

Measles Specific Immunoglobulin G Response in Children Aged 4-12 Year Who Received Two Doses of Measles Containing Vaccine in Infancy

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Objectives: To study the vaccine-induced measles specific immunoglobulin G (IgG) response in children aged 4-12 years immunized with two doses of measles containing vaccine in infancy. **Methods:** This cross-sectional study was done in a tertiary care centre for a period of 18 months from January, 2017. Measles specific IgG levels were assessed using ELISA technique in 80 children of age 4-12 years, [mean (SD) age, 7.5 (2065)] who had received two doses of measles vaccine in infancy. Measles-specific IgG levels >11 NTU were considered protective. **Results:** Protective levels of measles specific IgG were found in 86.4%. Significant association was found between negative immune response to measles vaccine and low socioeconomic status ($P=0.03$), under-nutrition ($P=0.001$), anemia ($P=0.03$), lack of exclusive breast feeding till 5 months of age ($P=0.007$) and higher parity ($P=0.002$). **Conclusion:** Less than one-seventh of children immunized with two doses of measles vaccine in infancy had measles-specific IgG below protective levels at the average age of 7.5 yr. Lack of exclusive breast feeding till 5 months of age, under-nutrition and anemia were the associated factors.

Keywords: Booster dose, Efficacy, Immunization, MR vaccine.

The global coverage with first dose of measles vaccine is 85% and that of second dose is 67%. [1]. Measles immunization has resulted in 73% worldwide reduction in measles death by year 2018 [2,3]. However, in 2010, India alone accounted for 47% of the global measles mortality [4,5].

Antibody response to measles immunization is affected by a large number of factors [6-10]. Over the last decade, there have been major advances in immunology, virology, molecular biology, bioinformatics, and related research fields and that have enhanced the understanding of measles vaccine-induced immunity [10,11]. It is important to understand the level and determinants of measles vaccine immunogenicity to guide public health measures for measles control/eradication. Thus, we carried out this study to determine the vaccine-induced measles-specific immunoglobulin G (IgG) in children.

METHODS

This cross-sectional study was done in the pediatrics department of a tertiary care public hospital in Kerala, India to find out the proportion of sero-protective measles specific antibody response and the factors associated in children of age 4-12 years, who had received two doses of measles containing vaccine at the ages of 9 month (measles vaccine) and 15-18 month (MMR vaccine). Children with prior natural measles infection, immune-compromised

children, those who had received blood products or immunoglobulin within the past 3 months, and those on steroid therapy or cancer chemotherapy were excluded from the study. Study was initiated in January, 2017. All consecutive cases satisfying the inclusion criteria attending our center during the study period were recruited for study. Informed consent was taken for each participant from parents or primary care taker. Institutional ethics committee clearance was obtained before starting the study.

Relevant history was taken from the mother or primary care taker of the child. Semi structured proforma was used for recording the information. History of measles immunization, and dates of vaccination were confirmed from the original immunization card of individual child issued from the hospital or health care setting from where the vaccine was taken. Vital signs and anthropometric measurements were recorded. Signs of vitamin and micronutrient deficiencies were noted and systemic examination was done. Venous blood (2 mL) was taken from each study participant and their mothers (after informed consent) for measles specific IgG titres. IgG levels were assessed by ELISA technique (Novatec immunodiagnostica) at Rajiv Gandhi Institute of Biotechnology, Thiruvananthapuram, Kerala. IgG levels <9 NTU (Novatec Units) were labelled negative, 9-11 NTU equivocal, and >11 NTU as protective/positive level according to manufacturers validation criteria.

WHAT THIS STUDY ADDS?

- 13.6% of children aged 4-12 years immunized with 2 doses of measles containing vaccine in infancy had no protective measles specific antibody titres.

Baseline haematology investigations were done for each study participant and WHO cut-off for blood hemoglobin level was used for diagnosing anemia. Proportion of sero-protective measles specific IgG level and the associated factors were the outcome variables. The associated factors studied were age, gender, socioeconomic status, prematurity, birth weight, antibiotic use in the first month after birth, anemia, exclusive breast feeding till 5 months of age, introduction of animal milk before 1 year of age, complementary feeding practices, balanced diet, vitamin deficiencies, maternal factors like maternal age at conception, parity, weight, anemia, maternal measles-specific IgG titre, and measles infection in mother before conceiving the child.

