

# Antibody against measles among first graders: Comparison of the antibody titer before and after the introduction of the two-dose measles-rubella vaccination program

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**To study the effectiveness of two-dose measles vaccination, we examined the antibody titer in the serum of first graders before and after the introduction of the two-dose measles-rubella (MR) vaccination program.**

**A total of 826 first graders (553 boys and 273 girls) who entered school from 2004 to 2009 were studied. We compared the measles IgG antibody in the serum (enzyme immunoassay) and measles antibody positive rate before and after the introduction of the two-dose MR vaccination program in 2007.**

**The measles IgG antibody titer ( $4.9 \pm 1.6$ ) (M  $\pm$  SD) and antibody positive rate (97.8%) after the introduction of the two-dose MR vaccination program were significantly higher than the values ( $3.3 \pm 1.9$  and 93.4%, respectively) recorded before its introduction.**

**We concluded that the implementation of two-dose measles vaccination for preschool children resulted in a significantly enhanced measles serum antibody titer among first graders. To eradicate measles, we recommend the two-dose MR vaccination.**

**Keywords:** measles, two-dose, vaccination

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## 1. Introduction

In Japan, periodic vaccination for measles was first formalized in 1978. While the nationwide average vaccination rate stands at more than 80%, some regions have recorded much lower vaccination rates of 50–60% according to a survey by the Ministry of Health, Labour and Welfare in 2000. After the last serious outbreak in 1984, smaller outbreaks have continued to recur yearly in various parts of Japan (Infectious Disease Surveillance Center [IDSC], 2008). The World Health Organization (WHO) set a goal to eliminate measles in the western Pacific region (which includes Japan) by 2012, and in line with this, Japan announced its Action Plan for the Prevention of Measles, amending the vaccination scheme in 2006

to meet its designated goal of eliminating measles (IDSC, 2008). On top of the existing phase one (12–24 months after birth) of vaccination, phase two (one year before entering elementary school) was added to change the vaccination of measles to a two-dose vaccination program based on the MR vaccine. In addition, phase three (13 years of age) and phase four (18 years of age) will be implemented from April 2008 to March 2013 with the goal of inoculating all under 18 years of age with the measles vaccine twice by March 2013 (IDSC, 2008). Research on the effectiveness of two-dose measles vaccination on first graders has been scant thus far.

To achieve our aim of examining the effectiveness of two-dose measles vaccination for this study, we compared the measles antibody titer of first graders

(who entered school between 2004 and 2009) to allow a comparison of the situation before (2004–2006) and after (2007–2009) two-dose vaccination was put into place.

## 2. Methods

### 2.1 Subjects

With the objective of preventing infection, as part of the group health management, an elementary school in Tokyo (School A) monitors the measles, rubella, varicella and mumps serum antibody titer of entering first graders who wish to have their antibody levels measured. The subjects for this paper are 826 first graders (553 boys and 273 girls) with no prior history of measles who entered School A between 2004 and 2009, and opted in for the blood test.

### 2.2 Methods

1) When the first graders entered school, their parents and guardians were surveyed using a health questionnaire on the number of times and periods in time at which their children had undergone vaccination for measles.

2) The enzyme immunoassay (EIA) test was used to test for measles IgG antibody in the serum (testing institution: Nakayama Laboratory, Kitasato Institute for Life Sciences, Kitasato University). Using a measles virus immunoglobulin test kit (the Measles IgG-EIA manufactured by Denka Seiken Co., Ltd.), the antibody titer was calculated and recorded by dividing the absorbance of the serum sample by the absorbance of the positive control. Regarding the cut-off, an antibody titer of one and above was considered positive while an antibody titer of less than one was deemed negative.

3) The average measles antibody titer and antibody positive rate for all the first graders in each year (2004–2009) were then compared. Following that, the data was regrouped according to the frequency of vaccinations received and compared. When comparing the difference between the values for two groups, the t-test and  $\chi^2$  test were used. For comparisons involving three or more groups, analysis of variance (ANOVA) was used, with multiple comparison tests conducted for cases that yielded statistically significant results. Cases that fulfilled the condition  $p < 0.05$  were deemed to be statistically significant.

