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Similar Antibody Levels in 3-Year-Old Children Vaccinated Against Measles, Mumps, and Rubella at the Age of 12 Months or 18 Months

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Background. Measles-mumps-rubella (MMR) vaccinations have been offered to Finnish children at 14–18 months and 6 years of age. In May 2011, the recommended age for the first vaccine dose was lowered to 12 months because of the European measles epidemic.

Methods. Fingerpint capillary blood samples were collected from 3-year-old Finnish children vaccinated once with MMR vaccine at 11–19 months of age. The immunoglobulin G (IgG) antibodies to all 3 MMR antigens were measured with enzyme-linked immunosorbent assay. Neutralizing antibodies and the avidity of antibodies were measured for measles virus.

Results. From April through October 2013, 187 children were enrolled. Equally high proportions of the samples were seropositive for measles virus, mumps virus, or rubella virus antibodies, and there were no significant differences in the IgG antibody concentrations in children vaccinated at 11–13 months of age, compared with those vaccinated at 17–19 months of age. However, among children vaccinated at 11–13 months of age, boys had lower antibody concentrations than girls. Neutralizing measles virus antibody titers were above the threshold for protective immunity in all 78 samples analyzed. The measles virus antibody avidity indexes were high for all children.

Conclusions. MMR induces similar antibody responses in 12-month-old children as compared to 18-month-old children, but in boys increasing age appears to improve the antibody responses.

Keywords. MMR; measles; mumps; rubella; vaccine; antibody; immune response; immunization; vaccination schedule.

Measles-mumps-rubella (MMR) vaccinations were included in Finland’s national immunization program in 1982 with a 2-dose vaccine schedule, in which the first dose was recommended to be given at 14–18 months of age and the second at 6 years of age. Measles vaccine was first introduced in 1975, administered at the age of 14 months. As a result of consistently high vaccination coverage (>95%) since 1987, endemic diseases targeted by MMR were eliminated by 1995 [1]. Since the elimination, only 1–5 imported measles cases have been reported annually. Although MMR vaccines have been available in most European countries for >30 years, measles and rubella epidemics still occur, mostly among unvaccinated populations [2]. The number of European measles cases reached a new peak in 2011, when >30 000 measles cases in 29 countries were reported to the European Centre for Disease Prevention and Control [3].

In the same year, an increased number of measles cases (n = 27) was also reported in Finland [4].

The recommended age for the first MMR vaccination in Europe varies from 9 to 18 months, according to the national programs in different countries. The optimal timing for the first MMR vaccination would be as soon as the child’s immune system is mature enough to effectively respond to the vaccine and when maternal antibodies have waned and no longer interfere with the vaccine response. Previous studies have reported that if the first dose of MMR vaccine was given before or at the age of 11 months, the proportion of children producing antibodies was lower [5–7], the vaccine induced a lower antibody response [8, 9], and the efficacy of the vaccine was inferior [10], compared with findings for children who received the vaccine at the age of ≥12 months.

It is known that measles virus infection induces higher antibody concentrations than measles vaccine [11] and that the persistence of vaccine-induced antibodies may be shorter than that for measles vaccine [9, 12–16]. The current vaccine recommendations are mostly based on data derived from the prevaccine era, when the mothers of the study children frequently had anti–measles virus antibodies induced by natural measles virus infection. In many developed countries, including Finland, where MMR vaccines have been included in the national immunization program for 3 decades, with high vaccination coverage, a large proportion of the women of childbearing age...
have antibodies to measles virus induced by vaccination, not by natural infection.

In May 2011, the National Institute for Health and Welfare in Finland lowered the recommended age from 14 to 18 months to 12 months because of measles outbreaks in Europe. Previously, the first dose of the MMR vaccine was most commonly administered at 18 months of age at a regular visit to a child healthcare clinic. The main aim of this observational study was to investigate whether differences exist in the levels of antibodies induced by the MMR vaccine, especially those against measles virus, in children vaccinated at the age of 12 months (range, 11–13 months) and 18 months (range, 17–19 months).

