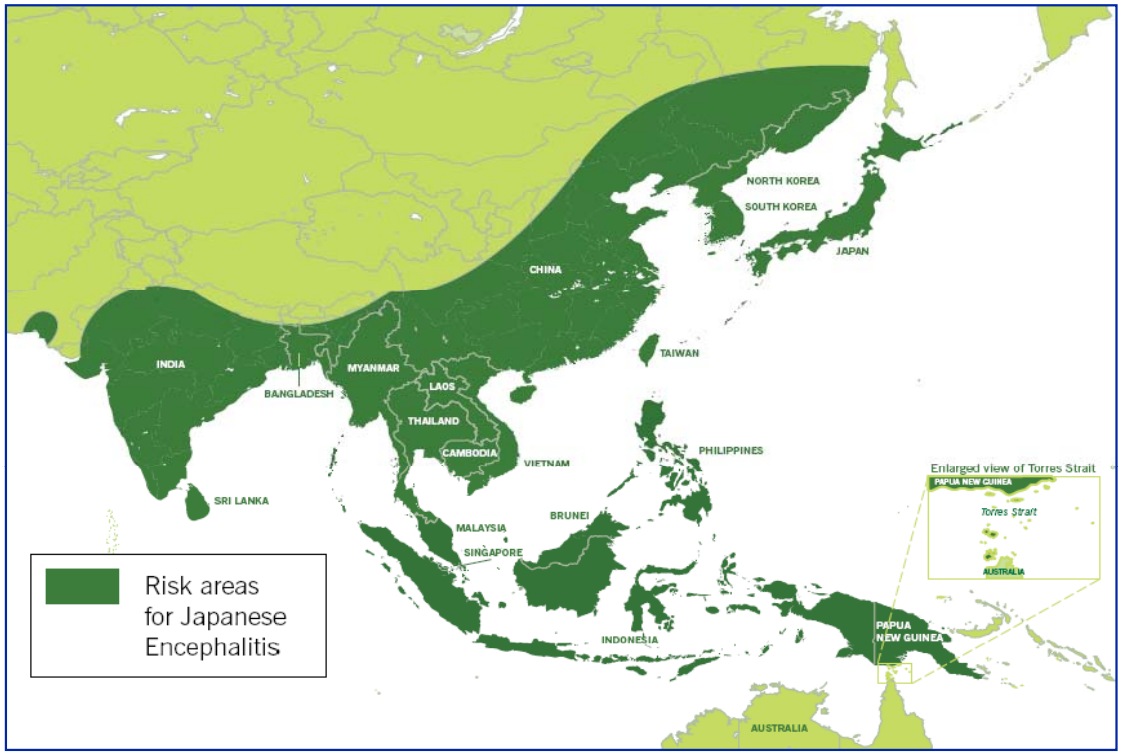
„... ...ine may be recommended based on

- **lo... incidence,**
- **... availability of appropriate anti-rabies biologicals,**
- **intended activity and**
- **duration of stay / repeat travel...“**

Basics on Japanese encephalitis (JE)

- Mosquito-borne flavivirus
- The leading cause of viral neurological infection and disability in Asia[1]
- 35,000–50,000 symptomatic cases reported each year among residents of endemic countries[2]
- Seasonality ?

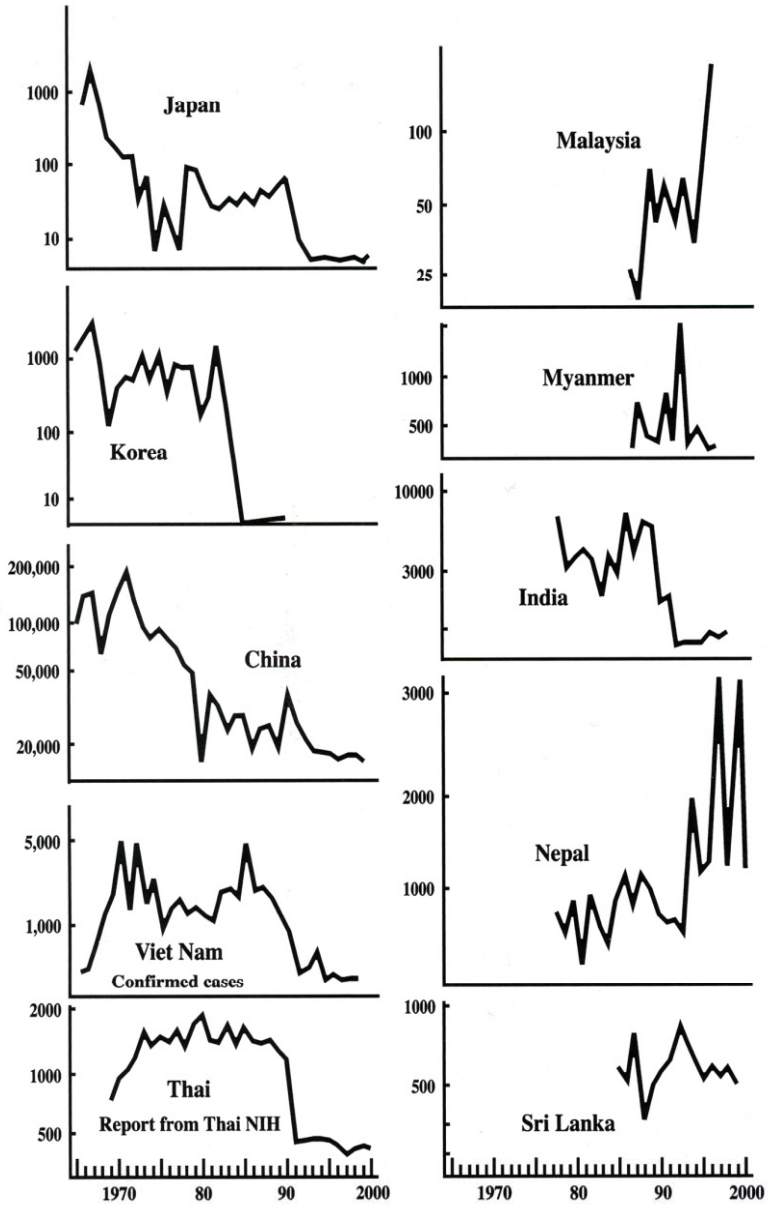
JE endemic areas: Asia and the Pacific



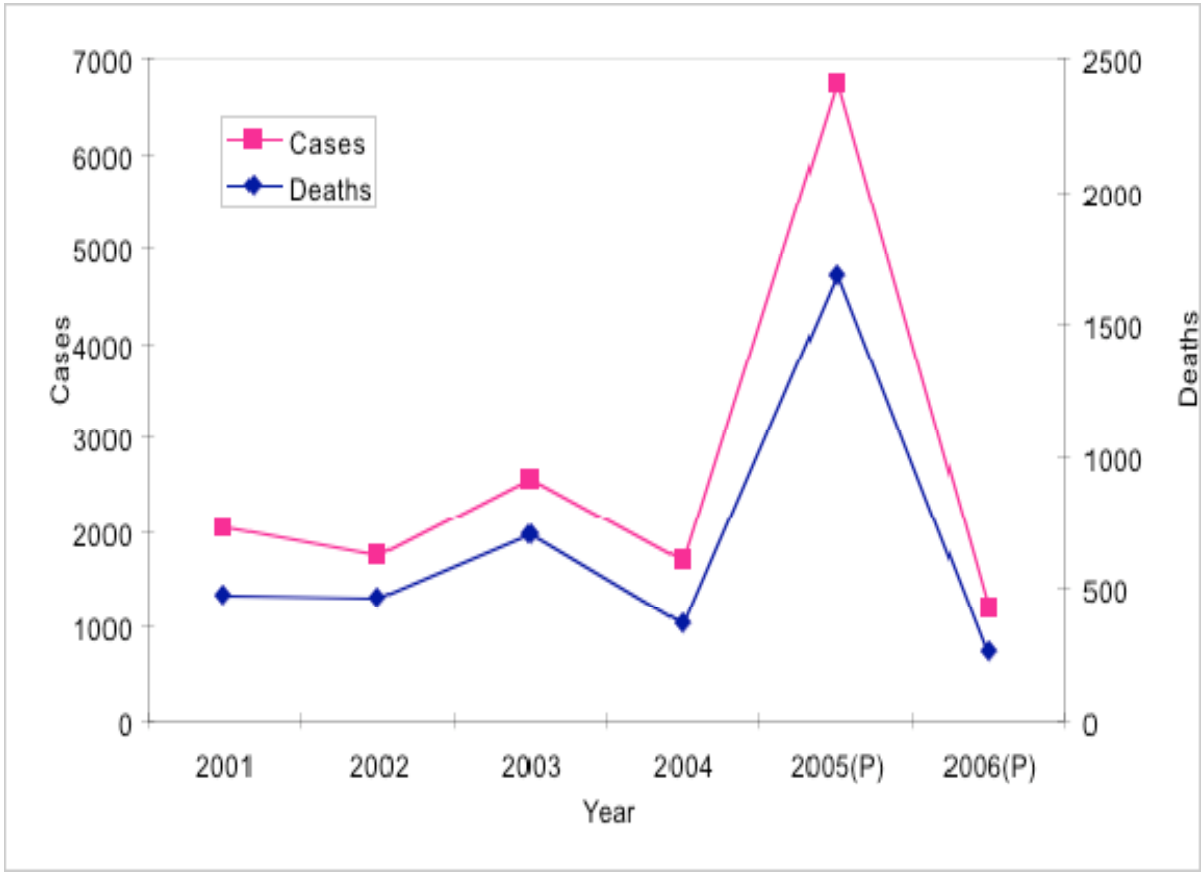
Adapted from CDC 2010[3]

1. PATH. 2008. http://www.path.org/projects/JE_in_depth.php
2. Solomon T et al. Lancet 2003; 361: 821-826.
3. Centers for Disease Control and Protection. Travelers' Health: Yellow Book. Chapter 2. 2010.

