

Measles Vaccine Failure in 9-month-old Infants

Dokuz Aylık Bebeklerde Kızamık Aşısı Yetersizliği

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Abstract

Objective: Lower seroconversion rates in live attenuated measles vaccines are detected in children aged 9 months or younger. We aimed to evaluate the effect of some infant characteristics (including growth status, yogurt consumption, infectious diseases, anemia, and serum zinc and selenium levels) on primary measles vaccine failure.

Materials and Methods: We enrolled 147 healthy 9-month-old infants who were being attended to in the Social Pediatrics Unit for measles vaccination. Parameters, including maternal history of measles infection, vaccination status, infant sex, birth weight, gestational age, pattern of breastfeeding, amount of daily yogurt consumption, growth parameters, and history of infectious diseases, were recorded. Serum anti-measles IgG titers on Days 0 and 42, serum zinc and selenium levels on Day 0, and serum tumor necrosis factor (TNF)- α levels on Day 42 were analyzed.

Results: Seroconversion rate was 62.6%. Among maternal and infant factors, the frequency of infant yogurt consumption of ≥ 75 mL/day was less in the non-seroconverted group ($p=0.018$). Multiple logistic regression analysis confirmed that the seroconversion rate was high in children with yogurt intake of ≥ 75 mL/day than in those with yogurt intake of <75 mL/day [OR:2.85 (95% CI:1.12–7.24)].

Conclusion: More than one in three infants who were vaccinated at 9 months of age had primary vaccine failure. Nutritional status, including anemia and serum selenium and zinc levels, did not affect vaccine response. In future studies, the effect of yogurt consumption on seroconversion might be investigated.

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Keywords: Yogurt, measles, vaccine failure, selenium, zinc

Özet

Amaç: Dokuz aydan küçük bebeklerde canlı zayıflatılmış kızamık aşısı sonrası düşük serokonversiyon oranları bildirilmiştir. Bu çalışmada, bazı anne ve bebek özelliklerinin (büyüme durumu, yoğurt tüketimi, enfeksiyon hastalıkları, anemi, serum çinko ve selenyum düzeyi) primer aşı yetersizliğine etkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Kızamık aşısı için Sosyal Pediatri Ünitesine başvuran 147 sağlıklı dokuz aylık bebek çalışmaya alındı. Annenin kızamık enfeksiyon öyküsü ve aşılanma durumu ile bebeğin gebelik haftası, doğum ağırlığı, cinsiyeti, emzirme durumu, günlük yoğurt tüketimi, büyüme parametreleri, enfeksiyon hastalıkları öyküsü ve aşı yan etkisi sorgulandı. Bebekten kan alınarak kızamık IgG düzeyi (aşının 0. ve 42. günü); tam kan sayımı, serum çinko ve selenyum düzeyi (Aşılama öncesi); serum TNF- α düzeyi (aşılamanın 42. günü) analiz edildi.

Bulgular: Serokonversiyon oranı 62.6%'dır. Anne ve bebek özelliklerinden sadece bebek yoğurt tüketiminin serokonversiyon oranını etkilediği görüldü ($p=0.018$). Çoklu lojistik regresyon analizi yoğurt tüketimi 75 mL/gün ve daha fazla olan bebeklerde serokonversiyon oranının yüksek olduğu görüldü [OR:2.85 (95%CI:1.12-7.24)].

Sonuç: Kızamık aşısı yapılan dokuz aylık her üç bebekten biri primer aşı yetersizliği göstermektedir. Serum selenyum ve çinko düzeyleri, anemi ve beslenme durumu aşı yanıtını etkilememektedir. Serokonversiyon üzerine yoğurt tüketiminin etkisi daha ileri çalışmalarla değerlendirilebilir. (*J Pediatr Inf* 2015; 9: 153-60)