**MATERIALS AND METHODS**

**Study Group**

Children born from November 2009 through October 2010 were recruited to the study from 2 cities in Finland (Helsinki and Tampere) in 2 phases; from April to June 2013 and from August to October 2013. Inclusion criteria were age of 34–44 months, receipt of 1 dose of the MMR vaccine between the ages of 11 and 20 months, understanding of Finnish by at least one of the child’s parents, and parental written informed consent. Exclusion criteria were fever (temperature, ≥38°C) within 72 hours before sample collection, receipt of immunosuppressive treatment after MMR vaccination, and a history of measles virus infection. The parents of the participants completed a questionnaire on the vaccination history (validated from the vaccination certificate of the child) and medical history of the child, as well as birth year and medical history of the parents. The study protocol has received a favorable opinion from the ethics committee for gynecology and obstetrics, pediatrics, and psychiatry of the Helsinki and Uusimaa Hospital District (198/13/03/2012). The vaccination history of the children participating in the study was confirmed from the national vaccination registry (THL/823/6.0200/2014). The M-M-RVaxPro vaccine (Sanofi Pasteur MSD), which contains the Edmonston strain of measles virus, the Jeryl Lynn strain of mumps virus, and the Wistar RA27/3 strain of rubella virus, was the MMR vaccine used in the national immunization program from May 2010 to March 2012.

**Sample Collection**

Capillary blood samples were collected by making a small incision to the fingertip with a lancet and by drawing a volume of 500 µL to 1 mL of blood into a microtube containing gel for serum extraction. The blood samples were kept at room temperature for 30 minutes, after which serum was separated by centrifugation for 1 minute 30 seconds at 10 000g. The serum samples were stored at −20°C.

**Measurement of Immunoglobulin G (IgG) Concentrations With an Enzyme-Linked Immunosorbent Assay (ELISA)**

IgG antibodies to the measles virus, mumps virus, and rubella virus strains in the MMR vaccine were measured by using commercial ELISAs (Enzygnost, Siemens, Germany) according to the manufacturer’s instructions. The quantitative cutoff was ≥150 mIU/mL for measles virus IgG, a titer of ≥230 for mumps virus IgG, and ≥4 IU/mL for rubella virus IgG, as determined by the manufacturer. Values equal to half of the concentration of the cutoff were assigned to samples containing antibody concentrations lower than the cutoff. Seropositivity was defined as an antibody concentration of ≥325 mIU/mL to measles virus, a titer of ≥570 for mumps virus, and a concentration of ≥7 IU/mL for rubella virus. Samples with equivocal IgG findings were not considered seropositive. This more stringent definition of seropositivity was used to compare the proportions of seropositive samples in children vaccinated at the age of 11–13 or 17–19 months. Protective-threshold ELISA values for IgG to measles, mumps, and rubella viruses have not been established.

**Avidity Determination of IgG Antibodies Against Measles Virus**

The avidity of measles virus antibodies was measured with the Euroimmun ELISA kit (Lübeck, Germany) according to the manufacturer’s instructions. The relative avidity index was calculated as a percentage \([\text{IOD of urea-treated specimen}/\text{IOD of untreated specimen}] \times 100\). Avidity index values of <40% were considered to indicate low avidity, values of 40%–60% indicated intermediate avidity, and values of >60% indicated high avidity of the antibodies in a sample.

**Plaque Reduction Neutralization Test (PRNT) for Anti–Measles Virus Antibodies**

The functional activity of anti–measles virus antibodies was measured using a modified plaque reduction neutralization test (PRNT) \([17]\), with four-fold dilutions of sera in duplicate from 1:2 to 1:128 dilutions. In short, sera were mixed with an equal volume of the defined amount (20–30) vaccine virus (genotype A) and incubated for 1 hour at +36°C and 5% CO₂. The mixture was incubated on 24-well plates (Falcon) with VeroSLAM cells (Robert Koch institute/WHO) at +36°C and 5% CO₂ for 30 minutes. Agarose with 1x DMEM (Dulbecco’s Modified Eagle Medium) and 4% fetal bovine serum was added to the wells and the plates were incubated for 6 days at +36°C and 5% CO₂. The plates were fixed with 30% Formalin and stained with crystal violet. The assay was standardized using the 3rd World Health Organization International Standard for Anti-Measles (National Institute for Biological Standards and Control code 97/648). An antibody concentration of ≥120 mIU/mL was considered protective \([18]\). Samples that had a neutralizing antibody titer higher than what could be accurately determined with the highest sample dilution used in the analysis were assigned a value of 1500 mIU/mL.

