Review

Japanese Encephalitis: Surveillance and Elimination Effort in Japan from 1982 to 2004

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SUMMARY: Japanese encephalitis (JE) surveillance has been conducted since 1965 as a part of the National Epidemiological Surveillance of Vaccine Preventable Diseases in Japan. Over 1,000 JE cases were reported annually in the late 1960s. The number of JE cases has since markedly decreased, with less than 10 cases reported annually from 1992 to 2004. A total of 361 JE cases were reported between 1982 and 2004. Prognosis was available for 320 cases; 58 (18%) died, 160 (50%) recovered with neuropsychiatric sequelae, and 102 (32%) completely recovered. Seventy-eight percent of these cases were 40 years old or over with a peak age group of 60-69 years old. JE predominantly occurred in unvaccinated populations. A high seroconversion rate among sentinel pigs was recorded every year. This suggests the presence of JE virus-infected mosquitoes during the summer in most areas of Japan, including the northern districts where no JE cases were reported from 1982 to 2004. Although JE cases have been reported in single figures since 1992, the risk of JE virus infection is still present. Thus, high immunization rates of JE vaccine should be maintained in Japan.

Introduction

Japanese encephalitis (JE) is a serious viral encephalitis with a high mortality rate and a high percentage of neuropsychiatric sequelae (1,2). JE occurs in annual epidemics in many Asian countries (3). Approximately 50,000 cases have been reported annually worldwide (4). However, the actual number of JE cases is considered to be significantly greater because JE surveillance systems are not effectively implemented in many developing countries. The epidemiological features of JE have dramatically changed over the past 3 decades in Japan, with a virtual elimination of clinical cases. In this paper, we analyze the records of JE surveillance in Japan from 1982 to 2004 and describe control measures taken in recent years.

Surveillance of JE in Japan

JE surveillance was first implemented in 1965 through the National Epidemiological Surveillance of Vaccine Preventable Diseases by the Ministry of Health and Welfare (currently the Ministry of Health, Labour and Welfare [MHLW]) (5). The surveillance includes (i) confirmation of notified JE cases, (ii) prevalence of JE antibodies among general populations, and (iii) seroconversion rates of sentinel pigs nationwide. Laboratory confirmation of JE has been performed by hemagglutination inhibition (HI) or complement fixation (CF) tests, according to the guidelines established in 1965. The cases were confirmed to be JE when HI or CF antibody titers were increased by 4 times or more in convalescent phase serum samples when compared to acute phase samples. In cases where only single patient samples were available, HI titers of 1:160 or greater and CF titers of 1:8 or greater were considered to be confirmatory laboratory data. Neutralization assay, polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA) have also been used recently for laboratory confirmation.

Annual numbers of confirmed human JE cases

The annual numbers of confirmed JE cases from 1965 to 2004 are shown in Figure 1. More than 1,000 JE cases were reported annually in the late 1960s. Since then, the number of cases dramatically decreased, with 20 to 90 cases reported annually from 1978 to 1991, and less than 10 cases reported annually from 1992 to 2004. A total of 361 confirmed JE cases were reported between 1982 and 2004.

Sex and age distribution of the JE cases

Of 361 confirmed JE cases, 184 cases were male and 177
were female (Table 1). Seventy-eight percent of the total cases were 40 years old or older with a peak in the 60-69 year age group (Figure 2). These data indicate that JE occurred mainly among elderly populations. The highest incidence rates were in the 50-59 year age group among males and in the 60-69 year age group among females.

Although JE occurred mainly in elderly populations from 1982 to 2004, there were a small number of JE cases in individuals younger than 10 years old (Figure 2). These cases accounted for 12% of the total JE cases.

### Geographical distribution of JE in Japan

Japan is geographically divided into 8 districts: Kyushu (the southernmost district including Okinawa Prefecture), Shikoku, Chugoku, Kinki, Chuubu, Kanto, Tohoku, and the northernmost district of Hokkaido (Figure 3). Of 361 JE cases, 165 cases (46%) were reported in the Kyushu district, 40 cases (11%) in Shikoku, 40 cases (11%) in Chugoku, 64 cases (18%) in Kinki, 24 cases (7%) in Chuubu, and 28 cases (8%) in Kanto (Figure 3). There were no confirmed JE cases in the northern districts of Tohoku and Hokkaido between 1982 and 2004. Therefore, JE occurred mainly in the southern districts of Japan.

