

AGE FOR MEASLES IMMUNIZATION SEROCONVERSION AFTER MEASLES VACCINATION AT 6-8 MONTHS OF AGE—A RANDOMIZED CONTROLLED TRIAL

N. Deivanayagam
N. Ramamurthy
P.V. Krishnamurthy
V.J. Shankar
T.P. Ashok
K. Nedunchelian
N. Mala
S. Shaffi Ahmed

ABSTRACT

The, objective of the study was to compare the effectiveness of measles vaccine by seroconversion in vaccinated children with non-vaccinated children of 6 to 8 months age group in a city slam community so as to study the feasibility of advancing the age of immunization. Live attenuated lyophilized Schwartz strain of measles vaccine was used. Hemagglutination inhibition (HI) antibody was estimated. Seroconversion was defined as either the conversion of negative to positive or a two fold rise in titre. One hundred and thirty two children completed the study. There was no difference in the age, sex and nutritional status between vaccinated and non-vaccinated groups ($p>0.7$). The seroconversion rate in the vaccinated group was 65% and in the non-vaccinated group was 26%. The age, sex and nutritional status did not significantly affect the seroconversion. Our data suggest that immunization with measles vaccine may be effective as early as 6 months of age. Immunization at 6 months may be needed at least for children in densely populated areas like cities and towns.

Key words: Seroconversion, Measles vaccine, Infants, Community.

The current recommended age for measles vaccination in India is after 9 months of age. About 10 to 15% of measles infection occurs in the age group of 6 to 8 months(1,2). The disease in infants has a high morbidity and case fatality. This study was conducted in the community to know the age specific effectiveness, as assessed by seroconversion to measles vaccine (Schwartz strain), at 6-8 months of age with a view to study the feasibility of immunization at an age earlier than 9 months.

Material and Methods

The study was a prospective randomized. trial conducted during 1988. All children between 6-8 months of age in an Integrated Child Development Services (ICDS) Project Area of Madras city were enumerated. Information regarding date of birth, measles immunization and infection were obtained by the Anganwadi workers and verified by one of the investigators from the records. Children with acute infections at the time of recruitment or those who had measles vaccination, measles infection or contact with measles within the past 2 weeks were excluded. Oral consent was obtained from the parents of these eligible children. Children were weighed to the nearest

From the Department of Clinical Epidemiology and Pediatrics, Madras Medical College; Department of Virology, King Institute of Preventive Medicine; and Advanced Centre for Clinical Epidemiological Research and Training (ACCERT) and Clinical Epidemiology Unit (CEU), Institute of Child Health, Madras.

Reprint requests: Dr. N. Deivanayagam, ACCERT/CEU, Institute of Child Health, Hall's Road, Egmore, Madras-600 008.

Received for publication May 7, 1990;

Accepted August 22, 1990

50 g. For nutritional assessment, Wellcome classification was followed. The individual centre in ICDS area was the unit of randomization.

Before immunization, 2 ml of venous blood was collected and 0.5 ml of live attenuated lyophilized Schwartz strain of measles vaccine 1000 TCID₅₀ was given to the study group. Adequate steps were taken for the maintenance of cold chain. Control group was not vaccinated at the time of recruitment. Children were observed at the end of one and two weeks for possible reactions. Second sample of blood was collected after 6 or more weeks. All control group children were vaccinated immediately after the second sample collection. Sera were coded and transported in ice box. They were stored at -20°C till they were tested at the King Institute of Preventive Medicine. Antibody titre was estimated using standard microtitration technique for hemagglutination inhibition (HI) antibody(3). Seronegatives becoming positive or a 2-fold rise in titre were considered as seroconverted and protective(2-4). Vaccine effectiveness was assessed as follows(5):

$$\text{Measles vaccine (seroconversion) effectiveness} = \frac{\text{Failure rate among non-immunized} - \text{Failure rate among immunized}}{\text{Failure rate among non-immunized}}$$

Out of 367 children enumerated in the study area, 205 were recruited, randomized and the first sample of blood was drawn. Six children, three in each group, had measles infection between first and second samples and were excluded. Fisher's exact test, Chi square test, t-test and analysis of variance were used for the analyses.