**Statistical Analysis**

The primary hypothesis of the study was that the log-transformed antibody concentrations to MMR vaccine antigens are similar in children vaccinated at 12 or 18 months of age. Based on the sample size calculation, we estimated that at least 70 participants (equal proportions of children vaccinated at 12
RESULTS

Profile of the Study Population

Overall, 187 children (97 boys and 90 girls) were enrolled, and all had received 1 dose of M-M-RVaxPro. The majority of the children had been immunized at the age of 11–13 months or 17–19 months (Table 1 and Figure 1). Boys were similar to girls in regard to age at immunization, time from immunization to blood sample collection, and age at blood sample collection (Table 1). The mean age of the children was 3 years, 3 months at the time of blood sample collection, and the mean interval between immunization and blood sample collection was 2 years (Figure 1). Of the 181 of 187 mothers who reported their birth-day and history of measles virus infection, 48 were born before 1975, the year when measles vaccine was introduced in the Finnish immunization program, and 92 were born after 1974 but before 1982, when MMR vaccine was introduced. None of the 41 mothers born after 1981 reported a history of measles virus infection, but 5 of 92 mothers born in 1975–1981 and 14 of 48 born before 1975 (11 of 37 born before 1974) reported having had measles.

Seropositivity to MMR Antigens

All 187 serum samples contained detectable antibodies to rubella virus (>4 IU/mL); all but 2 samples had antibodies to measles virus (≥150 mIU/mL), but in as many as 29 samples (16%) anti–mumps virus antibodies were below the limit of detection (titer <231). Equally high proportions of the children immunized at the age of 11–13 months and at

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>11–13 mo</th>
<th>14–16 mo</th>
<th>17–19 mo</th>
<th>( P ) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at immunization, mo, mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>12.4 ± 0.4</td>
<td>15.2 ± 0.9</td>
<td>18.3 ± 0.6</td>
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<tr>
<td>Among boys</td>
<td>12.4 ± 0.5</td>
<td>15.0 ± 0.8</td>
<td>18.4 ± 0.6</td>
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<tr>
<td>Among girls</td>
<td>12.4 ± 0.4</td>
<td>15.4 ± 0.9</td>
<td>18.3 ± 0.7</td>
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<tr>
<td>Participating children, no.</td>
<td>85</td>
<td>32</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>42</td>
<td>15</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>43</td>
<td>17</td>
<td>30</td>
<td></td>
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<tr>
<td>Age at blood sample collection, mo, mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>37 ± 1.6</td>
<td>39 ± 1.8</td>
<td>40 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Among boys</td>
<td>37 ± 1.8</td>
<td>39 ± 1.8</td>
<td>40 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Among girls</td>
<td>37 ± 1.5</td>
<td>39 ± 1.8</td>
<td>40 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Interval from immunization to blood sample collection, mo, mean ±SD</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>25 ± 1.6</td>
<td>24 ± 1.7</td>
<td>22 ± 1.6</td>
<td></td>
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<tr>
<td>Among boys</td>
<td>25 ± 1.8</td>
<td>24 ± 1.9</td>
<td>22 ± 1.5</td>
<td>NS</td>
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<tr>
<td>Among girls</td>
<td>25 ± 1.4</td>
<td>23 ± 1.4</td>
<td>22 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Anti–measles virus IgG GMC (95% CI)</td>
<td>2436 (1894–3134)</td>
<td>2835 (1990–4038)</td>
<td>2772 (2150–3574)</td>
<td>NS</td>
</tr>
<tr>
<td>Anti–mumps virus IgG GMT (95% CI)</td>
<td>942 (731–1214)</td>
<td>811 (505–1301)</td>
<td>817 (619–1078)</td>
<td>NS</td>
</tr>
<tr>
<td>Anti–rubella virus IgG GMC (95% CI)</td>
<td>59 (50–70)</td>
<td>57 (44–74)</td>
<td>73 (60–88)</td>
<td>NS</td>
</tr>
<tr>
<td>Anti–measles virus IgG avidity index, %, mean ± SD</td>
<td>91 ± 5.8</td>
<td>93 ± 5.0</td>
<td>94 ± 6.0</td>
<td>.0054</td>
</tr>
<tr>
<td>Anti–measles virus PRNT-based GMC (95% CI)</td>
<td>887 (715–1100)c</td>
<td>NA</td>
<td>1180 (1001–1391)d</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; GMC, geometric mean concentration; GMT, geometric mean titer; IgG, immunoglobulin G; NA, not available; NS, not significant; PRNT, plaque reduction neutralization titer; SD, standard deviation.

