

Effect of Second Dose of Measles Vaccine on Measles Antibody Status: A Randomized Controlled Trial

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Objective: To evaluate the effect of the second dose of measles vaccine on measles antibody status during childhood.

Setting: Immunization centre of Under-five Clinic of the Department of Community Medicine at a tertiary-hospital.

Design: Randomized Controlled trial.

Methods: Blood samples were collected from all subjects for baseline measles serology by heel puncture at 9-12 months of age. All subjects were given the first dose of measles vaccine. At second visit (3-5 months later), after collecting the blood sample from all, half the children were randomized to receive the second dose of measles vaccine (study group), followed by collection of the third sample six weeks later in all the subjects.

Results: A total of 78 children were enrolled and 30 children in

each group could be analyzed. 11(36.6%) children in the study group and 13 (43.3%) children in the control group had protective levels of measles IgG at baseline. Around 93.3 % of children in the study group had protective measles antibody titers as against 50% in the control group at the end of the trial. The Geometric Mean Titre (GMT) of measles IgG increased from 14.8 NTU/mL to 18.2 NTU/mL from baseline to six weeks following receipt of the second dose of the vaccine in the study group, as compared to a decrease from 16.8 NTU/mL to 12.8 NTU/mL in the control group.

Conclusions: A second dose of measles vaccine boosts the measles antibody status in the study population as compared to those who receive only a single dose.

Key words: Immunization, India, Measles, Prevention, Second-dose, Serology.

Measles is a leading cause of death among young children. Many experts now recommend two doses of the measles vaccine to ensure immunity, as about 15% of vaccinated children fail to develop immunity from a single dose [1]. In the past, there was a concern that early immunization of infants who still have the maternal antibody modified the immune response such that the infant would not respond adequately to a second dose. However, most studies have shown that the overall proportion of children who are seropositive after primary immunization before 12 months of age and re-immunized at age 15 months or later is at least 95%, similar to that after initial immunization at 15 months. Epidemiological data support the efficacy of a second dose in the presence of maternal antibody. Many countries have initiated a two dose Measles, Mumps and Rubella vaccine schedule with the aim of eliminating Rubella and Measles [2]. The rationale for the second dose has been to protect those who did not seroconvert after the first dose of measles vaccine. In an outbreak investigation in USA, attack rates were 30-60% lower in persons who

received two doses of measles vaccine as compared to those who received one dose only [3].

In India, one dose of measles vaccine is given under Universal Immunization Program at 9 months of age. As some developing countries have adopted a 2-dose schedule, Indian Academy of Pediatrics has now recommended second dose of measles vaccine at 15 months of age. There is paucity of literature regarding the effect of second dose of measles vaccination on serological status in developing countries, especially in the Indian subcontinent. Hence the present study was designed to evaluate the effect of second dose of measles vaccine on measles antibody status during childhood.

METHODS

This was a randomized controlled trial conducted in the Under-five Immunization Clinic of Department of Community Medicine at Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Kashmir; a tertiary-care hospital in northern India. The study was conducted from May, 2008 to February, 2009. The required sample size for

the study was calculated to be 30 in each arm [4]. A total of 78 subjects were enrolled in the study giving allowance for the attrition factor. The study was approved by the Ethical Committee of the Institute.

Every alternate infant (age 9-12 months) reporting for measles vaccination on the given day was enrolled in the study. These infant were divided into two groups, one designated as study group that received second dose of measles vaccine 3-5 months after the first dose at 9-12 months of age and the other as control group receiving similar dose of placebo (normal saline) after 1st dose of measles vaccine at 9-12 months of age. Since measles vaccination is done only once in a week, the average children vaccinated at the immunization center on each week's immunization day was 20-25 and the process of enrollment of the infants was completed in around eight sessions.

Infants with a history of measles, infants with a history of measles in the family or immediate neighborhood during the past one month, and infants whose age could not be ascertained were excluded. Written consent was obtained from the parents/guardians of participants on a form that provided relevant details of the study.

Pertinent information was collected from the mother and entered into a pre-designed proforma. The data information related to demography, breastfeeding, weaning, immunization and disease history. Subjects

were examined, their weight and height, head circumference, and mid-upper arm circumference, was measured. Weight was assessed using pan type weighing scale. Height was measured using an infantometer. Head circumference and Mid -arm circumference was assessed using an inch tape.

Three blood samples were collected from each patient and were processed as per the manufacturer's recommendations and results were expressed in Nova Tech units [5,6]. Chi square test and Fisher test were used for analysis.

