

# MEASLES AND MEASLES VACCINE IN JAPAN

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## ABSTRACT

Before the introduction of measles vaccine in 1971, measles was a common and well-recognized disease in Japanese children. Seroepidemiological studies conducted before the general use of the vaccine disclosed that measles epidemics differed from community to community; in rural areas, epidemics appeared at intervals of several years with the accumulation of susceptibles, and in urban areas, measles was endemic affecting younger children.

The measles vaccines developed in Japan showed excellent safety and efficacy in the clinical trials for general use. Since 1978 measles vaccines have been routinely given to children aged 12 months or older, and incidence of measles decreased dramatically. However, the vaccine acceptance rate has been only as high as 85% to 90% and small-scale outbreaks of measles have been observed periodically among unimmunized children: Measles is far from being eradicated in Japan. This is primarily due to the insufficient vaccine acceptance rate, and more efforts towards mobilization of parents to have their children vaccinated are now in progress.

Key Words: Measles, Measles vaccine, Immunization, Epidemiology

## INTRODUCTION

Over the last few centuries, measles has been one of the commonest communicable diseases in childhood in Japan. Because of the high attack rate and severity of the illness, there is an old Japanese proverb: "Measles is the determinant of children's fate." However, after the introduction of measles vaccine, the epidemiology of the disease markedly changed. The purpose of this paper is to give a brief sketch of measles and measles vaccines in Japan.

## EPIDEMIOLOGY OF MEASLES IN PREVACCINE ERA

Before the introduction of measles vaccine, measles was a common and well-recognized disease in Japanese children, with a specific Japanese name. Serological studies have shown a good correlation between a history of measles and the presence of specific antibody (Table 1.)

Table 1. History of Measles and Antibody Preservation.

	History of measles	
	Yes	No
Measles HI antibody		
$\geq 8$	768 (98.3%)	18 ( 2.4%)
$< 8$	13 ( 1.7%)	738 (97.5%)
Total	781 (100%)	756 (100%)

Studied in Nagoya, Japan in 1965, on children  $\geq 2$  years of age.

