Japanese encephalitis (JE) is a pernicious infectious disease widely spread in the western Pacific region where Taiwan is located.1-5 This disease formerly was quite prevalent in Taiwan, reaching epidemic proportions every summer. The earliest documented clinical record of JE in Taiwan can be dated back to 1931, although under the name of summer encephalitis.6 Kobayasi7 first succeeded in isolating JE virus (JEV) from fatal JE cases in 1938. The ecology of JE in Taiwan was first studied and addressed by Grayston and others8-13 in 1962.

It was promulgated in 1955 that JE was designated a notifiable disease on the island, but no systematic surveillance of any sort was set up at that time. Twelve years went by before an active surveillance was put into place in 1967 under the direction of Dr. T. Okuno, the then-World Health Organization consultant control of JE. Beginning in 1968, a mass vaccination program against JE for children was implemented in Taiwan, which, along with general improvements in living conditions over the past decades, has made a huge difference in the impact caused by the annual JE epidemics. Judging from the severity of suffering the disease inflicts on society, JE now seems to be under control in Taiwan.

A few cross-sectional studies have been published on JE epidemiology in Taiwan.8,14-20 However, as part of the staff of National Institute of Preventive Medicine, whose routine responsibilities in part encompass the registration, laboratory confirmation, active surveillance, and data processing of reported JE cases, we feel obligated to make known all pertinent information we have gathered over the years in an orderly, sensible, and analytical fashion. We do this in the hope that we may provide a somewhat broader comprehensive view of the real situation of JE in Taiwan in the past as well as of its current status, and we thus hope be of some help in preparing ourselves and other concerned health workers to deal with forthcoming JE epidemics.

**MATERIALS AND METHODS**

**Case definitions.** The following definitions were adopted when we commenced the active surveillance system for JE cases in 1967.

- **Suspected cases.** Suspected cases were defined as having fever of 38°C and above with one of the following symptoms: 1) meningeal signs and symptoms such as neck stiffness, opistotonus, and Kernig sign, accompanied or unaccompanied by nausea, vomiting, and headache; 2) cortical disturbance; 5) pyramidal and extrapyramidal signs, such as rigidity, spasticity, flaccidity, athetosis, and chorea.

- **Conﬁrmed cases.** Conﬁrmed cases were reported cases by the physician to health authorities.

- ** Reported cases.** Reported cases were suspected cases reported by the physician to health authorities.

**Reporting system.** Before 1967, health authorities monitored JE cases by merely following up physicians’ passive reports. The active surveillance system we have now was put into place in 1967. The system stipulates that before and during each epidemic season, health station personnel are to visit local hospitals and clinics, to provide information about case deﬁnition and surveillance statistics, to remind and exhort physicians to report suspected cases to health stations, and to collect serum samples for case conﬁrmation.

**Serum collection and transportation.** Paired serum samples, one of them taken in the acute phase and the other during convalescence, for each reported case have been acquired for serology testing purposes since 1966. All samples are refrigerated during shipping to the National Institute of Preventive Medicine and stored at −20°C once received at the laboratory.

**Serology testing.** A hemagglutination inhibition (HI) test has been used in serology testing. The method and reagents used in this test have remained the same throughout these years. Sucrose-acetone-puriﬁed JaGar01 strain JEV from infected suckling mouse brain is used as the antigen, and an acetone extraction method is used as serum treatment before the test.21 Paired sera are tested side by side simultaneously.

**Conﬁrmation standard.** A case is considered to be conﬁrmed based on the fulﬁllment of either of 2 criteria: the HI titer of the convalescent serum is ≥1:160 and has at least a 4-fold rise from titer in the acute phase serum, or the HI titer of either single serum is ≥1:320.18

**Mass vaccination program.** Since 1968, the ﬁrst year the
mass vaccination program against JE was implemented, vaccine has been given to children of certain age groups from March to May. Before 1987, an inactivated vaccine derived from Nakayama-NIH strain JEV-infected mouse brain was the only one used. An inactivated freeze-dried Beijing strain version was introduced in 1988, yet the Nakayama strain vaccine has remained dominant in the market to this day. Between 1968 and 1974, the vaccine was not given unless the child was 2 years old. In later years, the first dose of the vaccine was given to younger children. After 1980, the first dose was given at 1 year 3 months of age.

