EDITORIAL COMMENTARY

Boosting Japanese Encephalitis Vaccine

Christoph Hatz[1,2,3]

[1]Medicine and Diagnostics, Swiss Tropical and Public Health Institute, Basel; [2]University of Basel, and [3]Division of Epidemiology and Preventable Infectious Diseases, Institute for Social and Preventive Medicine, University of Zurich, Switzerland

(See the Major Article by Erra et al, on pages 825–34.)

Japanese encephalitis (JE), caused by a zoonotic flavivirus and transmitted by mosquitos during twilight and at night, is the most common vaccine-preventable viral encephalitis in rural areas from Eastern Pakistan to Northern Queensland in Australia and to Japan. Among the 3 billion people at theoretical risk of infection, an estimated 220 million people live in rice-irrigated areas where the risk may be considerably increased [1]. The impact of pig farming (amplifying host) on the epidemiology of JE infections is a matter of debate, particularly in periurban areas, but no conclusive evidence can be drawn from the existing literature [2]. Every year, up to 50 000 often severe JE clinical cases occur among the resident populations, in contrast with 1–2 cases among tourists, expatriates, and visiting friends or relatives in endemic areas [3].

The inactivated, mouse brain–derived wild-type Nakayama strain (JE-MB) vaccine, shown to be protective in endemic areas [4] but causing rare severe drug reactions, has widely been replaced by a new, purified, formalin-inactivated Vero cell culture–derived (IC51, JE-VC; attenuated SA_{14}-14-2) strain. Erra and colleagues provide a timely answer on how to boost JE–vaccinated subjects in a nonendemic population, filling a relevant gap of knowledge in travel medicine practice and beyond. A diligently chosen study design clearly shows that boosting the immune response following vaccination with 2–3 doses of the previously used JE-MB with a single dose of the JE-VC vaccine results in noninferior immunogenicity to boosting with a JE-MB vaccine. In addition, it confirms the validity of the known vaccination schedules with JE-MB and JE-VC. The decision to assess the immunogenicity of heterologous JE vaccines is scientifically sound. It shows that it is essential to rule out a potential bias that may result in favoring one vaccine over the other.

The interaction of concomitantly administered vaccines, including those against other flaviviruses, does not appear to negatively influence the immune response to JE-VC on the basis of the researchers' data.

A randomized controlled trial would be preferred. The small group size and the lack of ruling out the possibility of natural boosting are further limitations of the study. However, such complex studies are hardly feasible without substantial industry support. The study of Erra et al [5] also shows that investigator-driven studies are increasingly necessary to address practical questions that the user of medicinal products need to know, in order to provide the best and most cost-effective service to the client or patient.

Thus, a single dose of JE-VC will suffice to successfully boost previous priming with 2–3 doses of JE-MB vaccination. Two doses of JE-VC are not required in correctly prevaccinated travelers if the assumed correlate of a 50% plaque reduction neutralization test titer of ≥10 [6] is protective. The question remains how long the assumed protective level of antibodies will last in persons exposed to the wild-type virus and whether it is boosted by the respective exposure.

The true risk for travelers of suffering from the severe consequences of JE is under debate. The slight increase of reported JE cases among travelers over the past 36 years reflects the higher number of tourists rather than an increased risk for the individual traveler. The JE risk for 2 destinations with the highest risk for short-term travelers, Bali (Indonesia) and Thailand, is estimated to be 1 case in 1 million and 3.3 million travelers, respectively [3]. The respective risk estimates for Swedish (1 case per 400 000) and Finnish (1 case per 257 000) travelers to Thailand are higher [7, 8]. Even an assumed doubling of the number of cases will result in a low risk.

The fact that a new, apparently safe vaccine is now available is not necessarily a reason to boost its use in a population that may be at very limited risk. Thus, a careful assessment of the points in favor

Received 30 May 2012; accepted 1 June 2012; electronically published 13 June 2012.

Correspondence: Prof Dr Christoph Hatz, Medical Department, Swiss Tropical Institute, Socinstrasse 57, Basel CH-4002, Switzerland (Christoph.Hatz@unibas.ch).

