MATHEWS Open Access Journals

ISSN: 2572-6560

Research Article | Mathews Journal of Pediatrics

Should the Second Dose of Measles Vaccine be Performed at an Earlier Age?

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Received Date: 24 Jan 2017

Accepted Date: 08 Feb 2017

Published Date: 13 Feb 2017

Citation: Erkan VB, Altun D, Serdar MA and Sarici SU. (2017). Should the Second Dose of Measles Vaccine be Performed at an Earlier Age?. M J Pedi. 2(1): 008.

ABSTRACT

Background/Aims: An increase in the incidence of measles has recently been detected in our country because of migrations from neighboring countries. In this study, it was aimed to investigate whether performing the second dose of the measles vaccine at 4 years of age instead of 6 years of age would be more appropriate by comparatively measuring measles antibody titers in children aged 4 and 6 years who had not yet been vaccinated with the second dose of the measles vaccine.

Methods: Measles IgG antibody titers were measured in 48 case saged 4 years (Group I) and 43 cases aged 6 years (Group II) who had both previously been vaccinated with only one dose of the measles vaccine at 12 months of age according to routine immunization program of Ministry of Health and had not yet been vaccinated with a second dose of the vaccine.

Results: Mean measles antibody titers of Group I and II were 193,7 ± 49,8 IU/mland 106,1 ± 48,6 IU/ml, respectively, and mean IgG titer was statistically significantly higher in Group I when compared to Group II (p=0,001). Performing the second dose of measles vaccine at 4 years of age instead of 6 years of age is an early rappel and does not contribute to an increase in seropositivity according to results of our study.

Conclusion: The rappel dose of vaccine may be postponed to a further age, and further studies should be performed in further age groups in order to determine this critical age limit at which the second dose of measles vaccine is necessary.

KEYWORDS

Measles Vaccine; Immunization; Immunoglobulin.

INTRODUCTION

Measles is a highly contagious disease which is a significant cause of mortality and morbidity worldwide. The time between epidemics increased as vaccinations increased and the age for having the disease increased [1], whereas measles epidemics used to occur every 2-3 years in the prevaccination era. Although there is a reliable and effective vaccination program against measles, children who do not get the vaccine, or who cannot form sufficient level of antibodies with a single vaccine dose, remain susceptible to measles, which, in turn,causes the measles virus to be pandemic. Sensitivity to measles in school-age children is high, and school epidemics have an important role in measles outbreaks [1].

The age at which the administration of measles vaccine is performed is determined according to the age at which children lose maternal antibodies transferred from their mothers. This critical agevaries from society to society. Due to the low rate of vaccination in under developed or developing countries, the antibodies passing from the mother disappear early, and routine measles vaccination is madeat 6 or 9 months of age. Due to the higher vaccination rate in developed countries, the antibodies passing from the mother disappear later, and routine measles vaccination is performed at 12 or 15 months of age. However, in both situationsa second dose of vaccine is necessary [1]. The American Advisory Committee on Immunization Practice [ACIP] and the American Academy of Pediatrics [AAP] declare that 4-6 years of age is the ideal time for the second dose of vaccine, and in most countries a second dose of measles, mumps, and rubella [MMR] vaccine is given at this age [2, 3].

The significant decrease in mortality and morbidity provided by vaccinations confirms the success and significance of immunization programs. Preventive antibody levels can be measured serologically with various intervals after primary vaccination in order to establish appropriate immunization programs [1].

Due to immigration from neighboring southern countries, an increase in measles cases has recently been identified in Turkey. As measles cases have appearedin children of 4–6 years of age who have not had their second dose of vaccine, it has been suggested that the second measles vaccination be given at the age of 4 years instead of 6-7 years when children are in the first year of primary school [4]. However, to our knowledge, there is no comparative study investigating the effectiveness of vaccinations at this age based on the serologic measurement of preventive antibody levels. In this study our aim, thus, was to measure the measles antibody levels of children who have not yet had the second dose of measles vaccine at 4 to 6 years of age. We have also evaluated the necessity of a second dose of measles vaccine at 4 years of age instead of 6 years of age in a period when the risk for measles is increasing.