Dosages of vaccine vary for different birth cohorts. For those born between 1963 and 1969, 2 doses were given 1 week apart. For those born between 1970 and 1975, 3 doses were given. A booster dose was added 1 year after the 2-dose basal vaccination. For children born after 1975, 4 doses are given. A second booster (the added fourth dose) is administered when the child attends the first grade of primary school. Vaccination records are filed at local health stations for future reference.

Sequelae investigation. At end of the yearly epidemic, our laboratory personnel pay a personal visit to each patient with a new confirmed case to follow up the patient's prognosis and to complete a standardized questionnaire. This is done to determine whether the patient has a total recovery or is left with some impediments of neurologic functions (including numbness of limbs, muscle stiffness, slow movement of limbs, choreoathetosis, tremor, epilepsy, convulsion, dyslogia, facioplegia, dysphagia, dysacousia, and urine incontinence) or mental impediments (including emotional instability, changes in personality, mental retardation, and psychiatric disorder).

Other information. The vaccination history of the confirmed case is to be traced through the local health station file. The record of vaccination coverage rates cited in this study are provided by Taiwan Provincial Health Department, Taipei Municipal Health Department, and Kaohsiung Municipal Health Department.

Anti-JEV seroprevalence of the amplifying host. Two months before the epidemic season starts, 30 samples of swine serum are collected every week from assigned slaughterhouses in different northern and southern localities in Taiwan. Seroprevalence is determined by HI test results on those samples. Serum collection and testing are on going until 90% of seroprevalence is reached. Data from sources in central and eastern regions were also incorporated between 1978 and 1991.

RESULTS

Coverage rate of serum sample collection from reported cases. The coverage rate was at its lowest level in 1966 and 1967 (49 and 55%, respectively). The coverage rate was above 80% in the remaining years.

Variation of anti-JEV seroprevalence in the amplifying host. Variation in the annual date on which anti-JEV seroprevalence surpassed 50% in pigs in northern Taiwan is shown in Figure 1. Although fluctuating somewhat, the date tended to move forward gradually from July in the 1960s to May since the 1980s. The date that anti-JEV seroprevalence exceeded 50% in pigs in southern Taiwan was usually about 1–2 weeks earlier than the date associated with pigs in northern Taiwan. The results of investigation on pigs in central and eastern Taiwan were somewhat similar to that of pigs in northern Taiwan. Once anti-JEV seroprevalence has exceeded 50% in pigs, it will most likely rise to above 90% within 1 month.

Incidence rate. The annual incidence rates of JE since 1955 are depicted in Figure 2. The epidemic status of JE over the years can be roughly divided into 4 stages. Before 1968, the incidence rate was quite high. It was 2.05 per 100,000 for confirmed cases in 1967, which was the highest recorded year. From 1968 to 1975, the incidence rate noticeably was on the decline. The number of yearly confirmed cases ranged between 44 and 279. From 1976 to 1985, occurrence was low and steady. The annual number of confirmed cases was held between 36 and 67. After 1985, the incidence rate went on a further down slide. The number of confirmed cases varied from 6 to 35 each year. Six confirmed cases occurred in 1997, which is equivalent to an incidence rate of 0.03 per 100,000.

Mortality rate. The annual mortality rates of reported cases after 1954 are shown in Figure 3. The variation in the rate through the years bears a close resemblance to that of the incidence rate. The mortality rate in 1997 was 0.14 per 100,000, also the lowest ever recorded.

Residential locations of confirmed cases. Figure 4 indicates the residential distribution of confirmed cases in different epidemic stages in Taiwan. Although the incidence rate appears to be a little higher in northern and eastern Taiwan, confirmed cases took place sporadically in various districts. In 1997, for instance, the 6 confirmed cases came from 6 separate counties in central and southern Taiwan.

