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## A Survey of US Travelers to Asia to Assess Compliance With Recommendations for the Use of Japanese Encephalitis Vaccine

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### Abstract

**Background**—Japanese encephalitis (JE) vaccine is recommended for travelers to Asia whose itineraries increase their risk of exposure to JE virus. The numbers of travelers with such itineraries and the proportion of those who receive JE vaccine are unknown. We performed a survey to estimate the proportion of US travelers to Asia who receive JE vaccine according to the Advisory Committee on Immunization Practices (ACIP) recommendations.

**Methods**—We surveyed US residents 18 years old departing on 38 flights to Asia selected through a stratified random sample of all direct flights to JE-endemic countries from three US airports. We asked participants about planned itineraries and activities, sources of travel health information, JE vaccination status, and potential barriers to vaccination. Participants planning to spend 30 days in Asia or at least half of their time in rural areas were defined as “higher JE risk” travelers for whom vaccination should have been considered.

**Results**—Of 2,341 eligible travelers contacted, 1,691 (72%) completed the survey. Among these 1,691 participants, 415 (25%) described itineraries for which JE vaccination should have been considered. Of these 415 higher JE risk travelers, only 47 (11%) reported receiving 1 dose of JE

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### Declaration of Interests

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vaccine. Of the 164 unvaccinated higher JE risk travelers who visited a health care provider before their trip, 113 (69%) indicated that they had never heard of JE vaccine or their health care provider had not offered or recommended JE vaccine.

**Conclusions**—A quarter of surveyed US travelers to Asia reported planned itineraries for which JE vaccination should have been considered. However, few of these at-risk travelers received JE vaccine.

Japanese encephalitis (JE) virus, a mosquito-borne flavivirus, is the most common cause of vaccine-preventable encephalitis in Asia. Among an estimated 67,000 annual cases, 20 to 30% of patients die and 30 to 50% of survivors have neurologic sequelae.<sup>1–3</sup> JE virus transmission occurs primarily in rural agricultural areas. In most temperate areas of Asia, JE is seasonal and large epidemics can occur. In the subtropics and tropics, transmission can occur year-round, often intensifying during the rainy season. In endemic countries, JE is primarily a disease of children. However, travel-associated JE can occur among persons of any age.<sup>4</sup>

For most travelers to Asia, the risk for JE is very low but varies with destination, duration, season, and activities.<sup>1,4</sup> The US Advisory Committee for Immunization Practices (ACIP) recommends JE vaccine for travelers who plan to spend ≥1 month in JE-endemic areas during the JE virus transmission season.<sup>1,5</sup> JE vaccine should be considered for short-term travelers (<1 month) if they plan to travel outside of an urban area and have an itinerary or activities that will increase the risk of JE virus exposure. JE vaccine is not recommended for short-term travelers whose visit will be restricted to urban areas or occurs entirely outside a well-defined JE virus transmission season.

An inactivated mouse brain-derived JE vaccine (JE-VAX) was licensed in the United States in 1992 for use in persons aged ≥1 year.<sup>1</sup> JE-VAX was administered in a three-dose primary series at 0, 14, and 30 days. The vaccine was safe and effective but was associated with rare serious allergic and neurologic adverse events.<sup>1,2</sup> JE-VAX is no longer being produced and all remaining doses expired in 2011.<sup>6</sup> In 2009, the US Food and Drug Administration (FDA) licensed a new inactivated Vero cell culture-derived JE vaccine (IXIARO) for use in persons aged ≥17 years.<sup>1</sup> IXIARO is administered in a two-dose primary series at 0 and 28 days with a booster dose recommended ≥1 year later for persons who remain at increased risk of JE virus exposure.<sup>1,7</sup>

In 2004, there were an estimated 5.5 million entries of US travelers into JE-endemic countries.<sup>8</sup> The proportion of these travelers for whom JE vaccine should have been recommended and to whom the vaccine was administered is unknown. In 2007, we surveyed US travelers to Asia to estimate the proportion who had itineraries that put them at increased risk for JE and the proportion who received JE vaccine according to ACIP recommendations.