MATERİALS AND METHODS

The study sample consisted of 91 children between the ages of 4–6 years who were admitted to the Department of Pediatrics Ufuk University with any reason between February 2014 and March 2015. Cases were divided into 2 groups on the basis of the status of the vaccination of second dose of measles vaccine. Group I included 48 cases who had a mean age of 4 years, and were previously vaccinated with only one dose of measles vaccine according to the vaccination program of the Ministry of Health (at 1 year of age), but not had the second dose of the vaccine yet. Group II included 43 children who had a mean age of 6 years at the first year of primary school, and also not had the second dose of measles vaccine yet. Children were not included in the study if they had the second dose of measles vaccine, a chronic illness that affected immunization, any type of immune deficiencies, or weight and height percentiles below 5%. The vaccination cards of allocated children were checked, and the vaccination information was confirmed by their parents. Permission was obtained from the Ufuk University Medical School Local Ethics committee (on February 27, 2014) to conduct the study. Written informed consent was also obtained from thecases' parents. Blood samples were obtained during the child's first clinic application and treatment. The blood samples were centrifuged and blood serums were separated and stored at -80ºC until the time of the study. The measles antibody levels were evaluated with the Enzyme-Linked Immunosorbent Assay (ELISA) method, and a measles specific kit was used for this method. According to the suggestions of the kit manufacturer, values of ≤10 IU/mL were accepted as non-protective.

Statistical analysis of the data was performed using IBM SPSS Statistics 18.0 software. Definitive statistical and Mann-Whitney U tests were used for the evaluation of the mean value of intragroup antibody levels and analysis of anthropometric measurements and demographic data. A probability value less than 0.05 ($p<0.05$) was accepted as statistically significant.

RESULTS

Of the cases included in the study, 24 children were male [50%], and 24 were female (50%) in Group I. In Group II, 28 children were male (65.1%), and 15 children were female (34.9%). The mean age was 47.6 ± 1.5 months and 72.5 ± 1.9 months in Group I and Group II, respectively. The mean body mass index (BMI) was 15.2 ± 3.5 kg/m2 and 15.9 ± 2.9 kg/m2 in Group I and Group II, respectively. The demographic features and anthropometric measurements of the groups are given in Table 1.

Table 1: Demographic data and anthropometric measurements of the study groups.

	Group I†	**Group II†**
	(n=48)	**(n=43)**
Gender (M/F)	48 (24/24)	43 (28/15)
Age (months)*	47.6 ± 1.5 (45-50)	72.5 ± 1.9 (69-76)
Weight (kg)*	17.1 ± 2.6 (14-22)	23 ± 3.9 (17-31)
Height (cm)*	107.3 ± 8.9 (97-124)	120.6 ± 5.4 (110-130)
BMI (kg/m2) *	15.2 ± 3.5 (9.72-22.45)	15.9 ± 2.9 (13.88-22.71)

BMI: body mass index, M: male, F: female.

*: Values are given as mean ± standard deviation (min-max).

Measles antibody levels of Group I and II are given in Table 2, and the mean antibody levels were 193.7 ± 49.8 IU/mL and 106.1 ± 48.6 IU/mL in Group I and Group II, respectively. The mean antibody level was statistically significantly higher in Group I when compared to Group II ($p=0.001$), as shown in (Figure 1 and Figure 2). Mean antibody levels showed a decrease in Group II when compared to Group I due to increasing age.