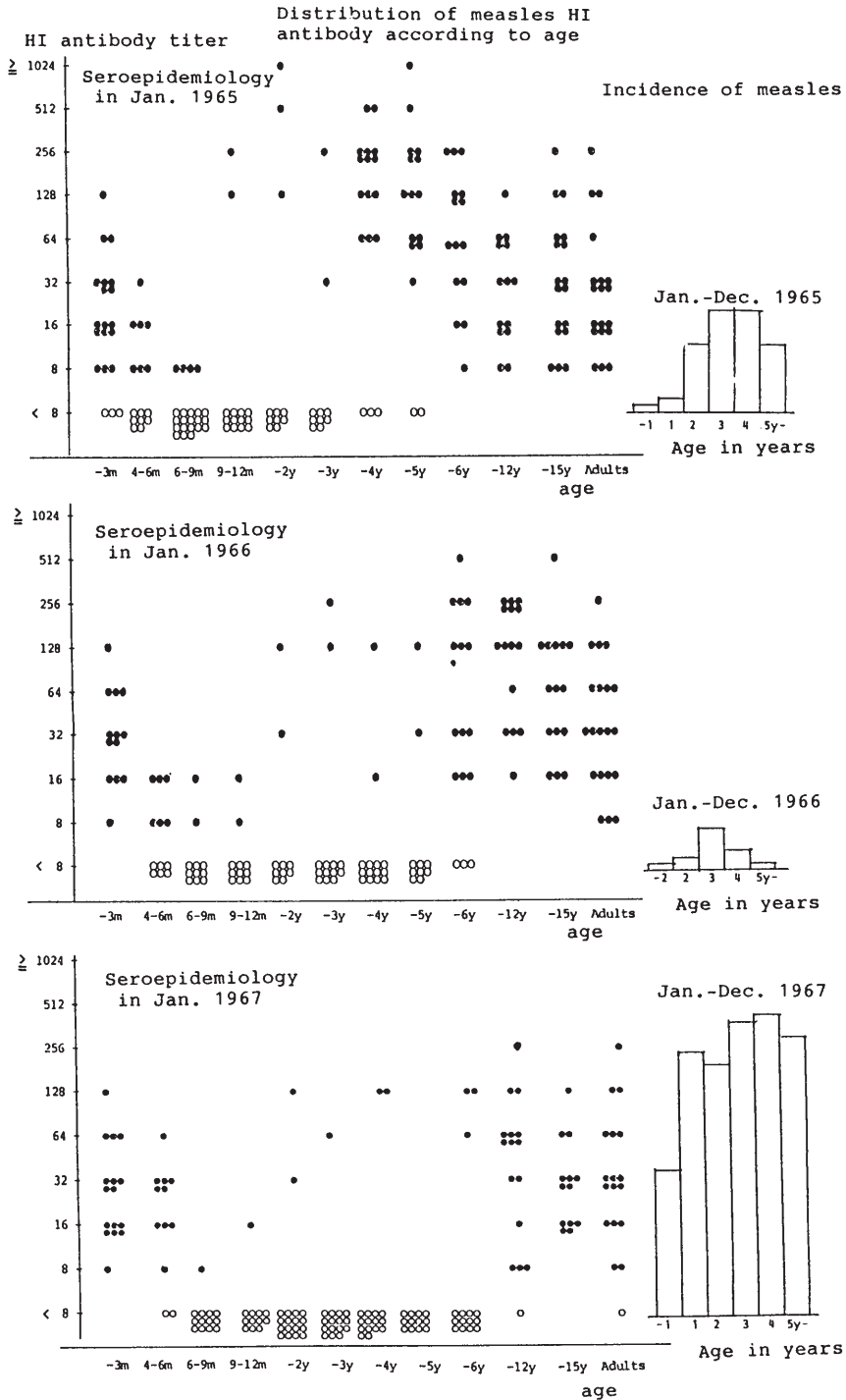


Fig. 1-a. Distribution of measles antibody and incidence of measles by age in a rural area in Aichi Prefecture.