The distribution of epidemic peak month. Figure 5 re-
Japanese encephalitis (JE) was officially classified as a notifiable infectious disease in 1955, and laboratory diagnosis was established in 1966. Reported cases are defined as suspected JE cases that were reported to health authorities by physicians. Confirmed cases are those reported cases that were diagnosed positive as JE by hemagglutination inhibition test.

The incidence rates in all age groups were mostly on downward slopes between 1966 and 1975 (Figure 6). Figure 7 depicts the track of the incidence rate for each age group since 1976. The incidence rates for age groups 0–9 and 10–19 years declined, whereas that for the age 40 and above group remained low but level. The incidence rate for age group 20–29 years first increased gradually, but then decreased after 1985. The incidence rate for age group 30–39 years increased after 1978, and the upward trend became more prominent after 1989.

Figure 8 shows the age-specific incidence rates of birth cohorts 1945–1954, 1955–1964, and 1965–1974, respectively, during the period 1966–1997. The birth cohort 1955–1964 had the highest incidence rates among the 3 birth cohorts for most age groups over 9 years of age.

Vaccination coverage rate. The coverage rates of the fourth dose (the second booster) given at primary school to
first graders, reached above 95%. The third dose coverage rates were 50.3% in 1974, 74–80% between 1975 and 1986, and over 80% after 1986. The second dose coverage rates were mostly above 80%, except for the years 1968 (only 14.1%), 1969 (56.1%), and 1970 (68.5%). These rates stayed over 90% after 1986.

**Vaccine efficacy.** The third dose (the first booster) of JE vaccine has been offered since 1974. In our efficacy study, the confirmed cases were divided into 2 groups based on the dosage availability of JE vaccine: group 1, born between 1970 and 1975, when 3 doses of vaccine were given, and group 2, born between 1976 and 1994, when 4 doses were given. The vaccine efficacy data for those who received more than 2 doses of vaccine are presented in Table 1. The efficacy is estimated to be about 85% on average and definitely exceeded 80%. No statistically significant differences were found among age groups.

**Sequelae investigation.** Table 2 shows the prognoses (investigated in the year of onset) in patients with confirmed cases who were born after 1969 and had their onset in 1975–1997. On average, 40% of the surviving patients had sequelae. The prognosis distribution of patients with confirmed cases between those who received more than 2 doses of vaccine and those who did not receive any was not different statistically ($\chi^2 = 1.42$, $P = 0.23$).

**DISCUSSION**

This report describes the epidemic situation of JE in Taiwan based on confirmed cases rather than reported ones. This may miss some fatal cases that did not have the chance to go through the confirmation process; also excluded are non-JE cases. Since 1966, confirmation of all reported cases by serology testing has been required. The coverage rate of paired serum sample collection from reported JE cases rose to above 80% after 1967, but more than 80% of the reported cases were diagnosed to be something other than JE after 1975 (Figure 2). That sufficiently explains why using the data of confirmed cases to evaluate the epidemiology of JE is better than using reported cases.
In last 3 decades, Taiwan has experienced a general improvement in many aspects of the living environment, coupled with a zealous and lasting immunization campaign for children. The net effect of these has been a change in the epidemic curve, reducing the incidence rate, and a shift of the average age of infection from young to older persons. In summary, enough epidemiologic evidence exists to demonstrate each of the following characteristics.

