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THE EVALUATION OF VACCINATION AGAINST MEASLES AT NINE MONTHS OF AGE
(Report of an epidemic)*

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SUMMARY: Ceyhan M, Kanra G, Vargel S, Işıkçelik Y. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). The evaluation of vaccination against measles at nine months of age (report of an epidemic). Turk J Pediatr 34: 127-133, 1992.

Sixteen measles cases were studied during an epidemic that broke out in Etimesgut district of Ankara. Eight of these children had never been vaccinated against measles while the remainder had been vaccinated at nine months of age. In the sera obtained during the course of the illness, anti-measles antibody was not detectable in six vaccinated children and in four unvaccinated children. Upon observing the siblings of the subjects, it was determined that one out of three who had not been vaccinated against measles and three out of seven who had been vaccinated at nine months of age contracted the disease within a month. However none of the siblings who had been vaccinated against measles at 15 months contracted the disease. In our cases, although vaccination at nine months of age could not prevent measles, it resulted in a milder form of the disease. It seems that measles vaccine administered to infants at around nine months of age does not prevent the occurrence of the disease in many children. *Key words: measles, vaccination, epidemic, anti-measles antibody.*

Measles continues to be a serious health problem in many countries of the world. Of vaccine-preventable diseases, measles remains one of the most important causes of childhood morbidity and mortality in developing countries. Almost all unvaccinated children contract measles, and over two million children die of this disease each year[1,2].

Immunization against measles with a live, attenuated virus vaccine saves lives. A single dose of measles vaccine can produce permanent immunity[3]. National public health recommendations for measles vaccination differ from country to country. In most developed countries, measles vaccine is administered at about the age of 15 months. By then, all maternal antibody has disappeared[4-6]. About 95 percent of children vaccinated at this age develop immunity against measles[7]. Because the disease is mostly seen during the latter part of the first year of life, measles cases continue to occur at a high rate despite successful immunization at 15 months of age[8]. The persistence of maternal antibody that interferes with the

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immune response to vaccination in very young infants hinders immunization at one month of age[9]. Following reports from a number of African, Latin American and Asian countries, suggesting that the optimal age for vaccination against measles in these areas should be about nine months of age, the World Health Organization has also recommended that infants in developing and underdeveloped countries should be immunized against measles at around nine months of age[10-13]. Soon afterwards, almost all developing and underdeveloped countries adopted the policy of vaccinating their infants at the said age. Turkey has also changed its immunization policy, whereby the minimum age for vaccination against measles has been lowered from 15 months to nine months. Since the efficacy of measles vaccination is mostly dependent on elimination of maternal antibody, vaccination administration to infants less than 12 months of age is controversial. The age at which infants completely lose maternal antibody against measles varies from country to country[14]. Since the elimination of maternal anti-measles antibody in Turkish children is not known, it is not possible to determine the optimal age for measles vaccination.

Although it had been previously thought that the incidence of measles had declined in Turkey after the initiation of mass measles immunization campaigns in which infants were vaccinated at nine months of age, we observed a measles epidemic between February and March 1989 in Ankara's Etimesgut district. To obtain data about the efficacy of measles vaccination programs in which infants are inoculated at nine months of age, we studied the clinical features of measles patients during that epidemic.

Material and Methods

This study was undertaken following the presentation of a febrile child with a rash in February 1989, whose symptoms resembled the clinical picture of measles. We then requested that midwives assigned to the Etimesgut district (20 km from Ankara) bring in all children with a rash to the Etimesgut Rural Hospital of Hacettepe University for evaluation. These children were examined by the first author of this paper, and their symptoms and signs were recorded. The vaccination status of the children was assessed by questioning the parents and examining the vaccination records of the Etimesgut Health Center which carries out the vaccination program for the Etimesgut area. Anti-measles antibody levels were determined from blood samples taken four weeks apart, the initial one obtained at presentation. Each child was monitored at home by a midwife who was instructed to bring in to the hospital any child who might be suspected of having signs of complications. All siblings of the subjects were monitored at home by midwives for symptoms of measles. Their vaccination status against measles was also evaluated.

