Japanese Encephalitis Debate: One in a Million?

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Japanese Encephalitis: Vaccine or No?

- *Japanese Encephalitis Vaccine for Travelers: Exploring the Limits of Risk*[1]
- The authors quote a popular movie at the time, *Chicken Run*, describing in a jocular fashion the 1 in a million chance of the imprisoned chickens mounting a successful escape.
- Rather than be deterred by this low probability one of the protagonist chickens instead exhibits hope saying, "Then there is still a chance."
- Article went on to posit that the risk for a traveler to Asia of contracting Japanese encephalitis is 1 in a million and because of this low probability it was not necessary to recommend the Japanese Encephalitis vaccine.

[1] Shlim DR, Solomon 2002:Clin Inf Dis

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INVITED ARTICLE TRAVEL MEDICINE
Charles D. Ericsson and Robert Steffen, Section Editors

Japanese Encephalitis Vaccine for Travelers: Exploring the Limits of Risk

David R. Shlim[1] and Tom Solomon[2,*]
[1]Jackson Hole Travel and Tropical Medicine, Jackson, Wyoming; and [2]Departments of Neurological Sciences and Medical Microbiology and School of Tropical Medicine, University of Liverpool, United Kingdom

The prevention of Japanese encephalitis in travelers presents the juxtaposition of 4 factors: a disease that is widespread throughout Asia, a disease with a low incidence in travelers, a vaccine about which there are safety concerns, and a clinical course that can result in death or permanent disability in two-thirds of symptomatic cases. Travel medicine practitioners often seem to be polarized into 2 groups: a group that gives more weight to the severity of the disease (and therefore often recommend vaccination) and another group that is more persuaded by the low occurrence of cases in travelers (and therefore rarely recommend vaccination). This review assesses the known risks of contracting Japanese encephalitis and the risks associated with the vaccine and tries to develop an appropriate way to recommend this vaccine to travelers who may be at significant risk.

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Japanese Encephalitis: Risk in Travelers

ONE IN A MILLION? REALLY?

- **Ask any travel medicine specialist and they will tell you:** The risk of Japanese Encephalitis in travel is:
  - ***One in a million***
- Where does that figure come from and what does it really mean?

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Japanese Encephalitis Vaccine

Original Sin:

- January 1993 ACIP recommendations
  - Adverse effects from available mouse brain ("Biken") vaccine considered unacceptable
    - Soldiers in Okinawa, Australian AE profile
- Decision made to evaluate potential risk of disease vs. risk of vaccine side effects
- T. Monath, T. Tsai and others at the CDC made a decision that the risk of JE was not sufficient to justify use of the vaccine unless the traveler was in a JE risk area for > 30 days during the transmission season
- CISTM Paris 1993 back of the envelope calculation

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Japanese Encephalitis Vaccine

- **Problem with this:**
  - In post marketing surveillance of the mouse brain JE vaccine in the US: no increased risk of adverse events
  - The "30 day" and "seasonal only" recommendations and one in a million risk of disease became codified in the recommendations ever since

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Japanese Encephalitis Vaccine

- This is despite the availability of a newer, even safer vaccine (Ixiaro)
- Accumulating evidence of wider distribution of enzootic areas of risk in Asia
- Availability of data showing cases in travelers during short term visits to Asia in areas (e.g. peri-urban) not previously considered endemic
- And in seasons not considered risk seasons for JE transmission

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Japanese Encephalitis Vaccine

- **JE Vaccines**
- **Vaccination of humans is the most effective means of preventing JE. There are three types of inactivated vaccines and one type of live attenuated vaccine currently used in the world:**
- mouse brain-derived, purified vaccine, which is based on either the Nakayama-NIH or Beijing-1 [P-1] strains
- primary hamster kidney (PHK) cell-derived, purified vaccine, based on the Beijing-3 [P-3] strain
- Vero-cell derived purified vaccine based on the P-1, P-3 or SA14-14-2 strains as virus seeds
- PHK cell derived live attenuated vaccine based on the SA14-14-2 strain of the JE virus

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Japanese Encephalitis Vaccine: Do Risks Outweigh the Benefits?

