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 ± 1.6) (M ± 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 ± 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

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 cutoff, 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 χ² 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](http://www.shobix.co.jp/sh/hp/main.htm)
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 ± 1.6) (mean ± standard deviation) was significantly higher than the average antibody titer recorded (3.3 ± 1.9) for the three years (2004–2006) before two-dose measles vaccination was introduced (Table 1).

The χ² 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 2004 and 2007, 2004 and 2008, and 2004 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 ± 1.5) was significantly higher than that of first graders who had been vaccinated once (3.4 ± 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 graders who had been vaccinated twice (5.2 ± 1.5) was significantly higher than that of first graders who had been vaccinated once (3.4 ± 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%).

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

<table>
<thead>
<tr>
<th>Year of school entry</th>
<th>Number of people</th>
<th>Measles antibody titer (Mean ± standard deviation)</th>
<th>Measles antibody titer 3 years before and after introduction (Mean ± standard deviation)</th>
<th>Multiple comparison</th>
<th>Measles antibody positive rate (%)</th>
<th>Measles antibody positive rate 3 years before and after introduction (%)</th>
<th>Regression analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>140</td>
<td>3.6 ± 2.0</td>
<td></td>
<td>a4 &gt; a5, a4 = a8, a9</td>
<td>99.3</td>
<td>93.4</td>
<td>b5 &lt; b8, b9</td>
</tr>
<tr>
<td>2005</td>
<td>131</td>
<td>3.0 ± 1.9</td>
<td>3.3 ± 1.9</td>
<td>a5 &lt; a7, a8, a9</td>
<td>87.8</td>
<td>93.4</td>
<td>b5 &lt; b8, b9</td>
</tr>
<tr>
<td>2006</td>
<td>138</td>
<td>3.3 ± 1.7</td>
<td></td>
<td>a5 &lt; a7, a8, a9</td>
<td>92.8</td>
<td>93.4</td>
<td>b5 &lt; b8, b9</td>
</tr>
<tr>
<td>2007</td>
<td>136</td>
<td>4.0 ± 1.6</td>
<td></td>
<td>a7 &lt; a8, a9</td>
<td>94.9</td>
<td>93.4</td>
<td>b5 &lt; b8, b9</td>
</tr>
<tr>
<td>2008</td>
<td>141</td>
<td>5.7 ± 1.4</td>
<td>4.9 ± 1.6</td>
<td>a8 &gt; a9</td>
<td>100.0</td>
<td>97.8</td>
<td></td>
</tr>
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</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Number of measles vaccinations</th>
<th>Number of people</th>
<th>Measles antibody titer (EIA test)*</th>
<th>Measles antibody positive rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccinated once</td>
<td>Vaccinated twice</td>
<td></td>
</tr>
<tr>
<td></td>
<td>486</td>
<td>3.4 ± 1.8</td>
<td>93.0</td>
</tr>
<tr>
<td></td>
<td>340</td>
<td>5.2 ± 1.5</td>
<td>99.4</td>
</tr>
</tbody>
</table>

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

Reference


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