Measles–Mumps–Rubella Revaccination; 18 Months vs. 4–6 Years of Age: Potential Impacts of Schedule Changes

by Mohammed Jafar Saffar,1 Golam Reza Fathpour,1 Mohammed Reza Parsaei,2 Abolghasem Ajami,3 Ali Reza Khalilian,4 Jalil Shojaei,2 and Hana Saffar5

1Department of Pediatric Infectious Diseases, Bouali-Cina Hospital, Pasdaran Boulevard, Mazandaran University of Medical Sciences, Sari-Iran
2Deputy of Health, provincial Center for Diseases Control and Prevention, Mazandaran Medical Sciences University, Sari, Iran
3Molecular and Cell Biology Research Center, Department of Microbiology and Immunology, Mazandaran Medical Sciences University, Sari, Iran
4Department of Biostatics, Mazandaran Medical Sciences University, Sari, Iran
5Pathology resident, Pathology Department, Sharaeiti Hospital Tehran Medical Sciences University, Tehran, Iran

Correspondence: Mohammed Jafar Saffar, Pediatric infectious diseases ward, Bouali-Cina hospital, Pasdaran Boulevard, Mazandaran University of Medical Sciences. Sari-Iran. E-mail: <saffar@softhome.net>.

Summary

Objective: The policy of administering the second dose of measles–mumps–rubella (MMR) vaccine (MMR2) has recently changed in Iran, at age 1.5 years instead of 4–6 years previously. The effects of such a change on the immune status of the individual are evaluated in this study.

Methods: Totally 249 and 228 children aged 18 months and 4- to 6-year-olds, respectively, with a documented receipt of primary MMR vaccine at the age of ≥1 year were enrolled. Before, and 4–6 weeks after MMR2 administration, anti-MMR IgG antibody levels were measured using ELISA method. IgM antibody levels were also assessed in measles–rubella seronegative children that responded to MMR2. Collected data for each component from both age groups were compared by using Fischer's exact probability and chi-square tests.

Results: Before revaccination, measles seroimmunity rate was similar between the two groups, but rates to mumps and rubella were significantly higher in younger children—measles: 74 vs. 78.3%; mumps: 82.3 vs. 68.4% and rubella: 75% vs. 67%, respectively. After administration of MMR2, all seroimmune subjects were IgG boosted. Except for rubella, older seronegative children showed significantly higher seroconversion rate to MMR2 and seroprevalence rates increased in vaccinees—measles: 98.2 vs. 94%, mumps: 97 vs. 94.4% and rubella: 87 vs. 92.4%, respectively. Only few measles–rubella seronegative children showed IgM response to MMR2. Conclusion: This study showed that the majority of younger children were susceptible to MMR infection before revaccination. Earlier age policy provides more protection against MMR in preschool-aged children. Rubella strain seems to be less potent than reported.

Key words: MMR vaccination, schedule change, MMR2, MMR revaccination.

Introduction

According to World Health Organization (WHO) and other recommendations, all children should receive a second dose of measles–mumps–rubella (MMR) vaccine (MMR2) to immunize them against primary vaccine failure (PVF) [1–3]. In addition, boosting antibody titres of primary responder may provide enhanced protection against secondary vaccine failure (SVF) [4–6]. High vaccination coverage with two doses of MMR vaccine after 1 year of age is needed to achieve satisfactory levels of immunity to interrupt the virus transmission [1, 7, 8]. Globally,
the most common time-point for delivering the MMR2 is at school entry (4–6 years of age), however, it may be given as early as 1 month after the first dose, depending on the local epidemiological and operational considerations [9–11]. Some countries now recommend two doses of MMR immunization before 2 years of age, in order to achieve better protection in young children, increase coverage and simplify the existing immunization schedules [1, 12–14].

Since March 2004, in Iran, two-dose monovalent measles vaccination schedule was replaced by two-dose MMR given at the age of 1 and 4–6 years. Despite high levels of vaccination coverage, this policy is recently changed to bring forward the age of the second dose to 1.5 years.