- **Possible Vaccine Side Effects**
  - Injection site reactions (redness, pain, swelling, or arm soreness)
  - Low-grade fever
  - Chills
  - Flu-like symptoms
  - Headache
  - Short-term fatigue
  - Nausea
  - Vomiting
  - Muscle pain
  - Abdominal pain
  - Mild itching, hives, or skin rash
- **Symptoms and Outcomes of the Disease In Travelers**
  - High fever
  - Chills
  - Headache
  - Nausea
  - Vomiting
  - Disorientation
  - Mental status changes
  - Seizures (especially in children)
  - Encephalitis
  - Permanent neurologic sequelae
  - **DEATH!**

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Japanese Encephalitis Vaccine: Real-Time Data

The vaccine **WORKS**: excellent seroprotection and no evidence that anyone who has received Ixiaro has ever contracted Japanese Encephalitis

The vaccine is **SAFE**: estimated overall AE rate 15.2/100,000 doses; serious AE rate 1.8/100,000 doses

The vaccine is **CONVENIENT**: 0, 7 days

The vaccine is **expensive**

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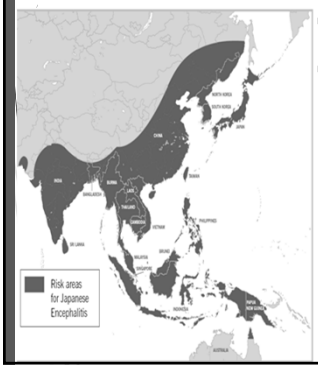
A large Area of Asia Is Endemic for JE



- Significant geographic expansion in Asia
- Almost half of the world's population lives in a country where JE is endemic

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Economic Development Has Led to More People Living in Higher-Risk Areas for JE

Urbanization of rural areas

- Economic and agricultural changes are blurring the boundaries of what is considered a 'rural' area[1]
- Increased migration to cities has led to urbanization of rural areas where natural enzootic cycles exist[2]
- Travelers who report they will only be staying in urban areas may be unaware of their true surroundings or decide, while traveling, to take side trips into more rural environments

Courtesy of David O. Freedman

Epidemiology conclusions

- Climate change, changes in horticultural and agricultural practices, expanding urban areas, and new data on JE vectors all mean that JE is an unpredictable threat

1. Yokohari M et al. Landsc Urban Plan 2008; 47: 159-171.
2. Petersen LR & Marfin AA. J Travel Med 2005; 12 (Suppl. 1): S3-11.

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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

1 Caramello P et al. J Travel Med 2007;14:346-8
2 The Olympian (Seattle) 28.3.2008

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JE Can Affect Travelers to Asia and can Have Severe Outcomes

Summary of selected published case studies between 1992–2013

Year	Country of Origin	Travel Destination	Duration/Travel itinerary	Outcome
1992[1]	UK	Malaysia, Thailand	9 weeks, 3 days trekking	Recovered
1994[2]	Sweden	Bali	10 days, one-day trip to the countryside	Recovered
1995[3]	Denmark	Bali	12 days, coastal, few trips inland	Fatal
2001[4]	Sweden	Java and Bali	3 weeks, outings to the countryside	Moderate sequelae
2004[5]	Finland	Thailand	2 weeks (1 week Khao Lak, 1 week Phuket, two-day trips rural area	Initially mild sequelae, after 3 years fully recovered
2004[6]	USA	Thailand	32 days	Recovered
2004[7]	New Zealand	Japan, China, and Hong Kong	5 weeks, urban and rural travel	Severe cognitive and motor sequelae
2005[8]	The Netherlands (two travelers)	Indonesia and Thailand	–	Both travelers recovered after long-lasting cognitive sequelae
2006[9]	Italy	Vietnam	3 weeks, rural travel	Recovered, slight deficit in recent memory
2008[10]	USA	Vietnam and Cambodia	Visiting family and friends, rural travel	Sequelae
2010[11]	Denmark	Cambodia	14 days, urban and rural travel	After initial recovery, died from cardiac arrest following generalized seizure
2010[12]	Canada	Thailand	1 month, urban and rural travel	Sequelae
2013[13]	Spain	Thailand	4 weeks, island, day trips to rural areas, two-day urban stay	Recovered, walk with an ataxic gait, minor memory impairment and emotional lability

