Japanese Encephalitis Debate: One in a Million?

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    Defense (DOD)

Japanese Encephalitis: Vaccine or No?

- Japanese Encephalitis Vaccine for Travelers: Exploring the Limits of Risk
- 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 protagonists 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.

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?

Japanese Encephalitis Vaccine

Original Sin:

- January 1993 ACIP recommendations
  - Advance 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
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

- 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

- 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

- Possible Vaccine Side Effects
  - Injection site reactions (redness, pain, swelling, or arm soreness)
  - Low-grade fever
  - Chills
  - Flu-like symptoms
  - Headache
  - Severe fatigue
  - Nausea
  - Vomiting
  - 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!

Japanese Encephalitis Vaccine: Do Risks Outweigh the Benefits?

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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

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
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.
- Increased migration to cities has led to urbanization of rural areas where natural enzootic cycles exist.
- 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.

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.

JE Can Affect Travelers to Asia and can Have Severe Outcomes

Summary of selected published case studies between 1992–2013

<table>
<thead>
<tr>
<th>Year</th>
<th>Country of Origin</th>
<th>Travel Destination</th>
<th>Duration/Travel itinerary</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>UK</td>
<td>Malaysia, Thailand</td>
<td>9 weeks, 3 days trekking</td>
<td>Recovered</td>
</tr>
<tr>
<td>1994</td>
<td>Sweden</td>
<td>Bali</td>
<td>10 days, one-day trip to the countryside</td>
<td>Recovered</td>
</tr>
<tr>
<td>1995</td>
<td>Denmark</td>
<td>Bali</td>
<td>12 days, coastal, few trips inland</td>
<td>Fatal</td>
</tr>
<tr>
<td>2001</td>
<td>Sweden</td>
<td>Java and Bali</td>
<td>3 weeks, outings to the countryside</td>
<td>Moderate sequelae</td>
</tr>
<tr>
<td>2004</td>
<td>Finland</td>
<td>Thailand</td>
<td>2 weeks (1 week Khao Lak, 1 week Phuket, two-day trips rural area)</td>
<td>Initially mild sequelae, after 3 years fully recovered</td>
</tr>
<tr>
<td>2004</td>
<td>USA</td>
<td>Thailand</td>
<td>32 days</td>
<td>Recovered</td>
</tr>
<tr>
<td>2004</td>
<td>New Zealand</td>
<td>Japan, China, and Hong Kong</td>
<td>5 weeks, urban and rural travel</td>
<td>Severe cognitive and motor sequelae</td>
</tr>
<tr>
<td>2005</td>
<td>The Netherlands</td>
<td>Indonesia and Thailand – Both travelers recovered after long-lasting cognitive sequelae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Italy</td>
<td>Vietnam</td>
<td>3 weeks, rural travel</td>
<td>Recovered, slight deficit in recent memory</td>
</tr>
<tr>
<td>2008</td>
<td>USA</td>
<td>Vietnam and Cambodia</td>
<td>3-weeks hotel and house, rural travel</td>
<td>Recovered</td>
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<tr>
<td>2013</td>
<td>Spain</td>
<td>Thailand</td>
<td>4 weeks, island, day trips to rural areas, two-day urban stay</td>
<td>Recovered, walk with an ataxic gait, minor memory impairment, emotional lability</td>
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JE among visitors to Bali

<table>
<thead>
<tr>
<th>Patient</th>
<th>Stay</th>
<th>Type</th>
<th>Outcome</th>
<th>Ref.</th>
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</thead>
<tbody>
<tr>
<td>10 F</td>
<td>Australia</td>
<td>14d / 1988</td>
<td>Beach hotel*</td>
<td>died</td>
</tr>
<tr>
<td>10 F</td>
<td>Sweden</td>
<td>10d / 1994</td>
<td>Beach hotel*</td>
<td>recovered</td>
</tr>
<tr>
<td>31 M</td>
<td>Danish</td>
<td>12d / 1994</td>
<td>Beach hotel*</td>
<td>died</td>
</tr>
<tr>
<td>30 M</td>
<td>Swedish</td>
<td>3 wk / 2001</td>
<td>Beach hotel*</td>
<td>sequela</td>
</tr>
</tbody>
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JE among visitors to Vietnam

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<td>3 wk / 2006</td>
<td>Tourist/hotel</td>
<td>few sequelae</td>
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<tr>
<td>9 M</td>
<td>U.S.A.</td>
<td>&lt;4 wk / 2008</td>
<td>VFR</td>
<td>sequelae</td>
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JE among visitors to Asia

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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.
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 travellers.
- 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!!

Guidance on Prevention of Japanese Encephalitis in Canadian Travellers

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

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 travelers 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 travelers to risk areas.

Guidance on Prevention of Japanese Encephalitis in Canadian Travellers

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

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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

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.

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

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

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

Subclinical JE

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

- Halstead SB, Grosz CR. Am J Hyg 1962;75:190-201
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:
- Severe persistent headache for 1 week, fever for 1 day
- Anorexia, abdominal pain, headache, fever
- Severe fatigue with narcolepsy, nausea
- Fever, fatigue and nausea

Many of these patients remained unwell for prolonged periods of time.

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 3-6 weeks.
- 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.

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.
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?

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

Study: Utilization of JE Vaccine in US Travelers

- 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

Results: Utilization of JE vaccine in US travelers

- >70% of identified higher-risk travelers never received JE vaccine
- Only 28.8% of higher risk travelers received the JE vaccine

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

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
“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.

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.

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.

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 be sexually transmitted once the individual is infected?
- If JE is in blood transfusions, is it in body fluids and for how long?

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.

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.