In the current study, we evaluated the status of anti-MMR seroimmunity before MMR2 in two age groups: 1.5 and 4–6 years, with well-documented primary MMR vaccination. Also, their immune responses to revaccination were assessed. To determine the PVF and SVF rates against measles and rubella in seronegative children who did respond to MMR2, anti-MMR-specific IgM antibodies were also measured.

**Subjects and Methods**

This study was conducted from January to November 2009 at the Well Baby Clinics affiliated to Mazandaran Medical Sciences University, North of Iran. The study subjects were healthy children aged ≥1.5 and 4–6 years calling to receive their scheduled MMR2. Children with documented primary MMR vaccination at ≥1 year of age were recruited consecutively. None of enrolled children had history of measles, mumps and rubella diseases or exposure, or any contraindication to MMR vaccination. Informed consent was obtained from the parent of each child before enrollment. Just before and 4–6 weeks after receiving MMR2 vaccine (revaccination) currently being used in Iran (combined MMR vaccine, Razi institute, Iran; measles component: Takahashi attenuated approximately 1000 IND50), sera were prepared and stored at −20°C until assayed at the university laboratory. Anti-MMR-specific IgG antibodies were determined quantitatively by ELISA method, using quantifiable MMR IgG ELISA kits (Euroimmune Medizinische Laboradiagnostika AG). Based on the manufacturer’s instructions, for this study the cut-off titre values of ≥275 mIU ml⁻¹, ≥22 U ml⁻¹ and ≥11 IU ml⁻¹ were considered positive for measles, mumps and rubella, respectively. For each component the numbers of the seronegative children were calculated for each age group. Seroconversion was defined as changing seronegative sera to positive. For each age group, mean concentration antibodies titres (MCTs) at before and after revaccination were calculated. To determine the ratio of PVF among initially seronegative children who responded to MMR2, measles- and rubella-specific IgM antibodies were assessed by using semi-quantitative ELISA kits (Euroimmune Medizinische Laboradiagnostika AG) according to the manufacturer’s instructions. Fisher’s exact probability test and chi-square test were used to compare collected data for components between the two age groups. The p-value of <0.05 was considered significant.

**Results**

During the study period, a total of 492 children were recruited and 477 analyzed in two age groups: 249 (52.2%) in 1.5 years age group [126 boys, mean age 19.11 (SD 3.10) months], and 228 (47.8%) in 4–6 years age group [113 boys, mean age 64.50 (SD 11.33) months].

**Measles immunity status**

Before the administration of MMR2, seroprevalence rate difference was not significant between the two age groups: 74 vs. 78.3%, p = 0.19, but MCA titres were significantly higher in children of 1.5 years age group: 890 (522) mIU ml⁻¹, than in children of 4–6 years age group: 1210 (684) mIU ml⁻¹, p = 0.01. Of 65 children, 50 (77%) seronegative 1.5-year-olds responded to revaccination and seroconverted compared with 44 of 48 (92%) 4- to 6-year-olds, p = 0.04. However, a statistically significantly higher proportion of older children become seroprotected compared with younger ones: 98.2 vs. 94%, p = 0.01, respectively. MCA levels achieved after MMR2 was not significantly different between two groups: 279 (1236) vs. 3124 (1479) mIU ml⁻¹, p = non-significant, respectively (Table 1).

**Mumps immunity status**

Seroprevalence rates were significantly higher in children aged 1.5 years than 4–6 years with a similar MCA levels: 82.3 vs. 68.4, p = 0.0004; 57 (27) vs. 51 (22) U ml⁻¹, respectively. Significantly more seronegative older children responded to MMR2 (65/72) than younger children (30/44) with seroprevalence rate of 97 vs. 94.4%, p = 0.17. Also, IgG levels were boosted in both age groups (Table 1).