1. Burdon et al 1994; 2. Wittesjo et al 1995; 3. Buhl et al 1996; 4. Ostlund et al 2004; 5. Lehtinen et al 2006; 6. Centers for Disease Control and Prevention 2005; 7. Cutfield et al 2005; 8. Dekking et al 2005; 9. Caramello et al 2007; 10. Centers for Disease Control and Prevention 2009; 11. Wirthmut et al 2011; 12. Langevin et al 2012; 13. Didi et al 2013

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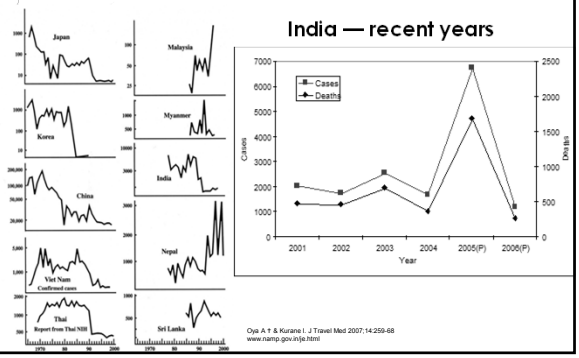
Outbreaks of JE — Often a Surprise



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

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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

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Measurements of Exposure

- In the absence of reliable incidence data
  - sero-epidemiologic methods can be used to measure exposure and make inferences about the endemicity of disease
- Serologic data in local populations tells us the risk of JE is present in a wider area than previously considered and JE is a lot more prevalent in endemic areas than previously suspected
- A recent study documents serologic evidence of JEV circulation in urban and peri-urban areas of Indonesia, Malaysia, the Philippines and Vietnam, countries with differing epidemiology in JEV risk

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Let's Discuss System-Wide Bias…

- The Canadians do not concur with the oft quoted figure of one in million for the risk of Japanese Encephalitis in travelers
- In a presentation at CISTM15 in Barcelona in 2017 discussing proposed CATMAT Guidelines on the use of the JE vaccine, Dr. Steven Schofield suggests that the risk of JE in travelers is actually:
  - **One in ten million!!**

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Guidance on Prevention of Japanese Encephalitis in Canadian Travellers

Steven Schofield
ISTM Conference – FC6.06
Tuesday, May 16th, 2017

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Likelihood of Japanese encephalitis infection (travellers)

The overall likelihood of travel-related clinical JE was estimated as ~ 1 case/10,000,000 trips (moderate confidence, risk of bias due to under ascertainment)

Region of embarkation	Cases	Estimated travel volume (millions) 2006-2016	Overall attack rate (cases/trips) for the travellers (95% confidence interval) 2006-2016
Canada	1	11.65	1/11,650,000 (1/65,996,483; 1/2,058,512)
United States	5	55.4	1/11,078,000 (1/25,035,276; 1/4,731,859
Europe	11	150	1/13,638,363 (24,420,2750; 7,614,582)

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Developing a Recommendation for CATMAT

We are going to make the decision for them. We know what Canadian travelers want…

"We believe that most, but not all, Canadian travellers would decide that the absolute protection afforded by JEV is worth the associated cost and inconvenience (including the possibility of AE) if the likelihood of JE was 1 case/100,000 trips or higher (low confidence)"

This threshold cannot be met for the majority of travellers to risk areas

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CATMAT Recommendation

- CATMAT suggests that JEV (IXIARO®) **NOT** be routinely used for travel to endemic areas (**Conditional recommendation, moderate confidence in estimate of effect**).