## Methods

We surveyed US residents aged ≥18 years departing on flights to Asia during August and September 2007. The timing of the survey administration corresponds to the risk period for

JE in temperate areas. Travelers who did not speak English were excluded. Surveyed flights were selected through a stratified random sample of all direct flights to JE-endemic countries from three US airports (John F. Kennedy International Airport, Chicago O'Hare International Airport, and Los Angeles International Airport). These airports are the most frequent origination points of US travelers to Asia from the eastern, central, and western United States, respectively. A pilot survey of passengers on eight flights to China and Thailand determined that 38% of eligible respondents reported a travel itinerary with increased risk for JE virus exposure. Using that point estimate and allowing for 50% oversampling to account for possible correlation (ie, passengers traveling together with similar itineraries and likelihood of vaccination), we determined that 1,500 respondents were needed to estimate the proportion of travelers for whom JE vaccine should have been considered [95% confidence intervals (CI)  $\pm 3\%$ ]. Assuming an average of 40 respondents per flight, we surveyed 38 flights to attain the desired sample size. The number of flights surveyed to each destination country was proportionate to the number of US citizen entries to those countries in 2004, the most recent year for which data were available (Table 1).<sup>8</sup>

Beginning at 2 hours prior to the scheduled departure, we approached all travelers in the waiting areas of the selected flights. Travelers were queried as to eligibility (ie, age  $\geq 18$  years, traveling on the selected flight, and ability to complete the survey in English). Eligible participants completed a self-administered questionnaire with questions asking about traveler demographics (ie, sex, age, education level, and household income), country of birth and residence, sources of medical advice and health care sought in preparation for the current trip, travel itinerary and planned activities, JE vaccination status, and potential barriers to vaccination. Travelers planning to spend  $>1$  month in JE-endemic countries or at least half of their time in rural areas were defined as persons for whom JE vaccination should have been considered because of increased risk of exposure to JE virus (ie, "higher JE risk"). Lower JE risk was defined as travelers planning to spend  $<1$  month in JE-endemic countries and less than half of their time in rural areas.

Data were entered into an Access database and analyzed using spss version 12.0 (SPSS Inc., Chicago, IL, USA) and R version 2.14 with the survey package.<sup>9,10</sup> For descriptive results, categorical variables were given as proportions and continuous variables were described by mean or median and range. For population inferences, proportions, prevalence ratios (PR), differences, and 95% CI were calculated accounting for the sampling design and using a finite population correction.<sup>11</sup> The proportions reported as population estimates were adjusted to account for differences in the numbers of direct flights to destinations in Asia and may not coincide with proportions computed using the raw counts. The survey was determined to be vaccine program evaluation and did not require human subjects' review.

## Results

All 38 randomly selected flights were surveyed. The proportion of travelers who planned to travel to each of the seven targeted countries was closely proportional ( $\pm 4\%$ ) to US citizen entries to those countries in 2004 with the exception of the Philippines. In 2004, 10% of US citizens who traveled to one or more of the seven targeted countries entered the Philippines, but 18% of travelers we surveyed planned to visit the Philippines (Table 1).

On the basis of airline manifests, 9,197 travelers boarded the 38 randomly selected flights. Among the 9,197 travelers, 5,239 (57%) were contacted by survey team members (Figure 1). Of these, 2,341 (45%) met eligibility criteria. Among the 2,341 eligible travelers contacted, 1,691 (72%) completed the survey.

Of the 1,691 surveyed travelers, 951 (56%) were male and the mean age was 44 years (range: 18–85 years); 1,257 (74%) had a college education and 486 (29%) reported an annual household income >\$100,000 (Table 2). Overall, 603 (36%) of the travelers were born in a JE-endemic country, 553 (33%) were returning to their birth country, and 403 (24%) planned to visit two or more countries. Of the 1,691 surveyed, 969 (57%) obtained travel medicine advice from various sources and 543 (32%) visited a health care provider to prepare for their trip. Travelers returning to their birth country were less likely to visit a health care provider to prepare for their trip (110/527, 19%) compared to other travelers (433/1,113, 34%) (PR 0.6, 95% CI: 0.5–0.7).

On the basis of their reported itineraries, 415 (25%) of the surveyed travelers were classified as having higher risk for JE virus exposure and 1,276 (75%) were classified as lower JE risk. Travelers with higher JE risk itineraries (mean age 41 years) were younger than travelers with lower JE risk itineraries (mean age 46 years; difference 5.1 years, 95% CI: 1.1–9.1). Higher and lower JE risk travelers were similar with regard to education level, household income, and planned destination countries. However, to prepare for their current trip, higher risk travelers were more likely to have visited a health care provider (185/415, 45%) than lower risk travelers (360/1,276, 28%) (PR 1.6, 95% CI: 1.2–2.1).

Of the 415 travelers with higher JE risk itineraries, 330 (84%, 95% CI: 79–88%) planned to spend 1 month in a JE-endemic country, including 115 (37%, 95% CI 26–47%) planning to spend 6 months in Asia. The remaining 85 (16%, 95% CI: 12–21%) higher JE risk travelers planned to spend <1 month in Asia but at least half of their time in rural areas; of these, 55 (62%, 95% CI: 49–77%) planned to spend more than half of their time doing outdoor activities in rural areas. Among the higher JE risk travelers, those returning to their birth country were again less likely to visit a health care provider to prepare for their trip (21% vs 56%; PR 0.4, 95% CI: 0.3–0.5).

