Persistence of Measles, Mumps, and Rubella Protective Antibodies 3 Years after Revaccination in HIV-Infected Children Receiving Antiretroviral Therapy

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Three years after measles, mumps, and rubella revaccination in 38 human immunodeficiency virus–infected children who had achieved immune recovery after antiretroviral therapy, the prevalence of protective antibody levels was 85% for measles, 61% for mumps, and 79% for rubella, compared with 88%, 84%, and 100%, respectively, 1 month after revaccination.

More than 90% of human immunodeficiency virus (HIV)–infected children live in developing countries where the prevalence of measles is high. In Thailand, measles vaccination is part of a compulsory immunization program with a nationwide coverage of 96% [1]. A dose of measles-containing vaccine is given to infants at 9–12 months of age followed by a second dose at the age of 4–6 years. Asymptomatic HIV-infected children are immunized on the same schedule as HIV-uninfected children.

The incidence of reported cases of measles, mumps, and rubella in Thailand in 2008 were 11.81, 0.98, and 21.9 cases per 100,000 persons, respectively [2]. Our previous studies showed that only 42% of HIV-infected children who had received measles-containing vaccine during early childhood had protective measles antibodies at the mean age of 10 years, and when revaccinated, 90% of these children had seroconversion [3, 4].

The objective of the present study is to determine the rate of persistence of protective antibodies against measles, mumps, and rubella 3 years after measles, mumps, and rubella revaccination among HIV-infected children receiving antiretroviral therapy and achieving immune recovery.

Patients, materials, and methods. This is a follow-up study of measles, mumps, and rubella revaccination among HIV-infected children receiving antiretroviral therapy. In brief, in October 2005, 51 HIV-infected children (mean age ± standard deviation [SD], 9.6 ± 2.8 years) with immune recovery after antiretroviral therapy (defined as a CD4 cell percentage >15% for >3 months) at Chiang Mai University Hospital (Chiang Mai, Thailand) were revaccinated with a single dose of the measles, mumps, and rubella vaccine Priorix (GlaxoSmithKline). The prevalence of protective antibody 1 month and 6 months after the revaccination were previously reported [4]. In the present study, these children were evaluated for the persistence of antibody levels 40 months after revaccination. The study protocol was approved by the research ethics committee of Chiang Mai University. Written informed consent was obtained from each child’s parent or guardian before enrollment.

Blood samples collected from participants at each visit were handled according to the same set of standard operating procedures. In brief, they were sent to the specimen-processing unit ≤4 h after collection and were centrifuged. Plasma aliquots were then kept at -70°C until shipment. The specimens were tested 1–3 months after specimen collection. The tests were performed at the Department of Medical Sciences of the Thai Ministry of Public Health (Nonthaburi, Thailand). The enzyme-linked immunosorbent assay was performed using Enzygnost reagent (Dade Behring), with an internal quality control performed on each run. The optical density readings were interpreted as negative if <0.1, equivocal if 0.1–0.2, and positive if >0.2. The positive optical density readings for measles and rubella were then converted to enzyme-linked immunoassay units, as reported by Ratnam et al [5]. Antibody levels of ≥320 mIU/mL for measles [6], >1:500 for mumps [7], and ≥10 IU/mL for rubella [8] were defined as protective antibody level. The most recent values of CD4 lymphocyte count and plasma HIV RNA level obtained within 3 months before or after the time of blood drawing were designated as current values. The mean decay of protective antibody at each time point (%) was determined by the following formula:

\[(\text{Antibody titer at specific time} - \text{baseline antibody titer}) \times 100 / \text{Baseline antibody titer} \]

Geometric mean titers were calculated with 95% confidence intervals for antibodies against each vaccine component at each
Table 1. Characteristics of the 38 Human Immunodeficiency Virus–Infected Children