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

Risk of JE among travellers

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.

Assessment of JE cases in travelers

- 1973 - 2008: total of 55 cases recorded

- BUT
  - 60% tourists — 16% expatriates, 11% soldiers
  - 35% less than 1 month stay abroad
  - Some just beach vacation with excursion(s)
  - **Thailand (n=19), Indonesia** (8), China (7), etc.
  - 18% case fatality rate / 44% with sequelae

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

Lessons learned:

JE may also occur

- in hotel tourists
  (Bali, Vietnam)
- in cities (Beijing, Hongkong)

Caramello P. et al. J Travel Med 2007;14:346-48

JE vaccine recommendations, travellers

Traditional:

- Stays in endemic zones ≥ 2-4 weeks
- With RURAL overnight stays

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

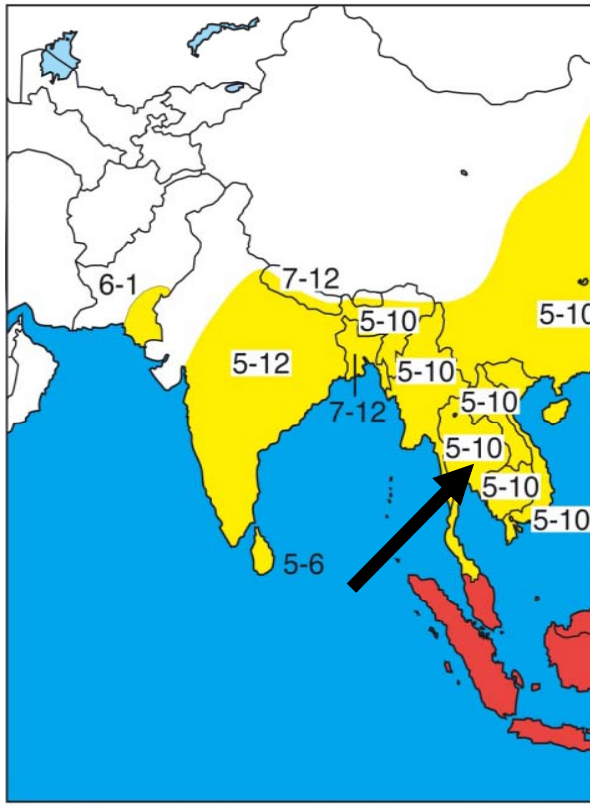
NEW (2010): *no more minimal stay*

- WHO: Extensive outdoor exposure: Camping, hiking
- Uncertain specific destination, activities, duration

Do we protect all at risk? Consider:
- Cumulative exposure
- Request for maximum protection

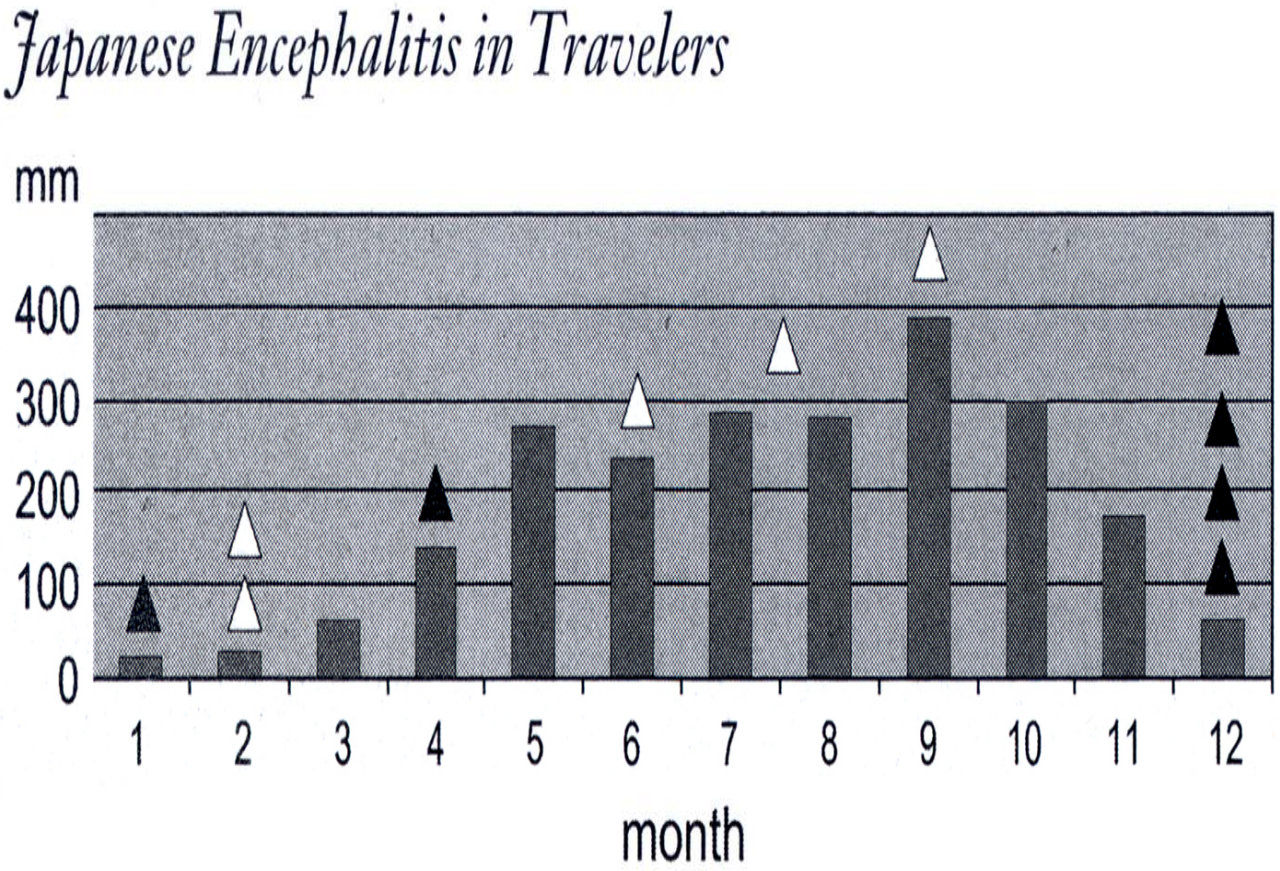
WHO: International Travel and Health, Geneva 2010, pp 115-7.
CDC: 'Yellow book' 2010,
wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/japanese-encephalitis.aspx

Is it evidence based to recommend JE vaccination only for the season of transmission?



Whole year transmission

Transmission months X-Y



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

JE vaccine:
Basic characteristics of JESPECT*

- contains 6 mcg of inactivated Japanese encephalitis virus (purified JEV proteins from attenuated strain SA_{14}-14-2)
- produced in Vero cells
- adsorbed on aluminum hydroxide
- 0.5 ml per dose
- Primary vaccination series: 0, 28 ± 4 days
- Accelerated schedule: no data yet
- Time to protection: 1 week after dose 2
  - NOTE: 1 dose results in limited seroconversion rates
- Booster: after 1 to 2 years (?)

* Name in Europe, Americas: **IXIARO**

Vaccination timelines

Primary vaccination series: 0, 28 ± 4 days

Accelerated schedule: no data yet

Time to protection: 1 week after dose 2

- NOTE: 1 dose results in limited seroconversion rates

Duration of protection: 1 to 2 years (?)

Booster: after 11 months to 2 years (?)

Contraindications

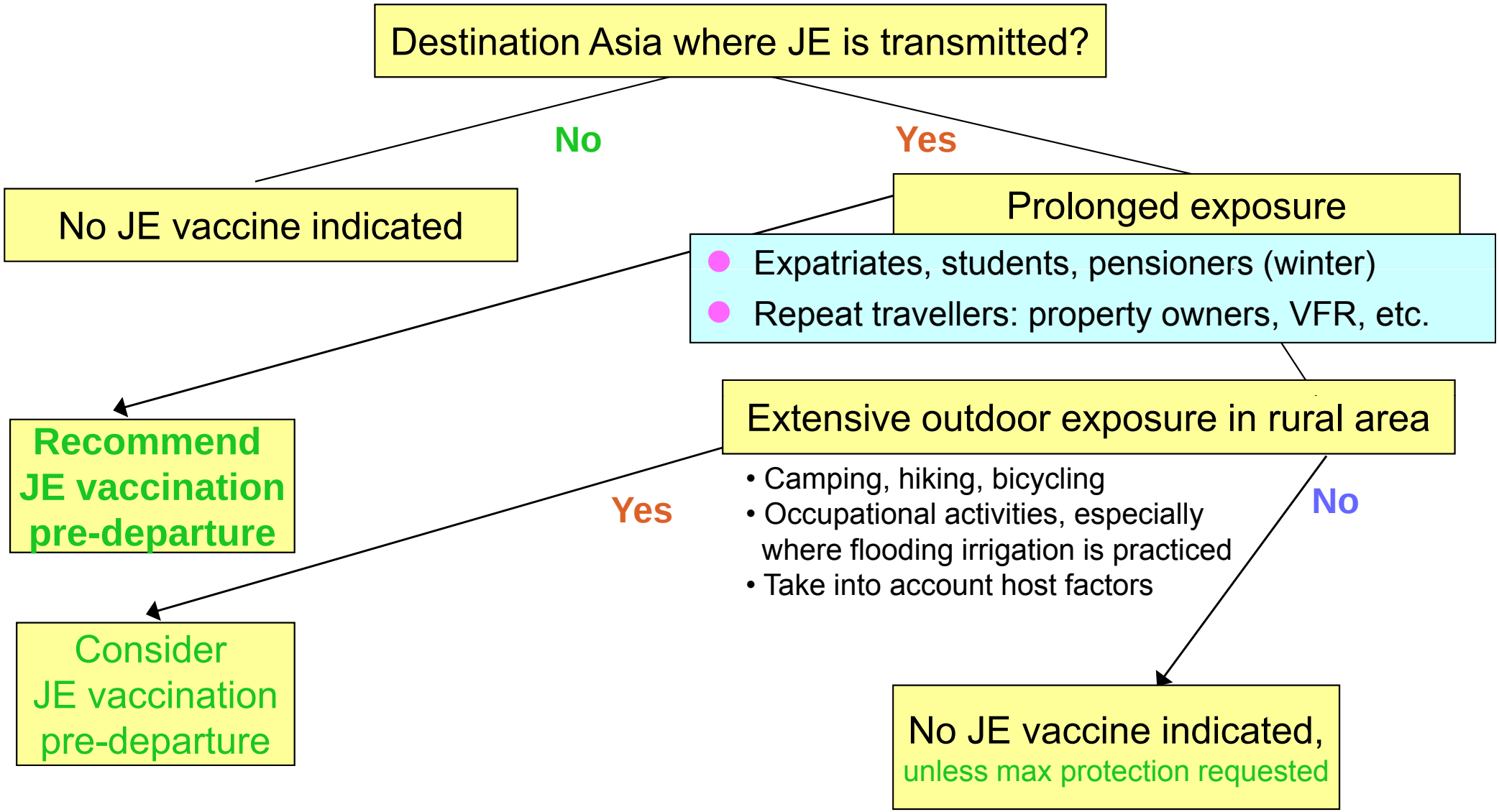
- Previous serious reaction to IXIARO/JESPECT
- Age < 18 years (no data)
- (Pregnancy: B1 — only if needed)
- (Lactation: only if needed)
- Where bleeding may occur following IM administration, IXIARO may be administered SC