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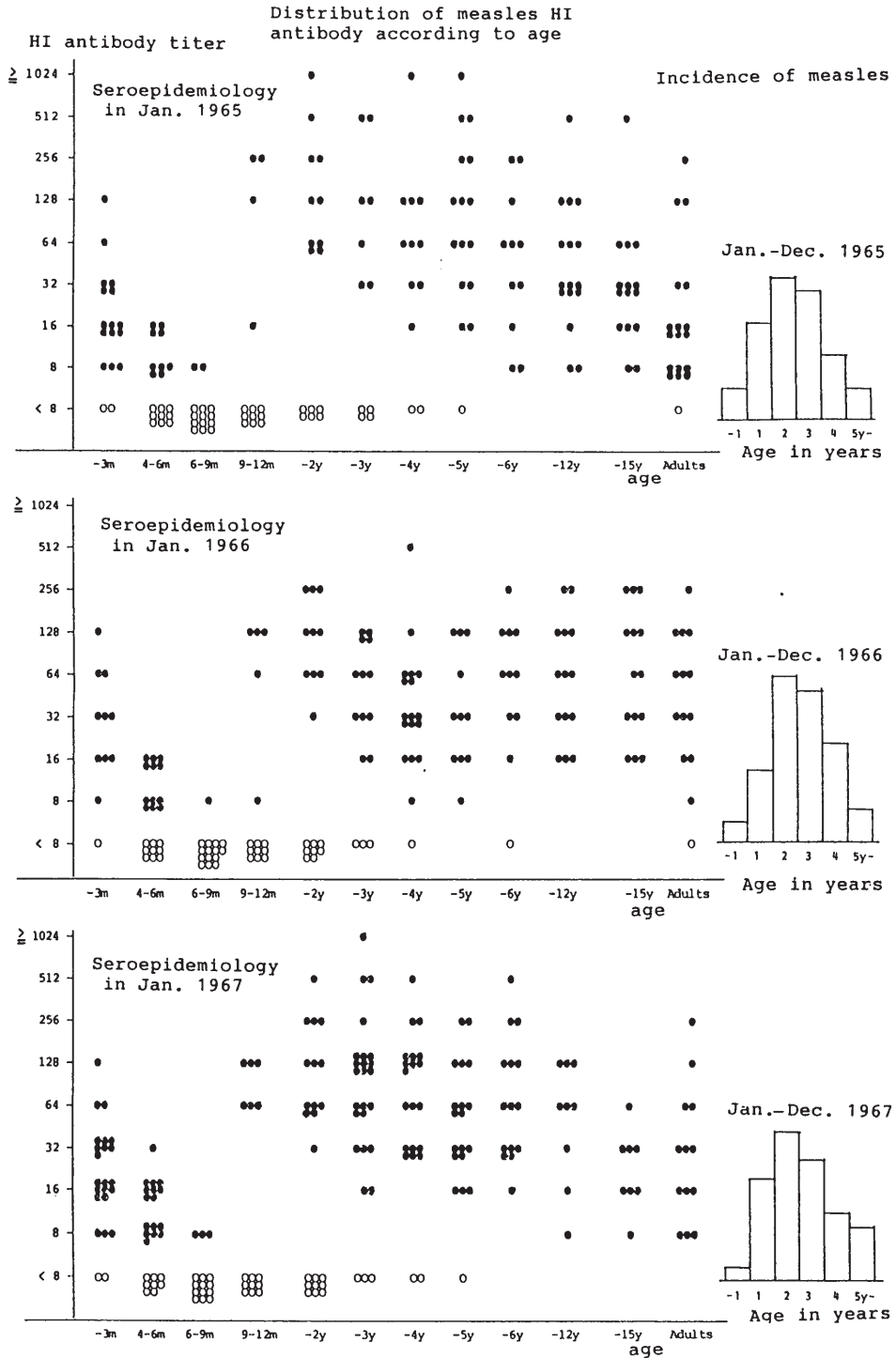


Fig. 1-b. Distribution of measles antibody and incidence of measles by age in an urban area in Aichi Prefecture.

Seroepidemiological studies, conducted in 1965 through 1967 shortly before the general use of the vaccine, showed that measles epidemics differed from community to community according to population density; in rural villages, epidemics appeared at intervals of several years with the accumulation of susceptible children (Fig. 1-a), and in urban areas, where new seronegative children were constantly being accumulated, measles was an endemic disease primarily involving children younger than those in rural areas (Fig. 1-b).

The estimated prevalence of seropositives and the incidence of measles by age from these studies are summarized in Table 2. In the prevaccine era, measles was prevalent in preschool children with a peak incidence at three to four years of age. More than 95% of children were seropositive by the age of six.

Table 2. Incidence of Measles and Seroprevalence of Measles Antibody in Prevaccine Era.

Age	Incidence of measles according to age	Prevalence of measles antibody
<6m	0 ( 0%)	247/412 (60%)
6-11m	79 ( 5%)	76/420 (18%)
1-2y	317 (20%)	173/456 (38%)
3-4y	619 (39%)	286/421 (68%)
5-6y	412 (26%)	377/423 (88%)
6y $\leq$	159 (10%)	390/398 (98%)
Total	1586 (100%)	1549/2530 (61%)

Aichi Prefecture, Japan, 1965-1967

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In April 1971, three live, further attenuated measles vaccines, Biken-CAM, Schwarz-FF8 and AIK-C, were licensed for general use after long and extensive field trials conducted by the Japanese Measles Vaccine Research Commission.<sup>1)</sup> Since 1978, children have been routinely immunized between 12 and 72 months of age according to the official immunization program. Results of field trials before licence conducted in Nagoya are summarized as follows:

### *Clinical and serological reactions to the vaccines*

There were no significant differences between the three vaccines in adverse reactions and antibody responses after inoculation (Table 3). Seroconversion rates were as high as 95% or more after a single injection. As for clinical reactions, mild fever for one to two days developed in 20%-30% and rash was observed in less than 20% of vaccinees.

