

Japanese Encephalitis: Defining Risk Incidence for Travelers to Endemic Countries and Vaccine Prescribing From the UK and Switzerland

Christoph Hatz, MD, DTM&H,^{*,†} Jutta Werlein, MD,^{*} Margot Mutsch, PhD, MPH,[†] Markus Hufnagel, MD,^{*,‡} and Ron H. Behrens, MD[§]

^{*}Medical Department, Swiss Tropical Institute, Basel, Switzerland; [†]Division of Communicable Diseases/Institute for Social and Preventive Medicine, University of Zurich, Zurich, Switzerland; [‡]Center of Pediatrics and Adolescent Medicine, University Medical Center Freiburg, Freiburg, Germany; [§]Travel Clinic, Hospital for Tropical Diseases, London, UK

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Background. Large numbers of Western travelers visit countries endemic for Japanese encephalitis (JE). The risk of infection is unknown. This study attempts at estimating a risk incidence for visitors from two European countries with the available data.

Methods. Using the total number of case reports between 1978 and 2008, the number of visits made by European tourists to endemic regions, and total doses of vaccines sold in the two study countries, the risk incidence of JE in travelers was estimated. The proportion of vaccinated visitors to endemic regions was retrieved from the data of two travel clinics (in London and Basel) and related to vaccine prescribing in UK and Swiss travelers.

Results. In 2004, an estimated 0.16% to 0.3% of UK and Swiss travelers were vaccinated against JE, with no surveillance reports of JE cases. Between 116,000 and 152,000 European travelers would receive vaccination. More than 99% travel to endemic countries without vaccination. Only 40 cases of JE infection have been reported in travelers for the past 30 years. The risk incidence is thus 1.3 per year in 7.1 million visits of the 17 million European travelers who are at a potential risk of JE infection.

Conclusions. This study and the analysis of the existing literature support the recommendation that all travelers should be informed about the risk of JE infection but also suggest that there is no evidence for justifying a general recommendation for JE vaccination in travelers to endemic areas.

Japanese encephalitis (JE) is caused by a zoonotic flavivirus transmitted by *Culex tritaeniorhynchus* and other mosquito vectors in many rural parts of Asia. Although 3 billion Asians are at theoretical risk of infection,¹ it is the 220 million people living in rice-irrigated areas who are at actual risk, where irrigation has led to increased outbreaks and cases.² The impact of pig farming (amplifying host) on the epidemiology of JE infections is a matter of debate, particularly in peri-urban areas.³ However, no conclusive evidence can be drawn from the existing literature.

Of all individuals infected, around 1% develop clinical disease, of whom one third will die and one third will develop permanent neurological sequelae.¹ An estimated 1:250 to 1:1,000 infected children and 0.04% of nonimmune adults living in endemic areas develop clinical disease following infection.⁴

Three vaccines were available for use until 2008: the Korean Green Cross Corporation vaccine, the Biken

vaccine (JE-Vax), and the JE vaccine from Denka-Seiken. All are inactivated Nakayama or Beijing strain virus grown from mouse brains. The protective efficacy of the mouse brain-derived strain vaccine was found to be 91% in Thailand.⁵

Adverse events following vaccination (mild-to-moderate redness, swelling, and/or tenderness around the injection site) were described in 55% of 509 German vaccinees, 2.2% sought medical advice, and 1.8% were judged unfit to work for an average of 2.2 days.⁶ Neurological and allergic reactions have also been reported in travelers with the same vaccine.⁷ Neurological sequelae following the mouse brain-derived inactivated vaccine have been reported in 1 of 1 to 2.3 million persons vaccinated in endemic areas.^{1,8} Hypersensitivity reactions are reported in 18 to 64 per 10,000 travelers vaccinated.¹

The exact risk for travelers contracting JE disease or infection in endemic areas is unknown. Reviewing the literature, we have identified 40 clinical JE case reports in travelers between the years 1978 and 2008.^{9,10} Sixteen cases in travelers (excluding soldiers or relatives of expatriates) were reported by the Centers for Disease Control and Prevention between 1972 and 1992.⁹ In the most