Sample size was calculated taking the proportion of 80% sero-positivity in children who have received 2 doses of measles vaccine based on an Indian study [6]. The calculated sample size was 80.

Statistical analyses: This was done using the software SPSS version 24. Chi square test/ Fishers exact test was used to study the association between categorical variables. Odds ratio (95% CI) were calculated for all variables. Significance level (P value) was set as <5 %.

RESULTS

Of the 81 children [54.3% females; mean (SD) age, 7.5 (2.65) y] recruited for the study, 38.3% were in the age group 4-6 years and 23.5% in 8-10 years. Of these, 75.3% were residing in rural areas, 61.% were from lower socioeconomic class, 25.9% were undernourished, and 51.9% were anemic. Previous history of small for gestational age (17.3%) preterm birth (4.9%), antibiotic use in the first month after birth (32.1%) were noted. Exclusive breast feeding till 5 months of age was done in 81.5% children; 59.3% had animal milk in diet before 1 year of age, and 49.4% had appropriate complementary feeding. Regarding the maternal factors, 7.4% were <20 years, 28.4% were <50 kg, 53.1% were anemic, 24.7% had prior measles infection, and 91.4% had sero-protective measles-specific IgG titre.

The proportion of sero-protective measles specific immunoglobulin G titre in children immunized with 2 doses of measles vaccine was 86.4%. after mean (SD) 6.06 (2.63) of the second dose of the vaccine [median (IQR) duration, 6.2 (3.7, 7.75) year].

On univariate analysis, significant association was found between absence of seroprotective IgG levels and lack of exclusive breast feeding till 5 months of age [OR (95% CI), 7.17 (1.45,35.71); $P=0.007$], anemia [OR (95% CI) 5.04 (95% CI), 1.86, 25.05]; $P=0.03$], under-nutrition [OR (95% CI) 11.69 (2.72, 50.12)]; $P=0.0001$], low socioeconomic status [OR 7.50 (95% CI 1.42, 61.83) $P=0.03$] and higher parity [OR 9.30 (95% CI 2.30, 37.59) $P=0.002$]. No significant association was found with age group of child, gender, place of residence, prematurity, birthweight, antibiotic use in the first month after birth, intake of animal milk before 1 year of age, complementary feeding practices and maternal factors like maternal age at conception, weight, anemia, measles specific immuno-globulin G titres of mother and prior natural measles infection of mother (**Table I**).

DISCUSSION

We found that the among children of age 4-12 years immunized with two doses of measles containing vaccine at 9 months and 15-18 months, 86.4% had protective level of measles-specific immunoglobulin G at around 7-8 year of age. Significant association was found between negative immune response to measles vaccine and under nutrition, anemia, low socioeconomic status, higher parity and lack of exclusive breast feeding till 5 months of age, on univariate analysis.

A previous study from India [5] had reported seropositivity of 21.4% after a single dose of measles

Table I Participants Characteristics and Measles Specific Immunoglobulin G Response (N=81)

Variable	Seroprotective titers ^a	P value
Exclusive breast feeding (5 mo), n=45	43	0.007
Anemia, n=42	33	0.032
Undernutrition, n=2	13	0.001
Upper socioeconomic status, n=31	30	0.032
Primipara, n=35	33	0.002
Protective maternal titer, ^b n=74	64	0.95
Antibiotic use in first mo, n=26	22	0.74
Preterm, n=5	4	0.46
Maternal measles, n=20	17	0.24

^aNTU (Novatec unit); ^bMeasles IgG.

vaccine at 9 months. In another Indian study [6], it was noted that sero-protection rate after two doses of measles containing vaccine was 80% in children of age 4-6 years and 83.3% in children aged 9-12 years. In another study from Kenya [8], 83% had protective antibody titres. In the study by Kizito, et al. [9] regarding risk factors of negative immune response after measles vaccination, significant association was found with malnutrition and maternal retroviral infections. Genetic factors have also been reported to have significant impact on the immune response after measles vaccine, with 2-10% of individuals immunized with two doses of measles, mumps rubella (MMR) vaccine not having protective titers due to genetic polymorphism associated with response [10]. There is a growing interest in applying novel vaccinomics approaches to understand and predict vaccine-induced immune responses [11]. Limitation of this study was a single-center setting, and lack of multivariate analysis.

