

Evaluation of the Antigenic Potency of Biken JEV Vaccine in Adults

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INTRODUCTION: This is a collaborative study between the United States Peace Corps in Thailand and the SMRL.

OBJECTIVE: To determine the antigenic potency of the killed Japanese B Encephalitis vaccine (Biken purified mouse brain) in a group of young adult Peace Corps Volunteers (PCV's) in Thailand.

DESCRIPTION: The Biken JE vaccine was first developed from formalin-treated, JEV-infected mouse brain tissue in 1936. Not until 1965, however, was the vaccine suitably purified and judged safe for use in Americans who reside in JEV endemic areas. No JEV vaccine currently exists other than the Biken vaccine for use in American personnel overseas. In 1965 a large field study in Taiwanese children indicated that the purified vaccine, given as two injections, can reduce clinical JE morbidity by 80%. Efficacy was much less apparent for those vaccinated with only one vaccine inoculation. Some immunity persisted for a year after immunization; the vaccine group without a booster dose still had 50% fewer cases of JE than their controls the second year after vaccination.

The only vaccine study reported in adults involved a group of young adult nursing students in the JEV endemic area around Tokyo in 1965. Greater than 90% of these students developed neutralizing antibody titers of 1:100 or more which persisted 4 months after a series of two injections one week apart, followed by a booster at one month. Only 50% of a comparative group who received only two injections one week apart had titers of 1:100 at 4 months; however 95% of this group had a titer of 1:10 at 4 months, which has been shown to be a protective titer in mice challenged with JEV. Since the adult vaccines in the 1965 study lived in an area endemic for JEV, some may have previously experienced a natural JEV infection, even though their neutralizing antibody titers were reported to be "negative" before vaccination. Thus the antibody response of Japanese living in an endemic area might differ in some instances from American adults who have resided in non-endemic areas. During the period Nov 1970-May 1971 the Peace Corps is offering Biken JE vaccine to all volunteers in Thailand for protection against Japanese encephalitis. Concurrently we are studying the antibody response of PCV's to the vaccination. The immune response in adults has not been adequately studied for extended periods (4-24 months) following immunization, and this study is designed to provide that information.

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PROGRESS: The vaccine has now been administered to several hundred PCV's on a voluntary basis. Before receiving the vaccine, each person was informed of the nature of the disease, the known effectiveness and risks of the vaccine, and its licensure status. The vaccine was given as two injections of 1.0 cc one week apart as recommended by the manufacturer (The Research Foundation for Microbiological Diseases of Osaka University). Each volunteer has donated a pre-immunization and one or more post-immunization serum samples for HI and PRNT determinations. A questionnaire completed on each volunteer includes a history of immunizations, allergies, viral illnesses, and areas of residence and travel preceding the study.

A different lot of vaccine is being used in each of three different groups of PVC's studied. Two vaccine lots were obtained from the manufacturer in Japan; the third lot was donated through the courtesy of Drs. T. Yamada and T. Fukunaga of the Research Institute for Microbial Diseases, Osaka University, who are working with the Virus Research Institute of the Department of Medical Science, Ministry of Public Health, Bangkok, Thailand.

Table 1 lists the three groups of PCV's studied, the vaccine lot given to each group, and the timing of immunizations other than JEV which are referenced around the time of JEV immunization. Schedules of immunizations other than JEV differ in each of the three study groups. Two of the groups received yellow fever and gamma globulin immunizations during training in Hawaii, which may augment or interfere with the response to JE vaccine given subsequently in Thailand. One group (34-35) will receive gamma globulin only after JE vaccine and no yellow fever vaccine.

We anticipated that a comparison of the varying intervals of time existing between vaccination with JE, yellow fever, and gamma globulin might provide data for evaluation of possible interference or augmentation of the JEV antibody response by these other immunoprophylactics.

Group 22-32 is composed of PVC's who have already been resident in Thailand for periods of 3-24 months before JE immunization. Group 33 was immunized with JE in Bangkok on arrival. Group 34-35 have not completed their immunizing course as of this progress report.

The preliminary serological results are summarized in Table 2. Twenty-two volunteers in group 22-32 were immunized and their post immunization serums collected 4-6 weeks later. Only two showed a 4-fold HI and PRNT antibody titer rise to JEV (see Table 3). Two of the twenty non-responders had a pre-immunization HI titer of 1:20; thus they failed to react anamnesticly to the vaccine. None of sixteen volunteers in group 33 responded to the vaccine as shown by undetectable HI antibody titers (<1:20) measured 4 weeks after immunization. The absence of detectable HI antibody response was confirmed by negative PRNT's ($\leq 1:5$) in 6 members of group 22-32, and in 5 members of group 33, all selected at random. No pre-existing antibody was demonstrable in members of group 33.

Thus, two different lots of vaccine, administered per the manufacturer's instruction, induced an antibody response in only 5% of the volunteers.

We are in the process of examining whether a third dose of vaccine, given as a booster dose 4-6 weeks after the initial 2-dose immunizing course, will provide a more satisfactory serological response. Examination of the potency of a third vaccine lot in group 34-35 is continuing.

Table 1. Peace Corps Volunteer Groups

<u>Study Group Number</u>	<u>Vaccine Lot No.</u>	<u>Immunization Schedule</u>
22-32	166	Yellow fever: 3-24 months prior to JE; gamma globulin: 2 weeks-6 months prior to JE
33	184	Yellow fever: 6 weeks prior to JE; gamma globulin: 2 week prior to JE
34-35	unknown	Yellow fever: not given; gamma globulin: 3-4 weeks after JE

Table 2. Serological Response of Peace Corps Volunteers to Biken JEV Vaccine

<u>Group No.</u>	<u>No. Immunized</u>	<u>No. Positive Responses*</u>	<u>Percent Response</u>
23-32	22	2	9%
33	16	0	0%
34-35	incomplete	—	—

* \geq 4-fold serum HI & PRNT antibody titer rise 4-6 weeks after the 2nd immunizing dose.

Table 3. Positive Immune Response in Two Volunteers Vaccinated with Biken JEV Vaccine

<u>Volunteer</u>	<u>Serum</u>	<u>Test vs JEV Antigen</u>	
		<u>HI</u>	<u>PRNT</u>
30-098	pre-immunization	1:10	<1:5
	post-immunization*	1:40	1:45
31-095	pre-immunization	<1:10	<1:5
	post-immunization*	1:20	1:16

* Drawn 4-6 weeks after the 2nd immunizing dose.