Forty-seven (11%, 95% CI: 7–15%) of the higher JE risk travelers reported that they received 1 doses of JE vaccine for this trip or a previous trip, while 368 (89%, 95% CI: 85–93%) indicated that they had never received JE vaccine. Higher risk travelers who received JE vaccine (mean age 34 years) were significantly younger than those who did not receive JE vaccine (mean age 41 years; difference 6.0 years, 95% CI: 0.1–12.9 years). Of the 368 travelers who were classified as higher JE risk but who had not received JE vaccine, 219 (60%) were unaware of or had not been advised to receive vaccine, and 104 (28%) did not think they needed JE vaccine for their trip. Overall, 164 (45%) of the 368 unvaccinated higher risk travelers visited a health care provider to prepare for the trip, but 113 (69%) still indicated that they had never heard of JE vaccine or their health care provider did not advise the JE vaccine (Table 3). Vaccine costs (7/164, 4%), inadequate time prior to travel (3/164, 2%), and concerns about possible adverse events (1/164, <1%) were uncommon reasons reported for not receiving the vaccine. Nine (19%) of 47 vaccinated and 55 (15%) of 368

unvaccinated higher risk travelers reported seeking advice from a travel medicine clinic. Education levels and household income were not associated with likelihood of vaccination.

Among the 1,276 lower JE risk travelers, 60 (5%) did not indicate vaccination status. Of the remaining 1,216 travelers, 17 (1.8%, 95% CI: 0.6–3.0%) indicated that they received the JE vaccine for this trip. Lower risk travelers who received JE vaccine were more likely to have sought advice from a travel medicine clinic (9/17, 53%) than lower risk travelers who did not receive JE vaccine (115/1,199, 10%) (PR 5.6, 95% CI: 2.4–13.2). Education levels and household income were not associated with vaccination.

## Discussion

We found that a quarter of US resident travelers to Asia had an itinerary for which JE vaccine should have been considered but only 11% of these travelers reported having received the vaccine. Of the travelers with higher JE risk itineraries, >80% planned to spend 1 month in a JE-endemic country and more than a third reported they would spend 6 months in Asia; the remaining higher JE risk travelers planned to spend at least half of their time in rural areas. These data suggest that US travelers who plan to have prolonged stays or extensive rural exposure in Asia may not be recommended or considered for JE vaccination according to ACIP recommendations. However, <2% of travelers with lower risk itineraries received JE vaccine, suggesting that it is not being inappropriately used in shorter term travelers to urban areas with little risk of disease.

This survey was performed in 2007, prior to the licensure of the new inactivated Vero cell culture-derived JE vaccine in 2009.<sup>12</sup> Given concerns about rare but serious adverse events associated with the previously available mouse brain-derived JE vaccine,<sup>1,2,13</sup> it will be important to see if JE vaccination increases among higher risk, and possibly lower risk, travelers. However, the new vaccine still requires a two-dose primary series administered 28 days apart and costs more than \$160 per dose.<sup>1,14</sup> Furthermore, the vast majority of travelers in this survey reported that they did not receive JE vaccine because they were not aware of it, were advised not to receive it, or had otherwise determined that they did not need it for their trip. Vaccine cost, inadequate time prior to travel, and concerns about adverse events were uncommon reasons reported for not being vaccinated. These data suggest that travelers and health care providers still need to be educated about the risks of travel-associated JE and itineraries for which JE vaccine might be indicated.

For most travelers to Asia, the risk for JE is very low but varies based on destination, duration, season, and activities.<sup>1,4</sup> During the 39 years from 1973 to 2011, only 62 cases of travel-associated JE among persons from nonendemic countries were reported in the literature, including 16 (26%) travelers from the United States. The majority of cases occurred among expatriates or tourists who visited JE-endemic countries for a month or longer and includes five (8%) travelers who returned to their birth country to visit friends and relatives.<sup>1,4,15–20</sup> Of the 62 reported cases, 12 (19%) patients died and 28 (45%) survived with sequelae. These reports are certainly not all the travel-associated JE cases that occurred during this period. However, the incidence of JE among persons from nonendemic countries traveling to Asia is estimated to be less than one case per 1 million travelers.<sup>1,4,21</sup>