4) Ethical concerns: The study population for this paper was drawn solely from test subjects who had opted in for the blood test and given their permission for the data amalgamated to be published. Furthermore, the data collected from the blood tests was anonymized to ensure that specific individuals cannot be identified. The possibility of subjects and their family members being adversely affected may be ruled out as the research findings contain no information that may aid in the identification of specific individuals.

## 3. Results

### 3.1 Trend in number of vaccinations among first graders before and after introduction of two-dose vaccination

Two-dose measles vaccination was introduced in 2007 and the proportion of first graders who had been vaccinated twice increased year-on-year (Fig. 1). For the three years running from 2007 to 2009, there were 337 first graders (80.2%) who had been vaccinated twice out of a total of 420, 80 first graders (19.0%) who had been vaccinated once and three unvaccinated

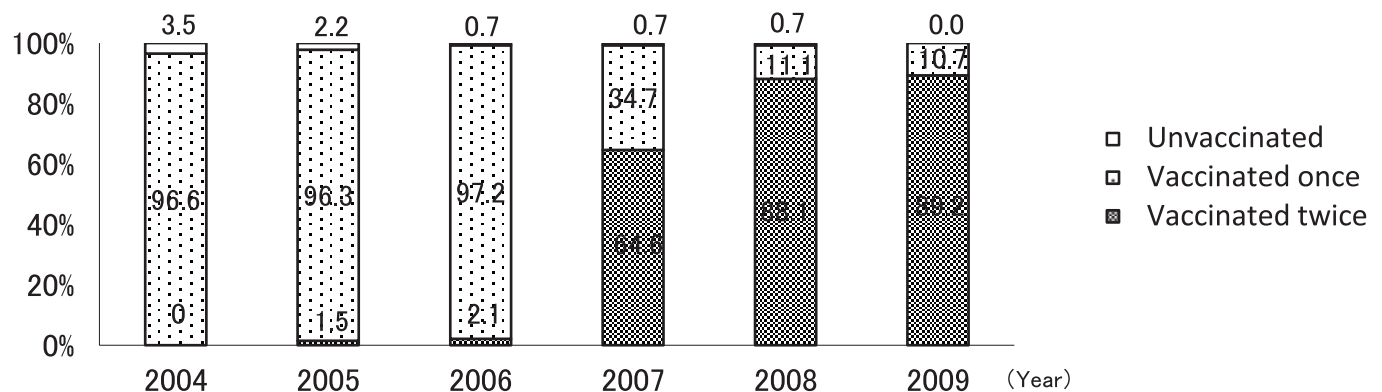


Fig. 1 Trend in number of vaccinations among first graders before and after introduction of two-dose vaccination

first graders (0.7%). In 2009, the number of unvaccinated first graders was zero, meaning that first graders as a whole had been vaccinated at least once.

### 3.2 Trend in measles antibody titer and antibody positive rate among first graders

The average measles antibody titer among first graders rose after 2007; the year two-dose vaccination was first introduced. While variance analysis did not yield statistically significant results from the differences between the average measles antibody titer for each year, the multiple comparison test yielded statistically significant results for all yearly data pairs except the following: 2004 and 2006, 2004 and 2007, and 2005 and 2006. In the three years after two-dose measles vaccination was introduced (2007–2009), the average measles antibody titer ( $4.9 \pm 1.6$ ) (mean  $\pm$  standard deviation) was significantly higher than the average antibody titer recorded ( $3.3 \pm 1.9$ ) for the three years (2004–2006) before two-dose measles vaccination was introduced (Table 1).

The  $\chi^2$  test yielded statistically significant results from the differences in measles antibody positive rate for all yearly data pairs, while regression analysis yielded statistically significant comparisons between

2005 and 2008, and 2005 and 2009.

In the three years after two-dose measles vaccination was introduced (2007–2009), the measles antibody positive rate (97.8%) was significantly higher than the antibody positive rate recorded (93.4%) for the three years (2004–2006) before two-dose measles vaccination was introduced (Table 1).