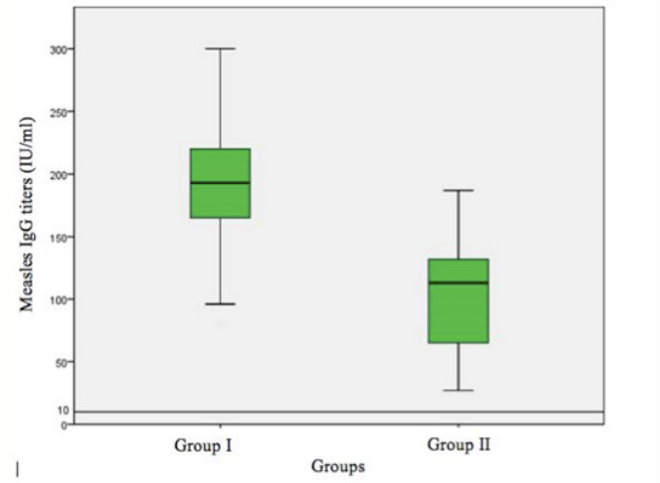

Figure1: Comparative distribution of measles antibody levels and mean values in both groups.

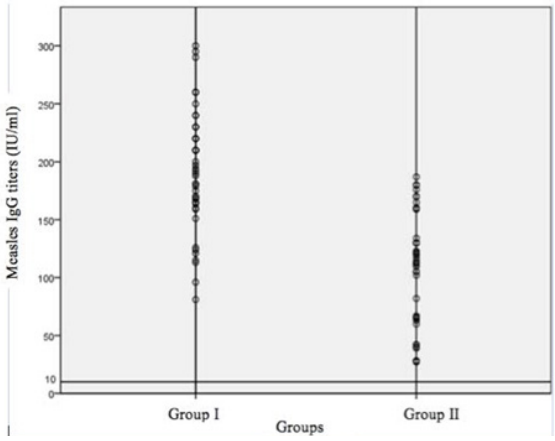

Figure 2: Distribution of measles antibody levels in groups.

Table 2: Measles IgG antibody levels of the study groups.

	Group I	Group II	p value$^{\alpha}$
	(n=48)	(n=43)	
Measles IgG antibody level (IU/mL)	193.7±49.8	106.1±48.6	0.001
Protectiveness (n/n) (%)	48/48 (100)	43/43 (100)	

α: Mann-Whitney U test.

When the antibody levels of both groups were compared in terms of gender, no significant difference was observed betweenthe groups with respect to gender as shown in Table 3.

Table 3: Comparison of the measles antibody levels of the study groups according to gender.

	Female	Male	p value$^{\beta}$
Group I (IU/mL)*	193.4±58.3 (81-300)	194±40.8 (115-260)	0.96
Group II (IU/mL)*	101.9±50.2 (28-180)	108.3±48.5 (27-187)	0.69

*: Values are given as mean ± standard deviation (min-max).

β: Mann-Whitney U test.

DISCUSSION

A goal of the World Health Organization is to stop domestic measles virus transmission. A primary strategy to meet this goal is to administer a routine second dose of measles vaccine with a high success rate and provide an opportunity for a second measles dose to populations susceptible to measles [1]. As a result of the successful administration of two doses of measles vaccination in Turkey, the prevalence of measles has decreased when compared to European countries [5, 6]. However, despite the Turkey's successful Measles Elimination Program, an increase in measles cases has been observed in Turkey due to immigrations from other countries since June 2012 [4]. In countries where measles cases are at peak levels, with frequent epidemic intervals, and where malnutrition is a common problem, babies younger than 12 months old will probably encounter measles and have measles with complications. In such countries, the first dose of measles vaccine is recommended at 9 months old [7]. Countries may prepare their own vaccination programs according to differing age groups, and they can adjust age ranges for their vaccination campaigns to be narrower or wider according to their own requirements [8]. At the meeting of the Measles Scientific Consultancy Board on March 10, 2013, and as a result of studies performed within the National Measles Elimination Program, it was advised to administer one additional dose of measles vaccine for all babies younger than 12 months. It was also advised that, after 12 months of age, routine dose of MMR vaccine should be administered provided that at least one month elapsed since the previous dose [4].