a By the unpaired Student t test (assuming unequal variances) for comparison of data from children aged 11–13 months to data from children aged 17–19 months.

b Measured in samples from 84 of 85 children immunized at 11–13 months of age.

c Measured in samples from 40 children immunized at 11.6–12.3 months of age.

d Measured in samples from 38 children immunized at 17.3–18.5 months of age.
17–19 months had detectable antibodies to measles virus (98% vs 97%), rubella virus (100%), or mumps virus (89% vs 81%; \(P = \text{NS, by the Fisher exact test}\)). The proportions of seropositive antibody concentrations to measles virus (≥325 mIU/mL), mumps virus (titer ≥570), and rubella virus (≥7 IU/mL) were also similar in children immunized with MMR vaccine at the age of 11–13, 14–16, or 17–19 months (Figure 2).

IgG Antibody Concentrations to MMR Vaccine Antigens
The geometric mean IgG antibody concentrations to measles, mumps, and rubella viruses measured with ELISA were similar in children immunized at the age of 11–13, 14–16, or 17–19 months (Figure 3 and Table 1). No significant differences (based on the unpaired Student \(t\) test, assuming unequal variances) were seen in geometric mean IgG concentrations to any of the MMR vaccine antigens between children immunized at 11–13 and 17–19 months of age. The geometric mean concentrations of antibody to measles virus were similar in children born to mothers with a self-reported history of measles (2834 mIU/mL; \(n = 20; 13\) boys) and in children whose mothers did not report having had measles (2514 mIU/mL; \(n = 167; 83\) boys). The mean age of the children was 15 months in both groups. No association was seen between the age at immunization and the concentration of antibodies to measles, mumps, or rubella virus (Figure 5).

Avidity of Anti–Measles Virus IgG Antibodies
All serum samples had high-avidity (avidity index, >60%) anti–measles virus antibodies (Table 1 and Figure 4A). The mean avidity index of children immunized at 17–19 months of age was slightly higher than that in children immunized at 11–13 months of age (94% vs 91%; Table 1 and Figure 4A). A significant positive correlation was observed between the avidity and the concentration of anti–measles virus IgG antibodies (\(r = 0.52; \ P < .0001\), by Pearson correlation). A weak but statistically significant positive correlation was observed between increasing age at immunization and avidity of anti–measles virus antibodies (\(r = 0.21; \ P < .005\), by Pearson correlation; Figure 5).

Neutralizing Anti–Measles Virus Antibodies
All tested samples of the children immunized at the age of 12 or 18 months had neutralizing anti–measles virus antibodies above...
the threshold considered to indicate protective immunity (PRNT titer, >120 mIU/mL). The PRNT-based geometric mean titer was similar in children immunized at 12 months (887 mIU/mL) and in children immunized at 18 months (1180 mIU/mL; Table 1 and Figure 4B).

Effect of Sex on the Antibody Concentrations

The serum concentrations of IgG against measles, mumps, and rubella viruses were significantly higher in girls as compared to boys immunized at 11–13 months of age but not in those immunized at 17–19 months of age (Figure 6). The geometric mean IgG concentrations in girls as compared to boys immunized at 11–13 months of age were 2-fold for measles virus (3450 mIU/mL vs 1720 mIU/mL) and mumps virus (1330 mIU/mL vs 660 mIU/mL) and 1.5-fold for rubella virus (73 vs 47 IU/mL). A trend of positive correlation was seen in boys but not girls between increasing age at immunization and a higher concentration of IgG antibodies to measles virus (r = 0.23; P = .024, by Pearson correlation) and rubella virus (r = 0.20; P = .002) and a higher avidity of anti–measles virus antibodies (r = 0.28; P = .005). The proportions of samples seropositive for anti–measles virus, anti–mumps virus, and anti–rubella virus were similar in 11–13-month–old boys, compared with those in girls (P not significant, by the Fisher exact test). The mean avidity index of anti–measles virus antibodies was equally high (>90%) in girls and boys immunized at 11–13 months or 17–19 months of age. The geometric mean concentration of neutralizing anti–measles virus antibodies was lower in boys immunized at 12 months (648 mIU/mL), compared with boys immunized at 18 months (800 mIU/mL).
(1270 mIU/mL) and with girls immunized at 12 months (1200 mIU/mL; Figure 6).