JE immunization recommendations for travellers, 2010

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	+ (*, **)	+ (*, **)	+ (***)	+ (**)
During **season** of transmission	+	+	+	(+)

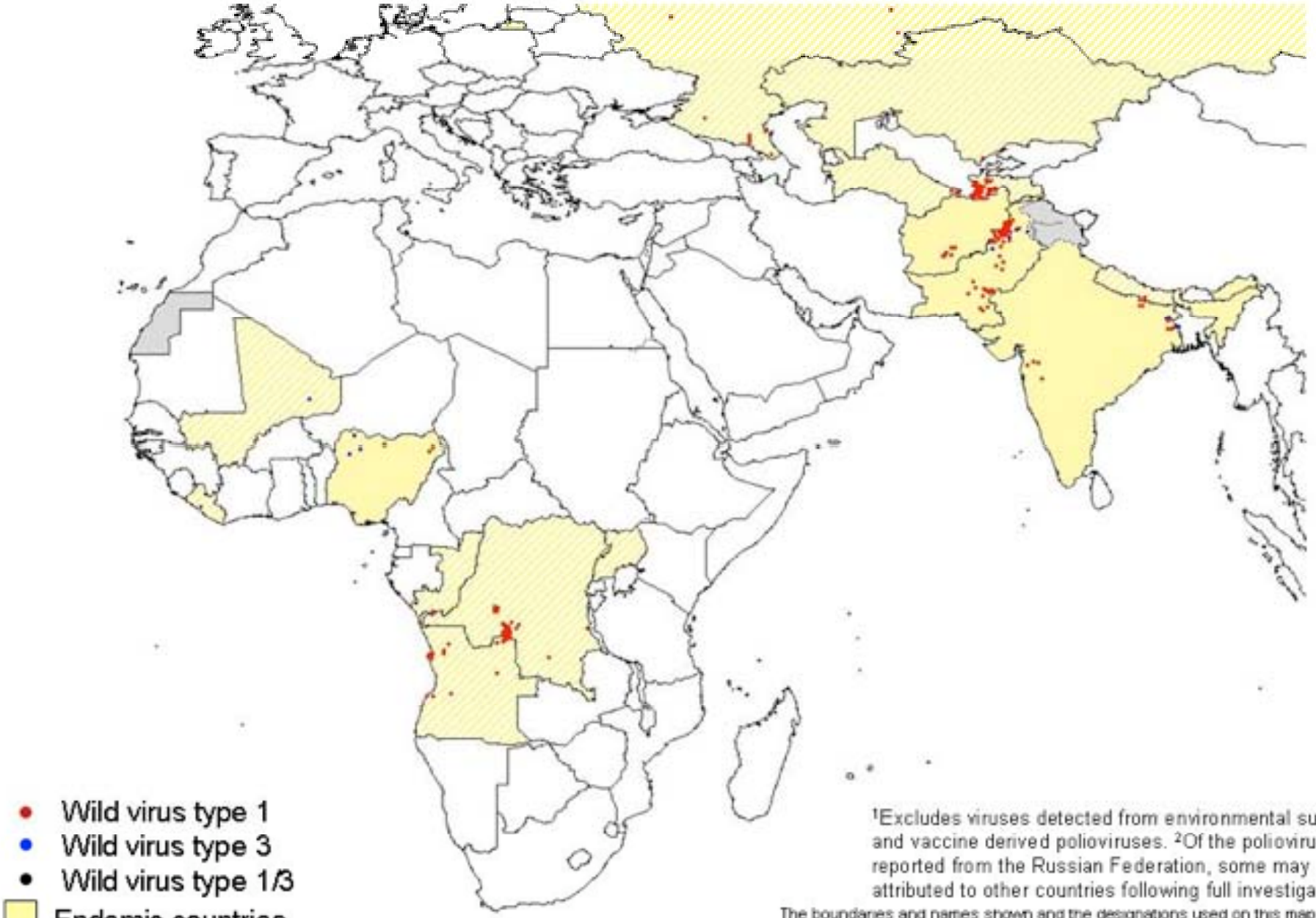
***** **Extensive outdoor, evening and nighttime exposure in rural areas**
****** **High individual risk (farming, camping, no bed nets)**
******* **Itinerary through rice fields and marshland; activities including fieldwork, camping, cycling**
+ **Immunization is recommended**

JE vaccination decision algorithm for travelers



Tick borne encephalitis (TBE)

Wild Poliovirus[1,2], 17 May 2010 – 16 Nov 2010



[1]Excludes viruses detected from environmental surveillance and vaccine derived polioviruses. [2]Of the poliovirus cases reported from the Russian Federation, some may be attributed to other countries following full investigation.

Influenza in travelers

Follow-up study:

Population: 1450 travelers to developing countries (1/1998 -3/ 2000)

Febrile illness: 289 (19.9%)

Two serum samples: 211 (73.0%) + 321 matched controls

Seroconversion for influenza virus infection (WHO CC London)

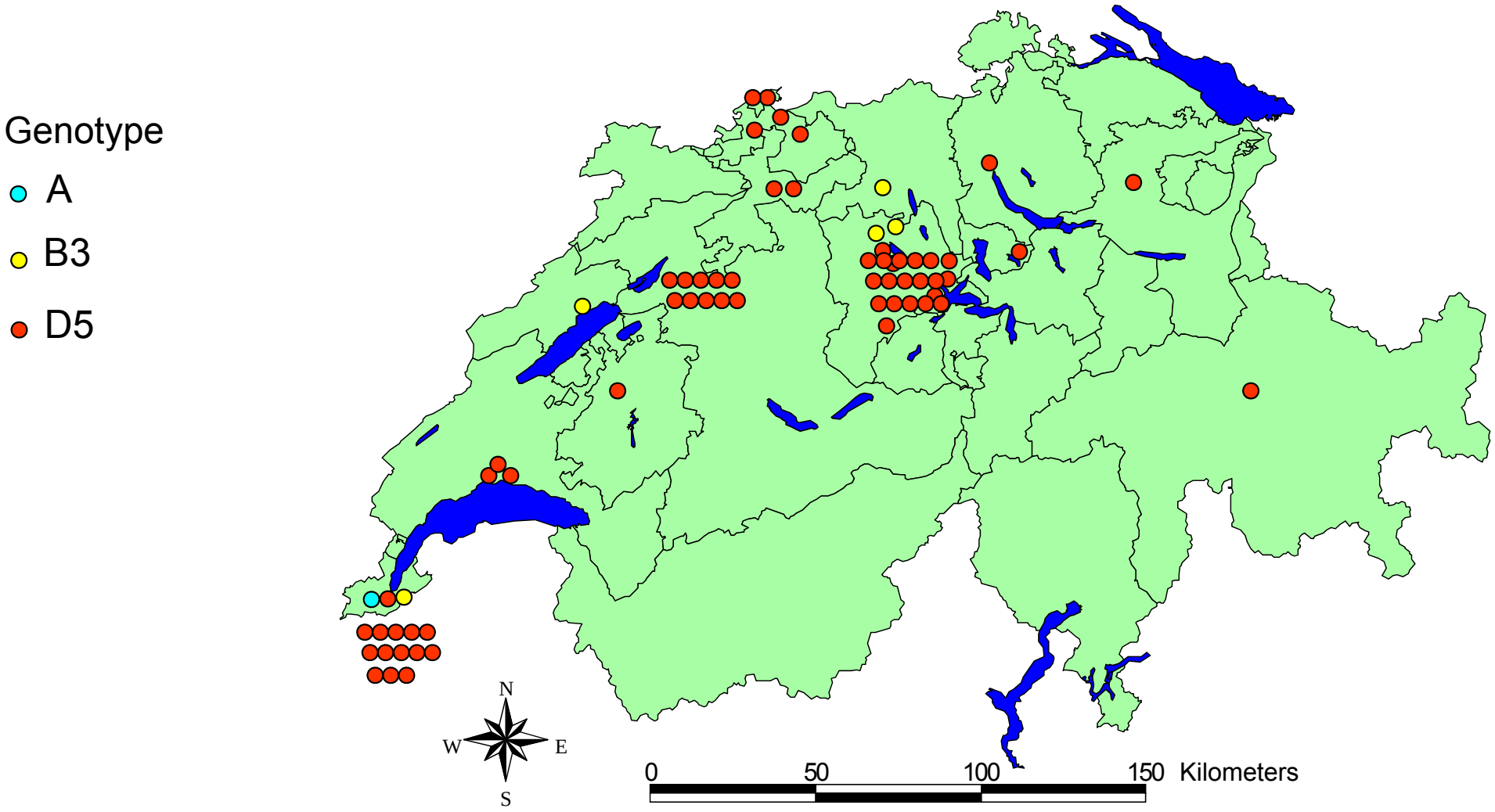
40 (67% with fever, 33% asymptomatic, 18 w/≥4x ab)

Incidence rate / 100 person-months: 1.0

2nd most frequent vaccine preventable infection!