For the large majority of travellers, the *likelihood of developing clinical JE in endemic areas is negligible (overall per trip attack rates estimated as approx. 1/10,000,000 for travel to endemic countries*) as is the estimated absolute benefit of JEV. We believe most travellers would choose not to receive JEV in this situation.

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Death of Canadian sickened in Thailand inspires daughter's vaccine crusade

Retired Edmonton firefighter Bill Hughes died four months after contracting Japanese encephalitis while in Thailand. (Photo courtesy of Jillian Hughes)

Meredith MacLeod, CTVNews.ca Writer

Published Friday, February 15, 2019 2:33PM EST

An Edmonton woman whose father died of a devastating mosquito-borne virus that caused fatal brain swelling is warning Canadians to take travel vaccines seriously.

Bill Hughes died in May 2016, roughly four months after he slipped into a coma after contracting Japanese encephalitis while in Thailand. He was a fit and healthy 62-year-old retired firefighter who did triathlons and loved to travel, says his daughter Jillian Hughes, who has made it her mission to raise awareness of the condition.

"My dad's death was preventable and I want to keep people from making the same mistake," she told CTVNews.ca in a phone interview. "No matter where you are travelling, educate yourself. I never thought this could happen to someone like my dad."

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Data Accuracy

- Let's start with the oft quoted figure of risk:
  - being one in a million or Dr. Schofield's figure of one in ten million
- Is this for all travelers to Asia?
- Is this for all travelers to at risk or endemic or enzootic areas for JE?
- Or some other calculation of numerator and denominator?
- Fact is, we do not have adequate numerator and denominator data

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Data Accuracy

- We know how many travelers visit Asia but we do not know precisely how many individuals travel to JE virus endemic regions
- And because of under-reporting of JE we really do not know how many actually acquire JE virus infection during travel
- Consequently, we cannot be certain that we have accurate numerator and denominator data.

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Facts

This is what is known:

- Japanese Encephalitis affects approximately 70,000 individuals each year despite implementation of childhood vaccination campaigns in many endemic countries
- This 70,000 incidence underestimates the true risk of disease as individuals infected by the bite of an infected mosquito and immune from vaccination will not develop overt clinical symptoms and will therefore not be counted as cases

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Do All Travelers Receive an Accurate Diagnosis?

- The risk in the non-immune traveler is also likely underestimated
- Returning travelers with signs and symptoms compatible with JE may be misdiagnosed as suffering from other viral illnesses, even if severe, and therefore go largely unreported to public health authorities
- Here a combination of low levels of suspicion by U.S. clinicians, especially in the face of a non-specific febrile illness, as well as infrequent use of reliable laboratory testing even if illness is suspected, make the diagnosis difficult

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Symptoms of JE

- Most individuals with JE infection are asymptomatic or have only mild flu-like symptoms (fever, headache)
- Only about 1 in 250 infections result in more severe systemic illness characterized by high fever, neurologic symptoms, and ultimately death

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Subclinical JE

Subclinical Japanese Encephalitis: Infection of Americans with a Limited Residence in Korea[1]

- Susceptible non-immune individuals seldom develop overt encephalitis but more frequently acquire undifferentiated febrile illness or inapparent infection
- Serologic surveys of Japanese and Koreans after WWII showing marked disparity between incidence of JE neutralizing antibodies and history of overt encephalitis
- In 1950 nearly 50% of survivors of the battle of Pusan were found to have JE antibody
- It became apparent that susceptible American adults were also more frequently infected subclinically or with an undifferentiated illness
- [1]Halstead SB Grosz CR. Am J Hyg 1962;75:190-201