### 3.3 Comparison of measles antibody titer and antibody positive rate among first graders (by number of vaccinations)

From 2004 to 2009, the average measles antibody titer for first graders who had been vaccinated twice ( $5.2 \pm 1.5$ ) was significantly higher than that of first graders who had been vaccinated once ( $3.4 \pm 1.8$ ) (Table 2). First graders who had been vaccinated twice also exhibited a significantly higher measles antibody positive rate (99.4%) than that of first graders who had been vaccinated once (93.0%).

## 4. Discussion

Based on the results of this study, in 2009, the third year since the implementation of two-dose measles vaccination, the number of first

**Table 1** Yearly comparison of measles antibody titer and antibody positive rate, comparison of values before and after introduction of two-dose vaccination program

Year of school entry	Number of people	Measles antibody titer (enzyme immunoassay test) (Mean $\pm$ standard deviation)	Measles antibody titer 3 years before and after introduction (Mean $\pm$ standard deviation)	Multiple comparison	Measles antibody positive rate (%)	Measles antibody positive rate 3 years before and after introduction (%)	Regression analysis
2004	140	3.6 $\pm$ 2.0	3.3 $\pm$ 1.9 <sup>†</sup>	a4 > a5, a4 < a8, a9	99.3	93.4 <sup>‡</sup>	b5 < b8, b9
2005	131	3.0 $\pm$ 1.9		a5 < a7, a8, a9	87.8		
2006	138	3.3 $\pm$ 1.7		a6 < a7, a8, a9	92.8		
2007	136	4.0 $\pm$ 1.6	4.9 $\pm$ 1.6	a7 < a8, a9	94.9	97.8	
2008	141	5.7 $\pm$ 1.4		a8 > a9	100.0		
2009	140	5.2 $\pm$ 1.4			98.6		

†:  $p < 0.05$  (Student's  $t$ -test), ‡:  $p < 0.05$  ( $\chi^2$  test), the inequality sign used with regards to multiple comparison and regression analysis denotes statistically significant differences ( $p < 0.05$ )

a4–a9: Measles antibody titer for 2004–2009 respectively, b4–b9: Measles antibody positive rate for 2004–2009 respectively

EIA: enzyme immunoassay, ANOVA: analysis of variance

**Table 2** Comparison of measles antibody titer and measles antibody positive rate by number of vaccinations

	Number of measles vaccinations		p
	Vaccinated once	Vaccinated twice	
Number of people	486	340	
Measles antibody titer (EIA test)*	3.4 $\pm$ 1.8	5.2 $\pm$ 1.5	$p < 0.05$ <sup>†</sup>
Measles antibody positive rate	93.0	99.4	$p < 0.05$ <sup>‡</sup>

\*: Mean  $\pm$  standard deviation, †:  $p < 0.05$  (vaccinated once vs. vaccinated twice) (Student's  $t$ -test), ‡:  $p < 0.05$  (vaccinated once vs. vaccinated twice) ( $\chi^2$  test)

EIA: enzyme immunoassay

grader who had never been vaccinated was zero, meaning that all first graders on the whole had been vaccinated at least once. According to a previous study conducted at School A (Kimura et al. 1999), the measles vaccination rate then had been lower than that of recent years. In 1998, the proportion of schoolchildren diagnosed with measles after entering school was 4.5% (the vaccination rate was 85.6% in the same year); similarly, in 1992, the proportion was 3.0% (the vaccination rate was 91.6%). Following then, efforts to actively recommend vaccination were stepped up. Since 2002, when the herd vaccination rate rose to 95%, no case of measles contracted after entering school has been reported. It is argued that vaccination rates of 90–95% are necessary in order to prevent outbreaks within a particular herd (Nokes et al. 1988). Further gains in the herd immunity are expected as a result of implementation of the two-dose vaccination program.