The findings from this survey suggest that the low risk of travel-associated JE likely reflects an inherently low risk of virus exposure and disease for most US travelers rather than high rates of protection owing to vaccine-induced immunity. Despite the apparent low risk of JE virus exposure for travelers, JE is a severe but preventable disease. All travelers to JE-endemic areas should be educated about personal protective measures to reduce the risks of vector-borne diseases. For travelers who will be in a high-risk setting based on season, location, duration, and activities, JE vaccine can further reduce the risk for JE virus infection.<sup>1</sup>

Although a majority of travelers to JE-endemic countries surveyed indicated seeking travel health advice, only one third sought advice from a health care provider. Among those with higher JE risk itineraries, less than half visited a health care provider to prepare for their trip, and people returning to their birth country were even less likely to see a health care provider. Travelers returning to their country of origin to visit friends and relatives are typically at greater risk than most tourists for travel-related infections but infrequently seek pre-travel health advice.<sup>15,22,23</sup> These findings highlight the fact that clear and accurate information about travel-related health risks and prevention methods needs to be readily accessible to the lay public through various sources with possible targeted outreach to certain higher risk groups.

This study was subject to several limitations. Although we attempted to obtain a representative sample of passengers to JE-endemic countries, our sample population was not randomly selected from among all US resident travelers to JE-endemic countries. In addition, <60% of travelers on the selected flights were contacted to participate in the survey, and those who were not available might have differed from the travelers we were able to approach. More than half of those who were contacted were not eligible to participate, with language being the most common reason. Therefore, our data likely underrepresented US travelers for whom English is a second language, which may include a higher proportion of immigrants and persons returning to visit friends or relatives. We could not evaluate each traveler's itinerary in detail and some might have been misclassified with regard to JE risk and indication for vaccination. JE vaccination status and whether JE vaccine was considered or offered were self-reported and could not be validated with health care providers or medical records. Finally, owing to differences in destinations, itineraries, and vaccine recommendations, these findings do not necessarily apply to travelers from other JE nonendemic countries.

When making decisions regarding the use of JE vaccine, health care providers need to weigh the individual traveler's risk of JE based on their itinerary, the high morbidity and mortality when JE does occur, the low probability of serious adverse events following vaccination, and the cost of the vaccine. We found that a quarter of surveyed US travelers to Asia reported planned itineraries for which JE vaccination should have been considered according to ACIP recommendations. However, few of these at-risk travelers received JE vaccine, even when they visited a health care provider to prepare for the trip. Clear and accurate information about travel-related health risks and prevention methods needs to be readily accessible to health care providers and the public. All travelers to Asia, including those returning to their country of birth, should be advised of the risks of JE and other vector-borne disease and the



importance of personal protective measures to reduce the risk for mosquito bites. Travelers who will be in a high-risk setting based on season, location, duration, and activities should receive JE vaccine according to current recommendations.

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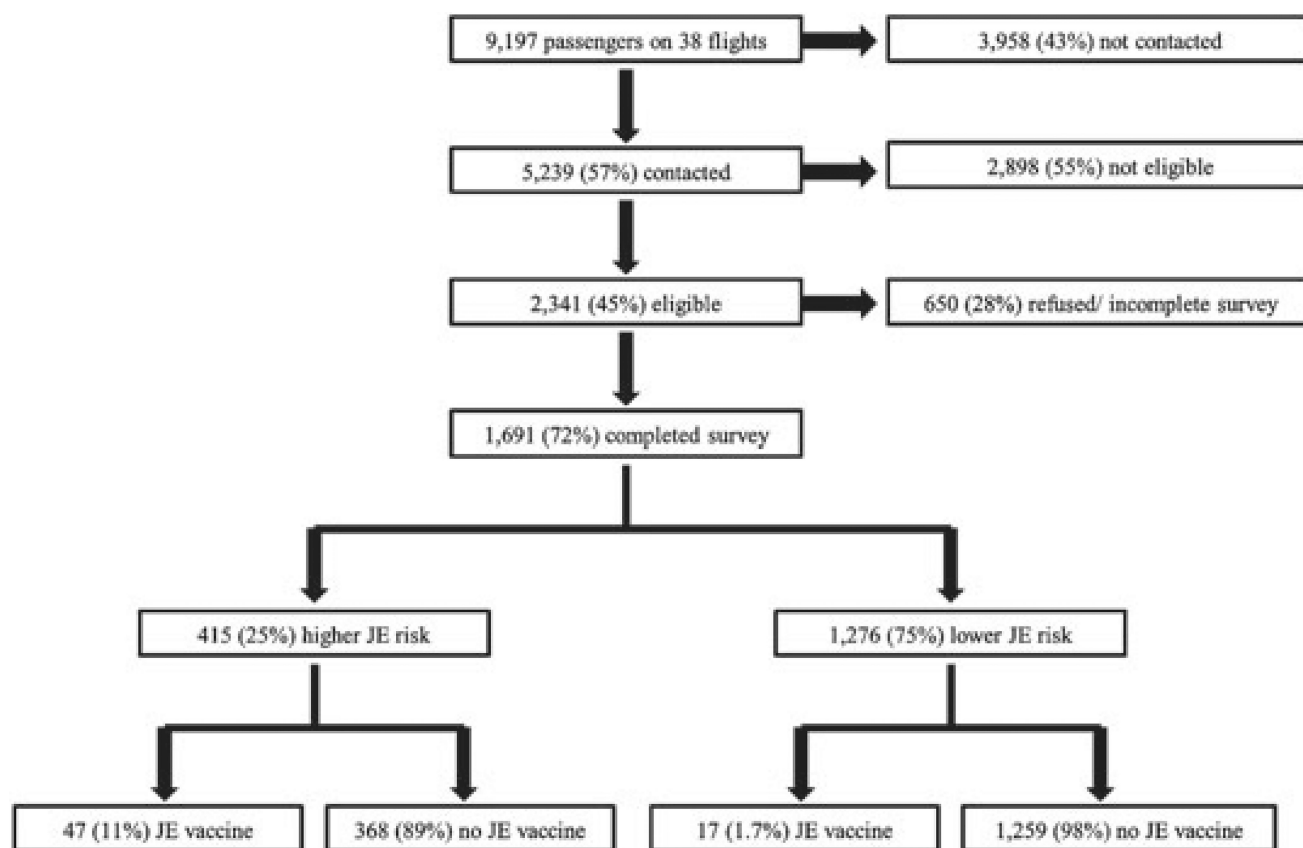
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**Figure 1.**  
Enrollment, eligibility, and classification of survey participants.