### *Serological and clinical efficacy of the vaccine*

Serological follow-up studies<sup>2)</sup> disclosed that antibody titers after measles vaccine were lower than those after natural infection (Fig. 2). However, there was no significant difference in long-term persistence of immunity between the two groups. In Fig. 2-a, two cases showed seronegative in the 8th and 10th year but they were seropositive by NT tests.

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Table 3. Adverse Reactions and Antibody Response of Children Immunized with Commercially Available Measles Vaccine in Japan.

Adverse reactions	Vaccine used		
	AIK-C	Biken	Takeda
Fever			
$\geq 37.5^{\circ}\text{C}$	21.4%	35.3%	24.0%
$\geq 39.0^{\circ}\text{C}$	3.4%	6.8%	5.7%
Rash	15.5%	10.5%	11.2%
Antibody response			
Seroconversion	98.0%	98.0%	97.5%
GMT of HI antibody ( $2^n$ )	5.8%	5.4%	5.7%

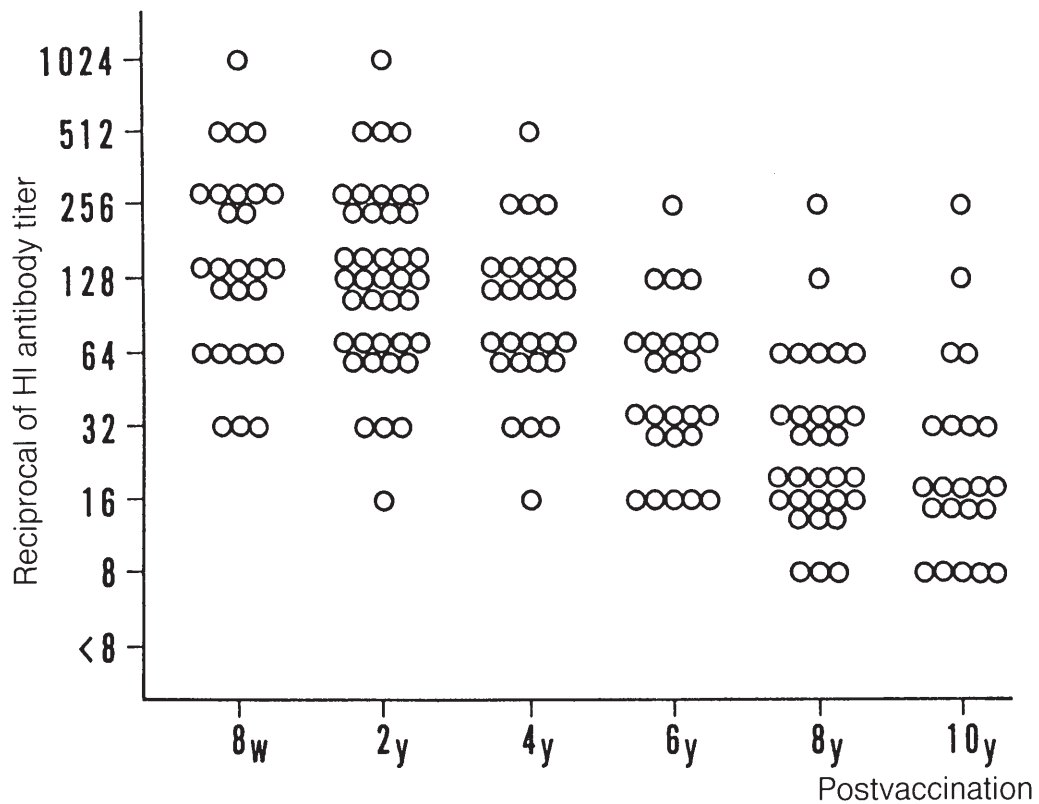


Fig. 2-a. Distribution of HI antibodies after immunization with FL vaccine.