Mütsch M et al Clin Infect Dis 2005;40:1282-87

Measles epidemic, Switzerland 2006-09
N = >4000, including 8 encephalitis



Courtesy: Prof. Ch. Aebi

Origin of the Swiss measles epidemic 2007-09 (n ≥ 4000, mostly genotype D5) ?

Courtesy: Prof. Ch. Aebi

Measles exportation from Switzerland

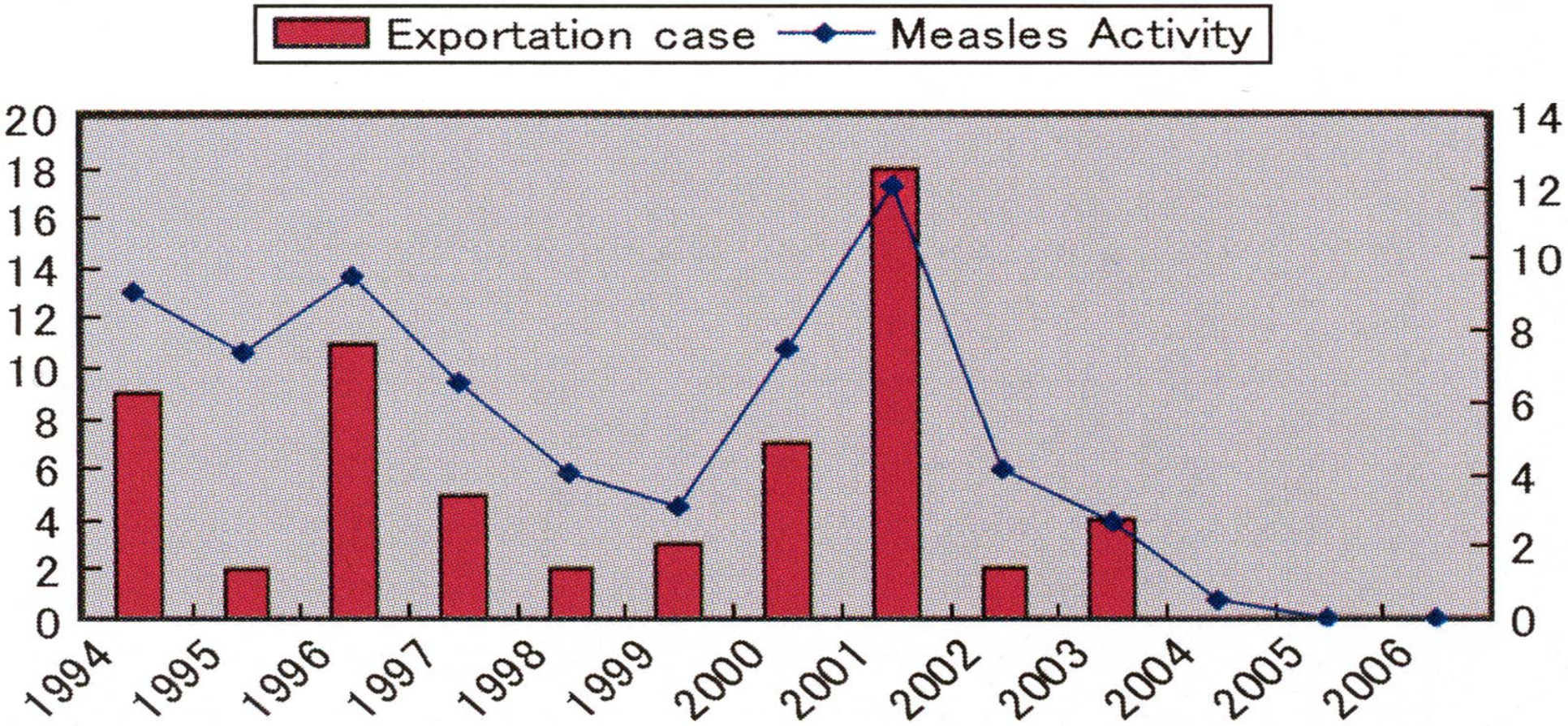


Figure 1 Index cases of exported measles ($n = 63$) from Japan to the United States (left scale) with annual measles activity (case per sentinel site, right scale), by year, 1994 to 2006.

Takahashi H. et al, J Travel Med 2008;15:82-86

Dr. Judy MacDonald of the Calgary Health Region stressed there is, so far, no indication that any members of the group are infectious.

Japanese tour group quarantined in Banff

Updated Mon. May. 28 2007 9:20 PM ET

CTV.ca News Staff

Health officials have quarantined about 130 Japanese tourists in a resort hotel in Banff after one sick member of the group who remained in B.C. tested positive for the measles.

The group, reportedly mostly high school students, arrived in Calgary from Vancouver on Sunday. The tour group then boarded buses and headed toward the Rocky Mountain resort town.

Imported cerebro-meningeal infections
French infectious disease unit, Saint-Mandré

Population:	35 M, 21 F, total n = 56
◆ 45% tourists	Aged 16 to 83 (mean 29)y
◆ 27% military	
◆ 16% immigrants	
◆ 12% expatriates	
Etiology confirmed:	42 (75%)
◆ Malaria	12
◆ Bacterial	4
◆Viral	**24**
– **Enteroviruses**	**11**
– **Herpesviridae**	**8 (1 fatal with HSV-1)**
– **HIV**	**2 (primary infections)**
– **Dengue**	**1**
– **Toscana**	**1**
– **EBV**	**1**

Rapp C. J Travel Med 2010;17:1-7

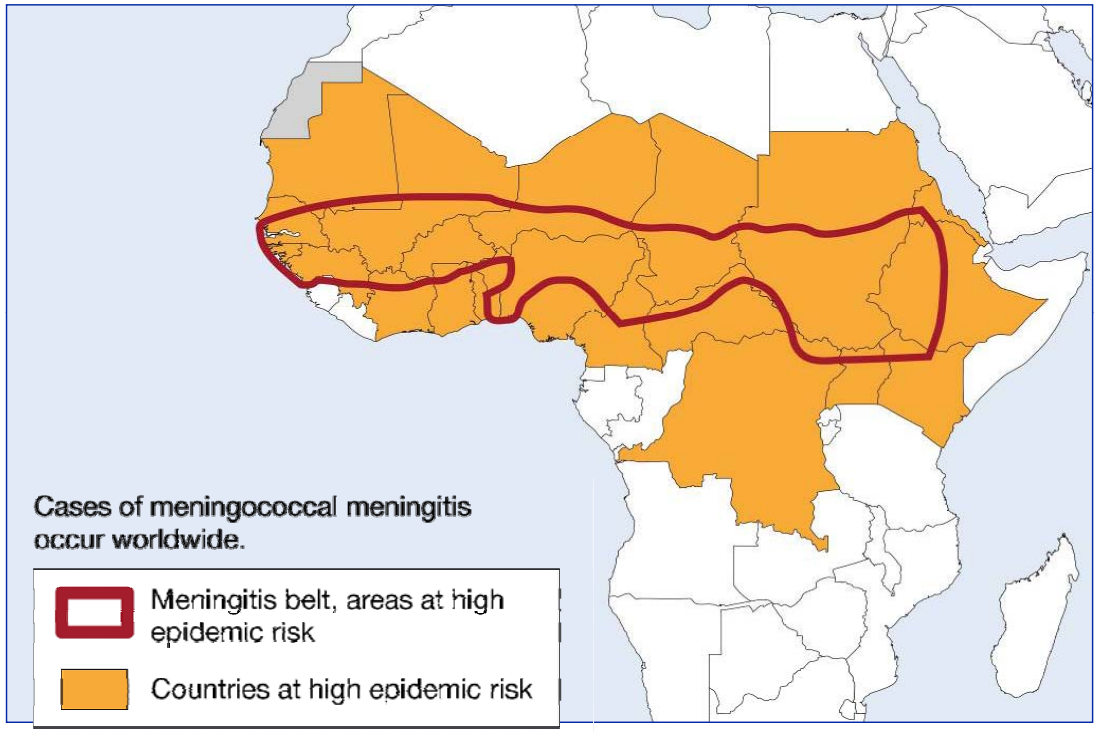
Meningococcal disease

Caused by the bacterium *Neisseria meningitidis*

- Most epidemics caused by serogroups A, B, C, W-135 and X
- Spread from person to person