**DISCUSSION**

In this study, we report persistence of high antibody concentrations to MMR vaccine antigens in 3-year old children immunized with 1 dose of the vaccine at 12 or 18 months of age. The concentrations of IgG antibodies to the MMR vaccine components were equally high in children immunized at the age of 12 or 18 months, yet we detected lower concentrations in boys immunized at 12 months. All children had high-avidity IgG antibodies. Levels of neutralizing antibodies were above the protective threshold for measles virus in all children, although the quantitative results were lower for boys immunized at 12 months.

Previous studies have indicated that vaccination at an older age tends to increase the antibody response to measles virus [20–23]. A positive linear relationship between age at immunization and anti-measles virus antibody titer was seen in 4–16-year-old Canadian children [24]. Reduced immune responses to measles virus in children younger than 6 months have been explained on the basis of the immaturity of the immune system [20, 25] and the presence of maternally derived anti-measles virus antibodies that interfere and weaken the immune response [26, 27]. Previous findings by Gans et al and Nair et al indicate that the capacity of the immune system to generate humoral responses to measles vaccine is impaired in 6-month-old infants even in the absence of maternal antibodies, suggesting immaturity of B-cell function, while (in the absence of maternal antibodies) the humoral response to the vaccine in 9-month-old infants is equivalent to that in 12-month-old infants [21–23]. De Serres et al reported that, during a measles outbreak in Canada in 2011, the number of measles cases observed among teenaged
children who had received their first MMR vaccine of a 2-dose schedule at 12 months was higher (38 of 660 children) than among the children who received their first vaccine dose at >15 months (4 of 198 children), resulting in a higher risk ratio for children first vaccinated at 12 months [28]. It was suggested that interference of maternal antibodies could explain their observation, because many of the mothers were likely to have encountered the wild virus [28], in which case the finding might not apply to children born to vaccinated mothers. In countries such as Finland, where the vaccine coverage has been consistently high for >3 decades and immunity is not boosted by exposure to the natural virus, antibody concentrations and avidity wane over time, even in individuals vaccinated twice with MMR vaccine [14–16, 29]. The majority of the children in this study were born to mothers born after 1974 and thus vaccinated, which means that the maternally received anti–measles virus antibodies in most of the children studied here have likely been induced by vaccination. Thus, the data from our study indicate that, in a population with high vaccination coverage, maternally transferred antibodies do not interfere with the immune response of the children if the vaccine is administered at the age of ≥11 months. In fact, most infants born to vaccinated mothers lack detectable antibodies to measles virus by 6 months of age [29]. The estimated age at which a child loses the protection by maternal antibodies and becomes susceptible to measles can be as low as 3.3 months in highly vaccinated populations [13].

A somewhat surprising secondary finding of our study was that the concentrations of antibody against measles, mumps, and rubella viruses were lower in boys as compared to girls vaccinated at 12 months of age. In a comprehensive review article, Klein et al concluded that clinical data support a role for sex in the response to viral vaccines [30]. Previous serological studies have also shown that sex and age at vaccination influence the immune responsiveness to MMR vaccination. Miller et al reported that the antibody concentrations to measles virus 4 years after vaccination were 2-fold higher in girls vaccinated after 14 months of age, compared with findings for girls vaccinated before 14 months of age, whereas in boys the antibody concentrations showed no age effect [31]. Miller et al also found that the anti–measles virus antibody levels were significantly higher (by 1.5-fold) in girls as compared to boys vaccinated after 14 months of age [31]. Mossong et al found that anti–measles virus antibody