Results

The baseline characteristics: Sex, age and nutritional status do not significantly differ between the 205 who were recruited, and 162 who were not recruited (p>0.2). The second sample was collected from 92 (70%) children between 6 to 11 weeks, and 40 (30 %) between 12 and 21 weeks. Thus only 132 children completed the study. There was no significant difference in the distribution of sex, age and nutritional status between those who completed and those who failed to complete the study.

The baseline characteristics between the study and control groups are compared in *Table I*. There was no significant difference between the groups in the distribution of the age, sex and nutritional status. The distribution of post-immunization titre values of the study and control

TABLE I –Comparison of Baseline Characteristics Between Study and Control Groups

| Characteristics | Study group (71) | | control group (61)* | |
|---------------------------|------------------|--------|---------------------|--------|
| | n | (%) | n | (%) |
| <i>Sex</i> | | | | |
| Male | 32 | (45.1) | 30 | (49.2) |
| Female | 39 | (54.9) | 31 | (50.8) |
| <i>Age</i> | | | | |
| 6 mo | 21 | (29.6) | 18 | (29.5) |
| 7 mo | 23 | (32.4) | 23 | (37.7) |
| 8 mo | 27 | (38.0) | 20 | (32.8) |
| <i>Nutritional status</i> | | | | |
| Normal | 23 | (32.4) | 20 | (32.8) |
| Under-nutrition+ | 48 | (67.6) | 42 | (67.2) |

*p>0.05 for all variables.

+Includes Marasmus, Study group 1 and Control group 3.

TABLE II- *Distribution of Post-immunization Titre Values of Study and Control Groups According to Age and Pre-immunization Titre Values (Reciprocals)*

| Age (mo) | Pre-imm titre | Study group | | | | | | | | | Control group | | | | | | | | | |
|----------|---------------|-------------|-----|-------------------------|---|----|----|----|-----|---------------------|---------------|-----|---|---|----|----|----|--|---|---|
| | | n | Neg | Post-immunization titre | | | | | | Second sample titre | | | | | | | | | | |
| | | | | 4 | 8 | 16 | 32 | 64 | 128 | 256 | n | Neg | 4 | 8 | 16 | 32 | 64 | | | |
| 6 | Neg | 8 | 2 | | | 3 | 2 | 1 | | | | | – | | | | | | | |
| | 4 | 2 | | | 1 | | | | | | | | 1 | 5 | 3 | 1 | 1 | | | |
| | 8 | 8 | 1 | 1 | | 3 | 2 | 1 | | | | | | 9 | 6 | 1 | | | 1 | 1 |
| | 16 | 1 | 1 | | | | | | | | | | | 1 | 1 | | | | | |
| | 32 | – | | | | | | | | | | | | 1 | 1 | | | | | |
| | 128 | 1 | | | | 1 | | | | | | | | 2 | 1 | | | | 1 | |
| | 256 | 1 | | | | 1 | | | | | | | | – | | | | | | |
| 7 | Neg | 4 | | 1 | | | 2 | 1 | | | | | 4 | 4 | | | | | | |
| | 4 | 6 | 2 | 1 | 1 | | 1 | 1 | | | | | 5 | 2 | 1 | | 1 | | | 1 |
| | 8 | 4 | 1 | | | | 2 | 1 | | | | | 2 | | | 1 | 1 | | | |
| | 16 | 7 | | 2 | 1 | 1 | 1 | 1 | 1 | | | | 6 | 1 | 1 | 2 | | | 1 | 1 |
| | 32 | 2 | | | | 2 | | | | | | | 2 | | | 1 | 1 | | | |
| | 64 | – | | | | | | | | | | | 2 | | 1 | 1 | | | | |
| | 128 | – | | | | | | | | | | | 1 | | | | | | | 1 |
| | 256 | – | | | | | | | | | | | 1 | 1 | | | | | | |
| 8 | Neg | 6 | | | 2 | 1 | 3 | | | | | | 7 | 4 | 2 | | | | 1 | |
| | 4 | 9 | 1 | | 3 | 1 | 3 | 1 | | | | | 3 | | | | | | | 3 |
| | 8 | 3 | 1 | | | 1 | | 1 | | | | | 5 | 4 | 1 | | | | | |
| | 16 | 6 | 1 | | | 3 | | 2 | | | | | 3 | | | 1 | | | 1 | 1 |
| | 32 | 2 | 1 | | | | | 1 | | | | | 1 | 1 | | | | | | |
| | 128 | 1 | | | | | | 1 | | | | | – | | | | | | | |
| | 256 | – | | | | | | | | | | | 1 | | | | | | | 1 |
| Total | | 71 | 11 | 5 | 8 | 17 | 16 | 12 | 1 | 1 | 61 | 29 | 8 | 7 | 4 | 5 | 8 | | | |

