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Immunogenicity and efficacy of one dose measles–mumps–rubella (MMR) vaccine at twelve months of age as compared to monovalent measles vaccination at nine months followed by MMR revaccination at fifteen months of age

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Abstract

Background and methods: measles is a common cause of morbidity and mortality in developing countries. Although the measles–mumps–rubella vaccine (MMR) is currently in use in developed countries, monovalent measles vaccine (MV) is routinely recommended by World Health Organization (WHO) at 9 months of age in Turkey, as in many other developing countries. In this study, 442 Turkish children received MV at 9 months of age and were revaccinated with MMR vaccine at 15 months of age. In the second group 495 children received MMR at 12 months of age with no earlier measles vaccination. Antibodies were measured before the first vaccination and 6 weeks after the MMR. All children had been followed for occurrence of measles infection for 60 months. Two vaccination schedules were compared for immunogenicity and protection rates. *Conclusions:* seroconversion and clinical protection rates were significantly higher in children who received only MMR at 12 months of age than in children revaccinated at 15 months of age. Seroconversion rate for measles was 69.9% in children who received MMR at 12 months of age and 90.3% in children revaccinated at 15 months of age ($P = 0.0003$). While there was no measles case in children who were revaccinated, 12 (2.7%) children in the first group acquired measles during the follow-up period. Vaccination at 12 months of age appeared to be better than the current national standard. The late elimination of maternal antibodies and the inhibitory effect of a weak antibody response after the first dose of vaccine at 9 months may explain the better immunogenicity and efficacy of the MMR vaccine given at 12 months of age. © 2001 Published by Elsevier Science Ltd.

Keywords: Monovalent measles vaccine; MMR vaccine; Developing countries

1. Introduction

Despite the advent of the measles vaccine (MV) in 1959, measles still remains as an important public health problem in the developing world. National recommendations for measles vaccination differ significantly between developing and developed countries. In areas without recurrent measles transmission, the first dose of measles immunization is recommended as measles–mumps–rubella vaccine (MMR) at 12–15 months of age. In areas with recurrent measles transmission, a two-dose schedule with monovalent measles vaccine at 9 months of age and a second dose, using MMR at 15 months of age is recommended [1]. MV was shown as immunogenic at 12 months of age (97% seroconversion) as at 15 months of age (98% seroconversion) in Australia [2]. In another study, 15–21% of vaccine recipients at 9–12 months of age failed to seroconvert in contrast to less than 6% of children immunized at 13–18 months [3]. The World Health Organization (WHO) recommends that immunization with a live attenuated MV should be carried out when

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the child is around the age of 9 months. At this age the transplacental antibodies in most children have disappeared [4]. Children can be vaccinated then in order to induce protection before the age of risk. Despite early vaccination at 9 months of age, measles continues to be a major child health problem in the developing countries [5]. Many children are now being revaccinated with measles or MMR vaccines at 15 months of age after initial vaccination. This two dose schedule is implemented in 12 of 22 countries in the Eastern Mediterranean Region of WHO including Bahrain, Islamic Republic of Iran, Iraq, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudia Arabia, Syrian Arab Republic, Tunusia, United Arab Emirates [5,6]. The Turkish Ministry of Health provides the monocomponent live MV to children at 9 months of age free of charge. Most of the pediatricians also recommend the administration of MMR (not covered under the government insurance policies) at 15 months of age, after this first dose of MV.

The effectiveness of early vaccination and revaccination against measles is not clearly established in developing countries. The purpose of this study was to investigate the immunogenicity and protection rate of revaccination with MMR vaccine at 15 months of age after initial vaccination at 9 months of age in comparison with children who received single dose of MMR vaccine at 12 months of age.

2. Materials and methods

2.1. Subjects

Study subjects were 1000 healthy infants aged 9 months (38–40 weeks) who had been given primary health care in five different maternity and child health care centers in Ankara, Turkey. Patients were enrolled in a 6 month period. Healthy children with no known history of chronic disease as immunodeficiency, asthma, atopy were recruited for the study. The infants that do not have these inclusion criteriae, infants younger than 9 months of age were excluded from the study. Approvals for this study were obtained from the ethic committees of Hacettepe University and Turkish Ministry of Health prior to the study. After obtaining written informed consents from parents, the infants were randomly allocated to either Group A or B. The systemic allocation was used for the randomization and 500 infants were assigned to each group. In Group A, 442 infants completed the study and 58 infants were excluded from the study (four immigration, four parental decision change, 50 due to the use of a different batch of vaccine). In Group B, 495 infants completed the study and five were excluded (three immigration, two parental decision change).

