

# Cumulative Vaccination Coverage for the 1st, 2nd, and Booster Doses of Stage I Japanese Encephalitis Vaccination in Japan: Results of Year 2009 Nationwide Survey

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Naohide TAKAYAMA,\*<sup>1</sup> Hiroshi SAKIYAMA,\*<sup>2</sup> Nobuhiko OKABE,\*<sup>3</sup> Satoshi UMEMOTO\*<sup>4</sup>

## Abstract

In May 2005, the Japanese Ministry of Health, Labour and Welfare instructed physicians to refrain from actively recommending the Japanese encephalitis vaccine. Since, a new Japanese encephalitis vaccine was developed using cell culture, which was approved in February 2009 and has been marketed since June of that year. But the new vaccine remained being refrained from general injection because of inadequate supply, and the drop in the national vaccination coverage for Japanese encephalitis is becoming a concern. For this reason, we conducted a survey in 2009 to examine the national cumulative vaccination coverage for the Stage I Japanese encephalitis vaccination for the first time. The survey revealed that the final cumulative vaccination coverages for the 1st, 2nd, and booster doses were 16.4%, 15.5%, and 6.2%, respectively, illustrating that the rates are rather low especially for the booster dose. In the future, the supply of cell culture-derived Japanese encephalitis vaccine would increase, and we expect the coverage to improve in Japan. An ongoing survey to examine the extent of any rise in the cumulative vaccination coverage will be essential.

**Key words** Cumulative vaccination coverage, Japanese encephalitis (JE), Stage I JE vaccination, Nationwide survey, Random sampling

## Introduction

Japanese encephalitis (JE) is acute encephalitis caused by infection with the Japanese encephalitis virus (JEV) that occurs throughout Asia. JEV, the pathogen, multiplies efficiently within the body of the pig, and the mosquito *Culex tritaeniorhynchus* that feeds on the pig acts the vector for JEV. Humans are infected with JEV by the bites of the infected mosquitoes, but the majority of infections are asymptomatic, with only about 1 in every 300 to 1,000 people

infected with JEV actually develop encephalitis.<sup>1</sup> In Japan, 2,301 JE cases were reported in 1966, of which 783 died. But since 1992, the number of JE patients reported has been remaining low, fluctuating below 10.<sup>1,2</sup>

JE prevention efforts include managing the pigs in which JEV proliferates, measures against the mosquitoes (the vector), and measures for the susceptible individuals. In order to address the issue of susceptible individuals, the amended Preventive Vaccination Law (also known as Preventive Vaccination Act) stipulates regular

\*1 Department of Pediatrics, Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital, Tokyo, Japan (ntkym2011@yahoo.co.jp).

\*2 Director, Sakiyama Pediatric Clinic, Tokyo, Japan.

\*3 Director, Infectious Disease Surveillance Center, National Institute of Infectious Diseases, Tokyo, Japan.

\*4 Director, Healthcare Marketing Intelligence Inc., Tokyo, Japan.

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vaccination of the JE vaccine for the small children at 6 to 90 months of age (Stage I), the children at age 9 to 12 years of age (Stage II), and the children at 14 to 15 years of age (Stage III).<sup>2</sup>

In July 2004, two children who received the mouse brain-derived JE vaccine for their Stage III vaccination contracted severe ADEM (acute disseminated encephalomyelitis). Considering that a new JE vaccine derived from cell culture that had no risk of contamination with nerve tissue was expected to be approved soon, the Japanese Ministry of Health, Labour and Welfare issued a notice in May 2005 to withhold the use of JE vaccine, and in July of that year the Stage III vaccination was abolished.<sup>3</sup> Subsequently, a new JE vaccine derived from cell culture was approved for production in February 2009,<sup>3-5</sup> and was made commercially available in June. But due to the limited supply of a new JE vaccine, medical and healthcare personnel continued to refrain from actively recommending the vaccine. Now, nationwide decreases in the JE vaccination coverage and antibody prevalence, as well as the risk of a JE outbreak among children, are becoming a growing concern.<sup>3,4,6</sup>

JE vaccination has been withheld since 2005, and JE vaccination coverage had not been surveyed for years now, which makes it impossible to ascertain the current vaccination status. Because the understanding of the current JE vaccination status provides an important piece of basic information in devising the future policy for JE vaccination, we conducted a nationwide random-sampling survey in Year 2009 to determine the cumulative vaccination coverage (CVC) for Stage I JE vaccinations in Japan.