groups according to age and pre-immunization titre values are shown in *Table II*.

The results of seroconversion and changes in geometric mean titre (GMT) are presented in *Table III*. The overall seroconversion rate differs significantly between study and control groups ($p < 0.05$). There was no difference in the conversion rates within the age group. There was no significant difference among the 6, 7 and 8 months of age, in their preimmunization GMT levels and also

post-immunization GMT levels in either group ($p > 0.05$). There was a significant increase in GMT after immunization in the study group and a significant decrease in the control group except in the 8th month. The nutritional status did not significantly affect the seroconversion or the change in GMT in the study group ($p > 0.2$). There were no untoward reactions among immunized.

Second sample of blood was collected in 43 and 28 children among study group

TABLE III— Comparison of Seroconversion Rates and Changes in GMT to Measles Vaccine Between Study and Control Groups

| Age (mo) | Study group | | | | Control group | | | |
|----------|-------------|-------------------|-------------|--------------|---------------|-------------------|-------------|--------------|
| | n | Seroconverted (%) | Pre-imm GMT | Post-imm GMT | n | Seroconverted (%) | Pre-imm GMT | Post-imm GMT |
| 6 | 21 | 14 (67) | 8.00 | 16.54* | 18 | 3 (17) | 10.08 | 5.9* |
| 7 | 23 | 13 (56) | 8.24 | 16.49* | 23 | 5 (22) | 12.96 | 8.5* |
| 8 | 27 | 19 (20) | 7.80 | 18.19* | 20 | 8 (40) | 8.00 | 10.2** |
| Total | 71 | 46 (65) | 8.00 | 17.13* | 61 | 16 (26) | 10.27 | 8.1** |

p<0.0001.

**p>0.05 (paired t-test)

and in 36 and 25 among control group after an interval of 6-11 and 12-21 weeks, respectively. The number of children seroconverted for the corresponding time intervals were 28 and 18 in the study group and 6 and 10 in the control group. There was no difference in the seroconversion rates between, the two different time intervals of blood collection in either group. There was no significant difference in the post-immunization GMT values between two time intervals in study group ($p>0.05$) but there was a difference in the control group.

Discussion

This study was done in the community. The laboratory personnel were not provided the clinical details to avoid expectation bias(6). The control group was used to assess the significance. The seroconversion was clinically significant as the conversion rate was 65 %. Measles vaccine effectiveness observed in our study in the field was $(45/61-25/71)/(45/61)=52\%$. Seroconversion rates in vaccine efficacy studies (4,7,8) (seroconversion at ideal conditions and/or for those who have been initially seronegative) are likely to be

higher than the rates in vaccine effectiveness studies (2,9-11) (studies carried out in actual settings and include all children for analysis).