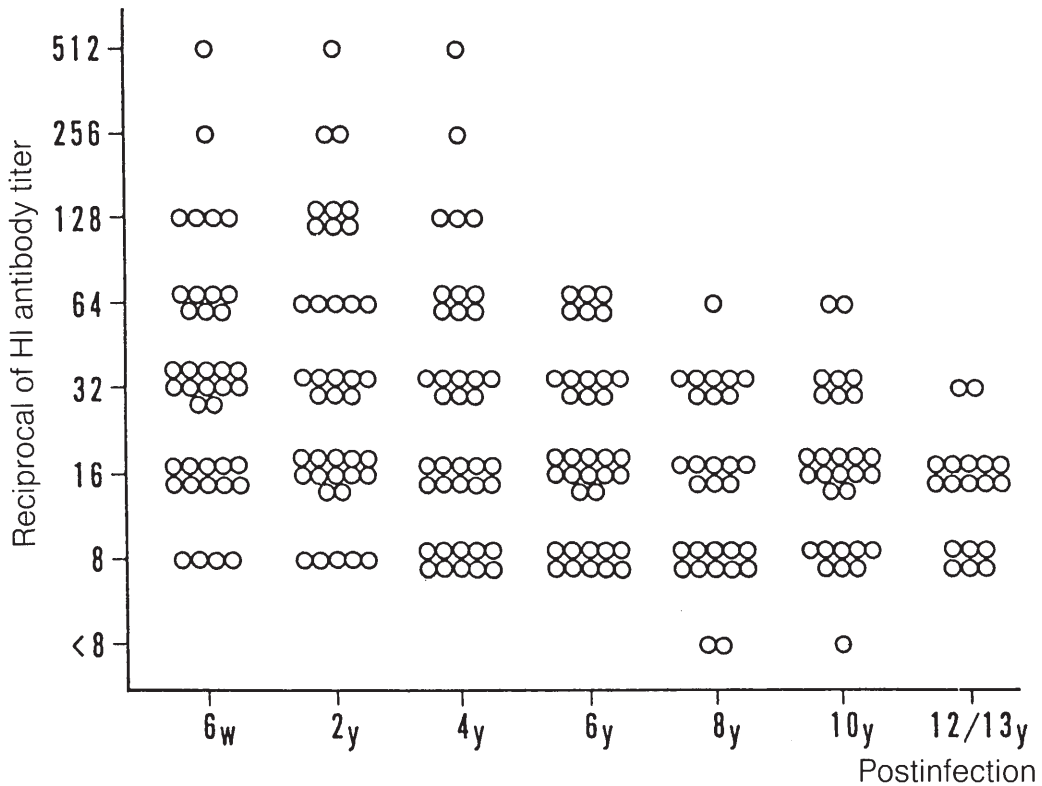


Fig. 2-b. Distribution of measles HI antibodies after natural infection.

Table 4. Clinical Efficacy of Measles Vaccine in Japan; Attack Rate of Measles after Household Exposure.

	No. of contacts	Measles after the contact		Attack rate
		Yes	No	
Children aged $\geq 6$ mo., unimmunized	308	296	12	96.1%
immunized with measles vaccine,				
in $\geq 1$ yr. of age	552	12	540	2.0%
between 6–11 mo. of age	54	18	36	33.3%

Aichi Prefecture, Japan, 1967–1971

Table 4 shows results of household contact studies to evaluate the clinical efficacy of the vaccine inoculation. Of unimmunized children 96% suffered from measles after household exposure to a measles patient. In contrast, the attack rate of measles was only 2% among children who had received measles vaccine after one year of age. The attack rate was 33% among children who had been vaccinated between 6 and 11 months of age. These results indicate that the vaccine provides excellent protective efficacy when used for children one year of age or older.

