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Prevention of Japanese Encephalitis (JE) by "BIKEN" Vaccine and Epidemiological Survey on JE in Dong Anh District, Hanoi, Vietnam

Tran Van TIEN[1], Hoan Thuy NGUYEN[1], Vu Sinh MAM[1], Phan Thi NGA[1] and Akira IGARASHI[2]

[1]*National Institute of Hygiene and Epidemiology 1 Yersin Street 10,000, Hanoi, Vietnam*

[2]*Department of Virology, Instite of Tropical Medicine, Nagasaki University, 12-4 Sakamoto-machi, Nagasaki City, Japan 852*

Abstract: From January 1986 to 1988, a total 27, 700 children between 3 months to 5 years old (85.7% of the target poopulation) in Dong Anh Distict, Hanoi, Vietnam, were immunized with JE BIKEN vaccine. The number of 24 JE cases reported from 1986 to 1988 after the vaccination was significantly less than the number of 131 cases reported in the years 1984 and 1985 before the vaccination. After the vaccination, annual number of JE cases was reduced more than 8−fold compared with previous years, and 21 of the 24 of JE cases (87.5%) were found among unvaccinated. Surveillances on swine antibodies and mosquito population in 1988−1989 indicated continued transmission of JE virus in the study area. By the hemagglutination-inhibition (HI) test, antibody positive swine were found all year round, and the positve rate fluctuated between 10 to 66% (average 43.5%) with gemoetrical mean titer between 11−47. *Culex tritaeniorhynchus* was the most abundant mosquito species and its density increased in hot season particularly in April and August, while its density was low in January to March and October to December.

Key words: Japanese encephalitis, Vaccine, Epidemiology, Vietnam

INTRODUCTION

JE has been one of the serious public health problems in several countries in Asian monsoon area where rice cultivation in watered paddy fields and swine raising are common features (Umenai *et al.*, 1985). In Vietnam, outbreaks of acute encephalitis syndrome (AES), clinically compatible with JE, have been reported every year since 1965 in more than 100 out of 214 Districts, in the country. Annual number of reported AES cases has been over 1,000 since 1969 (Nguyen *et al.*, 1990). Serodiagnosis on AES cases and virus isolation from clinical and field specimens hae shown the presence of JE cases among AES and JE virus circulation in nature (Ha *et al.*, 1977).

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In order to prevent this serious disease, JE vaccination was implemented in an endemic area, Dong Ahn District, Hanoi, from January 1986 to 1988. In order to show continued JE virus circulation after the vaccination, surveillances on swine antibody and mosquito population were performed in the study area in 1988−1989.

Materials and Methods

Study area

Dong Anh is a suburban District in Hanoi Metropolitan Area, with 23 communes and 185,949 population, situated at 21°N and 106°E (Fig. 1). Its climate is subtropical: the average temperature is high (23−28℃) from April to September, and relatively low (15−21℃) in January to March and from October to December. While precipitation over 100 mm has been recorded from May to October compared with less than 80 mm from November to next April. Majority of the inhabitants were farmers cultivating rice in watered paddy fields, while swine raising was commonly practiced. AES cases have been reported every year in hot season from May to September and JE virus was isolated at the National Insitute of Hygiene and Epidemiology (NIHE) since 1964. Large AES epidemics in 1984 and 1985 swept over entire 23 communes, calling for emergency intervention by JE vaccination which started from January 1986.