**Table 1**

Number of US citizen entries in 2004 and number of flights and travelers surveyed, by destination country

	<b>2004 US citizen entries (<i>N</i> = 4,599,477)</b>	<b>Flights surveyed (<i>N</i> = 38)</b>	<b>Surveyed travelers visiting country (<i>N</i> = 1,691)</b>
<b>Country</b>	<b>No. (%)</b>	<b>No. (%)</b>	<b>No. (%)</b>
China	1,308,627 (28)	11 (29)	489 (29)
Japan	759,753 (17)	7 (18)	250 (15)
Thailand	627,506 (14)	5 (13)	274 (16)
India	526,120 (11)	4 (11)	233 (14)
Korea	511,170 (11)	4 (11)	113 (7)
Philippines	478,091 (10)	4 (11)	301 (18)
Taiwan	380,210 (8)	3 (8)	103 (6)

**Table 2**

Characteristics of surveyed travelers and their planned itineraries

Characteristic	Surveyed travelers (N = 1,691)
	No. (%)
Male	951 (56)
Age group in years	
18–29	366 (22)
30–39	350 (21)
40–49	303 (18)
50–59	351 (21)
60	307 (18)
Unknown	14 (<1)
Highest education level	
High school	171 (10)
College or greater	1,257 (74)
Unknown	263 (16)
Annual household income	
<\$50,000	272 (16)
\$50,000–\$100,000	450 (27)
>\$100,000	486 (29)
Unknown	483 (28)
Number of countries planned to visit during current trip	
1	1,288 (76)
2	294 (17)
3	109 (6)
Sources of travel medicine advice for current trip <sup>*</sup>	
None	722 (43)
Primary health care provider	434 (26)
Travel medicine clinic	191 (11)
Friend, relative, or travel agent	315 (19)
Internet	309 (18)

<sup>\*</sup> Travelers could provide more than one response.

**Table 3**

Reasons travelers at higher risk for Japanese encephalitis (JE) virus exposure did not receive a JE vaccine prior to travel<sup>\*</sup>

	Visited a health care provider ( <i>N</i> = 164)	Did not visit a health care provider ( <i>N</i> = 204)
Reason for not receiving JE vaccine	No. (%)	No. (%)
Unaware of or not advised to receive JE vaccine	113 (69)	106 (52)
Did not think they needed JE vaccine	41 (25)	63 (31)
Traveling too soon to receive JE vaccine	3 (2)	8 (4)
JE vaccine too expensive	7 (4)	1 (<1)
Do not believe in vaccinations	1 (<1)	5 (2)
Afraid of sickness or side effect	1 (<1)	2 (1)
Medical contraindication	0 (0)	1 (<1)
None of the above	17 (10)	26 (13)

<sup>\*</sup> Travelers could provide more than one response.