Clinical Infectious Diseases 2012;55(6):835–6

DOI: 10.1093/cid/cis548

of and against JE-VC vaccination must be established. A serious and untreatable illness justifies its use. In contrast, the very low number of cases and the relatively low risk of exposure among travelers as well as the high cost speak against vaccinating. The scarce evidence of JE infections among travelers indicates that the majority of JE cases were recorded in subjects staying >1 month in endemic areas. However, 35% of the patients (n = 37) with a detailed descriptive risk analysis [3] had traveled for <4 weeks in an endemic setting. Two of 5 documented cases occurred outside the assumed transmission period in the respective countries [3, 7]. Despite these facts, 4 weeks' travel duration during the transmission period is the current cutoff for JE vaccine recommendation in many countries.

WHO SHOULD BE VACCINATED?

Beyond any doubt, all children living in endemic areas benefit greatly from JE vaccine [4]. For travelers, long-term expatriates, and visiting friends and relatives, the answer appears to be more complex and less straightforward. The presently available data on the risk of contracting JE in an endemic area are not adequate to give evidence-based advice.

Clearly, vaccinating all travelers to Asia is not cost-efficient [9]. Still, all travelers must be informed about this severe and often fatal disease. Exposure risks must be rationally assessed. Travelers sleeping at night in an open compound near unprotected water and close to pig rearing in Bali are at a higher risk than visitors to urban centers in Thailand. Families spending their holidays with local families in areas with known cases are likely to benefit from vaccination, although there are relatively few visiting friends and relatives among the reported severe cases.

Experienced travel medicine experts will base their recommendation on the differentiation of potential exposure (duration and season of travel, risk activities) and epidemiological knowledge (itinerary) of the literature and country reports, mixed with personal experience, and may be in the best position to counsel the traveler. Mosquito bite avoidance, although not scientifically confirmed, is a useful measure to protect travelers against JE. Using repellents on the skin and insecticides on bednets, fabrics, and clothing, and staying in accommodations with screened or air-conditioned rooms, will also protect from other endemic arthropod-born diseases (eg, malaria, dengue, and chikungunya). Finally, travelers will assess the benefits and risks for themselves and on that basis decide whether they want to spend a considerable amount of money on a vaccine against a disease that is very severe but exceedingly rare. If the travelers are aware that the risk of dying in a road accident is many times higher than suffering the severe consequences of a JE infection, they may make the informed decision to buy a helmet rather than spending money on the vaccine. If they choose to revaccinate after a previous priming JE-MB vaccination, they will only need a single booster dose of JE-VC.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Keiser J, Maltese MF, Erlanger TE, et al. Effect of irrigated rice agriculture on Japanese encephalitis, including challenges and opportunities for integrated vector management. Acta Trop **2005**; 95:40–57.
2. Ting SH, Tan HC, Wong WK, et al. Seroepidemiology of neutralizing antibodies to Japanese encephalitis virus in Singapore: continued transmission despite abolishment of pig farming? Acta Trop **2004**; 92:187–91.
3. Hills SL, Griggs CG, Fischer M. Japanese encephalitis in travelers from non-endemic countries 1973–2008. Am J Trop Med Hyg **2010**; 82:930–6.
4. Hoke CH, Nisalak A, Sangawhipa N, et al. Protection against Japanese encephalitis by inactivated vaccines. N Engl J Med **1988**; 319:608–14.
5. Erra E, Askling HH, Rombo L, et al. A single dose of Vero cell–derived Japanese encephalitis (JE) vaccine (Ixiaro) effectively boosts immunity in travelers primed with mouse brain–derived JE vaccines. Clin Infect Dis **2012**; 55:825–34.
6. Hombach J, Solomon T, Kurane I, et al. Report on a WHO consultation on immunological endpoints for evaluation of new Japanese encephalitis vaccines, WHO, Geneva, 2–3 September, 2004. Vaccine **2005**; 23:5205–11.
7. Buhl MR, Lindquist L. Japanese encephalitis vaccine for travelers: review of cases and seasonal risk. J Travel Med **2009**; 16:217–9.
8. Lehtinen VA, Huhtamo E, Siikamäki H, Vapalahti O. Japanese encephalitis in a Finnish traveller on a two-week holiday in Thailand. J Clin Virol **2008**; 43:93–5.
9. Hatz C, Werlein J, Hufnagel M, Behrens R. Japanese encephalitis and travel: defining risk incidence for travelers to endemic countries and vaccine prescribing from the UK and Switzerland. J Travel Med **2009**; 16:200–3.