**Rubella immunity status**

Seroprevalence rate for rubella with a similar MCA levels was significantly higher in younger than in older children at before revaccination: 75 vs. 66%, p = 0.02; 49 (18) vs. 47 (21) IU ml⁻¹, respectively.

After MMR2, although statistically non-significant, more younger seronegative children, seroconverted compared with older children: 43 of 62 (70%) vs. 48 of 78 (62%), p = 0.33, respectively.
Seroimmunity rates between the two groups were statistically significant: 92.4 vs. 87%, \( p = 0.01 \). All initially immune vaccinees were IgG boosted, with a similar MCA levels of 123 (52) vs. 120 (50) IU ml\(^{-1}\), respectively (Table 1).

### Discussion

The results of this study showed that at before the second dose of MMR administration, the IgG antibodies levels of a relatively higher number of children with a primary MMR vaccination at the age ≥1 years were below the putative value of protection against all three components of MMR vaccine. With vaccination the IgG antibodies titres were boosted, and the numbers of seroprotected vaccinees increased significantly. Also, findings indicated that earlier age revaccination provides higher immunity levels against MMR infections in Iranian pre-school aged children with a minor reduction in immunity among population.

Although there was no significant difference between the two groups regarding measles seroprevalence rate at before \( MMR_2 \), the difference was significant for mumps and rubella. These rates of seroimmunity are lower than expected [15–17] and put approximately a quarter of younger children at risk of MMR viruses, especially measles infection during pre-school years. Results of many serological studies indicated that MMR vaccination at ≥1 years of age provides >90 to 95% immunity against all three viruses and it may persist for many months to years [1, 2, 15–17] depending on the vaccine–virus strains [15–17]. In a USA study, the seroimmunity levels of children aged 4–6 years who had been MMR vaccinated at the age of 15–17 months were 90–93%, 93–96% and 90% before \( MMR_2 \) vaccination for MMR, respectively [10]. These rates for 1 and 2–4 years post primary MMR vaccination of infants aged 1 and ≥1–1.5 years were 83.6, 77.6 and 100% [12], and 80.5, 76.7 and 97.6% [18], respectively. In an earlier immunogenicity study of all components of MMR vaccine administered at ≥1 year of age in Iran, these levels were 90.5, 82 and 53% [19], respectively. The main reason for these relatively high levels of susceptibility to MMR viruses among both age groups, especially the younger children, is unclear. High rate of PVF with less potent vaccine due to inadequate cold chain or poor quality control during vaccine production, SVF with a duration of immunity shorter than vaccine used in other

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#### Table 1

**MMR seroimmune status in children of two age groups (1.5 to 4–6 years) at before \( MMR_2 \) and their immune response to \( MMR \) revaccination**

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- **Measles**
  - Seroprevalence rates
    - Before (%): 184 (74) vs. 180 (78.9), 0.09
    - After (%): 234 (94.4) vs. 224 (98.2), 0.01
  - Seronegative response rate (%): 50/65 (77) vs. 44/48 (91.7), 0.04
  - MCT levels (SD) (mIU ml\(^{-1}\))
    - Before: 1210 (684) vs. 890 (522), 0.01
    - After: 2793 (1216) vs. 3124 (1479), NS

- **Mumps**
  - Seroprevalence rates
    - Before (%): 205 (82.3) vs. 156 (68.4), 0.004
    - After (%): 235 (94.4) vs. 221 (97), 0.17
  - Seronegative response rate (%): 30/44 (68) vs. 65/72 (90.3), 0.002
  - MCT levels (SD) (U ml\(^{-1}\))
    - Before: 57 (27) vs. 51 (22), NS
    - After: 126 (55) vs. 112 (44), NS

- **Rubella**
  - Seroprevalence rates
    - Before (%): 187 (75) vs. 150 (66), 0.02
    - After (%): 230 (92.4) vs. 198 (87), 0.04
  - Seronegative response rate (%): 43/62 (70) vs. 48/78 (62), 0.33
  - MCT levels (SD) (U ml\(^{-1}\))
    - Before: 49 (18) vs. 47 (21), NS
    - After: 123 (52) vs. 120 (50), NS
countries, less sensitive assay used and/or some other factors may be responsible [20] for this susceptibility.