Separated first and second serum samples were stored at −20 °C until titration in the laboratory. Specific antibody titers against measles virus were determined by

a hemagglutination-inhibition test performed in 50 µl volumes in V well microtiter plates using standard procedures. Sera were inactivated at 56 °C for 30 minutes and then absorbed with washed rhesus monkey erythrocytes. Twofold dilutions in PBS (phosphate buffered saline) were prepared in 50 µl volumes to cover the range of 1:5 to 1:640. Following reaction with four units of measles hemagglutination (Behring) for 90 minutes at room temperature, 0.5% v/v erythrocytes were added and the plates were incubated at 37 °C for one hour. Negative control serum and the International Reference Preparation (IRP) of measles antibody were tested on each plate in all tests. End points were read as the highest dilution of serum which inhibited red cell agglutination.

Seroconversion for the diagnosis of acute measles infection in each patient was accepted as the appearance of a fourfold increase in the levels of anti-measles antibody in the second serum sample as against that in the first.

Results

Of the 20 children with fever and rash brought in to the hospital in Etimesgut district, we report 16 cases in whom measles was verified by immunological seroconversion. No seroconversion was demonstrated in the four remaining children, and they therefore were not enrolled in the study. Eight of the 16 subjects with measles had never received a measles vaccination while the remaining eight had been vaccinated at nine months of age (Table I).

As seen in Table I, all subjects demonstrated at least a fourfold increase in anti-measles antibody levels. The initial sera obtained during the course of the illness showed that only two children vaccinated at nine months of age and two unvaccinated children had a detectable antibody level. The antibody levels of the remaining 12 subjects, six vaccinated and six unvaccinated were nondetectable.

Although fever and rash were present in all children (Table II), the duration of the rash was less in the vaccinated group (4.3 ± 2.3 days versus 6.7 ± 3.7 days). During the first two days of the illness, Koplik's spots were present in all unvaccinated children, but were not evident in two vaccinees. The incidence of cough, conjunctivitis and coryza was 5/8 (62.5%), 4/8 (50.0%) and 7/8 (87.5%), respectively in the children who had been vaccinated at nine months of age while all of these signs were present in all unvaccinated children.

While complications such as convulsions (one case) and pneumonia (one case) were observed in the unvaccinated group, there were no complications noted in the vaccinated group.

There were four measles cases from two different families (two from each family) (Table I). The 16 patients in the study had a total 25 siblings who lived in the same house with the subjects during the epidemic (four of them were also subjects of the study). Three of the siblings had not been previously vaccinated against

TABLE I: Anti-measles Antibody Levels of Measles Cases and Vaccination Status of the Cases and their Siblings

Case No.	Age		Antibody Levels		Siblings	
	Infection (yrs)	At Vaccination (mo.)	First Sera	Second Sera	Age At Vaccination (mo.)	Measles
1	3	9	32	≧640	15	–
					15	–
2	9	–	20	320	–	–
					15	–
3	2	9	<5	320	15	–
					–	+***
4*	3.5	9	<5	160	15	–
					15	–
					9	+****
5*	10	–	20	160	15	–
					15	–
					15	–
6	3	9	5	160	9	–
7	9	–	<5	320	9	–
8	5	9	<5	80	15	–
9	11	–	<5	80		
10**	4	9	<5	80	9	+*****
11**	3	9	<5	≧640	9	+******
12	10	–	<5	20	–	–
13	7	–	<5	40	15	–
					9	–
14	2.5	9	<5	320	15	–
					15	–
15	9	–	<5	160	15	–
					15	–
16	13	–	<5	80	9	–

*,** Two separate siblings.
*** Case 5.
**** Case 4.
***** Case 11.
****** Case 10.