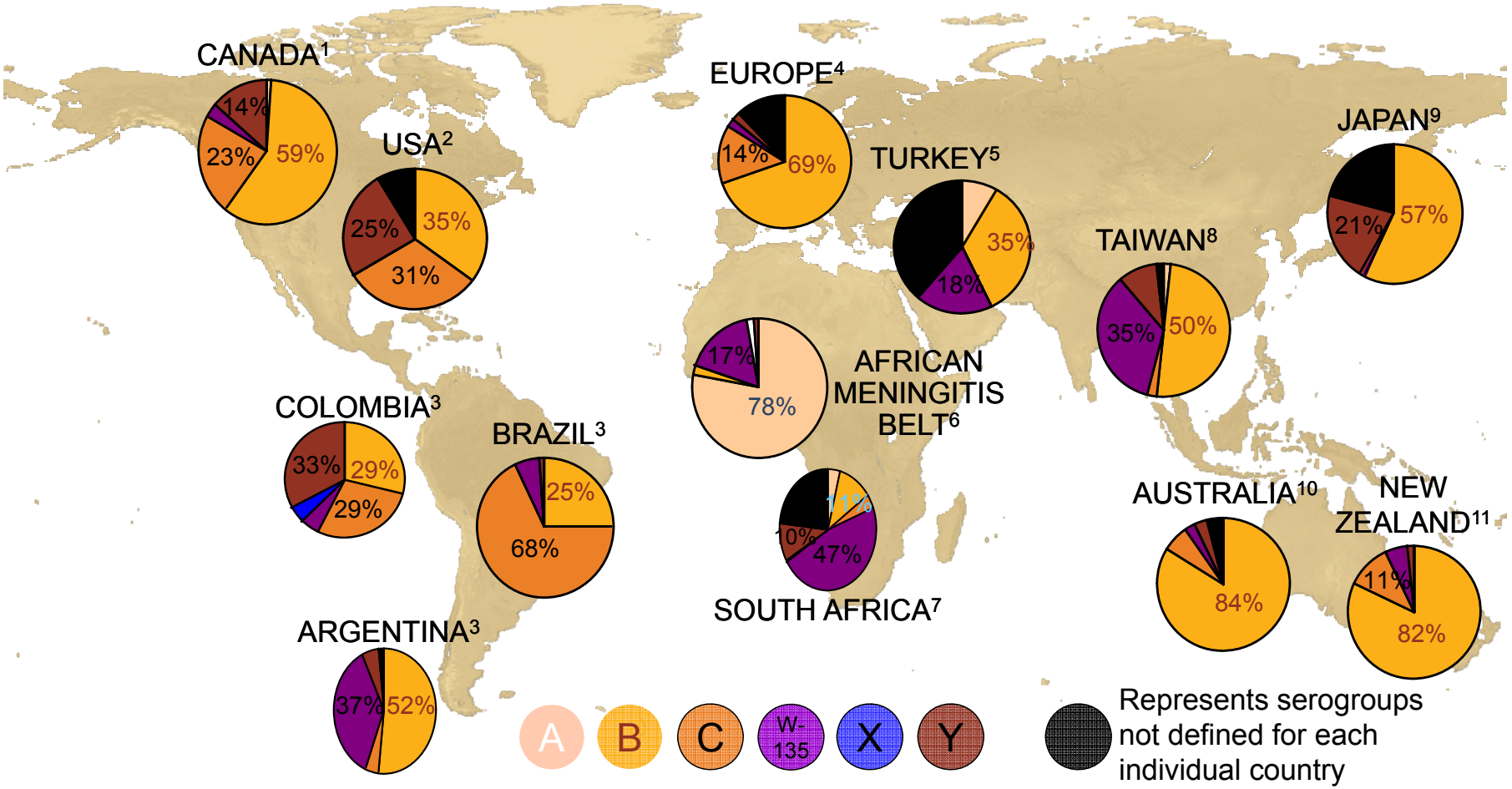
- Incidence is highest in the "African Meningitis Belt" (AMB) of sub-Saharan Africa
- Outbreaks have occurred in Hajj pilgrims (until 2003)
- Symptomatic disease is fatal in 5–10% of cases
- Up to 20% have permanent neurological sequelae

Meningococcal meningitis, countries at high risk, 2009



WHO: International Travel and Health 2010, pp. 117 -9;
Map: http://gamapserver.who.int/mapLibrary/Files/Maps/Global_MeningitisRisk_ITHRiskMap.png

Global *Neisseria meningitidis* Serogroup Distribution

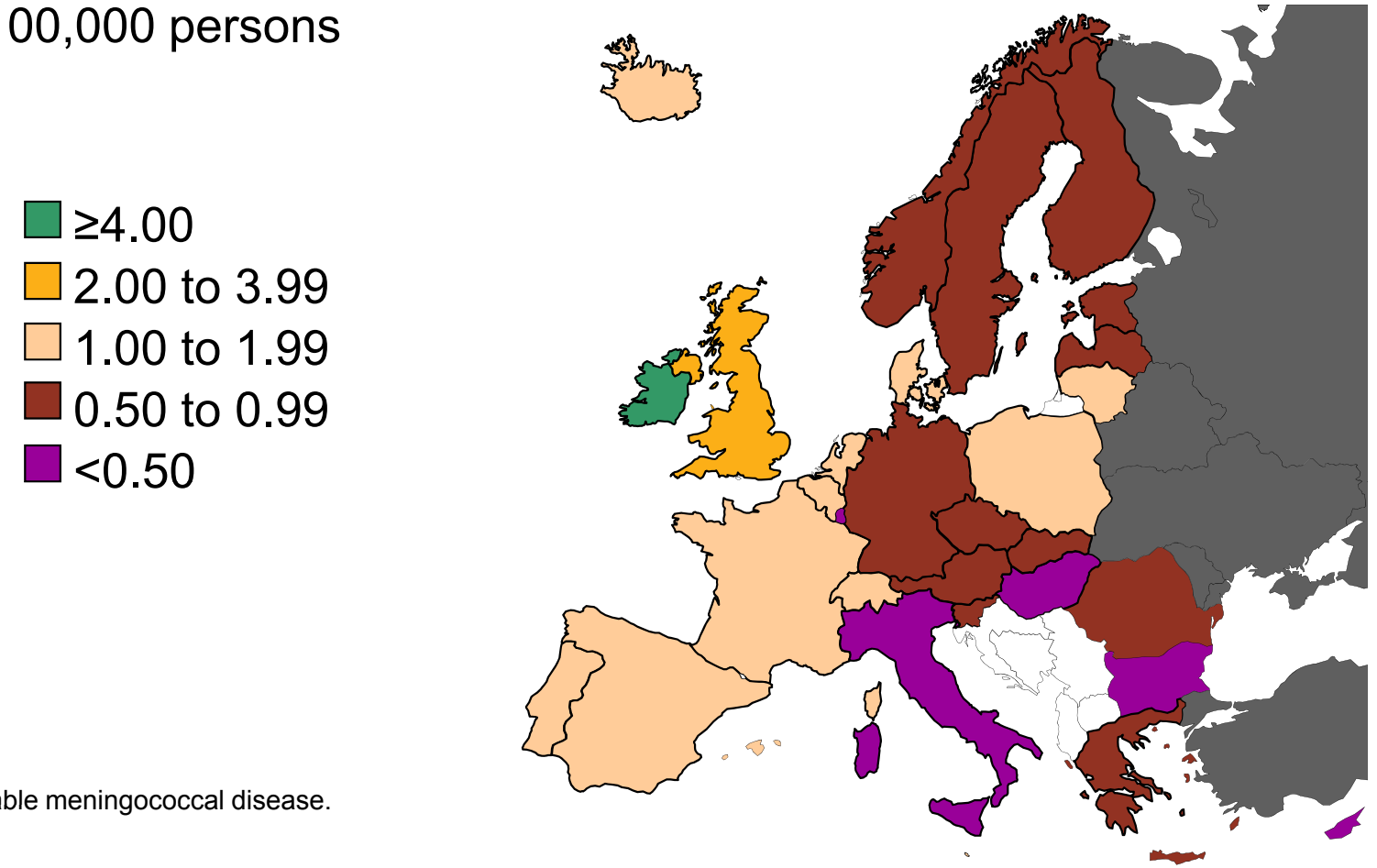


References upon request.

Incidence of Meningococcal Disease

Europe, 2007

Incidence*/100,000 persons



*Confirmed and probable meningococcal disease.

Czumbel I, et al. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden. 2009.

Meningococcal disease – Historical incidence estimates

Population	Attack rate (per million)	Cfr (%)
Travelers	0.4 to 3	>20
Pilgrims	77 to 2000	>20

Koch S & Steffen R, J Travel Med 1994;1:4-7
Jones DM & Sutcliffe EM, J Infect 1990;21:21-5
Moore PS et al, JAMA 1988;260:2686-9

Travel related environmental factors in meningococcal disease

Dormitories

- Educational institutions
- Military
- Trekking huts (Nepal 1980‘s)

Discotheque

Sport event (Rugby; not EURO)

Refugee camps

Pilgrimage

- Hajj, Umrah
- India (Prayag, Allahabad U.P.)