## Subjects and Methods

This CVC survey for Stage I JE vaccination followed the same procedure used in a nationwide measles-rubella vaccination coverage survey.<sup>7</sup> Specifically, 5,000 children who had reached 6 years of age by April 1, 2009, were randomly sampled nationwide. To the 1,223 local authorities where the sampled children resided, the letter of request, survey sheets, and the procedure manual were sent in June 2009. The persons in charge of preventive vaccination program in those local authorities were asked to inquire the dates on which the sampled children received JE vaccine. Based on the returned survey sheets, the number

of children who received JE vaccine was compiled at each age in months to determine the CVC.

## Results

### Survey sheets and record recovery rate

Of the 1,223 local authorities to which survey sheets and other materials were sent in June 2009, 1,051 replies were received as of September 16, 2009, bringing the recovery rate of 85.9%. Out of the 5,000 6 year-olds who had been randomly selected (sample pool), the records for 4,319 children were returned, giving the recovery rate of 86.4%.

Of the returned records, there were 6 cases that the local authorities were not cooperative with the survey in order to protect personal information ("non-cooperation"). Of the remaining records (4,313 children), 636 cases had received the 1st dose of Stage I JE vaccination, 3,248 had not received the vaccine, 109 did not note anything about the vaccination dates (no data), and 320 had been given the 1st dose but the exact date of vaccination was unknown. As regards the 2nd dose, 579 received the vaccine, 3,145 had not received yet, 337 had no data, and 252 received the vaccine but on unknown dates. As for the booster dose, 227 received the vaccine, 3,461 had not received yet, 372 had no data, and 253 received on unknown dates.

The records with no data or unknown dates for any of the 1st, 2nd, and booster doses and "no-cooperation" cases were all eliminated from the data analysis, and those that received the vaccine on known dates and those that have not yet received the vaccine were used for the analysis. Consequently, the sample size amounted to 3,884 for the 1st dose (77.7% of the sample pool), 3,724 for the 2nd dose (74.5% of the sample pool), and 3,688 for the booster dose (73.8% of the sample pool).

### Number of JE vaccinees at each age in months

According to Preventive Vaccination Law, Stage I JE vaccination consists of 3 doses and is given to children between the ages of 6 and 90 months (typically at 3 years of age) to build basic immunity. The first time vaccination include both 1st and 2nd doses (with 6 to 28 days apart), and the booster dose is given 1 year later (typically at age 4). Stage II JE vaccination is given once

to children between the ages of 9 and 12 years (typically, at age 9).<sup>2</sup>

In our survey, 44 children received the 1st dose of Stage I JE vaccine before reaching the standard age of 36 months (Fig. 1). The number of vaccinees begins to increase after the age of 36 months, and reaches its first peak at 40 and 41 months. The number again peaks at 50 months of age, 63 months, and 74 months. The most common age for vacci-

nation was 64 months of age with 49 vaccinees, followed by 43 vaccinees at 50 months and 62 months each. These fluctuations in the number of vaccinees likely occur because JE vaccines are primarily provided in the summer period.