In the three years since two-dose measles vaccination was introduced, the average measles antibody titer and antibody positive rate among first graders have risen significantly compared to that of the three years before two-dose vaccination was introduced. According to a report by the IDSC (2002), measles outbreaks have been recurring regionally in recent years among youths between 10–20 years of age. The reasons behind this are as follows: no past history of measles; not having been vaccinated against measles before; even with vaccination, under 5% of children are unable to acquire measles antibodies (primary vaccine failure); in addition, antibodies gained from vaccination decrease over the years (secondary vaccine failure), causing herd immunity to fall. It is a combination of these factors that accounts for 10–30% of youths having low immunity against measles. The results of this study have shown two-dose measles vaccination can be an effective countermeasure to primary and secondary vaccine failure by raising the herd immunity against measles among first graders.

In 2007, the year two-dose measles vaccination was introduced, the average measles antibody level and antibody positive rate reflected an upward trend as compared to before two-dose vaccination was introduced, but the increase was statistically insignificant. However, the results for 2008 (the second year after the implementation) onwards showed a more significant increase than that of 2007, and as a result, the average measles antibody titer

and antibody positive rate for the three years after the implementation (2007–2009) exhibit a significant increase from figures corresponding to the three years before the implementation (2004–2006). The two-dose measles vaccination rate in 2007 (64.6%), the first year of implementation, was lower than that of 2008 (88.1%) and 2009 (89.2%), and the higher average measles antibody titer and antibody positive rate recorded for 2008 onwards might also have been boosted by the nationwide measles outbreak that began in April 2007.

Among the subjects for this study, no instances of serious adverse reactions were reported. In their study of 75 children who underwent both MR vaccination at one year of age and two-dose vaccination before they entered elementary school, Terada et al. (2008) reported that after two-dose vaccination, measles antibody titer (neutralization test and enzyme immunoassay test) and rubella antibody titer (hemagglutination inhibition test) exhibited a significant increase with no cases of adverse reactions reported, indicating that MR two-dose vaccination is both safe and effective. A separate study of 199 children who had undergone single antigen measles and rubella vaccination at one year of age and MR vaccination before they entered elementary school was conducted by Takayama et al. (2009). They reported that measles antibody titer (hemagglutination inhibition test, neutralization test and particle agglutination test) and rubella antibody titer (hemagglutination inhibition test) exhibited a significant increase with no cases of adverse reactions reported. This indicates that MR vaccination is safe and effective even for children who have undergone single antigen measles and rubella vaccination at one year of age. Among the subjects for our study, 323 out of 340 people (95%) who underwent measles two-dose vaccination received the single antigen measles vaccine for their first vaccination and the MR vaccine for their second.

With the implementation of a comprehensive vaccination scheme, the United States has succeeded in eliminating measles in 2000, while Korea, which adopted two-dose measles vaccination in 2001, successfully eliminated measles in 2006 (MMWR, 2007). Although the WHO has set a goal to eliminate measles in the western Pacific region (which includes Japan) by 2012, 11,005 cases of measles were recorded in Japan when the nationwide measles survey was first introduced in 2008, and while the

figure has fallen sharply since then, there were 741 cases reported in 2009, 457 in 2010 and 434 cases in 2011 (IDSC, 2010). For measles to be completely eliminated within Japan in the future, it is essential that efforts at increasing awareness of the importance of vaccination before entering elementary school are stepped up to facilitate a target two-dose MR vaccination rate of 95% and above (Toyama et al. 2008). In addition, for children who have yet to undergo two-dose MR vaccination, it is important that sustained efforts are made to recommend that they be vaccinated even after they have entered elementary school.

## 5. Conclusion

To examine the effectiveness of two-dose measles vaccination, we have compared the measles antibody titer of first graders (who entered school between 2004 and 2009) to allow a comparison of the situation before and after two-dose vaccination was put into place. The average measles antibody levels and antibody positive rates were significantly higher among subjects who entered school in the three years after two-dose vaccination was introduced (2007–2009) as compared to subjects who entered school in the three years preceding its introduction (2004–2006). Two-dose measles vaccination is thus effective in raising the measles herd immunity levels of first graders.

## Appendix

The main findings of this paper were presented at the 56th Annual Meeting of Japanese Association of School Health (held on November 29, 2009, in Naha, Okinawa).

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