Our data is comparable to that of few studies for the age group of 6-8 months: Latin America (65%) and Halsey (63%)(7,8). However, our finding is different from that of others: lower rates were reported by Katiyar (52%), Dick (45%), Saha (34%) and Ruiz (47%) (9,10,12,13); higher rates were reported from South India (87%). Latin America (65% to 85%) and Kenya (87%) (4,7,14). Apart from other factors, the differences in the observations could be due to variations in the design, measurement and analysis of the studies. In the present study, if vaccine efficacy by seroconversion among seronegatives is alone considered, then the seroconversion rate in the study group was 29/35, i.e., 83 %, in the control group it was 9/24, i.e., 37% and the vaccine effectiveness in the field was 73 %.

If the interval between first and second blood sample collection, is too long, the possibility of subclinical infection contributing to enhanced seroconversion effect is a possible bias. This may be more so

in the control group and thereby reduce the *effectiveness* of the vaccine. There was a high increase in the GMT level among 8-months-old, in both the study and control groups. This could probably be due to sub-clinical infection. This study confirms the finding of others that seroconversion to measles is not influenced by the nutritional status (2,4,15,16).

Though the vaccine effectiveness is not high, it suggested that immunization in India may have to be considered as early as 6 months, at least for children living in densely populated areas like cities and towns where the outbreaks are more and spread of measles is rapid (17). They need another dose after 15 months of age, probably at 18 months of age, along with DPT and OPV (18,19). Close supervision is necessary to ensure that children immunized before the age of 9 months do in fact receive a second dose(20). It has been shown by many studies that low level of immune response in infants do not interfere with subsequent (second) dose of immunization (21-23).

Acknowledgements

The ACCERT project was fully funded by the Indian Council. of Medical Research. The valuable guidance, help and material assistance offered by the Tuberculosis Research Centre of Indian Council of Medical Research, Madras and the help and services offered by the ICDS project VIII personnel, particularly the Medical Officer and the ANMs is very much appreciated and acknowledged.

REFERENCES

1. Lobo J, Reddaiah VP, Kapoor SK, Nath LN. Epidemiology of measles in a rural community. Indian J Pediatr 1987; 54: 261-265.

2. Bhaskaram P, Radhakrishna KV, Madhusudhan J. Seroepidemiological study to determine age for measles vaccination. Indian J Med Res 1986, 83: 480-486.
3. DGHS, Ministry of Health and Family Welfare, Government of India, Manual on Laboratory Procedures of Common Epidemic-Prone Diseases: Measles. New Delhi, National Institute of Communicable Diseases; 1984.
4. Job JS, John TJ, Joseph A. Antibody response to measles immunization in India. Bull WHO 1984, 62: 737-741.
5. Orenstein WA, Bernier RH, Hinman AR. Assessing vaccine efficacy in the field; further observations. Epidem Rev 1988, 10: 212-241.
6. Sackett DL. Bias in analytic research. J Chronic Dis 1979, 32: 51-63.
7. Pan American Health Organization. Seroconversion rates and measles antibody titre induced by measles vaccine in Latin American Children 6-12 months of age. Bull Pan Am Health Organ 1982, 16: 272-284.
8. Halsey NA, Boulos R, Mode F, *et al.* Response to measles vaccine in Haitian infants 6-12 months old. Influence of maternal antibodies, malnutrition and concurrent illness. N Engl J Med 1985, 313: 544-549.
9. Katiyar GP, Kaur G, Agarwal DK, *et al.* Seroconversion response to Meviline-L measles vaccine at age 6-15 months. Indian Pediatr 1985, 22: 653-659.
10. Dick B, Smith T, Kipps A. A minimum age for measles vaccine administration to colored children. S Afr Med J 1975, 49: 1951-1954.
11. Bhatnagar SK, Man Mohan, Kumar P, *et al.* Optimum age for measles immunization: Study of pre- and post-immunization level of HI antibody titre. Indian Pediatr 1981, 18: 625-629.
12. Saha SM, Agarwal RK, Sood DK, Saxena SN. Seroconversion in different age groups after measles vaccination. Indian J Pediatr 1985, 52: 303-305.