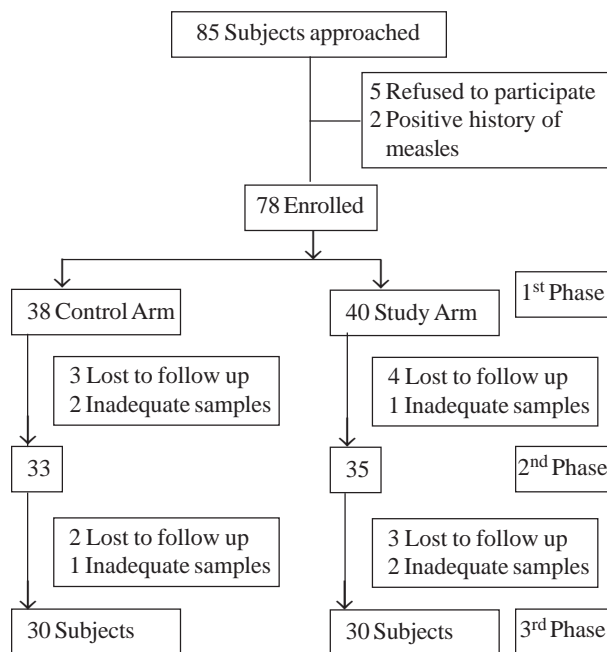
RESULTS

A total of 60 children were enrolled in the study, 30 for the study group and 30 for the control group. At enrollment, the baseline variables of children in two groups were comparable (**Table I**). The proportion of children with protective levels of measles IgG and the geometric mean titers (GMT) of measles IgG were almost similar in both groups at baseline. Measles IgG for study group was similar between the two groups, but it was significantly higher in the study group at third visit (**Table II**).

The GMT of measles IgG when compared between protected and non-protected children across two groups was higher for study group than control group, both at the second and third visit, though the difference was not statically significant (**Table III**).

DISCUSSION

The study found that a second dose of measles vaccine boosts IgG levels post-vaccination, as compared to children receiving one dose approximately 3-5 months earlier.



Flow chart showing flow of infants in the study.

TABLE I DEMOGRAPHIC DETAILS OF THE STUDY POPULATION (N=60)

	Study group	Control group
Females (%)	8 (26)	11 (36)
Age		
First phase	9.5 (0.73)	9.53 (0.68)
2 nd phase	13.8 (1.33)	13.4 (1.24)
Weight (kg) Mean ± SD		
First phase	8.08 (1.01)	8.14 (1.03)
2 nd phase	9.74 (1.37)	9.49 (1.11)
Height (cm), Mean ± SD		
First phase	68.9 (4.38)	70.3 (4.92)
2 nd phase	74.8 (5.16)	74.5 (4.34)
Literate mothers (%)	9 (30)	17 (56.6)
Working mothers (%)	1 (3.3)	2 (6.7)

TABLE II MEASLES IgG TITERS IN STUDIED CHILDREN DURING THREE PHASES OF THE TRIAL (N=60)

	Study Group n=30(%)	Control Group n=30(%)	P value
<i>First phase</i>			
No. with protected titers	11(36.6)	13 (43.3)	0.792
GMT (NTU/mL)*	10.60	11.21	
<i>Second phase</i>			
No. with protected titers	23 (76.6)	21 (70.0)	0.771
GMT (NTU/mL)*	14.93	12.11	
<i>Third phase</i>			
No. with protected titers	28 (93.3)	15 (50.0)	0.0004
GMT (NTU/mL)*	18.19	9.04	

The choice of the serological assay is important in evaluating the response to immunization. Both Plaque Neutralization assays and ELISA are more sensitive than the Hemagglutination Inhibition assays [6]. At present no serological test can differentiate between antibodies (whether IgG or IgM) produced by measles infection and that produced by immunization. The levels of antibody induced by immunization with attenuated measles virus vary with an approximately log-normal distribution.

The proportion of children having protective levels of measles IgG at 1st visit in this study was higher than 3.5%-17.6% reported in the literature [7-9]. The reason for our observation could be a pre-vaccination exposure to wild measles virus infection since measles is highly endemic in this region.

At the third visit, which was scheduled at six weeks following the receipt of second dose of measles vaccine in study group and a placebo in control group, a significantly higher number of children had protective levels of measles IgG in the study group. Similar results (93.7% vs 84.7%, respectively) have been reported from North Korea [10]. However, in our study, the proportion of protected children in the control group decreased from 70% to 50% from second to third visit. The explanation for this observation could be that since the proportion of children who had protective levels of measles IgG antibodies at base line was quite high (43.3%), which could either have been due to maternal antibodies or natural infection. Measles being highly endemic in this region, thus the proportion that could have responded to measles vaccine was actually less and the group which did not respond to measles vaccine at nine months continued with the waning phenomenon.

The GMT of IgG rose by 14.2 % from first visit to second visit and by 8.8 % from second to third visit in the

TABLE III COMPARISON BETWEEN GMJT OF (NTU/mL) MEASLES IgG OF THE STUDY AND CONTROL GROUP

	Study Group n=30(%)	Control Group n=30(%)	P value
<i>First phase</i>			
Protected	14.84	16.86	0.880
Not protected	8.78	8.52	
<i>Second phase</i>			
Protected	16.91	13.12	0.643
Not protected	9.38	8.36	
<i>Third phase</i>			
Protected	18.49	12.8	0.492
Not protected	10.13	8.97	

study group, while it gradually decreased in the control group. An attempt was made to compare the nutritional status of the children and immune status but a significant relation could not be established.

Our study proves that second dose of measles vaccine boosts the measles IgG status in the study population as compared to those who received only single dose. We also observed that in the control group the proportion of one dose vaccinated children initially increased and then returned to almost the same proportion protected at pre-vaccination levels. This justifies the need for a second dose of measles vaccine.

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