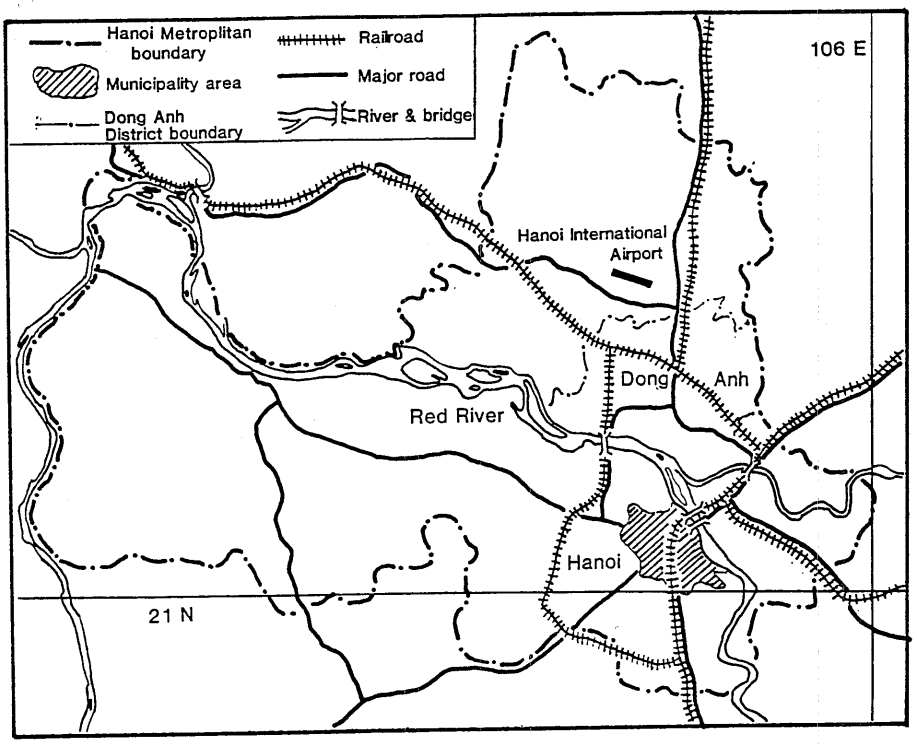

Fig. 1. Location of the study area: Dong Anh District, Hanoi, Vietnam.

JE vaccine and vaccination

Formalin-inactivated and highly purified "BIKEN" JE vaccine made from Nakayama Yoken strain in Japan (Takaku *et al.*, 1968) was kindly donated through international organizations. From January 1986, target population of children between 3 months to 5 years old, the most frequently affected age group, was indicated to receive 2 shots of vaccine with 1 week interval as primary immunization followed by a booster immunization in the next year.

Reported number of JE cases and serodiagnosis

Case records of AES in District Hospitals during 1984 to 1985 were examined to find out clinically compatible JE cases according to the diagnostic criteria of WHO (1988) and the Ministry of Health, Vietnam.

In 1986−1988, sera collected from JE−suspected cases were examined by the IgM-capture ELISA at NIHE for serodignosis (Bundo *et al.*, 1985).

Swine antibody survey

In 1986−1988, blood specimens were collected from slaughtered swine of 6−8 month old once a month, and separated sera were examined by the standard hemagglutination-inhibition (HI) test (Clarke and Casals, 1958) with microtiter modiffication at NIHE.

Mosquito collection

Resting mosquitoes were collected once a month in human dwellings and animal sheds by glass-suction tubes from 18:00 to 22:30 o'clock, and their species identification and counting were performed at NIHE. Density index of *Cx. tritaeniorhynchus* was calculated by dividing the humber of collected mosquitoes by the number of inspected houses or pigsties. Pools of *Cx. tritaeniorhynchus* and *Cx. annulus* were processed for virus isolation by mouse brain inoculation.

RESULTS

Vaccination target and coverage rate

Since young age groups were most frequently affected by AES, all 22,445 children between 3 months to 5 years old in January 1986 were indicated to receive 2 shorts of the vaccine in April 1986 before the epidemic season. The coverage rate of 87.2% was achieved including a booster immunization in the following year. In 1988, anothe series of immunization was performed on 5,255 children newly born after January 1986 until March 1988, and 79.8% coverage was achieved on this target population. Therefore, a total 27,700 children were immunized by JE vaccine with coverage rate of 85.7%.

The numer of JE cases before and afte JE vaccination

Table 1 shows the number of JE cases in variious age groups recorded in the study area from 1984 to 1989. In 1984 and 1985 before JE vaccination, 43 and 88 AES cases were

clinically compatible with JE, and averaged annual number of cases was 65.5. More than half of them (51.2% in 1984 and 58.0% in 1985, respectively) were in the age group of 1−4 years old, and the next frequently affected age group was 5−9 years old (30.2% in 1984 and 26.1% in 1985, respectively). While older age groups over 10 years were less frequently affected. After the vaccination, the number of JE cases (8, 4, and 12 in 1986, 1987, and 1988, respectively) were significantly less than those in previous years. The average annual number of cases after the vaccination of was 8.0 showing over 8−fold reduction compared with the figure before the vaccination. Serodiagnosis by IgM-ELISA was performed on 20 of the 24 cases (83.3%) and half of them showed positive results. Twenty one of the 24 JE cases (87.5%) after the vaccination were found among unvaccinated, and only 3 JE cases, one in each year, were reported among the vaccinated children. The age-specific attack rate of JE