Bruce et al. JAMA 2001;286:688-93

Mimouni D et al. Am J Infect Control 2010;38:56-8

CDC. MMWR 1985;34:119-25

Hauri AM et al. Epidemiol Infect 2000;124:69-73

Orr H et al. Commun Dis Public Health 2001;4:316-8
Gonçalves G et al. Euro Surveill 2005;10:86-9

Benca J et al. Neuro Endocrinol Lett 2007;28 Suppl 2:44

Anecdotal cases of meningococcal disease in travelers, from 1996 (selection)

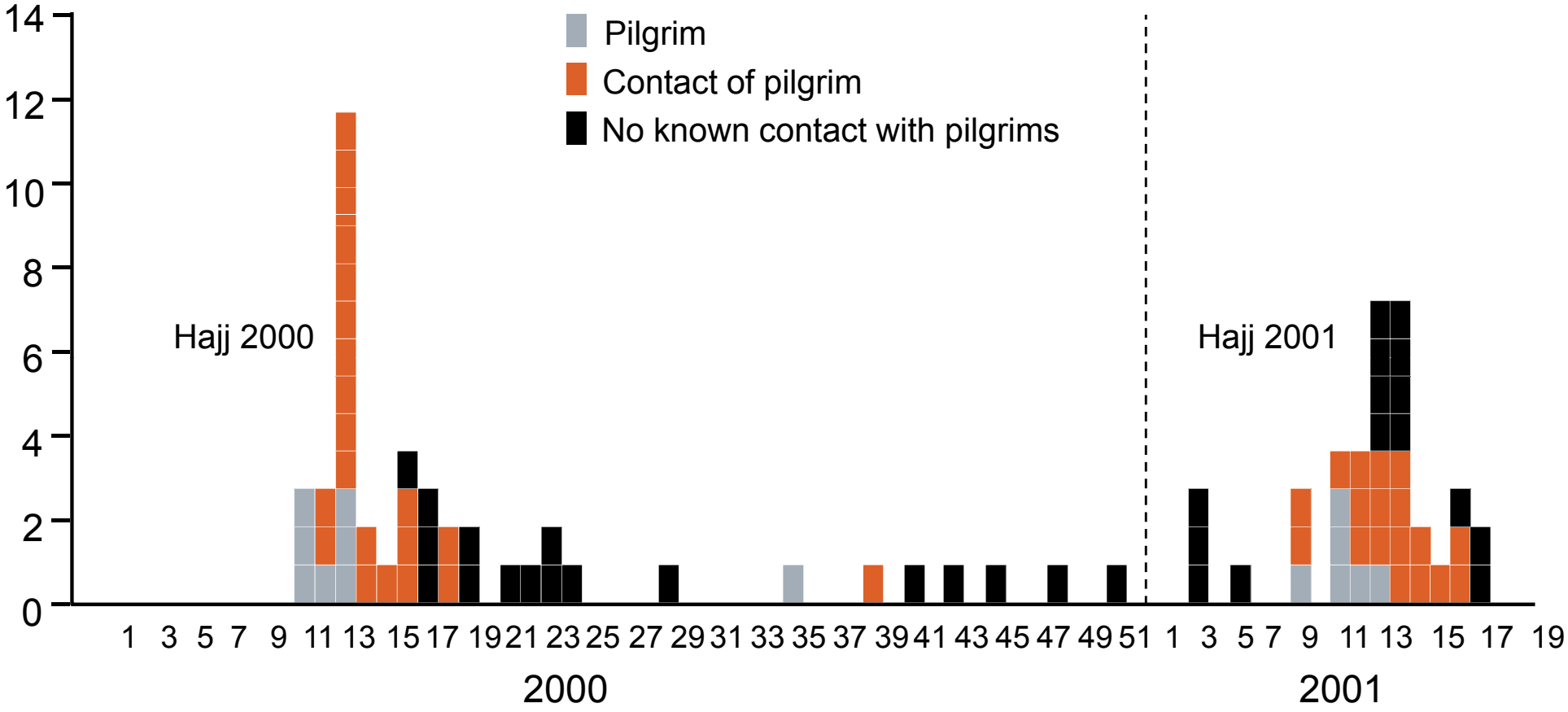
Type of traveler	Origin	Location	Outcome
Children PHLS. CDR Weekly 1996;6:191	UK, Germany	Majorca, Spain	2 died, 2 recovered (2 children died in same hotel)
Students (2) Zuscheid et al. Euro Surveill 2008, Nov 6; Rapp C et al J Travel Med 2010;17:1-7	Swiss / French	Germany	1 died, 1 recovered
Athlete Cummiskey J et al. J Sports Med Phys Fitness 2008;48:125-8	unknown	Jaca, Spain (1500 athletes from 43 countries)	recovered
Tourist Anonymous. NZZ 1 November 2006	Swiss	Tirol, Austria	died (only in public media)
Journalist Wilder-Smith A & Goh KT. J Travel Med 2003;10:59-60 (W135)	UK	Morocco > Japan > Singapore	recovered
Businessman Lapadula G et al. Emerg Infect 2009;15:52-54	Italy	Delhi, Chennai	recovered

The Hajj and global spread of disease

- Annual pilgrimage to Mecca, largest gathering in the world
- >2 million persons from many countries

But no meningococcal disease from 2004

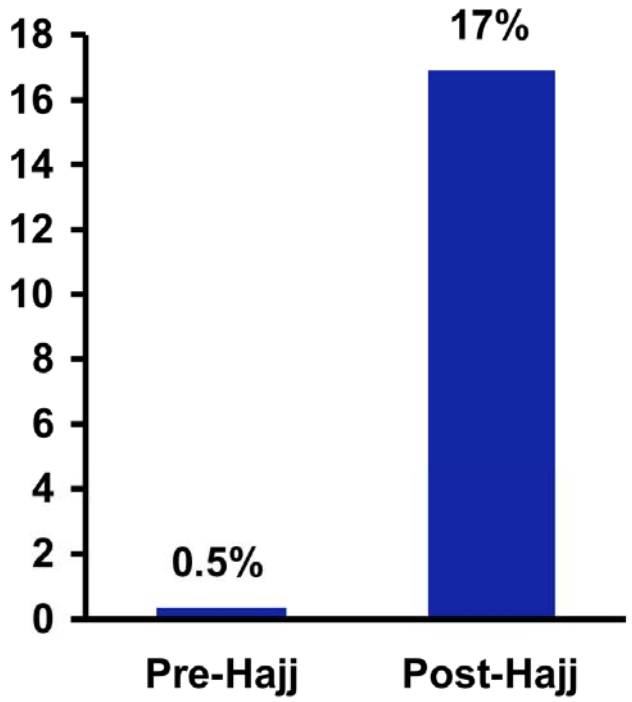
Exportation of Invasive W-135 Disease Among Pilgrims and Contacts – From the Hajj to England and Wales



Hahne SJ et al. *Lancet.* 2002;359:582-583.
Modified from: Prof. A. Wilder-Smith.

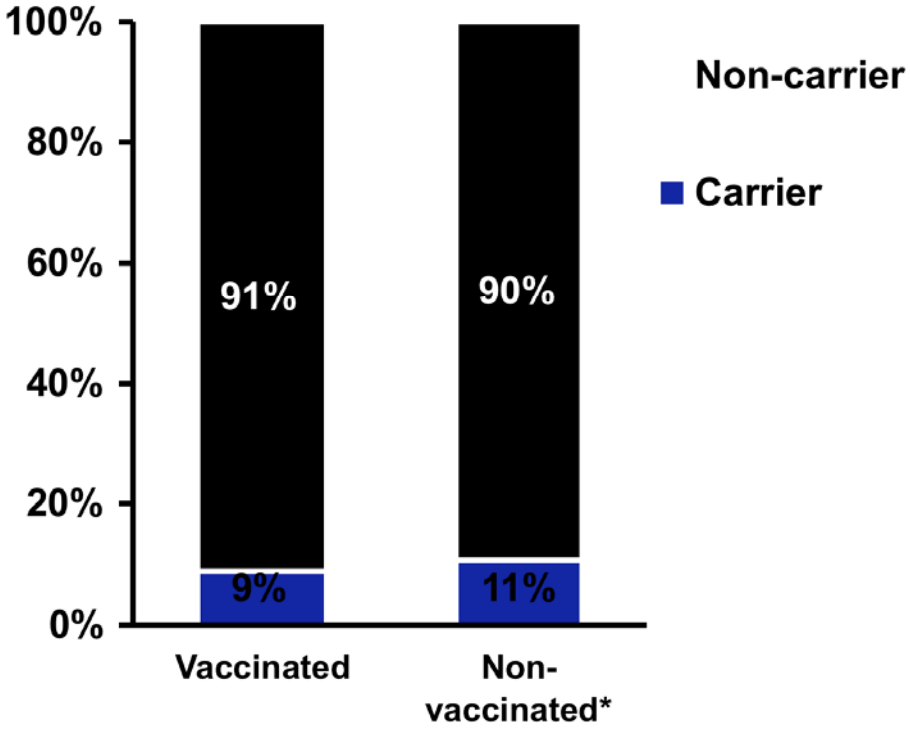
Post-Hajj carriage and effect of polysaccharide vaccination

Carriage rates before and after Hajj



Wilder-Smith A et al, *Emerg Infect Dis* 2003;9:123-6

Carriage rates amongst Hajj pilgrims returning home, 1987



Moore PS et al, *JAMA* 1988;260:2686-9

Available Meningococcal Vaccines

Class	Serogroups	Available vaccines
Polysaccharide vaccines	A, C, W-135, Y	Menomune®, ACWY Vax®, Mencevax®
	A, C	Mengivac®, AC Vax®
Polysaccharide-protein **conjugates**	C	Menjugate®, Meningitec®, NeisVac-C®
	A, C, W-135, Y	**Menveo®, Menactra®**
	C (+ Hib)	Menitorix®
Outer membrane vesicle (OMV) vaccines	B*	MeNZB®, MenBvac™
	B* (+ C polysaccharide capsule)	VA-MENGOC-BC®

Note: Availability of vaccines by country or region will vary.
*Strain specific.
Menomune and Menactra are registered trademarks of Sanofi Pasteur; AC Vax, ACWY Vax, Mencevax, and Menitorix are registered trademarks of GlaxoSmithKline; Mengivac is a registered trademark of Aventis-Pasteur; Meningitec is a registered trademark of Wyeth; NeisVac-C is a registered trademark of Baxter Healthcare; VA-MENGOC-BC is a registered trademark of Finlay Institute, Cuba; MenBvac is a trademark of Norwegian Institute of Public Health; Menjugate and MeNZB are registered trademarks of Novartis.

Granoff DM, et al. In: Plotkin S, et al, eds. *Vaccines*. 2008:chap 19.