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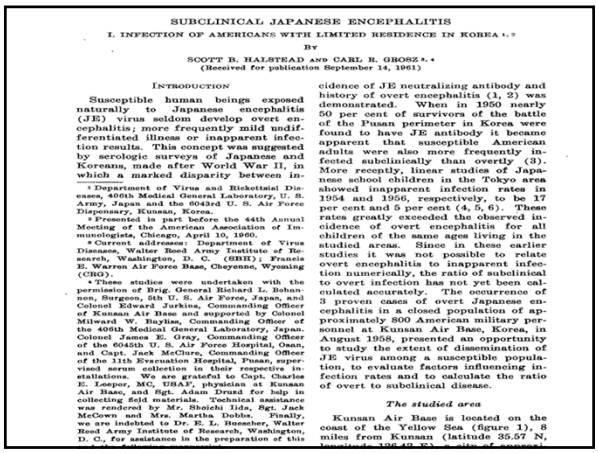

SUBCLINICAL JAPANESE ENCEPHALITIS

I. INFECTION OF AMERICANS WITH LIMITED RESIDENCE IN KOREA [1, 2]

By

SCOTT B. HALSTEAD AND CARL R. GROSZ [3, 4]

(Received for publication September 14, 1961)

INTRODUCTION

Susceptible human beings exposed naturally to Japanese encephalitis (JE) virus seldom develop overt encephalitis; more frequently mild undifferentiated illness or inapparent infection results. This concept was suggested by serologic surveys of Japanese and Koreans, made after World War II, in which a marked disparity between incidence of JE neutralizing antibody and history of overt encephalitis (1, 2) was demonstrated. When in 1950 nearly 50 per cent of survivors of the battle of the Pusan perimeter in Korea were found to have JE antibody it became apparent that susceptible American adults were also more frequently infected subclinically than overtly (3). More recently, linear studies of Japanese school children in the Tokyo area showed inapparent infection rates in 1954 and 1956, respectively, to be 17 per cent and 5 per cent (4, 5, 6). These rates greatly exceeded the observed incidence of overt encephalitis for all children of the same ages living in the studied areas. Since in these earlier studies it was not possible to relate overt encephalitis to inapparent infection numerically, the ratio of subclinical to overt infection has not yet been calculated accurately. The occurrence of 3 proven cases of overt Japanese encephalitis in a closed population of approximately 800 American military personnel at Kunsan Air Base, Korea, in August 1958, presented an opportunity to study the extent of dissemination of JE virus among a susceptible population, to evaluate factors influencing infection rates and to calculate the ratio of overt to subclinical disease.

The studied area

Kunsan Air Base is located on the coast of the Yellow Sea (figure 1), 8 miles from Kunsan (latitude 35.57 N,

[1] Department of Virus and Rickettsial Diseases, 406th Medical General Laboratory, U. S. Army, Japan and the 6043rd U. S. Air Force Dispensary, Kunsan, Korea.

[2] Presented in part before the 44th Annual Meeting of the American Association of Immunologists, Chicago, April 10, 1960.

[3] Current addresses: Department of Virus Diseases, Walter Reed Army Institute of Research, Washington, D. C. (SBIE); Francis E. Warren Air Force Base, Cheyenne, Wyoming (CRG).

[4] These studies were undertaken with the permission of Brig. General Richard L. Bohannon, Surgeon, 5th U. S. Air Force, Japan, and Colonel Edward Jurkins, Commanding Officer of Kunsan Air Base and supported by Colonel Milward W. Buyliss, Commanding Officer of the 406th Medical General Laboratory, Japan. Colonel James E. Gray, Commanding Officer of the 6045th U. S. Air Force Hospital, Osan, and Capt. Jack McClure, Commanding Officer of the 11th Evacuation Hospital, Pusan, supervised serum collection in their respective installations. We are grateful to Capt. Charles E. Lesper, MC, USAF, physician at Kunsan Air Base, and Sgt. Adam Druzd for help in collecting field materials. Technical assistance was rendered by Mr. Shoichi Iida, Sgt. Jack McCown and Mrs. Martha Dobbs. Finally, we are indebted to Dr. E. L. Buescher, Walter Reed Army Institute of Research, Washington, D. C., for assistance in the preparation of this

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Subclinical Japanese Encephalitis: Infection of Americans with a Limited Residence in Korea

