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Use of Japanese Encephalitis Vaccine in US Travel Medicine Practices in Global TravEpiNet


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Abstract. Few data regarding the use of Japanese encephalitis (JE) vaccine in clinical practice are available. We identified 711 travelers at higher risk and 7,578 travelers at lower risk for JE who were seen at US Global TravEpiNet sites from September of 2009 to August of 2012. Higher-risk travelers were younger than lower-risk travelers (median age = 29 versus 40 years, P < 0.001). Over 70% of higher-risk travelers neither received JE vaccine during the clinic visit nor had been previously vaccinated. In the majority of these instances, clinicians determined that the JE vaccine was not indicated for the higher-risk traveler, which contradicts current recommendations of the Advisory Committee on Immunization Practices. Better understanding is needed of the clinical decision-making regarding JE vaccine in US travel medicine practices.

BACKGROUND

Japanese encephalitis (JE) virus is a mosquito-borne flavivirus that is endemic in much of Asia and parts of the western Pacific. An estimated 70,000 JE cases occur per year; the case-fatality ratio is 20–30%, and 30–50% of survivors have neurologic or psychiatric sequelae.1–3 For travelers, the risk of disease is generally low but varies with destination, trip duration, season of travel, and planned activities.2 Fifty-five travel-associated JE cases were reported in the literature during 1973–2008.4

The Advisory Committee on Immunization Practices (ACIP) recommends JE vaccination for all travelers who plan to spend 1 month or more in JE-endemic regions during the transmission season. The ACIP further states that the vaccine should be considered for short-term (<1 month) travelers going to rural areas whose itineraries or activities place them at increased risk of JE virus exposure, short-term travelers going to areas with known outbreaks, and short-term travelers who are unsure of their itinerary.2 Two JE vaccines have been available for use in the United States: an inactivated mouse brain-derived vaccine (JE-VAX, Sanofi Pasteur, Swiftwater, PA) and an inactivated Vero cell culture-derived vaccine (IXIARO, Novartis Vaccines, Cambridge, MA).2 JE-VAX was associated with rare but serious hypersensitivity and neurologic adverse events.2 Production of JE-VAX was discontinued in 2006, and limited supplies were available until 2011. IXIARO, which is given as a two-dose series administered 28 days apart, was approved by the Food and Drug Administration in March of 2009. Until 2013, IXIARO was licensed for use only in people ages ≥17 years.

Few data regarding the use of JE vaccine in clinical practice are available. A 2007 airport survey of US travelers to Asia found that only 11% of higher-risk travelers (defined as those traveling to JE-endemic areas for ≥30 days or spending more than one-half their trip in rural areas) had received JE vaccine.5 Furthermore, 69% of these higher-risk travelers who had visited a healthcare provider before their trip indicated that JE vaccine had not been recommended during the clinical encounter.

In this study, we describe the demographic characteristics of US residents traveling to JE-endemic countries and evaluate the current use of JE vaccine in a large consortium of US clinical practices that provide pre-travel healthcare. We focused particularly on the time period since the introduction of IXIARO.

METHODS

Global TravEpiNet clinics. Global TravEpiNet (GTEN) is sponsored by the Centers for Disease Control and Prevention (CDC), and it is a consortium of US clinical practices that provide pre-travel care to international travelers.6 GTEN sites are distributed across the US and include academic practices, healthcare consortia, health maintenance organizations, pharmacy-based clinics, private practices, and public health clinics. An institutional review board at each participating site reviewed and approved the study.

