Disclosures (S. Schofield)
- Relationships with commercial interests: None
- Canadian Guideline centric (Canadian Committee to Advise on Tropical Medicine and Travel)


Risk of JE (CATMAT guideline; in press)

<table>
<thead>
<tr>
<th>Region of embarkation</th>
<th>Cases</th>
<th>Estimated travel volume (millions) 2006-2015</th>
<th>Overall attack rate for travellers (95% confidence interval) 2006-2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>1</td>
<td>1/11,650,000 (1/165,994,483; 1/2,056,512)</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>5</td>
<td>1/11,076,000 (1/25,935,276; 1/4,731,359)</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>11</td>
<td>1/11,636,363 (1/4,420,2750; 7.614,552)</td>
<td></td>
</tr>
</tbody>
</table>

"...(< 1 case/10,000,000 or approximately 1 case/1,000,000 with 10-fold underascertainment) ..."

What we want?
"Best" evidence/analyses to inform decision-making & recommendations

Benefits & harms, values & preferences

Different decisions/recommendations possible/expected

What is the risk?
Values and preferences of travellers?

Plausible contention (1)
JE vaccine (Ixiaro®) distributed (2009-present) in the US (ca. 1,500,000 doses) has not averted a single case of JE!
Risk = 1/million: estimated probability for no cases averted is 29% & no deaths averted is 73%

Risk = 1/10 million: estimated probability for no cases averted is 88% & no deaths averted is 97%

Binomial model: 2-dose primary series; no booster; distributed vaccine used, 50% of recipients take a second trip

Plausible contention (2)

Travelling to/from the clinic to get vaccine comes with about the same overall risk of death (MVA) as travel-associated JE

Plausible contention (3)

Many/most patients/practitioners believe that the benefit of receiving JEV is not worth its cost and inconvenience

Risk of dying JE, or driving car = 1/4 million trips
Risk of dying driving motorcycle = 1/266,666 trips
Lives saved by switching to car from motorcycle (per million trips) = 3.5
Lives saved per million vaccinated with JEV = 0.25
Relative protective benefit switching to car = 3.5/0.25 = 14.0

Assumptions: 100 km driven; Canada (driving in US more dangerous); 25% CFR for JE; JEV perfectly protective
Misleading towards a belief (1)

An overemphasis on disease severity vice absolute impact

Misleading towards a belief (2)

The assumption that benefits (disease protection) outweigh direct harms (AE) for a vaccine with a good safety profile

"What is most important in the discussion around vaccination in order to make an informed choice, is an emphasis on the severity of JE" (Turtle and Driver, 2018 Human Vaccines and Immunotherapeutics)

"Although cost remains a consideration, in a disease where the case-fatality rate among those with encephalitis is as high as 30%, and 30%-50% of those who survive suffer serious neurologic sequelae, the vaccine may be indicated for a greater number of travelers" (Connor et al., in press. Journal of Travel Medicine)

Possible Side-effects from Vaccines

"Any medication can cause a severe allergic reaction. Such reactions from a vaccine are very rare, estimated at about 1 in a million doses, and would happen within a few minutes to a few hours after the vaccination"

Source: https://www.cdc.gov/vaccines/safety/side-effects.htm

"In general, anaphylaxis is regarded as a rare event with accepted ranges of rates being between 1 event per 100,000 to 1 million vaccine doses. The case fatality rate of vaccine anaphylaxis is unknown but it would be reasonable to hypothesize that this would be similar to drug anaphylaxis (approximately 10%) and this would be in the region of 1 death per 1-10 million vaccine doses"
Misleading towards a belief (3)

Short shiff to alternatives....

“What is also missing from current recommendations is an appreciation of the changing epidemiology of JE infection” (Connor et al., in press. JTM)

“What is missing from Connor et al. is mention of insect bite precautions and the impact [if well executed] that they can have on risk (Scholfield, today)”

Summary

- Absolute benefit very small for the large majority (LM)
- “Indirect” harms outweigh benefit for LM (cost, inconvenience, travel to/from clinic)
- Travellers already choosing not to receive
- “Direct” harm equipoised with benefit for LM?
- No evidence that risk is increasing
- Alternatives, if used, cheaper and with broader benefit

Given above, who would choose to receive JEV?