3 cases of overt JE amongst a cohort of 800 soldiers provided an opportunity to evaluate American soldiers with "subclinical Japanese Encephalitis" as determined by development of acute JE antibodies

9.3% of this population developed acute JE antibodies

Clinical findings in these individuals included:

- Abdominal pain, diarrhea, headache, fever
- Severe persistent headache for 1 week, fever for 1 day
- Anterior chest pain, severe frontal headache, afebrile
- Severe fatigue with narcolepsy, nausea
- Fever, fatigue and nausea

Many of these patients remained unwell for prolonged periods of time

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GeoSentinel Data

In reviewing reports from the GeoSentinel Surveillance Network database in ill returned travelers from JE endemic areas:

- large number of cases of "viral syndromes" without a definitive diagnosis, with many lasting >3 weeks,
- and 48 cases of acute encephalitis reported without an etiologic diagnosis between 2009 to 2018.
- Many travelers returning from trips are seen by emergency doctors, primary care providers, hospitalists and others where JE may not be in their differential diagnosis.

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How Do We Make a Decision?

- **CATMAT:** The data are NOT GOOD ENOUGH TO DRAW THESE TYPES OF CONCLUSIONS!
- Let's agree there is a risk which is worth discussing with travelers
- There is a means to mitigate this risk: a safe and effective vaccine
- There is the peace of mind which comes from vaccinating travelers against potentially fatal travel related diseases

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How Do We Make a Decision?

- It is laudable to try to come up with Evidence Based Graded Recommendations
- There is bias introduced in deciding which data to use especially when the evidence is based on faulty, inaccurate or incomplete data

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The Decision to Recommend ***ANY*** Travel Vaccine

- **What factors should be considered when deciding *not* to immunize?**
  - Risk of disease is low
  - Vaccine is too risky
  - Vaccine is too costly (not the same as "cost effective")
  - Vaccine is of limited effectiveness
  - Vaccine effectiveness relies on inconvenient dosing
  - Competition with other pre-travel vaccine recommendations

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Other Diseases in Travelers

- **What is the risk of typhoid for a traveler to Asia?**
  - Is the typhoid vaccine effective?
  - Is the typhoid vaccine cost effective?
- **What is the risk of dying of rabies for a traveler to Asia?**
- **What is the risk of contracting measles for a flight attendant on an international flight?**
- **Malaria pills are expensive, do I really need them?**

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Other Diseases in Travelers

- **Vaccine preventable diseases with a lower risk than JE:**
  - Yellow Fever until recently: no cases in travelers for 10 years
  - Meningococcal meningitis
  - Deaths from Rabies

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How Travelers Make a Decision

What is the single most important factor in having a patient accept a therapy or intervention:

- The medical evidence supported by high-quality published studies?
- Recommendations from their friends and family?
- The conviction of the medical practitioner that this therapy or intervention is something important?
- Do not let our biases make the decision for the traveler

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Study: Utilization of JE Vaccine in US Travelers[1]

+ Retrospective (2009 -2012) data-base analysis of 8,289 US travelers >17 years (Global TravEpiNet (GTEN))
  - Collecting information on travelers itinerary, vaccinations and other parameters
  - If vaccines not given per ACIP guidelines, clinicians are required to provide a reason
+ Travelers grouped based on their JE risk:
  - Higher-risk travelers: traveling for ≥30 days during transmission season, or rural setting
  - Lower-risk travelers: traveling <30 days, or outside transmission season, or urban only

Travelers	Higher risk (n = 711)	Lower risk (n = 7,578)
Median travel duration, days (IQR)	50 (32-93)	14 (11-21)
Age 17-59 (%)	80.0	67.0
Purpose of travel: leisure (%)	49.4	59.0
JE-vaccination status: not vaccinated (%)	71.6	95.7

Deshpande et al., Use of Japanese Encephalitis Vaccine in US Travel Medicine Practices in Global TravEpiNet. AmJTropMedHyg 2014