Characteristics of Meningococcal Vaccines

Property	Polysaccharide	Conjugate
Effective in infants	No	**Yes**
Immune memory	No	**Yes**
Prolonged duration of protection	No	**Yes**
Booster effect	No	**Yes**
Reduction of carriage	No	**Yes**
Contributes to herd effect	No	**Yes**
Hyporesponsiveness with repeated dosing	**Yes**	**No**

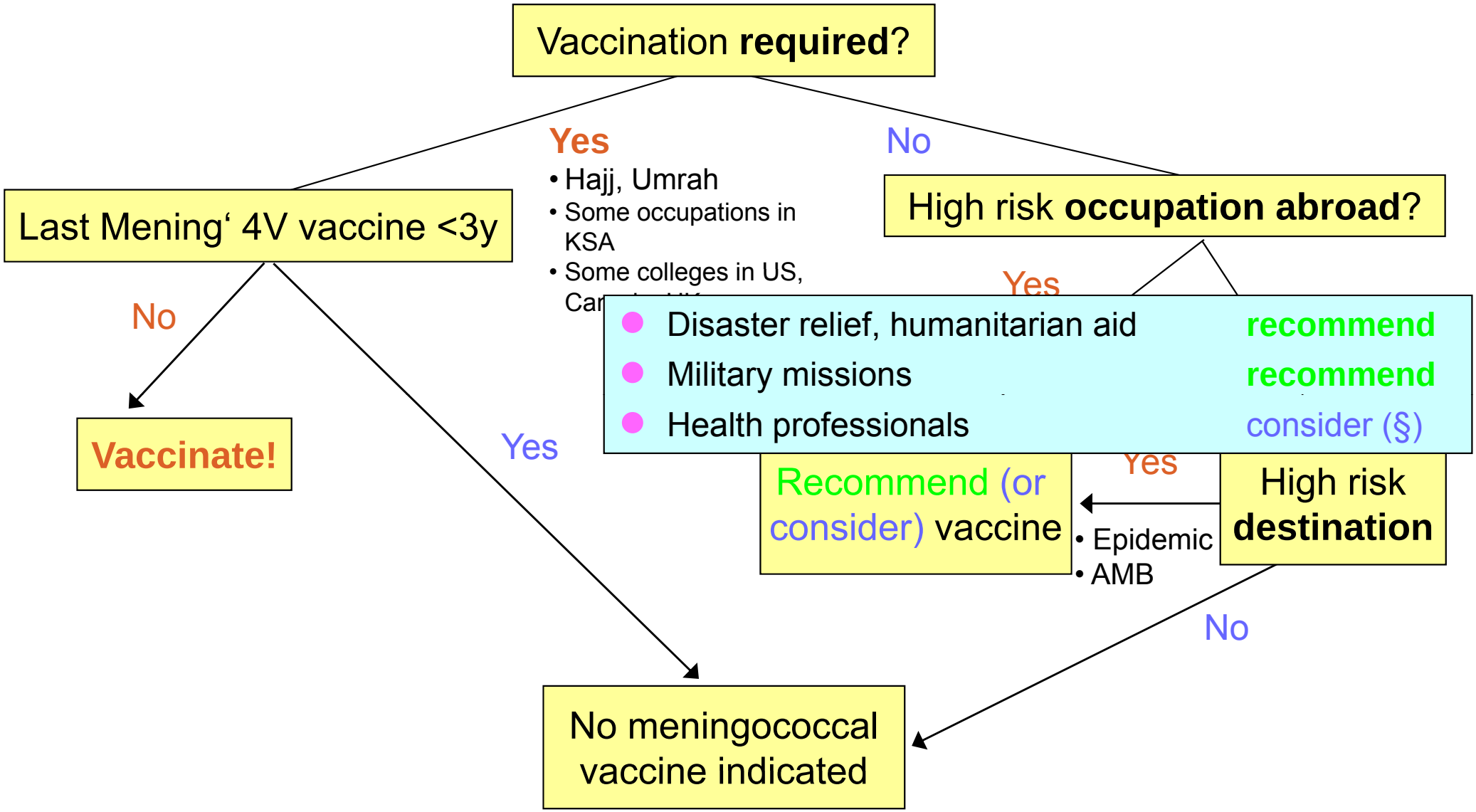
This is based on MenC conjugate experience and all attributes descried for conjugates may not necessarily to apply to Menveo

Harrison LH. *Clin Microbiol Rev*. 2006;19:142-164.

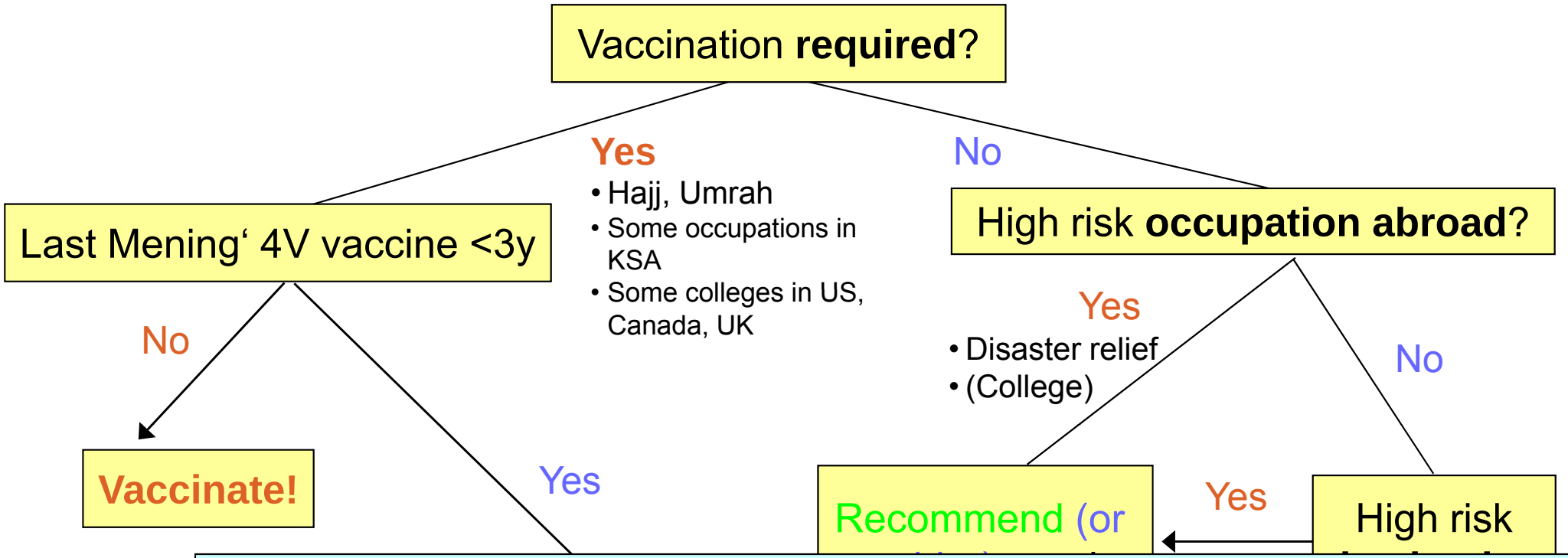
Meningococcal Vaccine Recommendations

	WHO	CDC (USA)	CATMAT (Canada)	NaTHNac (UK)	DTG / SWI (German / Swiss)
Hajj / Umrah	**Mandatory**	**Mandatory**	**Mandatory**	**Mandatory**	**Mandatory**
Occupation KSA	N/A	N/A	**Mandatory**	N/A	**Some required**
Military	At risk	N/A	N/A	N/A	N/A
Sub-Sahara MB					
All	Consider	**Recommend**	Consider	Risk groups	Consider
Dry season	-	-	**Recommend**	-	**Recommend**
Epidemiology					
Epidemic	Consider	**Recommend**	Consider	-	**Recommend**
Hyperendemic	N/A	**Recommend**	Consider	-	-
Prolonged contact w/locals	At risk	**Recommend**	Consider	**Indicated**	Consider
Other Young children	-	At risk	-	-	-
Healthcare work	-	-	-	**Indicated**	-
VFRs	-	-	-	**Indicated**	-

Meningococcal vaccination decision algorithm for travelers



Meningococcal vaccination decision algorithm for travelers



• Epidemic / outbreak, anywhere	**recommend**
• African meningitis belt (AMB)	consider (for any season — §)
– Prolonged contact with locals (VFRs, backpackers, etc)	**recommend**
– Prolonged duration of stay	**recommend**
– Host factors, e.g. immune deficiency	**recommend**
– Request maximum protection	**recommend**

Tetanus associated with travel

1 case only found: Spain to Germany

Werner GT. Sozial Präventivmed 1985;30:103-6

Routine immunizations in non-immune travelers for a stay in a developing country

Expert group	WHO *World*	CATMAT *Canada*	CDC *USA*	PHLS *UK*	NHMRC *Australia*	JAPAN *Vac. av.*
- tetanus/diphteria	***	***	***	***	***	+
- poliomyelitis	**	**	**	**	**	+
- measles	***	***	***	***	***	+
- influenza	*	*	?	*	?	+

*** = all, ** = all when visit in endemic country, * = risk group only, - = none

Conclusions

Travel related neurological infectious diseases are **RARE**

Underreporting! (often reporting not mandatory)