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## MEASLES IN THE POSTVACCINE ERA

Fig. 3 shows the number of cases of measles in Aichi Prefecture reported monthly to the Ministry of Health and Welfare from 1976 to 1984. Although surveys suggest that the officially reported cases represent only about 15% of the actual number of cases of measles, the scale of epidemics in the Prefecture seems well represented in the figure. During 1976–1977, when the measles vaccination was voluntary and its acceptance rate was as low as 40%, outbreaks of measles occurred every year, similar to those in the prevaccine era. In 1979–1980, after compulsory administration of measles vaccine started, vaccine coverage reached 70%–80% in pre-school children in the Prefecture and consequently the number of measles cases decreased markedly. However, the measles vaccine acceptance rate has remained around 85% and epidemics still occur at intervals of several years, primarily affecting unimmunized children.

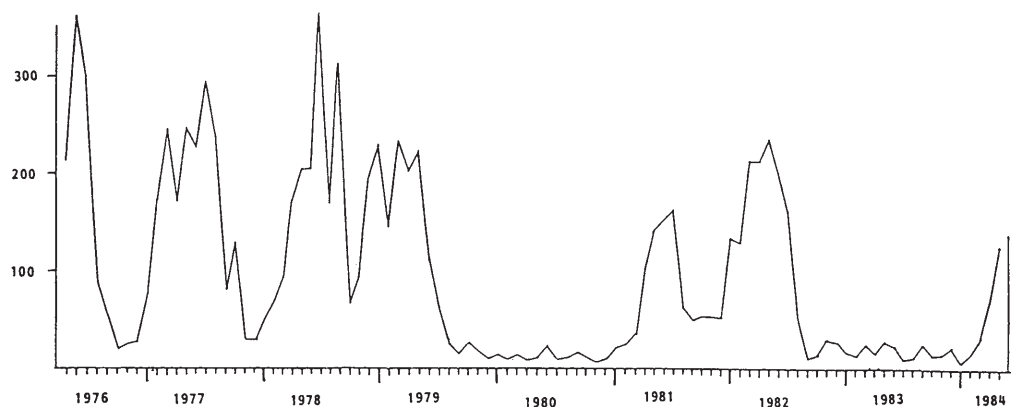


Fig. 3. Number of notified cases of measles in Aichi Prefecture.

## CURRENT SITUATION OF MEASLES IN AICHI, JAPAN

Out of 2,933 cases of measles reported to the Department of Hygiene, Aichi Prefectural Government in 1990, 863 cases were selected randomly and information was gathered through a direct household survey<sup>3)</sup>. As shown in Table 5, the peak incidence of the cases was at one year of age in the unimmunized group. As the age of attack became lower, the number of

Table 5. Age, Vaccine History and Severity of Clinical Course of Measles in Aichi Prefecture: Analysis of 863 Cases.

	Age							Total
	≤ 5m	6–11m	12–17m	18–23m	2y	3–5y	6y+	
Total	0	142	223	156	97	126	119	863
Vaccinated	0	0	0	2	6	8	15	31
Non-vaccinated	0	142	223	154	91	118	104	832
Hospitalised	0	25	35	18	9	13	7	107

Studied Jan.–Dec., 1991

complicated, severe cases increased. No case was reported among in infants before 6 months of age. With regard to the patients who had a history of measles vaccine, serological examination revealed that most of these vaccine failures were due to the inability to obtain seroconversion after vaccination (primary failure). In a few cases, however, their antibody level before and shortly after the attack suggested that a decrease of antibody titer after immunization caused substantial natural reinfection during epidemics (secondary failure<sup>4</sup>).

Of the cases analyzed, many children had been exposed in hospitals, both in the pediatric wards and outpatient clinic (Table 6).