2.2. Vaccines

MV (Rouvax®, batch no J1183, Schwarz strain, 1.000 $TCID_{50}$) and MMR vaccine (Trimovax®, batch no J1023; Schwarz measles strain, 1.000 $TCID_{50}$; Urabe Am 9 mumps strain, 5.000 $TCID_{50}$; Wistar RA 27/3 rubella strain, 1.000 $TCID_{50}$) of Pasteur-Merieux Serums and Vaccines, Lyon, France were administered subcutaneously into the right deltoid region.

2.3. Study plan

Infants in Group A received MV at 9 months of age and MMR at 15 months of age. Blood samples were collected just before measles vaccination and 6 weeks after MMR vaccination. Subjects in Group B received MMR at 12 months of age. Blood samples were collected just before and 6 weeks after the vaccination. After each vaccination, all vaccine recipients were visited by midwives in child health care at their homes on 7, 14, and 28th postvaccination days to collect adverse reaction records that the parents were asked to make notes. Adverse reactions were defined as a temperature of 39.4 °C (103 °F), cough, runny nose, diarrhea, any rash after vaccination, local reactions as redness and swelling and also change in the alertness and overall activity of the child, seizures, hypersensitivity reactions. Subjects were followed with phone calls and/or home visits every 3 months for 60 months after vaccination. A standard questionnaire including the possible adverse reactions was used during these phone calls. Parents were asked to report occurrence of measles in the vaccines and a measles case was defined as a subject diagnosed by a physician with pathognomonic enanthem (Koplik's spots), cough, coryza and conjunctivitis and maculopapular rash. In patients with no pathognomonic sign measles serologies were obtained. The severe cases were described as patients with acute encephalitis, bronchopneumonia, and respiratory distress.

2.4. Serological tests

Total specific levels of measles, mumps, and rubella Ig Gs were determined by commercial ELISA (Trinity Biotech Plc, Jamestown, USA). The test sera, positive and negative control sera, and calibrator were diluted 1:21 in serum diluent, 100 μl of them were added to the wells with additional 100 μl serum diluent to reagent blank well. Each well was incubated at room temperature for 20 min and aspirated, washed with wash buffer four times. Then, 100 μl conjugate was added to the wells followed by 20 min incubation at room temperature and washing five times with wash buffer. The wells were filled with 100 μl chromogen/substrate solution and incubated at room temperature for 10 min. Reaction was stopped by addition of 100 μl stop solution (1

Table 1
Adverse reactions after vaccinations

Reactions	Group A ($n=442$)		Group B ($n=495$)
	Measles	MMR	MMR
Systemic			
Fever	38 (8.7)[a]	40 (9.1)	55 (11.2)
Runny nose	19 (4.3)	7 (1.6)	22 (4.4)[b]
Cough	28 (6.2)	36 (8.1)	34 (6.8)
Rash	2 (0.4)	16 (3.6)	19 (3.8)
Diarrhea	5 (1.1)	2 (0.4)	5 (1.0)
Local			
Redness	7 (1.6)	14 (3.2)	19 (4.3)
Swelling	2 (0.4)	2 (0.4)	3 (0.6)

[a] Numbers in parenthesis indicate percentages.
[b] $P<0.01$.

N H_2SO_4). The developed color was read on ELISA plate reader at 450 nm. Calibrator value was calculated by multiplying the mean absorbance of the calibrators by the factor recorded on the kit packing (correction factor) and immune status ratio (ISR) was found by deviding the sample absorbance by the calibrator value. Then, ISR was changed to IU/ml using the formula specific for each lot as noted on the manufacturer's order. The cut off value was 0.29 IU/ml for measles antibodies, 0.83 IU/ml for mumps antibodies, and 5.1 IU/ml for rubella antibodies. The values below the cut-off were accepted as negative in calculation of seroconversion, but all measurable values were taken in account in GMT evaluations.

Seroconversion was defined as any positive antibody response in earlier seronegative infants and at least fourfold increase in antibody titers after vaccination for infants with positive pre-existing antibodies.