Study population. We evaluated international travelers seen at GTEN sites from September of 2009 to August of 2012. Clinicians collected data on travelers using a secure internet tool. For each clinic visit associated with a unique itinerary, travelers provided details about their medical history, destination countries, purpose of travel, geographic type of travel (urban, rural, or both), planned activities, planned accommodations, and duration and dates of travel. Clinicians verified the information provided by travelers and entered additional data on immunization history, health advice provided, vaccines administered, and medications prescribed during the pre-travel encounter. Clinicians were able to review additional geographic details of the itinerary, such as cities or regions visited within a destination country, but these details were not captured further for analysis. If a traveler had an indication for a vaccine according to ACIP guidelines that were current at the time of the clinic visit but the vaccine was not administered, the clinician was required to provide a reason for not administering the vaccine; available options included pre-existing immunity, vaccine not indicated, referred to primary care provider for vaccination,
Data analysis. For the purpose of this analysis, we consid-
ered the following countries to be endemic for JE in accor-
dance with the CDC definitions: Bangladesh, Brunei, Burma/
Myanmar, Cambodia, China, India, Indonesia, Japan, Laos,
Malaysia, Nepal, Papua New Guinea, Philippines, South
Korea, Sri Lanka, Taiwan, Thailand, and Vietnam. Australia,
Bhutan, Mongolia, North Korea, Pakistan, Russia, Singapore,
Timor-Leste, and the Western Pacific Islands were excluded
from this analysis, because JE cases are very rare or JE risk
data are limited. Transmission seasons for each country were
defined according to the CDC. We limited our analysis to
countries, whereas another 2,166 (7.2%) were traveling to
JE-endemic countries along with other countries not endemic
for JE. For this analysis, we focused only on the former
group; we classified 711 (8.6%) as higher-risk travelers and
7,578 (91.4%) as lower-risk travelers (Table 1). Higher-risk
travelers were traveling for a median of 50 days (inter-
quartile range = 32–93 days), and lower-risk travelers were
traveling for a median of 14 days (interquartile range = 11–21 days). Higher-risk travelers were significantly younger
than lower-risk travelers (median age = 29 years versus
40 years, P < 0.001). Leisure was the most frequent pur-
pose of travel for both categories of travelers. Travel for
research/education, to visit friends and relatives (VFR), and
for humanitarian service work represented a greater propor-
tion of higher-risk travel than lower-risk travel, and busi-
ness travel represented a greater proportion of lower-risk
travel. Higher-risk travelers sought pre-travel healthcare
earlier than lower-risk travelers (median = 28 days versus
23 days before departure, P = 0.004).
Of higher-risk travelers, 11 (1.5%) had received JE vac-
cine within the previous 2 years, whereas an additional

RESULTS

During the time period of this study, 29,885 travelers
ages ≥ 17 years were seen at GTEN clinics. The median
number of travelers seen at each clinic was 488 (interquartile
range = 215–1,691). Of 29,885 travelers, 8,289 (27.7%) were
planning to travel exclusively to one or more JE-endemic
countries, whereas another 2,166 (7.2%) were traveling to
JE-endemic countries along with other countries not endemic
for JE. For this analysis, we focused only on the former
group; we classified 711 (8.6%) as higher-risk travelers and
7,578 (91.4%) as lower-risk travelers (Table 1). Higher-risk
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earlier than lower-risk travelers (median = 28 days versus
23 days before departure, P = 0.004).
Of higher-risk travelers, 11 (1.5%) had received JE vac-
cine within the previous 2 years, whereas an additional

Table 1

Demographic and travel-related characteristics of higher and lower JE risk travelers

<table>
<thead>
<tr>
<th></th>
<th>Higher-risk travelers (N = 711)</th>
<th>Lower-risk travelers (N = 7,578)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>17–49</td>
<td>569</td>
<td>5,079</td>
<td></td>
</tr>
<tr>
<td>50–64</td>
<td>103</td>
<td>1,728</td>
<td></td>
</tr>
<tr>
<td>≥ 65</td>
<td>39</td>
<td>771</td>
<td></td>
</tr>
<tr>
<td>Gender (female)</td>
<td></td>
<td></td>
<td>0.059</td>
</tr>
<tr>
<td></td>
<td>400</td>
<td>3,968</td>
<td></td>
</tr>
<tr>
<td>Purpose of travel†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leisure</td>
<td>351</td>
<td>4,468</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Research/education</td>
<td>169</td>
<td>611</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Business</td>
<td>149</td>
<td>2,174</td>
<td>0.003</td>
</tr>
<tr>
<td>VFR</td>
<td>144</td>
<td>773</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Humanitarian service work‡</td>
<td>132</td>
<td>602</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Other§</td>
<td>11</td>
<td>150</td>
<td>0.193</td>
</tr>
<tr>
<td>Days to departure at clinic visit</td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>0–13</td>
<td>183</td>
<td>2,313</td>
<td></td>
</tr>
<tr>
<td>14–20</td>
<td>89</td>
<td>1,072</td>
<td></td>
</tr>
<tr>
<td>21–27</td>
<td>83</td>
<td>914</td>
<td></td>
</tr>
<tr>
<td>≥ 28</td>
<td>356</td>
<td>3,279</td>
<td></td>
</tr>
<tr>
<td>JE vaccination status</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Vaccinated within 2 years</td>
<td>11</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Received vaccine for this itinerary</td>
<td>188</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>Not vaccinated</td>
<td>512</td>
<td>7,250</td>
<td></td>
</tr>
</tbody>
</table>

* P value determined using a Somers' D-derived test adjusting for clustering among clinical sites.
† Travelers with multiple purposes of travel were included more than once; therefore, totals sum to > 100%.
‡ Humanitarian service work includes medical service work, non-medical service work, and missionary work.
§ Other reasons include travel to attend a mass gathering, for military purposes, to adopt, or for an explicitly stated other reason.
188 (26.4%) were administered the JE vaccine at their pre-travel visit (Table 1). Of lower-risk travelers, 28 (0.4%) had been vaccinated within the previous 2 years, and 300 (4.0%) were administered the JE vaccine at the pre-travel visit.