Thirty-three children received the 2nd dose of Stage I JE vaccination prior to reaching 36 months of age (Fig. 2). As with the 1st dose, the number of vaccinees began to increase after

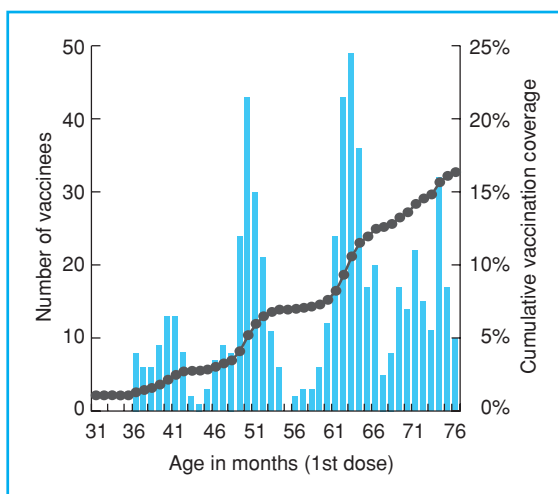


Fig. 1 Number of vaccinees of the 1st dose of Stage I Japanese encephalitis vaccination (bars) and the cumulative vaccination coverage (dots): results of Year 2009 survey

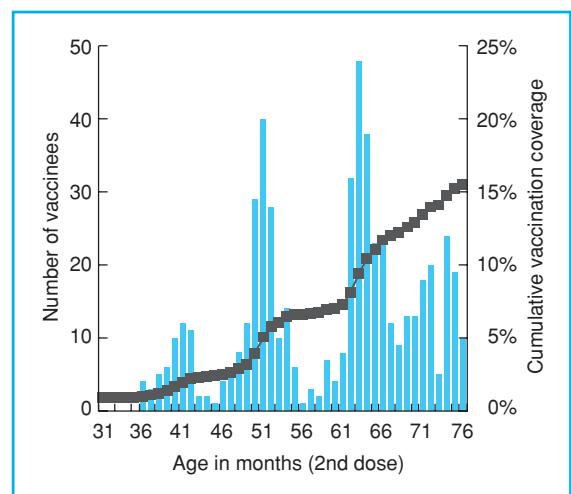


Fig. 2 Number of vaccinees of the 2nd dose of Stage I Japanese encephalitis vaccination (bars) and the cumulative vaccination coverage (squares): results of Year 2009 survey

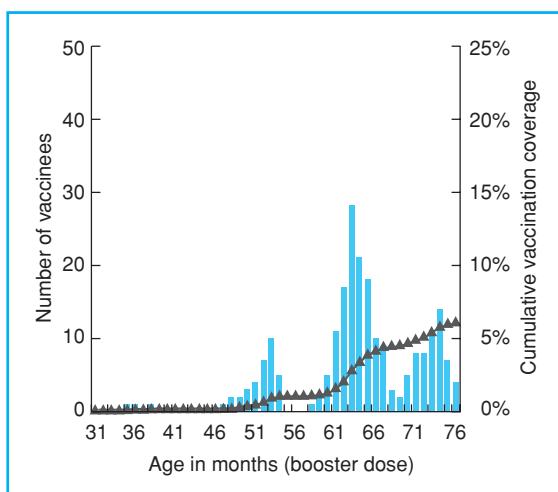


Fig. 3 Number of vaccinees of the booster dose of Stage I Japanese encephalitis vaccination (bars) and the cumulative vaccination coverage (triangles): results of Year 2009 survey

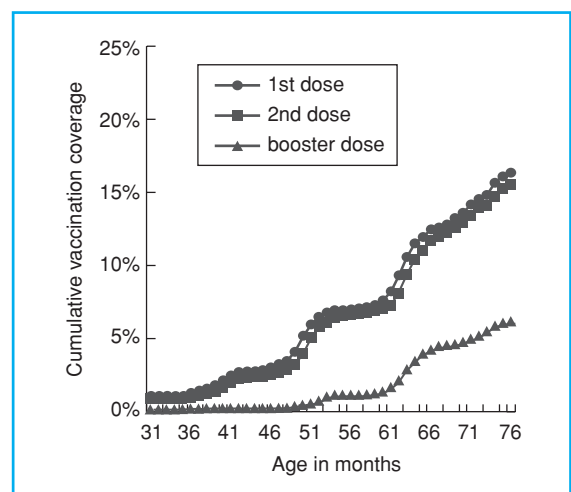


Fig. 4 Year 2009 survey results of Stage I Japanese encephalitis vaccination: comparison of the cumulative vaccination coverage curves among the 1st, 2nd, and booster doses

becoming 36 months of age, peaking at 41 months (1st peak), 51 months (2nd peak), 63 months (3rd peak), and 74 months (4th peak). The most common age for vaccination was 63 months of age with 48 vaccinees, followed by 40 vaccinees at 51 months.