Table 1. Number of JE patients in the years before and after JE vaccination in Dong Anh District, Hanoi, Vietnam

year	Total no. of cases	No. of cases (% to total) in age groups of				
		3−11 months	1−4 years	5−9	10−14 years	15− years
Before vaccination						
1984	43	5 (11.6)	22 (51.2)	13 (30.2)	3 (7.0)	0 (0)
1985	88	3 (3.4)	51 (58.0)	23 (26.1)	10 (11.4)	1 (1.1)
sum	131	8 (6.1)	73 (55.7)	37 (28.2)	13 (9.9)	1 (0.8)
After vaccination						
1986	8	3 (37.5)	0 (0)	4 (50.0)	0 (0)	1 (12.5)
1987	4	0 (0)	3 (75.0)	0 (0)	1 (25.0)	0 (0)
1988	12	1 (8.3)	8 (66.7)	3 (25.0)	0 (0)	0 (0)
sum	24	4 (16.6)	11 (45.8)	7 (29.2)	1 (4.2)	1 (4.2)
TOTAL	155	12 (7.7)	84 (54.2)	43 (27.7)	14 (9.0)	2 (1.3)

Table 2. Outcome of JE cases in Dong Anh Didtrict, Hanoi, Vietnam, 1984−1989

Year	Number (% to total) of		
	Total	Death	Sequelae
1984	43	5 (11.6)	8 (18.6)
1985	88	12 (13.6)	32 (36.4)
1986	8	2 (25.0)	1 (12.5)
1987	4	2 (50.0)	2 (50.0)
1988	12	2 (16.7)	3 (25.0)
1989	8	0 (0)	na(na)*
Total	163	23 (14.1)	46 (28.2)

*na: not available

was not significantly modified after the vaccination, showing highest rate in 1−4 years, followed by 5−9 years and 3−11 months groups.

Outcomes of these JE cases were shown in Table 2. Case fatality rate appeared to be less (11−13%) in 1984 and 1985 before the vaccination than those (16−50%) from 1986 to 1989 after the vaccination, however the difference was not statistically significant. The frequency of sequelae was almost similar before (18−36%) and after (12−50%) the vaccination.

Antibody survey on swine population

Table 3 shows the result of monthly surveillance on JE antibodies in swine sera. Antibody positive swine were found all year round in both years, and its positive rate fluctuated between 16−57% in 1988 and 36−71% in 1989, respectively. The annual average antibody

Table 3. Monthly surveillance on anti-JE HI antibodies among slaughtered swine in Dong Anh District, Hanoi, Vietnam, 1988 and 1989

Year	No. of sera	Month												
		Jan.	Feb.	Mar.	Apr.	May.	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Sum.
1988	tested	29	26	31	26	21	39	37	40	38	37	40	48	412
	positive	15	15	13	10	12	11	6	9	4	13	14	22	144
	(% +)	51.7	57.7	41.9	38.5	57.1	28.2	16.2	22.5	10.5	35.1	35.0	45.8	35.0
	GMT	45	41	47	49	39	34	31	36	31	36	11	15	35
1989	tested	37	38	35	39	44	38	39	44	37	25	40	32	448
	positive	20	14	15	19	30	27	26	16	18	12	15	14	226
	(% +)	54.0	36.8	42.8	48.7	68.2	71.0	66.7	36.4	48.6	48.0	37.5	43.7	50.4
	GMT	31	25	19	39	39	24	23	22	31	22	19	17	26

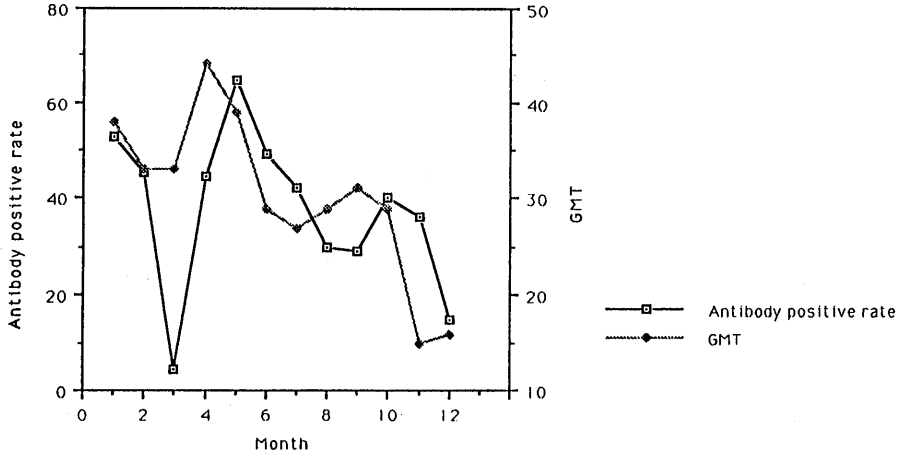

Fig. 2. Monthly change of anti−JE antibody positive rate and GMT among swine population in Dong Anh District, Hanoi, Vietnam, average in 1988 and 1989. Antibody positive rate (open square and solid line), and GMT (closed square and shaded line) in each month are shown.

