THE EFFICACY OF JAPANESE ENCEPHALITIS VACCINE IN HENAN, CHINA: A CASE–CONTROL STUDY

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Abstract. A population based case-control study to evaluate Japanese encephalitis (JE) vaccine efficacy was carried out in Gusi County, Henan Province, China from June to September in 1991. This study showed that the JE vaccine had a strong protective effect. The estimate of the vaccine efficacy was 78% (95% CI = 16-94%). An unimmunized child was at 4.54 times greater risk of developing JE than were fully immunized children during the study period. The present study may have underestimated the vaccine efficacy due to evaluation based on routine vaccination which might have been affected by vaccination management and the local cold chain system.

INTRODUCTION

Human immunization with inactivated Japanese encehalitis (JE) vaccine was initiated by United States military personnel in World War II (Sabin, 1964), and utilized for JE control in Japan in 1954 (Igarashi, 1992). With improved purification, JE vaccine has been widely used on millions of children around the world. However, only a few randomized placebo controlled evaluations of vaccine efficacy have been done so far (Hsu *et al,* 1971; Saenz *et al,* 1968; Hoke *et al,* 1988). JE vaccine derived from primary hamster kidney cells has been used since 1967 in China (Huang, 1982), over 70 million annual doses have been injected into children under 10 years old in the past two decades (Umenai, 1985). However, there are only limited data concerned with vaccine efficacy in places where JE vaccine is widely used. The present study aimed to estimate the vaccine efficacy through a case-control design.

MATERIALS AND METHODS

Study population and vaccination

The study was carried out in Gusi County, Henan Province, central China in 1991 from June to September. The county, with a total population of about 1.4 million, is an endemic area for JE. The disease is mainly transmitted in the summer from June to September. According to reports from the Health and Anti-epidemic Station in the county, the incidence rate of JE were 4.5 per 100,000 in 1989 and 8.3 per 100,000 in 1990, respectively. Cases are predominantly in children under 10 years old. JE vaccine has been used for the last two decades. The normal vaccine procedure is as follows: for primary immunization, children over six months and under one years old would be vaccinated with two doses of 0.25 ml, from 1 to 7 years old with two doses of 0.5 ml and over 7 years old with two doses of 1 ml, to be administered subcutaneously at intervals of about 10 days. A third injection (0.5 ml for 1-7 years old, 1 ml for over 7 years old) should be given in April, two months before the JE virus transmission. Children aged 1-10 years should then be boosted annually with the vaccine in April every year. The Health and Anti-epidemic Station in the county is responsible for the organization of vaccination and training of lower level doctors who administer vaccinations. There are 33 townships within Gusi County, each has its own hospital. Two to three doctors form a Disease Prevention and Vaccination Group within the township hospital which is responsible for supervision of vaccination and disease prevention in the township. Village doctors in the local community are responsible for vaccination. There are 10-15 administrative villages in each township, and each village with 2,000 to 3,000 population has one or two village doctors who are responsible for vaccination children. However, because of the shortage of the vaccine, it was estimated that less than 30% of the total susceptible population were protected by vaccination.

Case definition and selection

JE was diagnosed according to the following criteria: 1) Patients with fever, temperature > 39°C: 2) Abnormal mental state with focal neurological signs; 3) More than 5 leukocytes/mm^3 in cerebrospinal fluid (CSF); 4) No alternative diagnosis from history or from physical examination; 5) Detection of fourfold or greater increase in antibody titer in paired sera, or IgM antibody positive in CSF. The diagnosis was made without knowledge of the child's vaccination history. Children under 6 months or over 10 years old who were not permanent residents in the area were excluded from the study. Children under 6 months or over 10 years old are not normally recommended for vaccination. Two neighborhood controls matched by age within one years and of the same sex were selected at random for each case by interviewers during investigation. Exclusion criteria for controls were the same as for cases.

JE surveillance

Surveillance for JE was carried out in health facilities that provided health care for all the population. A team of field workers were organized to visit all hospitals in the country twice weekly to check case reports and to get specimens of sera and CSF from the beginning of June to the end of September. Each child admitted to an accessible hospital with a febrile central nervous system disorder was examined, and if possible, paired serum samples and CSF specimens were collected. The detailed serological tests have been reported elsewhere (Wang *et al,* 1992).

Data collection

Data were collected by 4 highly trained interviewers using a standard questionnaire, by interviewing the child's parents or a person who looked after the child. The data collection recorded a number of demographic variables parental income, parental education, use of bednets /bednets treated with pyrethroid insecticide, environmental description, and the presence of amplifier hosts of JE virus situation. Data concerning JE vaccination history were collected by consulting vaccination records with the village doctors who were responsible for the vaccination program in the local community. The cases and controls were considered as immunized if they received two primary immunizations with annual boosters.

Statistical analysis

The data were analysed using conditional logistic regession methods for a matched case-control study (Storer *et al,* 1983). Crude odds ratios with 95% confidence intervals were obtained after the variable of vaccination was put into the model. We examined whether potential confounding variables introduced into the model resulted in more than a minor change in the odds ratios estimates. The final model included all confounders under study besides JE vaccination. Maximum likelihood estimate of relative risk together with 95% confidence intervals and test for trends where appropriate were computed using the EGRET statistical package. The vaccine efficacy (VE) was caculated by using the formula VE = (1-OR) × 100.