### Table 1. Number of confirmed cases of JE in Japan during from 1982 to 2004, by sex, prognosis, and history of vaccination

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<tr>
<th>Year</th>
<th>No. of cases</th>
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Rate  51%  49%  28%  44%  16%  11%  1%  4%  51%  44%

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Fig. 1. Annual incidences of JE from 1965 to 2004 in Japan. Records of JE cases were collected using individual report cards by the Ministry of Health, Labour and Welfare, Japan. These reported cases included fatal cases and serologically and/or virologically confirmed survival cases.

Fig. 2. Sex and age distribution of JE cases from 1982 to 2004 in Japan. A total of 361 JE cases are shown based on ages at the development of symptoms.
All the JE cases were reported during a 5-month span, from July to November. The earliest onset of the disease was on July 12 in 2001 and the latest on November 1 in 2002. The majority of JE cases were reported in August and September with a peak in late August (Figure 4). When southern districts (Kyushu, Shikoku, Chugoku, and Kinki districts) and northern districts (Chubu, Kanto, Tohoku, and Hokkaido districts) were analyzed separately, a difference in monthly JE inception is observed. JE occurred from mid-July to early November with a peak in late August in the southern districts, while it occurred from early August to late October with a peak in early September in the northern districts.

**Monthly occurrence of JE**

All the JE cases were reported during a 5-month span, from July to November. The earliest onset of the disease was on July 12 in 2001 and the latest on November 1 in 2002. The majority of JE cases were reported in August and September with a peak in late August (Figure 4). When southern districts (Kyushu, Shikoku, Chugoku, and Kinki districts) and northern districts (Chubu and Kanto) were analyzed separately, a difference in monthly JE inception is observed. JE occurred from mid-July to early November with a peak in late August in the southern districts, while it occurred from early August to late October with a peak in early September in the northern districts.

**JE vaccination histories**

Records of JE vaccinations were available for 203 cases (Table 1). One hundred and eighty-three of the 203 cases were unvaccinated, and only 20 cases were vaccinated in full (5 times) or on partial vaccination schedules. The data suggest that JE predominantly occurred in the unvaccinated populations.

**Prognoses of the cases**

Prognoses were available for 320 of the 361 cases. Of the 320 cases, 58 (18%) died, 160 (50%) recovered with neuropsychiatric sequelae, and 102 (32%) completely recovered (Table 1). Prognosis was analyzed in 2 groups: cases younger than 40 years old and cases 40 years old or older. The percent-ages of JE cases with fatal outcomes and complete recoveries were 9% (7/78) and 38% (38/102), respectively, in the younger group, and 18% (51/283) and 29% (72/283), respectively, in the older group.
Prevalence of JE antibody among general populations in Japan

JE antibody prevalence was surveyed among general populations in the National Epidemiological Surveillance of Vaccine Preventable Diseases. The data for 2004 are shown in Figure 5. Neutralizing antibody titers equal to or greater than 1:10 were considered to be positive in the analysis. Antibody prevalence differed between age groups. The JE antibody-positive population was less than 50% for ages 3 years and younger, greater than 70% for ages 4 - 24 and 65 - 69, and between 20 and 70% for ages 25 - 64 and 70 years or more. It should be noted that the JE antibody-positive rate was also low in the population aged 45 - 49.

JE virus infection of sentinel pigs

The seroconversion rates among sentinel seronegative pigs were checked annually in most prefectures. Swine are known to be an amplifier of JE virus, and it is generally accepted that the seroconversion rates of sentinel pigs reflect the prevalence of JE virus in the area. Local public health institutes in most of the 47 prefectures surveyed pigs, which were brought to slaughterhouses, for positive rates of HI antibodies. Data in the representative 7 years including 1982, 1986, 1990, 1994, 1998, 2001, and 2004 are presented in Figure 6. Seroconversion usually began in May in Okinawa Prefecture and in July in other southern prefectures (data not shown). Seroconversion in the sentinel pigs moved to the north and occurred in all the prefectures by October with the exception of Hokkaido in some years. Seroconversion rates were somewhat lower in the northern prefectures.

Discussion

JE is an acute viral encephalitis transmitted by infected mosquitoes. Culex tritaeniorhynchus is the main vector in Japan. The ratio of asymptomatic to symptomatic infections is estimated to be 100:1 - 1,000:1 (3). Mouse-brain-derived, inactivated JE vaccine is available and internationally accepted (6,7). JE is, therefore, a vaccine preventable disease; however, this vaccine has not been used regularly in all the JE epidemic or endemic countries in Asia, mainly due to its high cost and to limitations in production capacity. The epidemic and endemic areas are located in East Asia, South Asia, and Southeast Asia (3,8). Approximately 1 billion children are believed to be at risk for JE virus infection in these areas. Additionally, JE cases have been reported in Papua New Guinea and Australia (9-12). JE is therefore no longer restricted to only Asian countries.

