Travel Medicine and Infectious Disease (2009) 7, 301–304

available at www.sciencedirect.com

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journal homepage: www.elsevierhealth.com/journals/tmid

A new inactivated Japanese encephalitis vaccine for adult travelers

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Received 25 March 2009; accepted 25 March 2009
Available online 12 July 2009

KEYWORDS
Japanese encephalitis;
Japanese encephalitis vaccine;
Travelers;
Travel vaccines;
Vero cell vaccine

Summary Current guidelines for Japanese encephalitis (JE) vaccine relate to an older mouse brain derived vaccine with an uncertain history of adverse events including delayed anaphylaxis. JE is widely distributed, including in urban areas. Underreporting is likely in many endemic countries, and atypical clinical forms exist. A new JE vaccine produced in Vero cells has become available, which appears equi-efficacious to the mouse brain derived vaccine. In development trials the new JE vaccine was as well tolerated as placebo. A review of existing guidelines for JE vaccine use in travelers should be considered.

> ''*Japanese encephalitis is a disease that pushes the limits of understanding risk and risk avoidance among travelers*''.[1]

Japanese encephalitis is a mosquito vectored flavivirus infection with a range that stretches from Pakistan to the Pacific Islands, and from China to Sri Lanka. Human infection may cause severe encephalitis, and is associated with approximately 30% mortality, and sequelae in survivors.[2]

The attack rate for Japanese encephalitis (JE) in travelers to rural areas of infected countries has been estimated at 1/5000/month,[1,3] but this represents average risk, and does not inform on the individual traveler's risk, which will vary with itinerary, activities, life style, accommodation, time of year, and climatic conditions.[4,5] It is generally held that infection is symptomatic in only 1 of every 250–1000 cases,[6] although the actual rate of infection demonstrated serologically amongst US troops in Korea was much higher: 1 in every 25.[7]

Current recommendations by CDC, Health Canada, and NathNac and others are to recommend immunization for travelers who will be spending at least four weeks in rural areas.[8–10] In contrast to Health Canada, the CDC and others state that infection may follow even brief exposure in rural areas.[11,12] However, transmission and reservoirs are not confined to rural areas, having been recorded both within urban areas, and on their outskirts[4,13]; JE virus sequences have additionally been detected in mosquitoes sampled in Tokyo and Osaka; interestingly, virus was detected in urban dwelling *Aedes albopictus* and *Culex pipiens* species.[14] Current guidelines for all contemplate vaccination with the only vaccine currently available in developed countries, which is derived from mouse brain. The advent of the new

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doi:10.1016/j.tmaid.2009.03.009

inactivated Vero cell derived vaccine and a reconsideration of JE's epidemiology should lead to a reassessment of existing guidelines.[2,15–24]

With 3 billion people at risk within the virus's range, the true incidence is likely to be higher than the frequently quoted figure of 50 000 cases per annum, given limited surveillance capacity in many affected countries.[24,25] A 1998 study estimated an annual pediatric incidence of 175 000 cases across the virus's range, which total would include 43 750 deaths and 78 750 cases with sequelae. A study from Bali, where the disease was previously thought to be very rare, found an incidence of 8.2 per 100 000 for children aged <10 years.[26] Cases were detected by hospital based surveillance, with case definition for confirmed cases including the presence of anti-JE IgM in cerebrospinal fluid. The authors concluded that the rate in Bali is similar to that in known endemic regions, and that vaccination should be introduced, stating, *''Our findings contradict the common wisdom that JE is rare in tropical Asia. Hence, the geographical range of endemic JE is broader than previously described. The results of the study support the need to introduce JE vaccination into Bali.''* A second and very recent study concluded JE to be endemic throughout Indonesia.[27]

Complicating incidence estimates, clinical presentations may not always resemble the classical encephalitic picture, contributing to underreporting and consequently underestimation of the true burden of disease: aseptic meningitis attributable to JE has been reported from Hiroshima,[28] and the clinical presentation may even be shifting from a predominantly encephalitic to a meningitic picture in Japan.[29] A poliomyelitis like syndrome in children has been attributed to JE in Vietnam, with 55% of cases in a series of 22 acute flaccid paralyses attributed to JE[30]; Taiwan reports a similar experience.[31] Other atypical presentations and clinical features, including isolated temporal lobe lesions and bilateral intracerebral hemorrhage, are reported and may potentially confound diagnosis.[32–34]

An important point to consider is that in countries where the population is routinely vaccinated against JE local incidence rates will not indicate the risk to unvaccinated travelers: a situation characterized as 'epidemiological silence', as man is merely an accidental host and the virus may continue to circulate in the absence of noticeable human disease. Erlanger et al. recently reviewed this topic, concluding that the incidence may decline in China and India in the wake of large scale vaccination programs.[35] A 2001 serosurvey in eight selected Japanese prefectures revealed a seropositivity of 4.4%, and a natural annual infection rate of 0.2–3.4%[36]; a similar serosurvey of racehorses confirmed continuing circulation of the virus in Japan, with an annual infection rate in racehorses of 15–67%.[37] The above suggests that risk to travelers from JE may be easily underestimated.