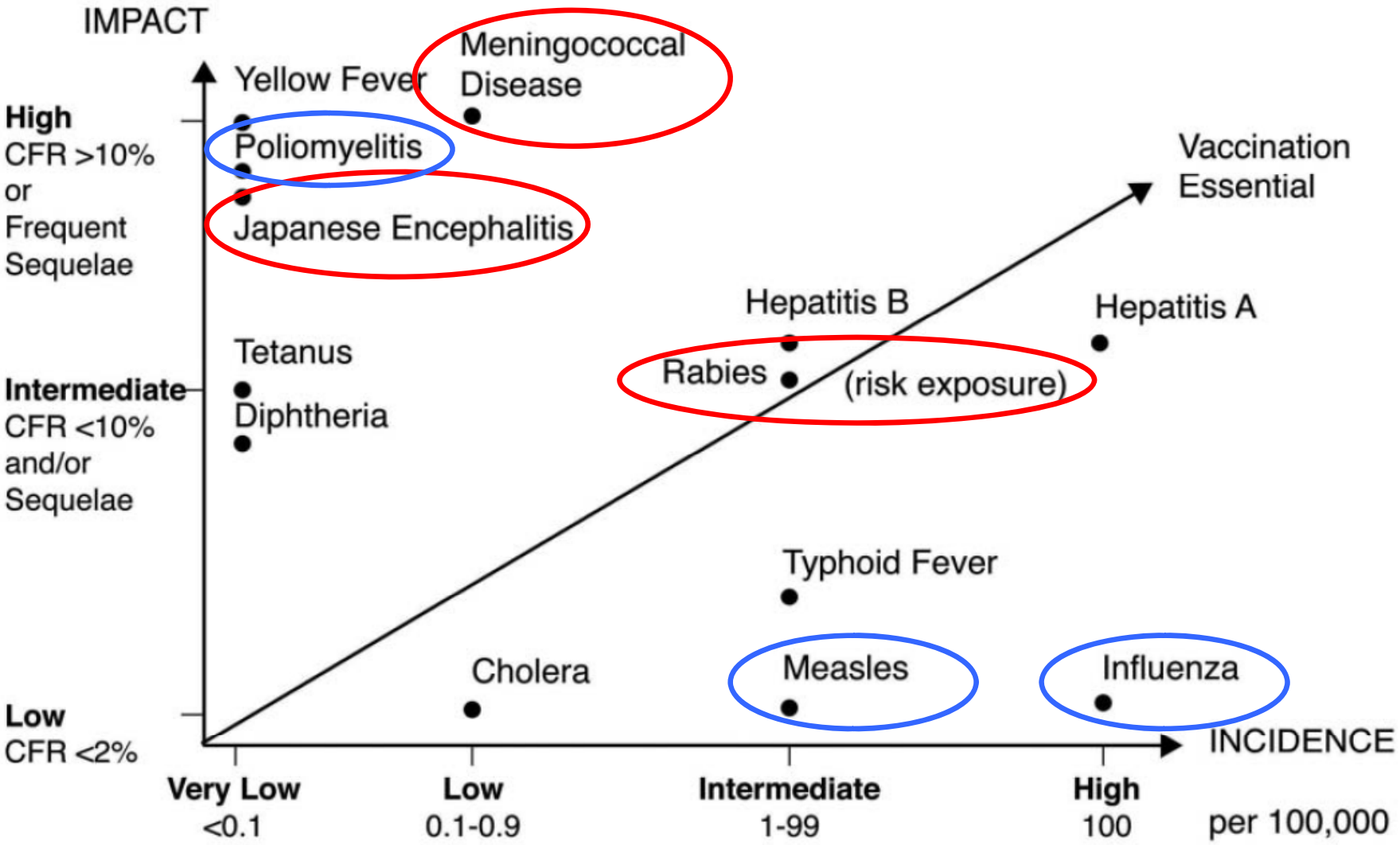
Often **no zero risk**

Some infections **vaccine preventable**

Difficult to determine who might become exposed

- Rabies
- Japanese Encephalitis
- Meningococcal Disease
- (Poliomyelitis) — *NOTE: in all exposed vaccine recommended...*

JE, rabies and meningococcal disease: in travelers rare, but have high impact



Steffen R & Connor BA. J Travel Med 2005;12: 26-35.

Reserve

Basic characteristics of IXIARO (=JESPECT)

contains 6 mcg of ina

encephali

f

cells

a bed on aluminum hydroxide

0.5 ml per dose

A new vaccine

IXIARO / JESPECT vs. ”traditional” JE vaccine

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.

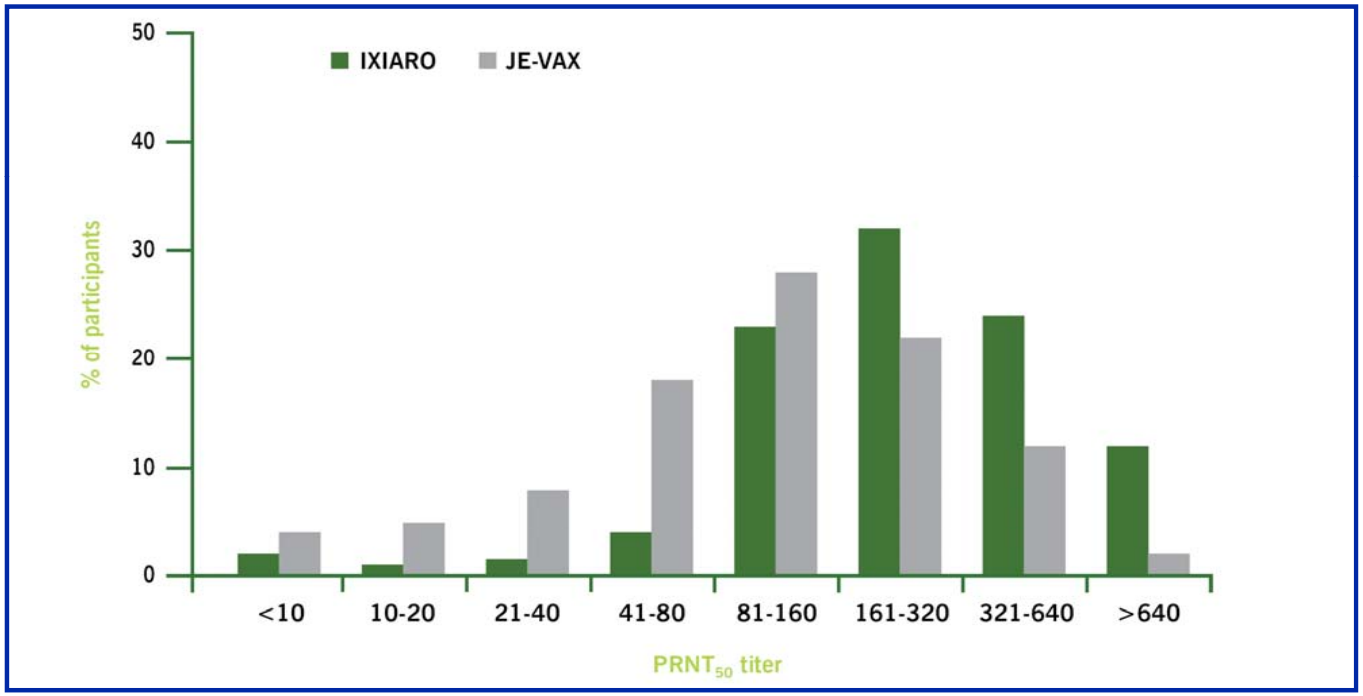
Immunogenicity: IXIARO / JESPECT vs. JE-VAX

IXIARO / JESPECT provided protective antibodies* in up to 98% of subjects [1]

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.

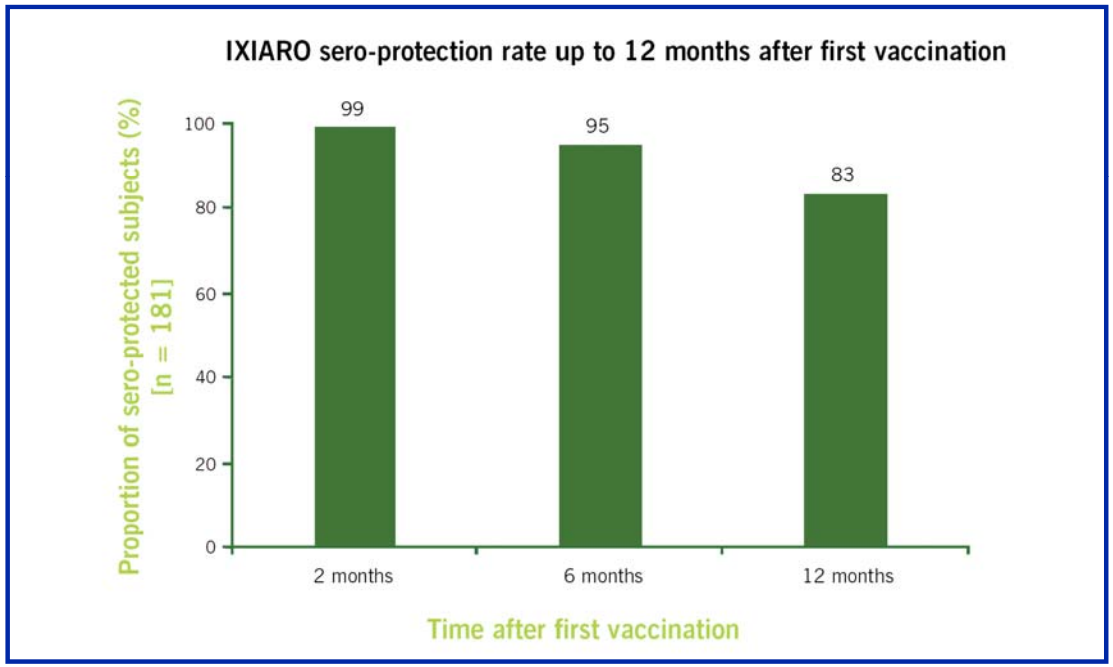
Tauber E et al. Lancet 2007; 370: 1847-1853.
Hombach J et al. Vaccine 2005; 23: 5205-5211.

Proportion with persisting protective antibody levels

83% (151/181) of subjects who received IXIARO / JESPECT maintained protective antibody titers* 12 months after vaccination [1]

A study investigating the ideal booster interval is ongoing

Protective antibody levels up to 12 months after first vaccination



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

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