Primary and Booster Immune Responses to Live Attenuated SA14-14-2 Japanese Encephalitis Vaccine in Korean Infants

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The attenuated SA14-14-2 JE virus strain, derived by serial passage in primary hamster kidney cells, was licensed and has been distributed in areas of southern China since 1989. Neuroattenuation of the vaccine strain was demonstrated in experimental animals and in several large scale human studies, of which the most recent, a controlled study of 25,000 children, found no cases of central nervous system infection in 13,000 immunized children. By some measures, the vaccine strain is overattenuated, since the antibody responses to one dos has varied from only 85% to 100% in children receiving vaccine containing $>10^{6.7}$ pfu/ml, the minimum vaccine infectious titer specified by Chinese licensing authorities, and geometric mean titers(GMTs) in these vaccinees generally have been low, on the order of 23～46. Although several field studies reported protective efficacies exceeding 95% after a single dose, based upon these immunogenicity data, public health authorities have recommended two doses, given in successive years, following the traditional approach of campaign vaccination each spring. This recommendation received support in a recent case-control effectiveness study that found an 85% vaccine effectiveness in children receiving one dose and 98%, after two doses. The SA14-14-2 vaccine currently is distributed only in China but the attenuated vaccine has been recognized as a potentially less costly and less reactogenic alternative to the inactivated mouse brain-derived vaccine, which now is the only internationally distributed JE vaccine.

In seeking licensure for SA14-14-2 vaccine in Korea, the manufacturer introduced certain changes in quality control procedures which are reflected in the production of the launch lot used in this study. This preliminary immunogenicity study in Korean infants sought to reconfirm the vaccine's immunogencity and safety and was the first clinical evaluation of the vaccine outside of China. We measured antibody responses in the primary immunization of children, one to three years old, the age interval when JE vaccine normally is recommended in the endemic area in Korea. Among the children who received a single dose as a primary JE vaccination, 95%(69/73) developed a neutralizing antibody response, with a GMT in responders of 21. From other studies, a second dose of SA14-14-2 vaccine would be expected to produce tenfold higher neutralizing antibody titers. Although we did not measure the immune response to a second dose, in children who previously had been

immunized with inactivated JE vaccine or in the single instance of a child who might have had a prior natural JE infection, SA14-14-2 vaccination produced a 50 - fold higher PRNT antibody response, consistent with an anamnestic response. This observation alleviates concern that children partially immunized with inactivated vaccine might have cleared the attenuated virus and abrogated a proper immune response. Although few subjects were studied, no significant adverse events occurred. However, further confirmatory studies are needed before booster immunizations with the SA14-14-2 vaccine can be recommended routinely in a public immunization program. Equally high anamnestic antibody responses were produced in children who had no detectable neutralizing antibodies after previous vaccination with the inactivated vaccine, suggesting the retention of memory T cells aiding the humoral response, and/or potentially, the presence of non-neutralizing enhancing antibodies.

In comparison to the 95% seroconversion among children immunized with the attenuated vaccine, only 38% of children who had received two doses of inactivated vaccine had detectable PRNT antibodies. However, antibody responses in these children were not studied prospectively and the post- immunization samples were obtained, on average, seven months later, when antibody titers might have diminished. On the other hand, other studies, principally in adults from developed countries, also have reported seroconversion rates of 45~67% after two doses of inactivated vaccine, leading to the current recommendation in the United States for three doses for primary vaccination. More importantly, the anamnestic response to live attenuated SA14-14-2 vaccine in children who had received two doses of inactivated vaccine supports observations from field studies that this two dose schedule is protective.

JE virus specific IgM antibodies were detected in only 12% of primary vaccinees, however, postimmunization serum samples were obtained four weeks after immunization and, in others, IgM antibodies might have declined to undetectable levels. Although, as might have been expected, no viral specific IgM was detected in the 11 children with prior immunization or infection, for the same reasons, no conclusion can be drawn about the absence of IgM as evidence of a secondary antibody response. The choice of the wild-type vaccine parent SA14 strain as the antigen in PRNT determinations in no way limits the generalizability of the results. Genomic sequence analysis has placed all JE vaccine strains, including SA14-14-2 and its SA14 parent, Nakayama, Beijing and P3 strains, in the genotype of JE viruses circulating in temperate areas of Asia but, no data indicate that these strains fail to protect against the disease occurring elsewhere in the region.

The excellent immune response to a single primary immunizing dose is encouraging but other data suggest that two doses may be needed to provide an adequate level of protection. In Korea and China, JE vaccine still is given in spring campaigns rather than at a chronological age. Additional studies are needed to determine how the SA14-14-2 vaccine should be integrated into pediatric immunization schedules in Asia.