The short report by Kanesa-thasan and others1 reopens debate on a provocative subject studied by leading arbo- 

ologists for decades: serologic cross-reactions and cross-

protection between closely-related members of the genus Flavivirus. Their paper addresses the question of whether “Jennerian” immunization with Japanese encephalitis (JE) vaccine elicits cross-protective immunity against a heterolo-

gous but closely related virus, West Nile (WN).

With WN virus on the march across the United States, and increasing numbers of laboratory workers engaged in surveillance and research exposed to this potentially lethal, BL3 agent, there is obvious interest in developing a vacci-
nation strategy. The availability in the United States of an a Food and Drug Administration–licensed inactivated JE vac-
cine (JE-VAX®, Aventis-Pasteur, Swiftwater PA), together with animal experiments showing cross-protection, have stimulated interest in use of the JE vaccine against WN vi-
rus. No critical appraisal of the risks and benefits associated with this approach has been put forward, in part because data are sparse and sometimes conflicting.

Kanesa-thasan and others report that human subjects com-

pleting the recommended three-dose series of JE-VAX® 

failed to develop cross-reactive WN virus-neutralizing anti-
bodies. The results suggest that vaccination of humans against JE may not provide protection against WN disease. While this conclusion is open to debate, as pointed out below, there is one practical certainty arising from the study: the absence of WN neutralizing antibody (the principal me-
diator of pre-exposure immunity and the accepted surrogate of protection5), does not support the use of JE-VAX® for off-label immunization against WN disease. Those respons-
able for occupational safety and public health interventions should take heed.

As pointed out correctly by Kanesa-thasan and others, the absence of neutralizing antibody does not exclude the pos-
sibility that humans primed with JE-VAX® could be pro-
tected against WN disease. Experimental data demonstrating cross-protection between JE and WN viruses are often cited as evidence in favor of heterologous vaccination. However, close examination of these data raise a number of questions. In some cases, the vaccination that elicited cross-protection against WN disease involved hyper-immunization regimens with live JE virus that could not easily be reproduced in humans. For example, in the study by Goverdhan and oth-
ers,3 which is always cited because it used nonhuman pri-

trates instead of rodent models, monkeys were immunized against JE with four doses of inactivated JE virus at weekly intervals, followed by four doses of live JE virus prior to WN virus challenge. Similarly, Hammon and Sather4 pro-
tected hamsters against WN virus challenge by three intra-
peritoneal inoculations of live JE virus. However, a recent study showed that hamsters given a single dose of live, at-

tenuated JE (SA14-14-2) vaccine or three doses of JE-VAX® 

according to the human vaccination schedule (0, 7, and 30 

days) had a cross-reactive anamnestic immune response and were significantly protected against WN challenge 4–6 weeks later (Tesh RB, personal communication). In fact the literature is replete with examples of both successes5,6 and failures8–10 of heterologous cross-protection between flav-
viruses, and schemes involving sequential immunization of multiple flaviviruses to induce a state of broad resistance,7 none of which have so far led to practical solutions. The conflicting experimental data are explained in part by dif-

ferent degrees of antigenic overlap, and by the relative vir-

ulence of the virus against which protection by heterologous immunity is sought.

Another problem of interpretation in the experimental studies is the relatively short interval (generally weeks or a few months) between immunization and challenge. It has been suggested that cross-protection between closely related flaviviruses, such as dengue serotypes 1 and 2, is exhibited only when the interval between primary and secondary in-
fec tions is less than a few months. There are few data on the durability of cross-protective immunity, but it is known 

that neutralizing antibodies produced following vaccination with JE-VAX® wane to low or even undetectable levels in many subjects within 1–2 years, and secondary vaccine fail-

ures are not known.11 The durability of heterologous cross-protection afforded by JE-VAX® against WN virus, if any, is uncertain, a problem confounded by lack of a sero-

logic marker, as shown by Kanesa-thasan and others.

The post-exposure, anamnestic immune response to infec-
tion is critical to protection induced by many vaccines, in-
cluding hepatitis A, hepatitis B, poliomyelitis, and measles. Persons whose vaccine-induced immunity has waned to undetectable levels may be protected against challenge because they are primed for a rapid recall response characterized by high-affinity antibodies. Prior immunization with one flavivirus primes for anamnestic immune responses (both B and T cell) to common antigens present in the virus causing the second infection. This phenomenon was first studied by Hammon and others,12 who inoculated inactivated JE vaccine (of very low antigenic potency) into children and horses with prior exposure to the closely related St. Louis encephalitis virus. The subjects responded with robust JE neutralizing antibody titers, whereas nonimmune controls failed to re-

spond. In a more recent study, protection of mice against JE was shown to depend on the post-challenge immune re-

sponse.15 Unfortunately, it is not practical to measure post-

exposure responses in humans, and assessments of cross-

protection afforded by JE-VAX® must be made on the basis of pre-exposure antibody levels. Kanesa-thasan and others 

found no measurable cross-reactive antibodies in subjects given JE-VAX®. Finally, it should be mentioned that prior immunization against JE could potentially subvert the im-

mune response following exposure to WN virus, with high 

neutralizing antibody titers to the primary and minimal re-

sponse to the challenge virus: the so-called phenomenon of
“original antigenic sin”. Clear examples of this phenomenon are provided in a recent study of sequential infections with members of the JE serocomplex.16

Another concern that cannot be addressed adequately by existing data is whether heterologous flavivirus vaccination is completely safe. Kanesa-thasan and others cite a recent study showing that passive immunization of mice with JE antibody potentiated disease caused by Murray Valley encephalitis virus.17 Other studies in which immunosuppressed mice were reconstituted with immune spleen cells showed that brain inflammation mediated by cellular immunity can enhance disease and shorten time to death.18 These experimental data suggest that a host with partial immunity (insufficient to prevent neuroinvasion) may suffer a worse outcome. It is unknown whether immunopathologic events seen under these artificial experimental conditions could occur in humans. If so, they are likely to be very rare events that could not be uncovered without very large clinical trials. While the experimental evidence and epidemiologic data suggest cross-protection between JE and WN viruses, rather than immunopathologic consequences, the burden of proof is on those proposing the treatment strategy.

Disclosure: The author wishes to disclose that he is an employee of Acambis, which is currently developing a vaccine against West Nile virus.

Author’s address: Thomas P. Monath, Research and Medical Affairs, Acambis, Inc., 38 Sidney Street, Cambridge MA 02139, fax: 617-494-0924, E-mail: thomas.monath@acambis.com.

REFERENCES