Corresponding Author: Christoph Hatz, MD, DTM&H, Medical Department, Swiss Tropical Institute, PO Box CH-4002 Basel, Switzerland. E-mail: christoph.hatz@unibas.ch

recent review of cases (published in this issue of the *Journal of Travel Medicine*), Buhl and Lindquist describe another 20 cases in travelers to endemic areas between the years 1992 to 2008.¹⁰ An additional four case reports from Russia¹¹ and France¹² have been published. For a 30-year period, these 40 cases represent an estimated incidence of 1.3 case reports per year in Western travelers. In analyzing data with respect to Swedish travelers, Buhl and Lindquist calculated a risk of 1:400,000 visits.¹⁰

Western travelers visit endemic regions in large numbers. Data from expatriates living in Kolkata¹³ suggest the risk of acquiring symptomatic disease in short- and long-term travelers to be very low.¹⁴ Our study was designed to estimate a risk incidence for visitors from two European countries to endemic regions. We estimated at-risk travelers using the total visits from the two countries to endemic regions, adjusting this by season of travel and proportion of travelers immunized. Immunization coverage was estimated from two travel clinics' vaccine use supported by national total vaccines sold. We examined policy and practice in the risk assessment in the two specialist travel clinics.

Methods

The number of travelers from Switzerland and the UK to endemic areas (India, Thailand, China, Sri Lanka, Malaysia, Bangladesh, the Philippines, Vietnam, Indonesia, Nepal, Cambodia, Burma, Laos, and Papua New Guinea)¹ was extracted from the official World Tourism Organization figures for the year 2004¹⁵ and for UK travelers from the International Passenger Survey.¹⁶ These data reflect foreign arrivals and therefore are a crude estimate of visitors to these regions. The seasonal trend in travel was available for UK travelers only. Estimates of the vaccination rates in the UK and Switzerland were based on annual doses sold. Because quarterly sales data were not available, the impact of seasonal travel on the vaccine prescription practice could not be determined.

The total number of doses of JE vaccination dispensed by the distributors in the UK and Switzerland during 2004 was used to calculate the total number of individuals vaccinated. Based on records from two large travel clinics in London, UK, and Basel, Switzerland, we estimated that 72% of vaccinees received three doses of vaccine, 14% received two doses, and 14% received one dose of vaccine.

Data from clients of the two travel clinics, each seeing around 10,000 travelers annually, were analyzed to determine respective vaccination coverage of travelers to endemic regions. In Switzerland, recommendations have been aimed at (1) those who knew that they would be exposed for more than 4 weeks with at least 13 nights in rice-growing areas during the JE transmission season; (2) travelers with special risks (visiting friends and relatives; high-risk exposure shorter than 13 d) or an adventurous travel style and uncertain itinerary based on individual assessment; and (3) international organization collaborators who were likely to be exposed during one of their

future assignments. In UK travelers, clinic policy was vaccine to be recommended if traveling for more than 3 months and during the peak transmission period of May to November.

Results

Overall, 17,282,000 European travelers visited JE-endemic countries in 2004.¹⁵ From our study denominator, an estimated 209,346 Swiss and 1,819,773 British travelers visited a country where JE was transmitted. A total of 764,060 British travelers (42%) made journeys during the peak transmission season. A total of 6,578 (UK) and 1,656 (Switzerland) vaccine doses were dispensed nationally during 2004 to an estimated 2,959 and 710 individuals, respectively. The 710 Swiss vaccine recipients represent 0.30% of all Swiss travelers to endemic areas. The respective figure for the 2,959 British recipients is 0.16%, of whom 0.39% traveled during the transmission season. No surveillance reports of JE cases from the national surveillance bodies in the UK and Switzerland were identified in 2004.