TABLE II: Clinical Findings of Measles Cases

Clinical Findings	Vaccinated		Unvaccinated	
	Positive Cases / Cases Examined		Positive Cases / Cases Examined	
Fever (38.5 °C)	8/8	(100 %)	8/8	(100 %)
Rash	8/8	(100 %)	8/8	(100 %)
Duration of rash (mean ± SE) (days)	4.3 ± 2.3		6.7 ± 3.7	
Koplik's spots				
1. day of rash	4/6	(66.6%)	4/4	(100 %)
2. day of rash	5/7	(71.4%)	7/7	(100 %)
3. day of rash	0/8	(0)	2/8	(25 %)
4. day of rash	0/8	(0)	0/8	(0)
Cough	5/8	(62.5%)	8/8	(100 %)
Conjunctivitis	4/8	(50 %)	8/8	(100 %)
Coryza	7/8	(87.5%)	8/8	(100 %)
Complications				
Pneumonia	0/8	(0)	1/8	(12.5%)
Febrile convulsion	0/8	(0)	1/8	(12.5%)

measles, 15 had a measles vaccination at the age of 15 months and seven at the age of nine months. While one of three unvaccinated children and three of seven children vaccinated at nine months contracted the disease, none of the 15 siblings who had been vaccinated at the age of 15 months showed any signs or symptoms of measles.

Discussion

The most important problem in measles immunization is the timing of vaccination. In spite of individual and geographic variations in patterns of maternal antibody transfer and antibody half-life, the World Health Organization recommends that measles immunization in developing and underdeveloped countries be undertaken when an infant reaches nine months of age[12,13]. Health officials in Turkey have adopted this policy. Since the immune response rate has been reported as 80-90 percent when vaccination is undertaken at nine months of age[3], a high vaccination rate was obtained, and therefore, no measles epidemic was expected. When we saw the first measles case in Etimesgut, where an effective vaccination program had been recently carried out, we were alarmed for there was a possibility that measles might crop up in older children because most of them had not been vaccinated. Contrary to our expectation of disease in the

unvaccinated group, half of the children who contracted measles had been vaccinated at nine months of age.

There is no doubt with regard to the preventive role of measles vaccine when administered at 15 months of age, the age at which many children in Etimesgut had been inoculated[15]. None of these children contracted measles during the epidemic. Despite the occurrence of measles in three of seven siblings of cases who had a measles vaccination at nine months of age and in one of three unvaccinated siblings, none of the 15 siblings vaccinated at 15 months contracted the disease.

The ineffectiveness of the vaccination at nine months of age is evident by low levels of anti-measles antibody during the illness. Failure to seroconvert is classified as primary vaccine failure and is generally attributed to neutralization of the attenuated vaccine virus by persistent maternal antibody in infants under 12 months of age or to inadequate immunization[16,17]. The latter may be a consequence of storage conditions and/or handling. On the other hand, secondary vaccine failure refers to the development of clinically apparent infection despite an immune response to vaccination[17,18]. In our subjects, low anti-measles antibody levels indicated primary vaccine failure. Because of a good "cold chain system" in Etimesgut district, neutralization of vaccine virus by maternal antibody is suspected as the reason rather than poor storage and handling conditions. Since we believe that the optimal age for immunization can be accurately predicted for any population by determining anti-measles antibody levels in children during the first few births of life to 12 months of age, another study is being carried out to observe the elimination of maternal anti-measles antibody.

Despite the absence of protective antibody levels, an obvious variation in clinical course was present in the vaccinated cases. The duration of rash was less and there was a lower incidence of cough, coryza and conjunctivitis in the vaccinated cases than in the unvaccinated cases. Koplik's spots were not present in two vaccinated cases. Although two unvaccinated cases developed complications, there were no complications noted in the cases who had been vaccinated at nine months of age. It seems that even if vaccination at nine months of age does not prevent the occurrence of measles, it results in a milder form of the disease.

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