Figure 6. A–C, Anti–measles virus (A), anti–mumps virus (B), and anti–rubella virus (C) immunoglobulin G (IgG) antibody levels measured by an enzyme-linked immunosorbent assay in serum samples from 3-year-old children (82 boys and 70 girls) immunized at the age of 11–13 or 17–19 months. D, Neutralizing anti–measles virus antibody levels were measured by the plaque reduction neutralization test (PRNT) in 46 boys and 32 girls immunized at 12 or 18 months of age. Statistically significant differences were seen in geometric mean antibody concentrations between girls and boys immunized at 11–13 months of age and between boys immunized at 11–13 and 17–19 months of age. *P < .05, **P < .01, ***P < .001, by the unpaired, 2-tailed Student t test, assuming unequal variances.
titers in girls were 13% higher than those in boys [24]. In our study, the mean IgG concentrations to mumps and rubella viruses but not measles virus were slightly although not significantly higher in girls as compared to boys also when the children were immunized at 17–18 months of age. Davidkin et al found that girls and boys who received their first MMR vaccine dose at the age of 14–18 months had similar antibody levels soon after the second vaccine dose at the age of 6 years; however, 8 and 15 years after the second dose, the antibody levels to measles and mumps viruses were significantly higher in female vaccines, compared with male vaccines [12].

Martins et al studied the measles virus–specific serum antibody levels of children in Guinea-Bissau before immunization and found that girls lost maternal anti–measles virus antibodies more rapidly than boys; at 4.5 months of age, girls were less likely than boys to have protective maternal antibody levels [32]. Niccol et al, in contrast to Martins et al, observed no significant differences according to sex in maternal antibody concentrations to measles, mumps, or rubella virus in Swiss infants [33]. It would be convenient to hypothesize that, if maternal antibodies wane at an earlier age in girls than in boys, girls would have less interference with vaccination than boys of the same age. This could explain the higher antibody concentrations seen in girls as compared to boys immunized at 12 months of age in this study. However, it is highly unlikely that the children of this study would have had maternal antibodies left at the age of 11–13 months. Furthermore, we found that the measles IgG antibody concentrations measured in children born to mothers with a self-reported history of measles were equally high as those in the rest of the study children. This study was primarily designed to compare the immunogenicity of the MMR vaccine in children immunized at the age of 12 or 18 months. Nevertheless, despite the relatively small sample sizes, we were able to detect significant differences with regard to age at immunization in the immunogenicity of the MMR vaccine between sexes. This finding indicates that the biological differences associated with sex may affect immune responses to MMR vaccination, even though the mechanisms causing these differences remain unexplained.

The main conclusion of our study is that the MMR vaccine induces high concentrations of high-avidity antibodies to measles virus, with neutralizing antibody titers well above the protective threshold in both girls and boys immunized at the age of 12 months. Even though increasing age at immunization appeared to improve the antibody responses in boys, the concentration of neutralizing anti–measles virus antibodies was well above the protective threshold in all children at the age of 3 years. The immunity to measles, mumps, and rubella will be further boosted with the second dose of MMR vaccine, given at the age of 6 years. The potential benefit of better immunogenicity of the first vaccine dose when delivered at an older age should be carefully balanced against the additional risk of acquiring measles virus infection before children are due to receive the first vaccine dose. As an increasing proportion of the mothers will have been immunized in childhood, newborns will have lower maternal antibody levels and are likely to become susceptible earlier. In the current epidemiologic situation, in which measles epidemics still occur in Europe, MMR vaccination at 12 months instead of 18 months is recommended to narrow the unprotected window during which maternal antibodies have disappeared and the child does not yet have vaccine-induced immunity. Further follow-up investigations, including analysis of clinical protection, both for vaccine-specific and nonspecific outcomes [34], and of potential sex-based differences, is warranted.

Notes

Acknowledgments. We thank the children and families who participated in this study; study nurses Teija Jaakkola and Päivi Siren, for their valuable contributions to the implementation of the study; and Julka Jokinen and Jonas Sundman, for their helpful advice in the design of the study.

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Potential conflicts of interest. M. M. has received funding and worked in collaboration with GlaxoSmithKline Vaccines in studies of pneumococcal protein vaccine antigens. A. A. P. and R. K. S. are investigators in studies for which the National Institute for Health and Welfare has received research funding from GlaxoSmithKline Vaccines. O. V. has been an employee of AstraZeneca R&D since August 2014 and has received salary from AstraZeneca. AstraZeneca has not contributed to the present study. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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