Ten children received the booster dose for the Stage I JE vaccine prior to reaching the standard age of 48 months of age (Fig. 3). The number of vaccinees peaked 3 times; first peak was at 53 months of age, second one at 63 months, and the third one at 74 months. The most common age for vaccination was 63 months with 28 vaccinees, followed by 21 vaccinees at 64 months. Because this survey targeted children who had recently turned 6 years of age, there were no booster vaccinees of over 77 months of age in our data.

#### National cumulative vaccination coverage of JE vaccination

The CVC curves for the 1st and 2nd doses of Stage I JE vaccination (Figs. 1 and 2, respectively) gradually rise in a staircase pattern from 36 months of age, but their overall rate of increase remained small. The CVC for the 1st dose is 16.4% at 76 months (95% confidence interval [CI]: 15.2–17.6%) and 15.5% for the 2nd dose (95% CI: 14.4–16.8%). The CVC for the booster dose gradually increases from 50 months of age in a staircase pattern, but the increase is extremely moderate, and the CVC at 76 months was 6.2% (95% CI: 5.4–6.9%) (Fig. 3).

#### Comparison of cumulative vaccination coverage (CVC) for the 1st, 2nd, and booster doses of Stage I JE vaccination

The CVC curves for the 1st and 2nd doses of Stage I JE vaccination closely resemble each other; they both show similar pattern of increase, and the difference between their final CVC figures was only about 1% (Fig. 4). On the contrary, the curve for the booster dose showed about one-third of the pattern of increase observed in the 1st and 2nd doses, and the final CVC was also more than 9% lower than that of the 1st and 2nd doses.

#### Discussion

At the end of May 2005, the Japanese Ministry of Health, Labour and Welfare issued an emergency notice that the active recommendation of JE

vaccination should be refrained, and regular vaccination program was essentially suspended. Initially, it was expected that the new JE vaccine derived from cell culture would be approved shortly, but its approval took longer than expected. The new vaccine was finally approved in February 2009, and its sale launched in June. However, the vaccine's production volume remains low and fails to meet the quantity needed to vaccinate all eligible targets in Japan. Moreover, the safety of the new vaccine had not been adequately confirmed,<sup>5</sup> so physicians continue to refrain from actively encouraging with the JE vaccine.

In the case of the 6 year-old children who were the subjects of this survey, physicians were already withholding JE vaccine by the time these children had reached the standard age of 3 years for Stage I JE vaccination. Therefore, we would surmise that only the children whose parents strongly desired the JE vaccine for some reason were vaccinated. We also believe that the CVC curves for the 1st and 2nd doses were identical because those who were eager enough to receive the 1st dose also received the 2nd dose with very few cases of dropouts. On the other hand, it is not clear why the CVC for the booster dose was only two-fifths of that of the 1st or 2nd doses.

Once the production volume of the new cell culture-derived JE vaccine increases and a sufficient supply to cover regular vaccination for all target children can be secured, there would be no reason to refrain from actively recommending the vaccine. Accordingly, we expect the situation to change for the better in the future. However, the final CVC figures for other regular vaccinations all exceed 90%—namely, that of BCG vaccine at 6 months of age is at 97.7%,<sup>8</sup> the 1st dose of oral poliomyelitis vaccine at 24 months of age is at 93.4%,<sup>9</sup> the 1st dose of DPT (diphtheria/pertussis/tetanus) vaccine is at 95.4%,<sup>8</sup> and Stage 1 MR (measles-rubella) vaccine at 24 months is at 96.2%.<sup>10</sup> We believe this survey should be conducted on continuous basis from next year to examine the extent of any fluctuation in the CVC curve during a year and whether the coverage rises to the level of other regular vaccines.

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