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>At antiretroviral therapy initiation</th>
<th>At MMR revaccination</th>
<th>At 40 months (~3 years) after revaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years ± SD</td>
<td>7.4 ± 2.2</td>
<td>9.4 ± 2.1</td>
<td>13.2 ± 2.2</td>
</tr>
<tr>
<td>Median CD4 lymphocyte percentage (IQR)</td>
<td>2.5 (1.0–9.0)</td>
<td>26.5 (22.0–30.0)</td>
<td>30.0 (24.8–33.5)</td>
</tr>
<tr>
<td>Duration of antiretroviral therapy, median months (IQR)</td>
<td>...</td>
<td>31 (30–35)</td>
<td>72 (70–75)</td>
</tr>
<tr>
<td>No. (%) of children with viral suppression</td>
<td>...</td>
<td>37 (97)</td>
<td>37 (97)</td>
</tr>
</tbody>
</table>

**NOTE.** IQR; interquartile range; MMR, measles, mumps, and rubella.

follow-up time point. With respect to geometric mean titers, the mean of log-transformed titers was first obtained assuming that log-transformed titers were normally distributed with unknown variance. The 95% confidence intervals were then obtained by exponential transformation of the 95% confidence intervals for the mean of the log-transformed titers.

SPSS software, version 16.0 (SPSS Inc), was used for statistical analysis. Comparisons of continuous variables were performed by the independent sample $t$ test, and those of categorical variables were performed by the $\chi^2$ or Fisher exact test. Statistical significance was set at a 2-tailed $P$ value $<.05$.

**Results.** Thirty-eight (75%) of 51 HIV-infected children who had been revaccinated with measles, mumps, and rubella in 2005 were studied in February 2009. These 38 children were approached to volunteer for a hepatitis A vaccine efficacy study because they did not have protective antibody to hepatitis in their 2005 baseline serum samples and were offered to co-enroll in the present study. The characteristics of the 13 children who did not participate were not different from the study group in terms of sex, age, CD4 cell percentage, and duration of antiretroviral therapy at the time of revaccination, but their baseline CD4 cell percentage was higher (mean ± SD, 8.2% ± 5.2% vs 4.1% ± 4.0%; $P<.01$; data not shown). Table 1 presents the characteristics of the 38 children. Nineteen children (50%) were receiving nevirapine-based antiretroviral therapy, and the rest were receiving efavirenz-based antiretroviral therapy. Four children lived in an orphanage and were exposed to a measles outbreak in 2008, when they received additional doses of mea-

Table 2. Prevalence of Protective Antibodies to Measles, Mumps, and Rubella in Human Immunodeficiency Virus–Infected Children 1, 6, and 40 months after Measles, Mumps, and Rubella Revaccination

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of children</th>
<th>Time after revaccination</th>
<th>$P$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 month</td>
<td>6 months</td>
<td>40 months (~3 years)</td>
</tr>
<tr>
<td>Measles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) of children with protective antibody levels</td>
<td>34$^a$</td>
<td>30 (88)</td>
<td>29 (85)</td>
<td>29 (85)</td>
</tr>
<tr>
<td>Geometric mean titer, mean mIU/mL (95% CI)</td>
<td>...</td>
<td>2291 (1380–3802)</td>
<td>1414 (871–2138)</td>
<td>871 (589–1288)</td>
</tr>
<tr>
<td>Mumps</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) of children with protective antibody levels</td>
<td>38</td>
<td>32 (84)</td>
<td>25 (66)</td>
<td>23 (61)</td>
</tr>
<tr>
<td>Geometric mean titer (95% CI)</td>
<td>...</td>
<td>1:1660 (1:1175–1:2399)</td>
<td>1:1122 (1:741–1:1698)</td>
<td>1:741 (1:490–1:1122)</td>
</tr>
<tr>
<td>Rubella</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) of children with protective antibody levels</td>
<td>38</td>
<td>38 (100)</td>
<td>34 (90)</td>
<td>30 (79)</td>
</tr>
<tr>
<td>Geometric mean titer, mean IU/mL (95% CI)</td>
<td>...</td>
<td>74 (52–102)</td>
<td>45 (31–66)</td>
<td>32 (22–47)</td>
</tr>
</tbody>
</table>

**NOTE.** A measles antibody level $\geq 320$ mIU/mL was defined as a protective level, a mumps antibody of $\geq 1:500$ was defined as a protective titer, and a rubella antibody level $\geq 10$ IU/mL was defined as a protective level. CI, confidence interval.