The number of susceptible subjects among population should be kept below 5% for control of measles (WHO). Since sub-optimal level of seropositivity in mid-childhood was seen in this study, the need for an additional dose of measles containing vaccine for Indian children may be explored in further studies. Under-nutrition, anemia, and lack of exclusive breast feeding are modifiable risk factors for poor immune response, and may be targeted through appropriate interventions.

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REFERENCES

- World Health Organization: New Measles Surveillance Data for 2019. Accessed August 15, 2019. Available from: <http://www.who.int/immunization/newsroom/measles-data-2019/en/>
- Patel MK, Orenstein WA. Classification of global measles cases in 2013-17 as due to policy or vaccination failure: A retrospective review of global surveillance data. *Lancet Glob Health*. 2019;3:313-20.
- Melissa M, Coughlin, Andrew S, Beck, Bankamp B, Rota PA. Perspective on global measles epidemiology and control and the role of novel vaccination strategies. *Viruses*. 2017;9:11.
- Vashishtha VM, Yewale VN, Bansal CP, Mehta PJ. IAP perspectives on measles and rubella elimination strategies. *Indian Pediatr*. 2014;51:719-22.
- Gomber S, Arora SK, Das S, Ramachandran VG. Immune response to second dose of MMR vaccine in Indian children. *Indian J Med Res*. 2011; 134:302-6.
- Hansashree P, Verma S, Rawat A, Sankhyan N, Bharti B. Long-term seroprotection rates following second dose of measles as MMR vaccine at 15 months in Indian children. *Indian Pediatr*. 2018; 55:405-7.
- Torre GL, Saule R, Unim B, et al. The effectiveness of measles mumps rubella vaccination in the prevention of paediatric hospitalization for targeted and untargeted infections: A retrospective cohort study. *Hum Vaccin Immunother*. 2017;13:1879-83.
- Kanga AJ, Kaggia S, Ongusi J, Lwembe RM. Seroprevalence and risk factors associated with measles outbreaks among children in Kwale, Lamu and Narok Counties in Kenya. *J Hum Virol Retrovirol*. 2014;5: 00172.
- Kizito D, Tweyongyere R, Namatovu A, et al. Factors affecting the infant antibody response to measles immunisation in Entebbe-Uganda. *BMC Public Health*. 2013;13:619.
- Haralambieva IH, Kennedy RB, Ovsyannikova IG, Whitaker JA, Poland GA. Variability in humoral immunity to measles vaccine: New Developments. *Trends Mol Med*. 2015;21:789-801.
- Ovsyannikova IG, Pankratz S, Vierkant RA, Jacobson RN, Poland GA. Human leukocyte antigen haplotypes in the genetic control of immune response to measles-mumps-rubella vaccine. *J Infect Dis*. 2006; 193:655-63.
- Morris SK, Awasthi S, Kumar R, et al. Measles mortality in high and low burden districts of India: Estimates from a nationally representative study of over 12,000 child deaths. *Vaccine*. 2013; 31:4655-61.
- Perry RT, Gacic Dobo M, Dabagh A. Progress towards regional measles elimination worldwide. *Morb Mortal Wkly Rep*. 2014; 63:1034 -8.
- Vashishtha VM, Choudhury P, Kalra A, et al. Indian Academy of Pediatrics (IAP) Recommended Immunization Schedule for Children Aged 0 through 18 years – India, 2014 and Updates on Immunization. *Indian Pediatr*. 2014; 51:785-800.
- Haralambieva IH, Ovsyannikova IG, Shane Pankratz S, Jacobson RM, Poland GA. A large observational study to concurrently assess persistence of measles specific B-cell and T-cell immunity in individuals following two doses of MMR vaccine. *Vaccine*. 2011;29:4485-91.