Administration of JE vaccine at GTEN clinics increased during the time period of the study. Overall, 7.2% of all travelers who were exclusively visiting JE-endemic countries received the JE vaccine in the first year of the study (September of 2009 to August of 2010) compared with 8.6% of such travelers in the final year (September of 2011 to August of 2012, \( P = 0.04 \)). The proportion of travelers to JE-endemic countries who were deemed higher-risk according to our study criteria did not significantly change over the time period of the study (8.9% in the first year versus 8.3% in the final year, \( P = 0.42 \)).

Figure 1 shows the countries visited by higher-risk travelers. Overall, India was the most common destination country for both higher- and lower-risk travelers. The top five destination countries were the same for both higher- and lower-risk travelers and included India (48% of higher-risk travelers and 40% of lower-risk travelers), Thailand (17% of higher-risk travelers and 20% of lower-risk travelers), Cambodia (14% of higher-risk travelers and 18% of lower-risk travelers), Vietnam (13% of both higher-risk and lower-risk travelers), and China (11% of higher-risk travelers and 12% of lower-risk travelers).

In total, 512 (72.0%) higher-risk travelers neither received JE vaccine during the clinic visit nor had been previously vaccinated (Table 1). Table 2 shows the reasons that clinicians provided for not administering JE vaccine to these higher-risk travelers. In the majority of instances (55.1%), clinicians stated that JE vaccine was not indicated for the higher-risk traveler; 116 (22.7%) travelers declined the vaccine, and 85 (16.6%) travelers had insufficient time (< 28 days) to complete the JE vaccine series before departure. Thirty (35.3%) of eighty-five travelers with insufficient time to complete the JE vaccine series were seen by a clinician 14–27 days before their departure date.

We performed a multivariable analysis to identify factors associated with a clinician’s determination that the JE vaccine

Figure 1. Frequency of visits to JE-endemic countries by higher-risk travelers. Travelers who visited more than one country are included more than one time; 10 travelers to South Korea (8) and Taiwan (2) were excluded because of missing data.

| Table 2 |
|-------------------------|--------|--------|
| **Reason** | **Number** | **Percent** |
| Vaccine not indicated | 282 | 55.1 |
| Patient declined | 116 | 22.7 |
| Insufficient time | 85 | 16.6 |
| Vaccine not available | 11 | 2.1 |
| Referred to other provider | 5 | 1.0 |
| Medical contraindication | 3 | 0.6 |
| Unknown* | 10 | 2.0 |

*Data were missing for 10 higher-risk travelers to South Korea (8) and Taiwan (2).
Travelers who plan to spend time in rural areas. ACIP recommends JE vaccination for travelers to countries during the transmission season and planning to spend more than one time. Clinicians were more likely to consider JE vaccine to not be indicated for VFR travelers and travelers to India (Table 3). Because not all regions of India are endemic for JE, we performed the same multivariable analysis, but we excluded travelers to India; this change did not affect the findings.

**DISCUSSION**

Travel to Asia has been increasing in recent decades, placing more travelers at potential risk for JE. This work is the first description of the use of JE vaccine in a large clinical consortium in the United States since the introduction of IXIARO in 2009. Approximately one-quarter of all travelers in our study were adults who were visiting countries that are endemic or partially endemic for JE. Most of these travelers were considered to be at lower risk for JE according to our classification scheme.

We defined travelers as being at higher risk for JE if they were traveling long-term (30 days or longer) to JE-endemic countries during the transmission season and planning to visit rural areas. ACIP recommends JE vaccination for travelers who plan to spend ≥1 month in endemic areas. However, we found that only slightly more than one-quarter of these higher-risk travelers received JE vaccination in association with their clinic visit. In the majority of cases, JE vaccine was not administered because the clinician reported that the vaccine was not indicated. Clinicians were more likely to consider JE vaccine to not be indicated for VFR travelers and travelers to India.