Very infectious forms of measles and low effectiveness of a single vaccine dose complicate measles elimination. Epidemiological data show that a second dose of vaccine is required for children who are vaccinated in the presence of antibodies passing from the mother. Numerous countries have started to administer a second dose of measles vaccine at various ages [9]. The protectiveness of the second dose is 95% including the cases who do not respond to the first dose. MMR vaccination at 12 months provides vaccination protection for babies who have not yet been vaccinated against measles or for babies who were previously vaccinated against measles but did not respond to the first vaccination (primary vaccine failure). With this strategy, the desired immunity level for measles can be achieved in the population [9].

The AAP and ACIP recommend a second dose of measles vaccination between 4-6 years old to address primary vaccination failure. Thus, secondary vaccination failure is not discussed for 4-6 year old children or for first "classers" in primary school. In other words, loss of vaccine-related immunity at these ages in individuals known to have developed antibody response aft vaccine seems to be impossible [3].

Johnson et al. have shown that measles antibodies that developed following vaccinations administered at 15 months were

maintained at the protective level until about 11 years old [10]. Approximately 8-10 years after vaccination, antibodies-are observed in more than 85% of vaccinated individuals [10]. In our study, we observed antibody levels-in all the cases of both groups-that were considerably above protective limits, with no primary vaccination failure. This indicates that vaccination in the first year of primary school at 6 years of age-except for cases of primary vaccination failure-will not provide any benefits when performed at 4 years of age in terms of secondary vaccination failure. The statistically significant higher antibody levels of Group I (4-year-old) in comparison to Group II (6-year-old) is also in correlation with the natural course of antibody levels (that decreases with increasing age).

Liuve et al. [11] accepted 0.20 IU/mL as the protective antibody level in their study, and found the highest protective antibody levels in the age group of 13 months - 4 years (>95%) in children vaccinated with only one dose of measles vaccine at 8 to 12 month old. The authors showed that this protective level was kept relatively fixed until 15 years old and it decreased to 88.4% in the 15-29 year age group [11]. Based on the high measles frequency in adults between 20-29 years old, some researchers have suggested that vaccination program with an additional dose beyond the primary school age prevents the circulation of measles virus among adolescents [12,13].

Wang et al. examined 1015 cases from ten age groups in China (0-7 months, 8-12 months, 2-4 years old, 5-9 years old, 10-14 years old, 15-19 years old, 20-29 years old, 30-39 years old, 40-49 years old, and ≥ 50 years old) [14]. Participants in this study had the primary dose of measles vaccine administered at 8 months and the secondary MMR dose administered between 18 and 24 months, based on China's vaccination program. Based on their study, they have recommended a primary vaccination at the age of 8 months and a secondary vaccination at the age between 18 and 24 months. Their results showed protective antibody levels at the following levels: 71.5% for unvaccinated babies younger than 7 months, 98.3% for cases in whom a single dose was administered, 95.3% in 2-4 year olds, and 99% in 5-9 year olds. In all age groups over 9 years old, protective antibody levels were calculated to be at a minimum of 96.1% [14]. In our study, the protective antibody level was accepted as 10 IU/mL and higher, limited cases were studied, and no cases with low antibody levels were observed. When there searchers examined the impact of gender on antibody levels, they found statistically significant antibody level differences in the 20–29 age group and inthe 30–39 age group, but no significant differences in other age groups [14]. In our study, no statistically significant difference was observed when the intragroup antibody levels were compared with respect to gender.

In their study, Çelik et al. made age groupings of 9-11 years, 12-14 years, and 15-16 years, and they determined protective antibody levels at 17.17, 18.6, and 18.7 IU/mL, respectively [15]. Lower antibody levels in that study when compared to the levels in our study may be explained by the differences that mean age of the cases in our study is younger and antibody levels decrease with increasing age.

According to our study results, performing the second dose of measles vaccine at 4 years of age instead of 6 years of age is an early rappel and does not contribute to an increase in seropositivity according to results of our study. Currently 6 years of age is seemingly the optimal age for the second dose of measles vaccination. The rappel dose of vaccine may be postponed to a further age, and further studies should be performed in further age groups in order to determine this critical age limit at which the second dose of measles vaccine is necessary.

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