2.5. Statistical tests

Statistical evaluation was done by using SPSS (Version 6, SPSS Inc, Chicago, IL, USA) and Statistica (version 5, Stat Soft Inc, Tulsa, OK, USA) computer programs. Mann–Whitney U test for comparison of mean titers, t-test for comparison of seroconversion rates and χ^2-test for comparison of nominal attributes were used for statistical analysis.

3. Results

There was no significant difference between the two groups with regard to sex and age ($P=0.24$ and 0.38, respectively). The time interval between immunization and postvaccination blood sample collection was 42.7 ± 3.6 days for Group A and 42.5 ± 4.1 days for Group B. Adverse reactions to vaccinations are shown in Table 1. With the exception of runny nose which was more common in Group B ($P<0.01$), there was no difference for systemic or local adverse events between the two groups.

The geometric mean titers (GMT) of specific antibodies against measles, mumps, and rubella before and after vaccination for both groups are given in Table 2. Prevaccination measles GMT was higher in Group A in which children were younger (9-month-old) during the blood sample collection ($P<0.0001$). Postvaccination antibody titers were higher in Group B ($P<0.0001$). No difference was detected between the two groups for

Table 2
Antibody titers before and after vaccinations, seroconversion and clinical protection

	Group A ($n=442$)		Group B ($n=495$)		P
	Pre	Post	Pre	Post	
Measles					
GMT	0.082	0.360	0.035	0.742	<0.0001 (Pre)
95% CI	0.063–0.111	0.323–0.395	0.001–0.050	0.670–0.814	<0.0001 (Post)
Seroconv	NA	69.9	NA	90.3	0.0003
Infection	NA	12 (2.7%)	NA	0	<0.0001
95% CI		1.20–4.23			
Mumps					
GMT	0.045	1.074	0.039	1.096	0.27
95% CI	0.003–0.076	0.873–1.259	0.005–0.066	0.965–1.248	0.19
Seroconv	NA	98.4	NA	97.3	0.24
Rubella					
GMT	3.645	7.649	3.761	7.527	0.38
95% CI	0.130–4.86	4.96–9.018	0.163–4.754	5.001–8.88	0.36
Seroconv	NA	95.2	NA	93.7	0.21

CI, confidence interval; GMT, geometric mean titer (IU/ml); NA, not applicable; Pre, prevaccination; Post, postvaccination; Seroconv, seroconversion (percentage).

Table 3
Seropositive infants before vaccination

	Group A[a] ($n = 442$)	Group B[a] ($n = 495$)
Measles	36 (8.1)[b]	7 (1.4)
Mumps	14 (3.1)	7 (1.4)
Rubella	9 (2.0)	2 (0.4)

[a] Group A, 9 months of age; Group B, 12 months of age.
[b] Numbers in parenthesis indicate percentages.

pre- and postvaccination mumps and rubella antibodies ($P = 0.27$ and 0.38, respectively, for prevaccination and 0.19 and 0.36, respectively, for post vaccination).

Seroconversion rate was 69.9% in Group A and 90.3% in Group B for measles and this difference was statistically significant ($P = 0.0003$) (Table 2). Clinical protection was also significantly better in Group B ($P < 0.0001$). While there was no measles case in Group B, 12 (2.7%) children in Group A acquired measles during the follow-up period. These cases were confirmed with serological testing. None of these cases had severe measles and they did not require hospitalization. All of these children were shown to have seroconversion prior to developing disease. They were diagnosed with measles 12–36 months after vaccination. The diagnosis was confirmed with serologic testing and no further serologies were obtained from these patients. These cases were scattered between the five different centers and there was no known epidemiologic link between these cases. There was no difference in seroconversion for mumps and rubella ($P = 0.24$ and 0.21, respectively).

The ratio of seropositive infants before vaccination is given in Table 3. Ratio of seropositive infants for measles was 8.1% in Group A and 1.4% in Group B. This ratio was 3.1 and 1.4% for mumps and 2.0 and 0.4% for rubella in Groups A and B, respectively.