A detailed analysis of clients traveling to JE-endemic countries during 2004 and who used specialist travel clinics in Basel and London during that year revealed that 1,243 clients visited the Basel clinic and 4,254 clients visited the London clinic. A total of 546 (44.7%) itineraries met the Swiss vaccination recommendations, and a total of 26 (4.64%) were immunized. Of the 26 recipients (16 males), the average age was 31 years (range 21–60 y). India was the most frequent destination,¹³ followed by Thailand.¹⁰

Of the 4,254 clients attending the London travel clinic and traveling to JE-endemic countries, 59 individuals (1.39%) were vaccinated based on their risk assessment and consent to vaccination. All travelers visited multiple countries, including Thailand (86%), Cambodia (73%), and India and/or Vietnam (68%).

Discussion

While the public health importance of mass JE vaccination of the local children population in endemic areas is undisputed,¹ the majority of travelers are at a very low risk of infection by comparison. The risk of disease in tourists and expatriate residents is, however, unclear, and an individual risk assessment is required to identify those who should be vaccinated. Current policy for recommending vaccine is focused on purely theoretical risk factors for acquiring infection and traveling for longer periods in rural settings during peak transmission seasons. Based on travel data from the UK (adjusted by season of travel), this study has estimated that 42% of the 17 million European travelers (ie, 7.1 million) visit endemic countries during the peak transmission season and could be considered at risk of infection. The national vaccine sales suggest that vaccination coverage is around 1% of travelers to endemic countries (UK and Swiss). Using the

Table 1 Factors to be considered when vaccinating travelers and expatriates

Points in support of vaccination	Points against vaccination
Serious and untreatable illness	Very low number of cases among travelers, expatriate residents, and military personnel
Available relatively safe vaccine	Risk regions probably not visited by most travelers and expatriates
Few Japanese encephalitis cases during short stays in endemic settings	Seasonal risk—highest seasonal risk coincides with low travel period
Efficacious vaccine	Adverse events associated with vaccine
Unknown exposure during travel	High cost of vaccination
Possible risk outside typical transmission season	
Underreporting of cases?	
Undetected cases during travel (incubation: 4–20 d)	
Travelers “off the beaten track”	
Repeated trips, visiting friends and relatives in rural areas	

lowest vaccination rate of 0.16% (UK clinic) and the highest rate of 0.3% (Swiss clinic), an estimate of between 116,000 and 152,000 Europeans visiting endemic countries would have received vaccination. This highlights that more than 99% of travelers are not vaccinated (protected).

The published literature details 40 cases for the past 30 years, an average of 1.3 cases per year. Although this is likely to be a significant underestimate of cases, from underreporting and disease during travel, the risk incidence based on this crude numerator gives an overall disease risk incidence of 1.3 cases per 7.1 million European travelers. We have not added visits from North America, Australia, and New Zealand, although we have included the published case reports from these continents. A risk assessment for JE should include the incident risk of developing the disease, financial cost of the vaccine, risk of adverse events of vaccination, and benefits of avoided disease (not infection). The factors to be considered when making the decision are listed in Table 1.

Seventy percent of the 20 reported symptomatic cases were described in persons who had traveled 10 days to 5 weeks in endemic areas. The presentation of 35% of the 20 cases indicates that they had traveled outside the transmission season.¹⁰ These figures highlight that long-term travel or expatriate status as well as classical transmission season do not correlate with the case reports.

Adverse events of the currently available vaccine range from 55% for mild local reactions to an estimated risk of 1 of 1 to 2 million for more severe neurological events.⁷ The cost is significant but not detailed in this study.

A reasonably priced and safe vaccine for use where JE epidemics occur may influence the risk perception and lower the threshold for vaccinating travelers in future. All travelers should be informed about the potential but low risk of JE as well as about both the potential and the incidence of adverse effects of the vaccine. This study suggests there is little to support the current policy of targeting the vaccine at any one group or recommending the vaccines be used generically by region. The potential benefits and costs of JE vaccination need to be decided by each fully informed traveler. The incident risk should now be

an important consideration in the risk assessment. The use of personal protection measures with repellents, sprays and vaporizers, insecticide-treated clothing, and bed nets should be the mainstay of JE and other vector disease avoidance.

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Declaration of Interests

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