GTEN sites care for a large number of international travelers, and we speculate that the providers in this study are likely to be familiar with ACIP recommendations for JE vaccine use. This suggests that factors other than lack of awareness of ACIP recommendations influenced their clinical decision-making. Healthcare providers must consider a number of factors when deciding whether to administer a travel-related vaccine, including the details of the traveler’s itinerary and risk of exposure to disease, vaccine cost, morbidity, and mortality of the disease, and potential adverse events after vaccination. Although JE can be a fatal disease with high morbidity, the risk of infection for travelers is low. A review of published cases of JE in travelers during 1973–2008 estimated the incidence rate for travelers from non-endemic areas to be 0.2 cases per million. Although current ACIP recommendations are formulated based on these low-incidence rate estimates, clinicians who chose not to administer JE vaccine may have considered this low infection risk in their decision-making. Alternatively, clinicians might have considered the JE vaccine to be too costly, and therefore deemed it not indicated. Country-specific details of the traveler’s itinerary that were not included in our analysis may also have influenced the clinicians’ risk assessments. Lastly, clinicians may have hesitated to administer JE vaccines given the adverse event profile that was previously associated with JE-VAX. The temporal increase in use of JE vaccine observed in our study suggests that the improved tolerability of IXIARO or increased awareness associated with the licensure of a new vaccine may have influenced clinical decisions.

IXIARO is administered in two doses separated by 28 days. For approximately one-sixth of higher-risk travelers who did not receive JE vaccine, the clinician indicated that there was insufficient time to complete the vaccine series before departure. A sizable number of these travelers had clinic appointments 14–27 days before departure. Availability of a more accelerated JE vaccine schedule might, therefore, increase the number of travelers who are able to receive the vaccine before departure.

Our study has some limitations. Although GTEN is the largest consortium of clinics providing pre-travel care in the United States, GTEN sites may not be representative of all travel medicine practices. GTEN does not collect data regarding clinician demographics, educational background, or years in practice, and hence, we cannot relate clinician-specific factors to decision-making regarding JE vaccine administration. We also did not collect details on the rationale behind clinical decision-making about JE vaccine, and hence, we cannot determine why clinicians diverged from ACIP recommendations for use of JE vaccine. An in-depth survey of clinician knowledge, attitudes, and practices regarding JE vaccine would be useful for exploring this area.

In summary, we found that many travelers whose itineraries placed them in a category for which JE vaccine is clearly recommended by the ACIP were not offered the vaccine by clinicians, who deemed the vaccine to not be indicated. The failure of clinicians to adhere to practice guidelines is an area in need of additional research. Clear and accurate information about travel-related disease risks and prevention options needs to be available to healthcare providers and the public. Web-based decision support tools for patients have been useful for improving uptake of other vaccines, such as the measles-mumps-rubella vaccine. A better understanding of JE vaccine administration practices since the advent of IXIARO is necessary, with a particular focus on understanding why clinical practice differs from current guidelines.

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**Table 3**

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Odds ratio (95% confidence intervals)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose of travel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humanitarian service work</td>
<td>0.59 (0.35–0.99)</td>
<td>0.045</td>
</tr>
<tr>
<td>VFR</td>
<td>1.69 (1.03–2.77)</td>
<td>0.039</td>
</tr>
<tr>
<td>Business</td>
<td>0.55 (0.33–0.93)</td>
<td>0.026</td>
</tr>
<tr>
<td>Research/education</td>
<td>0.50 (0.31–0.82)</td>
<td>0.006</td>
</tr>
<tr>
<td>Leisure</td>
<td>1.20 (0.81–1.80)</td>
<td>0.376</td>
</tr>
<tr>
<td>Traveling to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cambodia</td>
<td>0.73 (0.37–1.45)</td>
<td>0.369</td>
</tr>
<tr>
<td>China</td>
<td>1.83 (0.96–3.48)</td>
<td>0.067</td>
</tr>
<tr>
<td>India</td>
<td>1.90 (1.22–2.95)</td>
<td>0.005</td>
</tr>
<tr>
<td>Japan</td>
<td>0.22 (0.35–1.45)</td>
<td>0.117</td>
</tr>
<tr>
<td>Myanmar (Burma)</td>
<td>0.23 (0.22–2.32)</td>
<td>0.211</td>
</tr>
<tr>
<td>Thailand</td>
<td>0.99 (0.55–1.79)</td>
<td>0.968</td>
</tr>
</tbody>
</table>

*Travelers with multiple purposes of travel or multiple destinations were included more than one time.†Obtained from a multivariable random effects logistic regression model.
REFERENCES