Misleading towards a belief (3)

The inference that the changing epidemiology of JE increases risk to travellers

“...farming methods and patterns are changing. Some areas that were traditionally dominated by crop planting have changed to growing commercial crops, such as fruit trees, which require less irrigation, and thereby reduce the level of mosquito breeding. The measures described above have also reduced the level of natural circulation of JEV between mosquitoes and pigs and thus have decreased the risk of JEV infection amongst the human population”

Source: ACIP presentation, October 26, 2017

“...The epidemiology of JE and risk to the traveller has changed and continues to evolve. The spread of JEV into new environments, changes in agricultural practice and animal vectors, climate change, peri-urban growth, changes in international travel to Asia, personal risk factors, mosquito vector free transmission, interactions with other flaviviruses and better information on infections without encephalitis and other factors make JE an underappreciated risk” (Conner and Bunn, 2016. Tropical Diseases, Travel Medicine and Vaccines)

“What is also missing from current recommendations is an appreciation of the changing epidemiology of JE infection” (Connor et al., in press. JTM)
Risk Assessments and Guidelines

About ½ a case per year per 5 million trips = 1 case/10 million trips

Estimate of risk for U.S. travelers to Asia

- Risk estimate based on reported U.S. cases
  - 12 U.S. travel-associated JEV cases in the 25 years from 1993 to 2017 (<1 per year)
  - 4-5 million U.S. citizen trips to Asia per year since 2004 (NTTO)
  - < 1 case per million trips to Asia
- Risk varies based on season, destination, duration, and activities

Source: ACIP presentation, October 26, 2017

Balancing “Harms and Benefits” (1)

“...most travelers would be willing to accept the harms, cost and inconvenience of vaccination if JEV risk was 1/100,000 or higher, but not at lower risks. This threshold for vaccine use is several orders of magnitude higher than the overall risk estimate for JEV. Thus, we recommend against routine use of JEV for travel to endemic areas” (CATMAT, in press)

Balancing “Harms and Benefits” (2)

“.the relatively likelihood of acquiring JEV is likely elevated for some populations (e.g., long-term travel, exposure in rural areas, multiple trips to endemic areas and/or travel to an areas suffering an outbreak) and that more travellers would choose to receive vaccine in such circumstances (risk factor evidence was not evaluated using GRADE...)” (CATMAT, in press)

Estimate of risk: limitations

- Calculation based on number of trips as number of travelers not available
- Rate of underdiagnosis and underreporting unknown; assuming 10 times as many cases
  - 120 U.S. traveler cases (~5 case per year)
  - 100-125 million U.S. citizen trips to Asia
  - ~1 case per million trips to Asia

Source: ACIP presentation, October 26, 2017

VOTE: Proposed JEV vaccine recommendations

JE vaccine is recommended for persons moving to a JE-endemic country to take up residence, longer-term (e.g., 21 month) travelers to JE-endemic areas, and frequent travelers to JE-endemic areas.

JE vaccine also should be considered for shorter-term (e.g., <1 month) travelers with an increased risk of JE based on planned travel duration, season, location, activities, and accommodations (Box). Vaccination also should be considered for travelers to endemic areas who are uncertain of specific duration of travel, destinations, or activities.

JE vaccine is not recommended for travelers with very low risk itineraries, such as shorter-term travel limited to urban areas or travel that occurs outside of a well-defined JE virus transmission season.

Source: ACIP Presentation, February 27, 2019
What would we do for a similar disease @ home (say WNV)?

Other risk factors
The available evidence did not allow for the reliable estimation of the incremental impact of risk factors such as duration of travel, age, rural exposure

CATMAT recommendation (in press)
“...CATMAT suggests that JEV (IXIARO®) not be routinely used for travel to endemic areas [Conditional recommendation against use]...for the large majority of travellers, the likelihood of developing clinical JE in endemic areas... is negligible... balanced against cost, inconvenience and the potential risk of adverse effects, most travellers would choose not to receive JEV”
Permethrin on clothing
Topical repellent
Tick checks
Bed nets