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The efficacy of mouse-brain inactivated Nakayama strain Japanese encephalitis vaccine—Results from 30 years experience in Taiwan

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Abstract

An intensive mandatory vaccination program has been underway, combating Japanese encephalitis (JE) since 1968 in Taiwan. Long-term collection of immunization records has been developed from 1967 to 2000 in this study to retrospectively assess the efficacy of the mouse-brain inactivated Nakayama JE vaccine. The vaccine efficacy (VE) of completing at least two doses of the JE vaccine was 96.98%. Among 1 to 14-year-old children, the efficacy of completing 1, 2, and 3 doses of immunization was 85.59%, 91.07% and 98.51%, respectively. Furthermore, the long-term efficacy for a single dose vaccinated at least 25 years was 86.79%, and for 2 and 3 doses it was 88.10% and 95.54%, respectively. In contrast to previous studies that recommended at least two doses of JE vaccination to acquire necessary protection, the empirical results in this study indicated that even immunization with one single dose provides sufficient protection to the population. However, a single dose of JE vaccine might still be beneficial for some JE epidemic or endemic developing countries with limited resources for infectious disease control.

Keywords: Mouse-brain inactivated Nakayama strain JEV; Vaccine efficacy; Long-term observation

1. Introduction

Japanese encephalitis (JE) is the leading cause of viral encephalitis in Asia with 50,000 cases reported annually [1]. Only supportive therapy was available for JE treatment. The case-fatality rate of JE ranges from 0.3 to 60%, and most patients who recovered from the infection with the clinical symptoms often displayed sequela of physical, mental, behavioral and intellectual deficits [2,3]. Mass immunization has been believed to be one of the most effective preventive measures against JE in Asian countries, and the Nakayama strain vaccine has been widely used in these countries [4].

A mass vaccination campaign combating JE has been launched since 1968 in Taiwan. Vaccine is given to children of certain age groups during March to May (prior to the epidemic season) every year. Between 1968 and 1974, only two doses (primary basal vaccination) were given one week apart to children older than 2 years. Since 1974, a booster dose (the third dose) was added 1 year after the primary basal vaccination. Beginning in 1983, children attending the first grade of elementary school (7 or 8 years old) received the second booster vaccination, which means a complete JE immunization comprising of a total of four doses [5] were given.

The Nakayama strain of the JE virus, which was isolated from the cerebral spinal fluid of a patient in 1935 and maintained by continuous mouse-brain passage, has been the principal strain used in mouse-brain-derived vaccines produced throughout Asia [6]. In Taiwan, the alcohol–protamine purified, inactivated vaccine was domestically manufactured and administered [7]. The Nakayama strain vaccine has been the dominant vaccine in the market, except for the Beijing strain product, which was introduced in 1988 from Japan [5].

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Although some studies indicated that the Nakayama strain of the JE vaccine was efficacious in the field [8], others demonstrated that there were some antigenic differences among viral strains [9], and the current vaccine strain(s) may not be completely effective against certain wild-type isolates [10]. In addition, a seroprevalence study of the JE neutralization antibody suggested insufficient protection among 15 to 19-year-old based on a 37.9% seroconversion rate tested by a plaque reduction neutralization test (PRNT) [11]. The neutralizing antibody titer higher than 1:10 estimated by PRNT is generally accepted as evidence of protection and post-vaccination seroconversion. Based on the results of neutralization antibodies examination, more studies concluded that booster doses were required to prolong the immunity duration [12,13].

The efficacy of the Nakayama strain vaccine varied in different reports [14,15]. In 1999, Wu et al. [5] estimated that the efficacy among people receiving more than two doses vaccination in Taiwan exceeded 85% on average during 1970–1994. The incidence of JE had decreased from 2.05 confirmed cases per 100,000 population in 1967 [5] to 0.11 confirmed cases per 100,000 population in 2003 [18]. Their results triggered the current study of the protective efficacy of the Nakayama JE vaccine used over the past 30 years in Taiwan. In this study, immunization records of 1261 JE confirmed cases and vaccine coverage rates from 1971 to 2000 were collected from the National Institute of Preventative Medicine (presently known as Center for Disease Control, Department of Health, Taiwan) to evaluate the efficacy of the Nakayama JE vaccine.