positive rate was 34% in 1988 and 50% in 1989, respectively. The geometrical mean titer (GMT) of HI appeared to be generally low (11−49%), and the titer was higher in January to October (31−49%) than November and December (11−15%) in 1988. Low HI−GMT in November and December (17−19) was observed again in 1989 (Fig. 2).

Surveillance on mosquito species

The results of mosquito surveillance in Dong Anh District in 1988 and 1989 were shown in Table 4. The most abundant species in 1988 was *Cx. annulus* (39.1%) followed by *Cx. tritaeniorhynchus* (36.2%), and *Anoopheles* spp. (9.3%). While, in 1989, *Cx. tritaeniorhynchus* (45.9%) was most abundant followed by *Cx. quinquefasciatus* (25%), *Cx. annulus* (19%), and *Anopheles* spp. (7.2%). Since collection in 1988 was not performed in all months, the result in 1989 with monthly collection provides more reliable information on mosquito population (Table 4).

The seasonal variation of *Cx. tritaeniorhunchus* density in a pigsty and in a human dwelling was shown in Table 5. In 1988, mosquito collection was not performed all year

Table 4. Composition of mosquito species collected in Dong Anh District, Hanoi, 1988 and 1989

Species of mosquitoes	No. (%) of species in the year of	
	1988	1989
Culex tritaeniorhynchus	477 (36.22)	865 (45.89)
Cx. annulus	515 (39.1)	359 (19.05)
Cx. quinquefasciatus	131 (9.95)	471 (24.99)
Cx. gelidus	0 (0)	2 (0.11)
Cx. fuscocephalus	10 (0.76)	1 (0.05)
Cx. bitaeniorhynchus	4 (0.3)	0 (0)
Aedes albopictus	0 (0)	3 (0.16)
Mansonia annulifera	44 (3.34)	30 (1.59)
Mn. indiana	10 (0.76)	14 (0.74)
Armigeres subalbatus	3 (0.23)	4 (0.21)
Anopheles spp.	123 (9.34)	136 (7.21)

Table 5. Monthly changes of *Cx. tritaeniorhynchus* desity index in a pigsty and a human housing in Dong Anh District, Hanoi, Vietnam, 1988 and 1989

Year	Density index	Month											
		Jan.	Feb.	Mar.	Apr.	May.	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
1988	Pigsty	0.28	−	0	−	0	−	2.92	2.41	4.86	2.84	1.75	0.45
	House	0.03	−	0	−	1.1	−	0.56	0.23	0.70	0.27	0.17	0
	Total	0.31	−	0	−	1.1	−	3.5	2.64	5.66	3.11	1.92	0.45
1989	Pigsty	0	0.07	0.64	8.95	6.66	2.89	3.85	8.26	2.91	0.72	0.04	0
	House	1.17	0.07	0.03	0.43	0.37	0	0.1	0.37	0.03	0	0	0
	Total	1.17	0.14	0.67	9.38	7.02	2.89	3.95	8.63	2.94	0.72	0.04	0

round, however, the mosquito density was higher in a pigsty than in a human house. Same tendency was observed also in 1989 except in January and February.

The monthly changes of antibody positivve rate and GMT among swine population and *Cx. tritaeniorhynchus* density index in 1989 were compared in Fig. 3A, with monthly temperature and rainfall in Fig. 3B, respectively. The density of *Cx. tritaeniorhynchus* was high during hot season from April to September compared with low density in cool season from January to March and November to December. Two mosquito density peaks were observed in April and August, while the peak of rainfall was in June. Therefore, the mosquito density did not directly depend on the rainfall, but appeared to be related with the inundation of rice fields for 2 rice harvests in May-June and November-December. The first larger peak of the mosquito density in April appeared to be followed by increased swine antibody positive rate in May to July and increased GMT in April and May. However, the second smaller peak of the mosquito density in August was followed by less remarkable increase of antibody positive rate or GMT. Temperature in October to next March was not