The mode of transmission has remained unchanged. *Culex tritaeniorhynchus* was and still is the main vector, and swine are the amplifying hosts. Swine amplify the virus in late spring, which causes the human epidemic that follows. Studies in the 1960s indicated *C. tritaeniorhynchus* and *Culex annulatus* were the 2 vectors for JEV transmission in Taiwan.10,22–25 Later studies suggested *Cx. tritaeniorhynchus* to be more prominent.26 Surveys made in 1978 and during 1981–1983 fortified the latter notion by affirmative isolation of JEV from *Cx. tritaeniorhynchus* and *Culex annulatus* were the 2 vectors for JEV transmission in Taiwan.10,22–25 In our laboratory, we were able to isolate JEV from field-caught *C. tritaeniorhynchus* in every summer from 1986 to 1990 (Wu YC and others, unpublished data). According to the investigation in the 1960s, peak densities of *Cx. tritaeniorhynchus* were reached in the months of July and August.9,28 This pattern was found little changed in 1990–1992.29 This evidence implies that both the vector identity and the peak distribution of its density had little disparity over the past 30 years. Hurlburt30 established the pig–mosquito amplifying cycle of JEV in Taiwan in 1964. Figure 1 indicates a close correlation between the median of onset dates of confirmed cases in any particular year and the date in that year when swine seroprevalence exceeded 50%, which suggests the pig–mosquito amplifying cycle of JEV on Taiwan also remained the same despite the passing of 3 decades.

The incidence rate of confirmed cases has dropped dramatically. We believe several reasons exist for the decrease. First, many changes have occurred in the living environment in Taiwan, such as urbanization, shrinkage of rice fields, the use of insecticides, and centralization of the pig feeding industry which relocated pig farms away from residential areas. These changes effectively lessened the exposure of humans to vectors. Indeed, the incidence rate in nonvaccinated infants decreased from 6.04 per 100,000 in 1966 to 0.37 per 100,000 in 1980, and stayed very low afterward (Wu YC and others, unpublished data). Second, the mass vaccination has had a definite impact. As shown in Figures 6 and 7, the incidence rate in children under 10 years of age dropped markedly after 1967. Third, the epidemic season has shifted forward (Figure 5). The peak density of *C. tritaeniorhynchus* invariably occurred in July to September over the years; however, the epidemic in humans has moved forward into June since the 1980s, and thus the vector density at the time is comparatively lower.29 Fourth, other minor factors exist, such as improvement in nutrition and a decrease in outdoor activities at night for most young children. The mortality rate also decreased along with the incidence rate. Another possibility is the increase in the average age of JE patients, who might have experienced cross-reacting antigens to JEV in their early life and acquired some protection.

Confirmed cases are found all over Taiwan. The residential distribution of confirmed cases is shown in Figure 4. The wide distribution of cases might be due to the occurrence of both the vector (mosquito) and the amplifying host (pig) in neighborhoods of nearly the entire island.

The current epidemic season lasts from May to October each year. The reasons for the forward shift in the epidemic peak month need to be elucidated here. Chang and others31 noticed new infections in pigs in southern Taiwan during January and March. Also, sporadic confirmed human cases occur in winter all over the island. The timing of annual JEV emergence has been demonstrated to not exactly correlate with the density of vectors.10,30,32 In a study done in 1981–1983, Rosen and others26 found 2 peaks of positive JEV isolation from *Cx. tritaeniorhynchus* in northern Taiwan each year. These peaks were 4 months apart. Our investigation of anti-JEV seroprevalence of swine also shows a regular pattern of JEV emergence every year across Taiwan. The virus emerges in southern Taiwan first, then appears across the rest of Taiwan without a fixed order. This suggests a high possibility of JEV presence during winter throughout Taiwan. Ecological studies in Hokkaido and Okinawa demonstrate that JEV does overwinter locally.33,34 Several hypotheses exist for JEV overwintering; however, none of them can explain why the epidemic peak month has moved forward in Taiwan.35 Although the clustering of pigs may lead to more rapid spread of JEV, the spread of JEV in the 1960s was already at a comparable, if not greater, speed, and thus the influence of consolidation of pig farms should be limited. Japanese encephalitis virus can remain in the human nervous system and cause latent infection and recurrence.36,37 If latent infection of JEV also occurs in pigs, the forward movement of the epidemic peak month would be explained to some extent. A female pig with JEV infection could become latently infected. If JEV reactivates when the pig is pregnant, the virus would pass to newborn pigs, as it does in mice.38,39 Both the mother and the newborn pigs would then serve as reservoirs for the periodic occurrence of JEV. The advancement of pig feeding technology from the 1960s to the 1980s, which has apparently shortened the period between pregnancies of female pigs, might be responsible for earlier JEV emergence.