$^a$ Four children were excluded because they received an extra dose of measles vaccine during a measles outbreak prior to this study.

$^b$ Determined by the Fisher exact test.

$^c$ Determined by the paired $t$ test.
sles vaccine as a part of the outbreak response [9]. None of the 38 children experienced any serious illness or needed hospitalization during the 40 months prior to this study.

Forty months after measles, mumps, and rubella revaccination, the prevalence of protective antibodies was 85% for measles, 61% for mumps, and 79% for rubella. The prevalence decreased significantly at month 40, compared with months 1 and 6, after revaccination for mumps and rubella, but not for measles (Table 2). Of the 4 children who received additional second doses of measles vaccine during the measles outbreak in July 2008, all had protective antibody. At month 40, a total of 2 children who had been seropositive for measles at 6 months after revaccination became seronegative (the levels at month 6 were 888 and 3953 mIU/mL). Two other children who had no protective measles antibody at month 6 were found to have protective anti-measles antibody at month 40. Mumps antibody levels increased in 2 other children (from 1:190 to 1:599 in one child and from 1:142 to 1:712 in the other). No subject demonstrated an increase in rubella antibody levels.

The median annual decay rates for protective antibodies were −12.2% (interquartile range [IQR], −1.9% to −33.8%), −24.8% (IQR, −5.4% to −54.5%), and −16.4% (IQR, −2.2% to −23.9%) in the first 5 months after revaccination for measles, mumps, and rubella, respectively. The annual decay rate decreases in the subsequent month up to year 3. They were −2.7% (IQR, −1.2% to −4.6%), −3.6% (IQR, −0.5% to −6.2%), and −2.8% (IQR, −0.5% to −4.2%) for measles, mumps, and rubella, respectively.

**Discussion.** This study demonstrated the persistence of antibodies to measles, mumps, and rubella among HIV-infected children who achieved immune recovery after antiretroviral therapy for at least 40 months after revaccination. The prevalence of protective antibodies was 85% for measles, 61% for mumps, and 79% for rubella. There was a significant decrease in geometric mean titers over time, but the proportion of children with protective antibodies remained unchanged from 6 months to 40 months for measles.

Our study showed higher prevalence of protective antibody against measles after revaccination (85% at 40 months) versus those in 15 HIV-infected Swedish children (60% at 1 year) [10] and 18 HIV-infected American children (73% at 1 year) [11]. Although all children in these 3 studies were in immune recovery after having received antiretroviral therapy for a similar period of time (2–2.5 years), at the time of the study, 97% of our children were experiencing HIV suppression, compared with 51%–66% and 79% of children in the Swedish and US studies, respectively.

In our study the proportion of children with protective antibody to mumps slightly decreased from 66% to 61% three years after revaccination. These percentages are slightly lower than in the normal population, for which seropositivity to mumps is 74%–77% four to 20 years after vaccination [12, 13].

We found that the percentage of children with protective antibody against rubella decreased from 90% at 6 months to 79% at 3 years after revaccination. The persistence of rubella antibody after measles, mumps, and rubella vaccination in the normal population is variable. Studies from Luxembourg and Finland revealed that >95% of vaccine recipients were still seropositive for rubella 7–20 years after vaccination [12, 14], whereas a study of American children reported the decrease in seropositivity rate from 90% among 4–6-year-old children to 67% among 11–13-year-old children [15]. Although rubella is a rather mild disease, infection during pregnancy could lead to serious congenital anomalies. Proper counseling of older children and consideration of additional rubella vaccination when they reach adolescence may be warranted.

In conclusion, we have documented the persistence over a period of 3 years of measles, mumps, and rubella protective antibodies in HIV-infected children with immune recovery after antiretroviral therapy. From our data, it appears that revaccination of all HIV-infected children with measles, mumps, and rubella vaccine after immune recovery is indicated especially in countries with a high prevalence of measles. Nevertheless, only longer follow-up of revaccinated HIV-infected children could clarify how often the revaccination should be scheduled in these patients.

**Acknowledgments**

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**Potential conflicts of interest.** All authors: no conflicts.

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