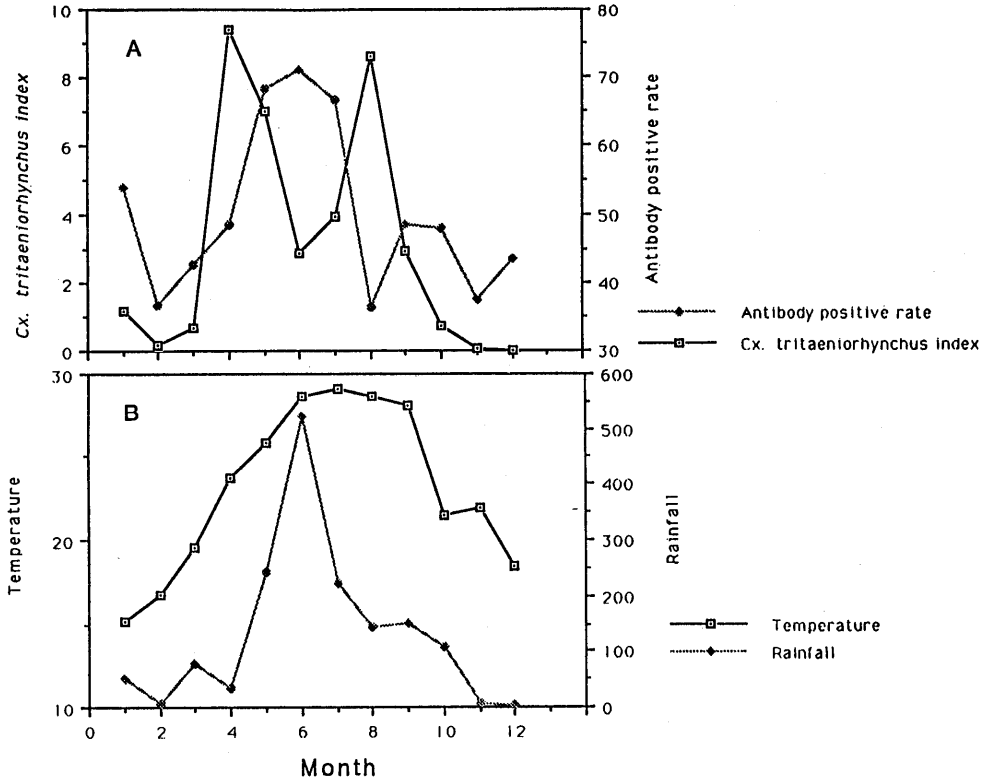

Fig. 3. Monthly change of *Cx. triteniorhynchus* density index, swine anti−JE antibody positive rate, temperature and rainfall in Dong Anh District, Hanoi in 1989. *Cx. tritaeniorhynchus* index (open square and solid line) and swine antibody positive rate (closed square and shaded line) in panel A, and temperature (open square and solid line) and rainfall (closed square and shaded line) in panel B are shown for each month in 1989.

high enough for the activity of *Cx. tritaeniorhynchus.* While, most of the human JE patients were found in July in north Vietnam (Nguyen *et al.,* 1990).

Virus isolation

Ten pools of 377 *Cx. tritaeniorhynchus* and 6 pools of 366 *Cx. annulus* were processed for virus isolation, however the result turned out to be negative.

Discussion

Our results showed that the number of AES cases clinically compatible with JE was significantly reduced by JE vaccination. Although the study was not designed as a placebo−controlled double−blind test (Hsu *et al.,* 1971; Hoke *et al.,* 1988), efficacy of JE vaccination was shown by reduced number of cases and the high proportion of unvaccinated children among JE cases after the vaccination. This reasoning was supported by the epidemiological observation on swine antibodies and mosquito population which indicated continued circulation of JE virus in the study area even after the vaccination. Although JE virus was not isolated from limited number of potential vector mosquitoes and presence of swine antibody did not necessarily indicated recent infection, significant proportion of swine, the most efficient amplifier of JE virus, was antibody positive, and *Cx. tritaeniorhynchus,* known JE vector, was the most abundant mosquito species and its density increased significantly during epidemic season in the study area. Two peaks of *Cx. tritaeniorhynchus* in April and August did not coincide with the peak of human JE cases in July. Probably in April, when the mosquito density reached to its first peak, JE virus was not yet introduced into swine-*Culex* cycle. It would be necessary to follow up the montly change of JE virus-infection in *Cx. tritaeniorhynchus* and to examine IgM-class swine antibodies.

The result in this study would be regarded as a rationale for JE vaccination as an efficient control measure for AES or JE in Vietnam.

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