JE was a serious cause of morbidity and mortality in Japan for many years. There were more than 1,000 JE cases reported annually in the late 1960s. The number of JE cases has decreased dramatically, and less than 10 cases have been reported annually since 1992 (Figure 1). The majority of the cases were in the elderly population with a peak in the 60 - 69 year age group. The JE antibody-positive percentage, however, is not lower in the elderly population than in the younger population. We assume that the high incidence of JE among the elderly population is mainly due to impaired immune responses. However, it should be noted that the age distribution of JE patients in Table 1 is a sum from 1982 to 2004, and the antibody positive rate in Figure 5 is that observed in 2004. Thus, a direct comparison between these two data may not be appropriate. Although the percentage was low, there were
JE cases among children younger than 10 years old. In Japan, primary JE vaccination is to be given twice at 1- to 4-week intervals between 6 and 90 months of age, and the current standard schedule usually starts at 3 years old. The first booster immunization is given 1 year after the primary vaccination (usually at the age of 4 years), and the 2nd and 3rd booster immunizations are given at ages 9-13 years and 14-15 years, respectively. (The 3rd booster immunization was terminated as of July 29, 2005.) The small cluster of cases between the ages of 0 and 4 years most likely reflects lower levels of antibody prevalence among this age population. Thus, immunization at ages younger than 3 years old should be considered in order to prevent JE in children aged 3 years old and younger. The JE antibody-positive rate was also low in the population 45-49 years of age. It is possible that this population was not vaccinated with JE vaccine at a high rate and was not naturally infected at a high rate as in the elderly populations.

There have been reports of acute disseminated encephalomyelitis (ADEM) after immunization with mouse brain-derived JE vaccine. The MHLW of Japan halted the recommendation of JE vaccination as of May 30, 2005, because of the occurrence of severe ADEM. However, the JE vaccination system has not been changed, and JE vaccine is available for those who request the vaccination. The incidence of ADEM is estimated to be less than one case per 1 million doses ([13] and data not shown), and this rate is not higher than those induced by other vaccines. Further investigation is needed to define the relationship between JE vaccine and ADEM. The development of Vero cell-derived JE vaccine is underway (14).

Extensive vaccination with mouse brain-derived, inactivated vaccine is considered to be the main factor in the significant decrease in the number of JE cases in Japan. The JE virus Nakayama strain was originally used for vaccine production in Japan, but since 1989 the Beijing-1 strain has been used instead. The protective efficacy of the vaccine was evaluated in placebo-controlled studies. The efficacy was estimated to be 80% in Taiwan in 1965 (15) and 91% in Thailand in 1988 (16). Neutralizing antibody titers of 1:10 or greater, which are generally considered to be protective levels, were maintained for at least 3-4 years after the first booster immunization (17-20).

It is believed that in addition to extensive JE vaccination, there are other multiple factors which also contributed to the decrease in the number of JE cases in Japan. These factors include a decrease in the areas of the irrigation fields where Cx. tritaeniorhynchus breed and changes in rice cultivation methods. These changes decreased the population of Cx. tritaeniorhynchus (21). Other factors also include the segregation of pigs, which are amplifiers of JE virus, from residential areas (21) and fewer pig farms (22). Due to these factors, JE virus-infected mosquitoes have fewer chances to bite humans.

A high seroconversion rate among sentinel pigs is consistent with the occurrence of JE cases in southern districts (Figure 4). It should, however, be noted that sentinel pigs are seroconverted even in northern districts with the exception of Hokkaido in some years. The data suggest that JE virus-infected mosquitoes are present during the summer in most areas of Japan, including the northern districts where no JE cases were reported from 1982 to 2004. Therefore, caution is still necessary with respect to JE in Japan. It was reported that anti-JE virus NS1 antibody was detected in 10 and 5% of the residents in rural and urban areas, respectively, in Hyogo Prefecture (23). It was also reported that anti-JE virus NS1 antibody was detected in 0.2 to 3.4% of the residents in 8 prefectures (24). Additionally, anti-JE virus NS1 antibody was detected among residents nationwide (25). Anti-JE virus NS1 antibody is induced only by JE virus infection, not by immunization with inactivated JE vaccine. These results indicate that humans and horses are naturally infected with JE virus at low but significant levels today. Therefore, JE vaccination is still recommended throughout Japan. For many countries that have been suffering from serious JE epidemics, the Japanese experience is a good example of successfully fighting the battle against this devastating disease.

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APPENDIX


REFERENCES