Following MMR2 revaccination, a high boosting of IgG antibodies levels occurred. Significantly more seronegative older children responded to measles and mumps components. However, the response rate to rubella was not different between the two groups. Despite high percentage of IgG response to measles and rubella among seronegative children, only a few showed IgM seropositivity. These high levels of IgG response coupled with a lack of a significant IgM response suggest that most of these children had been primed immunologically with a lower antibody titre achieved by the primary MMR vaccination. Therefore, their seronegativity at before MMR2 seems to be due to waning antibody levels (SVF), or it is likely that the IgM assay used was less sensitive to detect IgM (PVF) [18].

In the absence of repeated boosting, both vaccine-induced and naturally acquired antibodies may wane during time [21, 22]. As a consequence, the number of susceptible individuals increases progressively. To interrupt measles virus circulation, achieve and maintain measles control and elimination, the number of susceptible subjects among population should be kept <5% over a long period of time [23–26]. In this study, measles seroprevalence rates acquired by two doses of MMR vaccine were lower than expected, especially in young children, along with the risk of antibody level waning over time may influence the WHO goal for control and elimination of measles in the region and world [26, 27].

Significantly younger children were seroimmune to mumps infection at before MMR2 administration. However, the response rate to revaccination was significantly higher in seronegative older children, and mumps seroprevalence rate of two age groups become similar although, lower than reported worldwide, especially for younger children. Based on the findings of this study, it can be suggested that earlier age revaccination does not influence the long-term vaccine-induced immunity levels of the population.

The main goal of rubella vaccination programme is to protect women of childbearing age from rubella infection, and to prevent congenital rubella syndrome (CRS) [1, 17, 26]. The chief concern though is that infant rubella vaccination with inadequate coverage may lead to increase in CRS [17, 25–26]. The rubella seroprevalence rates detected in this study at pre- and post-MMR2 vaccination were lower than that reported worldwide [1, 2, 17]. Several comparative immunogenicity studies were done with different rubella strains showing >90 and >99% immunity rates with one and two doses of rubella-containing vaccine [17, 27–28]. Because of the consistent immunogenicity, induction of resistance to re-infection and low rates of side effects, the RA 27/3 strain is the most widely used rubella vaccine throughout the world, except in Japan [17]. The MMR vaccine and strain used in our study ‘Takahashi’ was obtained from India. The low seroprevalence rate (53%) detected in this study is in accordance with an earlier immunogenicity study of the MMR vaccine in use in Iran [19]. This suggests a low potency of the rubella strain of MMR vaccine currently being used in the country, and hence a need to improve its immunogenic potency or it being replaced by a more potent strain such as RA 27/3. Considering the possibility of waning vaccine-induced antibody titres over time [29–31] and the relative percentage of seroimmunity levels acquired after receipt of the two doses of MMR vaccine, it is likely that the number of susceptible women of childbearing age will increase progressively, indicating that the risk of CRS may continue in future in the community [17, 25, 26].

**Conclusion**

It can be suggested that earlier administration of the second dose of MMR may be more desirable than at school entry. However, the impact of this policy change will be influenced by the extent of waning of vaccine-induced immunity. If this occurs following the two-dose schedule [1, 29–31], a later administration of MMR2 revaccination is favored. However, if earlier age is planned, two-dose vaccination policy associated with high-levels of coverage (>95%), periodic seroepidemiological studies to determine population immune status and if necessary supplementary vaccination and conducive effective case finding are fundamental. Low levels of rubella seroimmunity achieved after two-dose vaccination necessitates improving the potency of rubella component of the MMR vaccine in use in Iran. Further studies for documenting these findings are recommended.

**References**