Table 6. The Source of Infection: Analysis of 863 Cases.

Household contact; Sibling(s)	5.7%
Indoor playmate(s)	5.2%
Classmate(s) in school	8.6%
Hospital-acquired; Contact in the ward	13.7%
Hospital-acquired; Contact in OPD	31.3%
Unknown	35.7%

Studied Jan.—Dec., 1991

Table 7 relates to the results of monitoring activity on clinical efficacy of recent measles vaccines. From January through December 1991, 559 children aged 6 months or older had been exposed to household contact with measles patients. Attack rates after the exposure were 94.7% in the unimmunized group and 2.6% in the vaccinated group. Measles vaccines in current use have excellent clinical efficacy.

Table 7. Attack Rate of Measles after Household Exposure.

	No. of contacts	Measles after the contact		Attack rate
		Yes	No	
Children aged $\geq$ 6 mo., unimmunized	133	126	7	94.7%
immunized with measles vaccine, in $\geq$ 1 yr. of age	426	11	415	2.6%

Studied Jan.—Dec., 1991

In spite of the excellent efficacy of these vaccines, the coverage of the measles vaccine, mono-valent or measles-mumpus-rubella (MMR) triple vaccine, was 88% in 1991 in Aichi Prefecture and nationwide coverage of the vaccine in 1990 in Japan was as low as 66%. These figures are far from showing eradication of measles since a herd immunity of more than 90% to 95% is needed to control the disease<sup>5</sup>. Several factors have been known in regard to the insufficient acceptance of measles vaccine, such as lack of information,<sup>6</sup> mother's unawareness of the severity and complications of the disease,<sup>7</sup> and ignorance about the vaccine.<sup>8,9</sup> Since these factors might differ from community to community we gathered information through interviews with mothers attending a well-baby clinic for children three years of age.<sup>10</sup> The reasons why children were left unimmunized are summarized in Table 8. Mothers stated many reasons, but most of them were



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not contraindicated for measles vaccine. In Table 9 we summarized the knowledge of mothers on measles. Only less than half of the mothers replied that measles causes encephalitis and is sometimes fatal. As to measles vaccine, many of them did not have accurate knowledge on the efficacy of measles immunization. Such an active survey should be conducted on mothers' concept of measles and measles vaccine in each community, along with the promotion of an immunization campaign.

Table 8. Reasons Children were Left Unimmunized

Total # studied	2,621
Acutely ill	37.4%
Chronically ill	6.6%
Too busy	21.6%
Afraid of side effects	7.0%
Thought needless	3.7%
Did not know	5.8%
Attacked before 1 yr	8.8%
Others	9.1%

Nagoya, 1988-91

Table 9. Mothers' Knowledge of Measles and Measles Vaccine (Percent of YES Answers).

Total # studied: 2,144 mothers	% of YES
Long lasting high fever	77.2%
Severe cough and eye discharge	33.2%
Anorexia and malnutrition possible	32.4%
May be complicated by pneumonia	35.5%
May be complicated by encephalitis	30.4%
Sometimes fatal	30.2%
Vaccine efficacy is excellent	59.3%

1990, Aichi

In April 1989, the MMR vaccine developed in Japan was licenced for general administration. However, the triple vaccine has still remained for voluntary use since cases of aseptic meningitis as a complication of the mumps vaccine were reported with higher incidence in Japan than in other countries.<sup>11,12</sup> Detailed epidemiological investigations on the complications are now in progress.

## CONCLUSION

Incidence of measles cases has prominently decreased with compulsory administration of measles vaccine in Japan. However, small outbreaks of the disease have still occurred periodically. This is clearly related to an insufficient vaccine acceptance rate in children among whom

measles has been principally prevalent. More efforts towards encouraging nationwide use of the vaccine are now in progress. Concurrently, we should contribute towards the worldwide effort for global eradication of measles conducted by the World Health Organization (WHO) in the Expanded Programme on Immunization (EPI).

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