The onset age of the average confirmed case shifted grad-

### Table 2

<table>
<thead>
<tr>
<th>Vaccination status</th>
<th>Recovered (%)</th>
<th>Recovered with sequelae (%)</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unvaccinated</td>
<td>96 (56.8)</td>
<td>73 (43.2)</td>
<td>169</td>
</tr>
<tr>
<td>1–2 doses</td>
<td>34 (61.8)</td>
<td>21 (38.2)</td>
<td>55</td>
</tr>
<tr>
<td>≥3 doses</td>
<td>35 (66.0)</td>
<td>18 (34.0)</td>
<td>53</td>
</tr>
<tr>
<td>Total</td>
<td>165 (59.6)</td>
<td>112 (40.4)</td>
<td>277</td>
</tr>
</tbody>
</table>

* Patients surviving confirmed Japanese encephalitis cases were all paid a visit to investigate their prognosis each December. Only those who were born after 1969 are included in this table. No statistically significant difference was found in distribution of prognosis between the unvaccinated group and the group vaccinated with > 2 doses (χ² = 1.42, P = 0.23).

† Sequelae included neurolologic function impediments, such as numbness of limbs, muscle stiffness, slow movement of limbs, choreoathetosis, tremor, epilepsy, convulsion, dysphagia, dysarthria, and urine incontinence; mental impediments, including emotional instability, changes in personality, mental retardation, and psychiatric disorder.
ually from under 10 years of age toward adulthood. The 1955–1964 birth cohort has the highest incidence rates for age groups over 9 years old throughout the study (Figure 8). Several reasons exist for the high incidence rates in the 1955–1964 birth cohort. General improvement in the living conditions on the island decreased the odds of people’s exposure to JEV. This cohort, with less childhood exposure and less immunity, would have a higher incidence rate at older ages when compared to the earlier, more exposed 1945–1954 birth cohort. The fact that most members of the 1955–1964 birth cohort did not receive any JE vaccine also results in the higher incidence rate at older ages in that group when compared with the younger vaccinated 1965–1974 birth cohort. This result coincides with the findings of a 1991 JE seroepidemiologic study in Taiwan.46 Similar shifting of onset age was also observed in Korea and China after initiation of JE vaccination programs.41,42

Vaccine efficacy after more than 2 doses of vaccine is estimated to be about 85%. Hsu and others43,44 reported the efficacy of the first 2 basal doses of JE vaccine in the same year after administration was about 80%, but dropped to 58.7% the next year. Therefore, to get a more complete picture, we conducted a survey and a calculation on vaccine efficacy in those who received more than 2 doses of JE vaccine in our study (Table 1). The efficacy for each age group did not seem to be very consistent, perhaps due to an overall incidence rate that was too low. However, on average, efficacy remained above 80% within 10 years after the third dose of vaccination (the 95% confidence interval for those born in 1970–1975 was 76–90%, and the interval was 79–92% for those who were born after 1975). However, further investigation is called for to determine the exact endurance of vaccine protection. About 40% of all patients who survived confirmed JE cases had sequelae (Table 2). Although confirmed cases seem to include nonvaccinated cases, the difference is not statistically significant (P = 0.23), which was consistent with findings in China.45 This may indicate that JE vaccine is effective in blocking viremia by neutralizing antibodies, but the vaccine cannot modify the disease outcome once the virus has invaded the central nervous system.46

Japanese encephalitis virus is still wide spread and eradication in Taiwan seems remote, unless some abrupt immense changes in living conditions that are capable of effectively eliminating or breaking the JE transmission cycle. For the time being, a more effective and convenient vaccine is needed to ensure that JE is controlled and suppressed to minimize its human impact.

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