2. Materials and methods

2.1. Proportion of target population vaccinated with the 1st, 2nd, 3rd, 4th dose JE vaccine

In general, the proportion of target population vaccinated with any dose of JE vaccine between 1970 and 2000 was above 85% [16,17]. The formula to calculate the proportion of target birth cohort completed the 1st or 2nd or 4th dose was taken from?? the vaccinated size of the target birth cohort divided by the total population size of the target birth cohort. The denominator of proportion of target birth cohort completed third dose were those who finished the second dose. The average proportion of the target population vaccinated with the 1st, 2nd, 3rd, and 4th dose of JE vaccine between 1971 and 2000 are displayed in Fig. 1.

2.2. Confirmed cases definition and data collection

Confirmed cases were defined as satisfying any of the following two criteria: the hemagglutination-inhibition (HI) titer of the convalescent serum is ≥1:160 and has at least a fourfold rise from titer in the acute phase serum, or the HI titer of either single serum is ≥l:320 [5].

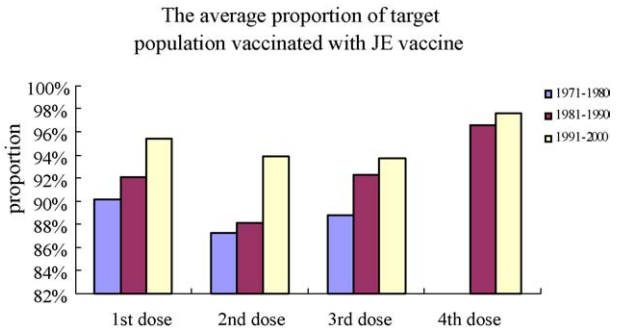

Fig. 1. The average proportion of target population vaccinated with 1st, 2nd, 3rd and 4th dose of JE vaccine between 1971 and 2000.

There were 1261 confirmed cases during 1970–2000 collected from the National Institute of Preventative Medicine.

2.3. Data analysis

The confirmed cases were classified by vaccination history into two groups, including group A (receiving at least both the 1st and 2nd dose of JE vaccine) and group B (receiving less than two doses). Since the proportion of the target population vaccinated with at least two doses of JE vaccine between 1970 and 2000 was above 85%, the proportion of the target population was assumed conservatively as 85% in group A and 15% in group B. Vaccine efficacy (VE) is estimated as one minus the relative risk (RR = incidence of vaccinated group divided by incidence of unvaccinated group) between the two interested groups (VE = 1 − RR) [18].

To clearly understand the efficacy of immunized with a single, 2 or 3 doses JE vaccine in 1 to 14-year-old population, the incidence of the four groups which were group 0 (unvaccinated group), group 1 (vaccinated with only one dose), group 2 (vaccinated with two doses) and group 3 (vaccinated with three doses) during 1970–2000 were calculated. The incidence of groups 1, 2, and 3 were compared with group 0 to obtain the RR and VE values. In this study, the annual incidences from 1970 to 2000 of groups 0–3 were compared to each other by *t*-test.

The long-term protective efficacy of the Nakayama strain of JE vaccination were demonstrated by estimating the cumulative incidence following JE vaccine immunized for 1–4, 5–9, 10–14, 15–19, 20–24, 25–29, and 30–31 years. Each cumulative incidence was estimated by Σ[age-specific confirmed cases/(age-specific population × age-specific proportion of target population vaccinated)].

3. Results

A total number of 719 JE confirmed cases occurred during 1971–2000 were selected. These confirmed cases were born after 1966, and the birth cohorts between 1986 and 1990 were excluded because they were vaccinated with Beijing strain JE