4. Discussion

Measles continues to be an important cause of morbidity and mortality in Turkey. Since routine vaccination against measles at 9 months of age is provided to most of these children, primary vaccine failure in addition to the unvaccinated population needs to be considered for the measles endemicity [7,8]. Risk factors for primary vaccine failure are mostly due to improper vaccine handling, use of killed virus vaccine, concomitant use of immune serum globulin, and interference by maternally acquired measles antibody [9]. Killed virus vaccine has not been used in Turkey for a long time and concomitant use of immune serum globulin could obviously not be considered for this high rate of vaccine failure. In our study, 8.1% of children at 9 months of age was seropositive when MV was administered, in contrast to 1.4% seropositivity rate at 12 months of age when one dose MMR was administered. The possibility of contracting measles before or at the time of vaccination seemed unlikely given the low titers and comparison of the seroprevalance of both groups. Passive transfer and interference by maternal antibodies appeared to be the most important reason for primary vaccine failure.

Persistence of maternal antibodies could be a major cause of reduction in seroconversion rates to live MV administered to infants under the age of 12 months. Albrecht et al. [10] reported measles neutralizing antibodies in children up to 12 months of age and a direct correlation between persisting levels of maternal antibody in the infant and response to vaccination. Similar results were observed in an animal model using macaques in the presence of passively acquired antibodies [11].

The results of our study indicated a higher vaccine failure rate (30.1%) after early (9 months of age) measles vaccination followed by MMR vaccine at 15 months of age than MMR vaccination at 12 months of age (9.7%). Although much higher than the first group, the seroconversion rate of 90.7% in children who were vaccinated at 12 months of age with a single batch of the vaccine appear to be less than in some of the earlier reported studies for unknown reasons [12,13]. The early vaccination seemed to alter the immune responses to revaccination. The results of the early studies for determining the immune response to the vaccination at 15 months after measles vaccination at 9 months of age were conflicting. Two studies including small numbers of children indicated that the immune responses of some infants vaccinated before 10 months of age were altered enough to suggest lower protection rates even with revaccination after one year of age [14,15]. Murphy et al. [16] found good measles antibody responses after immunization with MMR vaccine at 15 months of age in children who had been vaccinated with MV at 5–10 months of age. They suggested that the reason for lower antibody response after reimmunization in the other studies, was related to the different serological method. They used a more sensitive method (ELISA) instead of hemagglutination inhibition assay. In our study, we used ELISA and found lower antibody response after reimmunization than that after one dose vaccine at 12 months of age. Similarly, in another study comparing antimeasles antibody titers in German and Nigerian cohort of paired mothers and newborns Hartter et al. [17] found that the passively acquired antimeasles antibodies decayed rapidly. The cause of

this confliction might be purely due to the geographic and regional differences of maternal antibody elimination, not the serological method. In these studies, the vaccines were not followed after vaccination and the only parameter for vaccine protectiveness was the serological response. Stetler et al. [18] revaccinated 254 infants who had received MV at less than 10 months of age and determined immune responses 3 weeks and 8 months later. Despite almost equal antibody responses at 3 weeks postvaccination in both groups, infants who received their first doses of MV at or after 15 months of age had higher antibody responses 8 months after the vaccination. The authors suggested that infants who did not respond were also protected after revaccination. No comparative studies for efficacy of revaccination after early measles vaccination including clinical protection have been done before our study. Although serologic testing was not done in the end of the study for all subjects, and theoretically few cases could be missed, we followed the subjects for 60 months and observed that one dose MMR was apparently more protective than early vaccination/revaccination (zero versus 12 cases).

The role of transplacental antibodies in primary vaccine failure may vary in different populations. Although maternal malnutrition can result in lower maternal measles antibody titers in many underdeveloped countries, most of the children are still expected to have maternal antibodies derived from maternal infection in developing and underdeveloped countries. Elimination of high maternal antibodies secondary to infection is expected to be later than that of maternal vaccine induced antibody responses. Thus, maternal antibody transfer may have a more important inhibitory effect in early vaccination in developing regions than in the underdeveloped regions. These results do not exclude the need for early vaccination during measles epidemics to prevent the infants younger than one year of age until development of a new potent MV for infants younger than 12 months of age. Higher incidence of running nose observed in one dose MMR vaccine group may be related to seasonal variations of vaccination.

In conclusion, seroconversion and clinical protection of MV at early ages and revaccination at or after one year of age may differ between countries depending on the maternal antibody status. The elimination time of maternal antibodies might be related to vaccine coverage and infection prevalence of mothers and may vary in different geographic locations. Since most of the mothers who live in developing countries have high measles antibody levels gained by infection, their children were expected to lose maternal measles antibodies later than children of developed countries.

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