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Reduction of neutralization antibody against heterologous circulating strains in adults immunized with Japanese encephalitis live vaccine

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Japanese encephalitis (JE) remains the most important cause of viral encephalitis in Asia and the Pacific region, and an estimated 50,000–70,000 human cases resulted in about 10,000 deaths worldwide annually.1 Vaccination has been well proven the most successful strategy to reduce morbidity and mortality. The Chinese live attenuated vaccine derived from Japanese encephalitis virus (JEV) strain SA14–14–2 has just achieved the World Health Organization prequalification and now been recommended for use in all JE endemic countries.2 To date, more than 300 million children have been immunized with the SA14–14–2 vaccine. Neutralizing antibody titers against the vaccine strain SA14–14–2 (GIII strain) and a number of circulating strains including FJ03 (GIII strain isolated in Fujian, China, 2003), SC04 (GI strain isolated in Sichuan, China, 2004), SH53 (GI strain isolated in Shanghai, China, 2001), and SX06 (GI strain in Shanxi, China, 2006), were determined by using the standard 50% plaque reduction neutralization test (PRNT), respectively.

As shown in Figure 1, the PRNT50 titers against the 4 circulating strains were significantly lower than that against SA14–14–2. Notably, the PRNT50 titer against SC04–17 (<1:10) was significantly lower than the other JEV strains. Our preliminary results in vaccinated population demonstrated that there is a significant reduction in protective antibodies against JEV circulating strains especially heterologous GI strains. Previously, mice challenge experiments indicated that the SA14–14–2 vaccine could confer protection against the challenge of different JEV isolates,8 while neutralizing antibodies against selected strains also decreased. Recent results from vaccinees with inactivated vaccines also suggested potential reduction in neutralization capacity against heterologous JEV genotypes.9,10

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Although the population size is relatively small, these results deserve extensive concerns. For most JE vaccine clinical trials, only neutralizing antibody against the homologous strain is detected. This probably would lead to unfaithful results in areas where the circulating strains were quite different from the vaccine virus. Heterologous circulating strains should be included for immunogenicity and efficacy studies in any immunogenicity and efficacy trials. Furthermore, efforts should be warranted to identify the potential genotype-specific neutralizing epitopes of JEV, which have been extensively investigated for dengue viruses.\(^{11,12}\)

Especially, structural and reverse genetic studies would help reveal the relevance between protection and antigenic variations among JEV genotypes.

Finally, a novel vaccine that derived from genotype I or multivalent vaccine that includes several genotypes of JEV strains may be beneficial in the context of vaccine development in the future.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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