RESULTS

A total of 51 cases fulfilled the case definition and inclusion criteria during the study period, of whom one could not be investigated because the child and her parents were unavailable for interview. Two neighborhood controls were selected at random for each of the remaining 50 cases. The mean (± SD) age of cases was 3.15 ± 1.86. The controls was 3.20 ± 1.77. That more boys than girls suffered from JE suggested that boys might have higher risk; children of lower income families and lower parental education also tended to have a higher risk of JE (Table 1).

JE vaccination strongly decreased the risk of in fection (Table 2). The odds ratio of children who received the complete vaccine procedure was 0.22 (95% CI = 0.06 – 0.84) compared with those children who were never vaccinated, after adjusting for confounding variables. The adjusted odds ratio of children who had been vaccinated but did not completely follow the vaccine procedure was 0.33 (95% CI = 0.08 – 1.29). The vaccine efficacy was 78% for children who completely followed the vaccination procedure, and 67% for those who were not completely vaccinated. An unimmunized child was at 4.54 times greater risk of developing JE than a fully immunized child; those who did not receive the full vaccine course were at 3.12 times greater risk in 1991.

DISCUSSION

The study showed a protective effect of JE vaccine against JE among children under 10 years old. The vaccine efficacy in those who followed the com-

Table 1

Age, sex, income and parental education distribution in cases and controls.

	Cases (%)	Controls (%)
Age in years		
0.5-0.9	5 (10)	5 (5)
1.0-3.9	29 (58)	55(55)
4.0-9.9	16 (32)	40 (40)
Sex		
Male	29 (58)	58 (58)
Female	21 (41)	42 (42)
Income[a]		
< 50%	31 (62)	51 (51)
50-99%	15 (30)	30 (30)
≥ 100%	8 (16)	19 (19)
Parental eduation (years)		
≤ 5	40 (80)	67 (67
6-8	9 (18)	19 (19)
≥ 9	1 (2)	14 (14)
Total	50 (100)	100 (100)

[a] Expressed as multiples of average income in China (US $ 60)

plete vaccination procedure was much stronger than that of those who did not follow the complete vaccination procedure. The efficacy was lower than that of an American-Thai study in Thailand in 1984, which used an inactivated-mouse-brain-derived vaccine (Hoke *et al*, 1988). The present estimate of vaccine efficacy was much lower than previous studies in China (Huang, 1982). However, none of the previous studies involved randomized placebo controlled trials. Their results could not eliminate the effects of biases and confounders.

A randomized placebo controlled trial should be ideal for investigating the vaccine efficacy of JE vaccine. This approach, however, has several drawbacks. Firstly, a controlled trial of this kind may be both costly and difficult to justify ethically because of prior evidence of some efficacy of vaccination. Secondly, what is often required is an estimate of the vaccine efficacy by the routine health sevices rather than that in the carefully controlled situation of a randomized trial. Thirdly, JE is a disease with very low incidence, therefore, a randomized place bo controlled trial needs to recruit a large susceptible population in order to get enough cases to evaluate protective efficacy.

One limitation of the present design in estimating the vaccine efficacy is selection bias. As regards case selection, to ensure they represent a homogeneous group, strict diagnostic criteria were esta-

Table 2

Odds ratios and vaccine efficacies with their 95% confidence interval for fully and non-fully vaccinated children under 10 years old.

	Case (%)	Control (%)	OR (95% CI)		Vaccine efficacy
			Crude	Adjusted [a]	(%)
Vaccination [b]					
None	39 (78)	44 (44)	1.00	1.00	
Non-fully	7 (14)	26 (26)	0.18 (0.05 – 0.60)	0.32 (0.08 – 1.29)	68 (– 29 92)
Fully	4 (8)	30 (30)	0.12 (0.04 – 0.42)	0.22 (0.06 – 0.84)	78 (16 94)
Likelihood ratio test [c]			p < 0.001	p = 0.012	

[a] Adjusted for bednet impregnation, house location, socio economic status and parental education.
[b] None = children did not receive Japanese encephalitis vaccination; Fully = children received tow primary immunzations with annual boosters; Non-fully = children did not completely receive two primary immunization and/or annual booster.
[c] Test for trend

blished with inclusion and exclusion criteria, which may affect both exposure and disease. A surveillance system was set up to ensure all cases would be recruited into the study. A second source of bias is information bias. Parents of children with JE may have a better recall of the children's vaccination history than do those of children without JE. We attempted to avoid this bias by checking the children's vaccination history record at local village doctors' clinics. All other variables such as socio-economic status and environmental variables are objective questions which leave little opportunity for misinterpretation by interviewers. Therefore, it is unlikely that our conclusions are due to recall bias and interviewer bias. Extensive control was made in analysis for factors thought to be confounding the association. Nevertheless, the present study might underestimate vaccine efficacy due to evaluation based on routine vaccination which might be affected by vaccination management, administration and the local cold chain system.

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