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Results: Utilization of JE vaccine in US travelers[1]

>70% of identified higher-risk travelers never received JE vaccine

+ Only 26.8% of higher risk travelers received the JE vaccine

Travelers	Higher risk (n = 711)	Lower risk (n = 7,578)
Days to departure at clinic visit (%)		
0–13	25.7	30.5
14–20	12.5	14.1
21–27	11.7	12.1
>28	50.1	43.3
JE-vaccination status (%)		
Vaccinated within previous 2 years	1.5	0.4
Received vaccine for this itinerary	26.8	4.0
Not vaccinated	71.6	95.7

Deshpande et al., Use of Japanese Encephalitis Vaccine in US Travel Medicine Practices in Global TravEpiNet. AmJTropMedHyg 2014

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Results: Utilization of JE vaccine in US travelers[1]

Reasons for not receiving JE vaccine

+ For the majority of higher risk travelers, clinicians did not vaccinate because they deemed the JE vaccine was not indicated

Reasons	Percent
Vaccine not indicated	**55.1**
Patient declined	22.7
Insufficient time	16.6
Vaccine not available	2.1
Referred to other provider	1.0
Medical contraindication	0.6
Unknown*	2.0

* Data were missing for 10 higher-risk travelers to South Korea (8) and Taiwan (2).

Deshpande et al., Use of Japanese Encephalitis Vaccine in US Travel Medicine Practices in Global TravEpiNet. AmJTropMedHyg 2014

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"No-One Told Us..."

- At a symposium at CISTM15 a UK organization "The Encephalitis Society" presented videos of family members whose children contracted JE while traveling on short holidays in Asia
- These parents uniformly expressed regret that "no one even discussed the risk of JE with us"
- And given the risk, albeit small, but coupled with the potential consequences each would have opted for vaccine, irrespective of cost
- Do not assume because something is expensive your traveler does not want it

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The U.S. Advisory Committee on Immunization Practices (ACIP)

The U.S. Advisory Committee on Immunization Practices (ACIP) recently updated its policy recommendation for U.S. travelers:

- JE vaccine is recommended for persons moving to a JE-endemic country to take up residence, longer-term (e.g. ≥1 month) travelers to JE-endemic areas, and frequent travelers to JE-endemic areas
- JE vaccine should be considered for shorter-term (e.g. less than one month) travelers with an increased risk of JE based on planned travel duration, season, location, activities and accommodations
- Vaccination also should be considered for travelers to JE-endemic areas who are uncertain of specific duration of travel, destinations or activities

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World Health Organization

World Health Organization (WHO) states:

- Even if the number of JE-confirmed cases is low, vaccination should be considered when the environment is suitable for JE virus transmission, and that there is little evidence to support JE reduction disease burden from interventions other than human vaccination.

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Special Population Considerations

- Are there particular risks in pregnancy that may be similar to that seen with Zika virus or other arboviruses? There is evidence that JE virus is found in aborted fetal tissue.
- Can JE by sexually transmitted once the individual is infected?
- If JE is in blood transfusions, is it in body fluids and for how long?

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Unanswered Questions

Risk in Pregnancy

- In the risk assessment, we also should consider whether JE virus could, like other arboviruses, represent a serious threat during pregnancy, both to the mother and fetus.
- As data accumulate about the sexual transmission of Zika virus, acquisition during pregnancy, and the disease's sequelae, as well as problems associated with Chikungunya infection during pregnancy, we wonder whether there are similar risks associated with JE virus.
- In fact, there is evidence that JE virus is found in aborted fetal tissue. Blood and blood product transfusion during viremia may also carry risk.

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Summary

- JE is an unpredictable threat for travelers
- Case studies show that travelers visiting for a short time, with little or no rural exposure, and outside of the established transmission season have contracted JE
- The risk is greater than we think!
- Human vaccination is the best protection against JE
- All travelers to Asia should be assessed for their risk of contracting JE and an informed discussion should be part of every travel consultation

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