Historically the prime barrier to greater vaccine uptake in developed countries has been concerns over the safety of existing mouse brain derived vaccines, especially delayed anaphylactic type reactions and neurological adverse events: Danish authorities estimated an incidence of 1 serious adverse event for every 50 000–75 000 vaccinees,[38] while other estimates give incidence an order of magnitude higher[6]; demyelination events have been estimated at up to 2.3 per 1 000 000 vaccinees in Japan.[39] It has also been suggested that the risk of adverse events was more common with particular batches, but other reports suggest that risk was not confined to certain batches.[40–42] Stricter case definitions may account for differing adverse event rates between countries.[40] Japan employs a stricter case definition and reports a rate for systemic hypersensitivity reactions of 0.8 per 100 000 doses in Japan, versus 6.3 per 100 000 doses in the United States.[41] Of interest, urticaria and wheezing were shown in Japan to be associated with antibodies to gelatin contained in the vaccine.[43]

Safety concerns with the existing mouse brain derived vaccine obviously impact negatively the risk-benefit ratio for vaccination against JE. The literature however supports the risk of disease as being underestimated. Practitioners are thus faced with a dilemma: should they vaccinate against a potentially devastating disease, with a vaccine that has had its safety questioned, given that disease may be commoner than originally believed?

Safety concerns, especially possible neurological adverse effects, have led the manufacturer of the currently licensed inactivated mouse brain derived JE vaccine to no longer produce it for developed countries, where it is likely to eventually become unavailable.[46] The impending availability of the new IC51 Vero cell culture derived inactivated vaccine (JE-Vero) is likely to fill this gap. It is apposite therefore to consider the safety and immunogenicity of this vaccine.

In a randomized open label unblinded phase II study comparing inactivated Vero cell vaccine (JE-Vero) against the currently registered mouse brain derived vaccine (JE-VAX), 2 doses of intramuscular (IM) 6 μg JE-Vero on days 0 and 28 ($N = 24$) produced a GMT on day 56 of 327.2 (95% CI: 253.3–422.8) versus 128.3 (95% CI: 76.3–215.8) for 3 subcutaneous (SQ) doses of JE-VAX ($N = 21$) on days 0, 7, and 28. There was no significant difference in seroconversion rates at day 56 (JE-Vero 95%, JE-VAX 74%, $P = 0.09$); 7/8 (87.5%) of JE-Vero subjects were seropositive on day 720 (GMT 89.1; 95% CI: 56.3–141.0); 4/6 (67%) of JE-VAX subjects were seropositive on day 720 (GMT 27.9; 95% CI: 12.7–61.2). No serious adverse event was reported in either group, and there was no significant difference in systemic adverse event (AE) type or incidence between the 2 vaccines: commonest systemic AEs comprised headache (13 [54%] for JE-Vero and 11 [52%] for JE-VAX) and myalgia (10 [42%] for JE-Vero and 9 [43%] for JE-VAX); local reactions comprised redness, swelling, and arm pain, and were equally distributed between the 2 vaccine groups.[45]

A phase III multi-centre observer-blinded randomized controlled study compared 2 IM doses of 6 μg each on days 0 and 28 of JE-Vero ($N = 400$) against 3 SQ doses of JE-VAX on days 0, 7 and 28 ($N = 400$); a placebo dose was given to the JE-Vero group on day 7. On day 56 the GMT for JE-Vero was 244 (range 5–19 783), significantly higher than the GMT of 102 (range 5–1864) for JE-VAX (ratio 2.3 [95% CI: 1.97–2.75]). There was no significant difference in seroconversion rates at day 56 (JE-Vero 98%; JE-VAX 95%); reassuringly, immune sera from vaccinees were tested across a panel of different JE virus strains, and found active against all. There were no significant differences found in systemic AE rates or types between the 2 vaccine groups: headache (113 [26%] for JE-Vero and 125 [29%] for JE-VAX); myalgia (88 [21%] for JE-Vero and 69 [16%] for JE-VAX);