Anahtar kelimeler: Yoğurt, kızamık, aşılanma etkinliği, selenyum, çinko

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Introduction

Although the measles vaccine has been part of routine national childhood vaccination programmes for at least 20 years, measles remains a public health concern for outbreaks that challenge basic measles control (1-3). In a review of

published studies regarding measles outbreaks during the last decade, approximately 10.5% (range=0.25%–83%) of all measles cases occurred in children younger than the recommended age for the first vaccine dose in Europe (2). Younger infants are losing maternal antibodies earlier, and thus, become susceptible to

measles before routine immunization at 12 months of age in developed countries (3, 4). As a result of this shift, the risk of measles mortality among infants remains high in countries with ongoing transmission, and thus, the measles vaccine should be administered at 9 months of age (5). In some countries, vaccination of infants as young as 6 months is recommended during outbreaks to reduce the burden of the disease. However, studies indicate low measles specific humoral immunity, both neutralizing antibody titers and avidity, in young infants who are immunized even in the absence of passive antibodies. The barriers of earlier vaccination have been the presence of maternal antibodies and dysmaturity of the neonatal immunological system (2). These limitations are age dependent and appear to mature around 9 months (4). In several studies, with respect to the response to live attenuated measles vaccines, lower seroconversion rates were observed in children at 9 months of age or younger than in those at 12 months (2). Primary vaccine failure, which has been mainly attributed to suboptimal humoral immune responses to the measles vaccine, is the major source of vaccine failure (1). Approaches to eradicate measles should include the management of primary vaccine failure.

Some factors might influence vaccine efficacy, including host factors, such as age at immunization, presence of passive antibody, infectious diseases, nutritional status, and vaccine-specific issues (1, 4, 6-9). There are some controversial studies regarding the nutritional status or presence of illnesses on immune response (7, 8, 10-15). Micronutrients, including zinc and/or selenium, have important roles in the function of the immune system (16, 17) because they have been demonstrated to be improved in zinc- and/or selenium-deficient populations who have been administered supplements. However, there are limited studies regarding the effect of zinc and selenium levels on antibody responses to vaccines (11, 16-18).

A number of studies have demonstrated that some pro- and prebiotic formulations reduce the risk and in some cases, the duration or severity of infections. In addition, consuming some probiotic strains may enhance vaccine responses in children (19-23), adults (24-28), and elderly (29), although evidence is not entirely consistent (30, 31). Youngster et al. (23) found that infants (8–10 months old) who were administered probiotics as a powder [*Lactobacillus acidophilus* ATCC4356, *Bifidobacterium bifidum* DSMZ20082, *B. longum* ATCC157078, and *B. infantis* ATCC15697 (Altman Probiotic Kid Powder)] for 5 months, starting 2 months prior to the mumps, measles, rubella, and varicella vaccination, had more frequently protective IgG antibody titers at 3 months post-vaccination compared with infants in the placebo group. Vaccine-specific IgA titer to an oral poliovirus vaccine was

increased after consuming yogurt-containing LGG and *L. paracasei* ssp. *paracasei* during a 5-week intervention, with the live attenuated poliomyelitis vaccine being administered on Day 8 (24). Conventional commercially available “yogurt”, which is a fermented milk product by *L. bulgaricus* and *S. thermophilus*, is the main component of complementary food in infants in Turkey (32). Daily yogurt intake has been reported to have some stimulating effects on immune functions (33, 34). However, there is no published study regarding the effect of yogurt consumption on the measles vaccine failure.

Infants, aged 9 months, are high-risk groups for the measles vaccine failure and any intervention which support appropriate infant growth and improve immune status evaluated. If some causes of vaccine failure are determined, efforts could be made to overcome some of the obstacles that are associated with immunizing young infants during outbreaks. We have planned this study to evaluate the role of some maternal and infant factors (including breastfeeding, dietary yogurt intake, growth status, infectious diseases, anemia, and serum zinc and selenium levels) on primary vaccine failure, which is an important problem for measles eradication. In addition, we investigated the effect of seroconversion on serum tumor necrosis factor (TNF)- α levels.

Material and Methods

Study Participants: Healthy 9-month-old infants who were being attended to in the Children’s Hospital Social Pediatrics Unit for measles vaccination were enrolled. Infants were excluded if they had a history of allergic or other reactions to any previous vaccination; had a history of epilepsy or immunodeficiency; used chronic drug therapy; or were administered immunosuppressive therapy or blood products or immunoglobulins at 3 months before enrolment. A total of 147 infants of voluntary parents were suitable for the enrolment criteria.

This study was approved by the Ethical Committee (LUT 05/21).

Enrolment visit: After acquiring informed consent, some characteristics of mothers (vaccination status and history of measles infection) and infants (sex, gestational age, birth weight, duration of total and exclusive breastfeeding, and weight and height on admission) were obtained with a questionnaire at enrolment. On Day 0, pre-vaccination blood sample was drawn. Then, one dose of live attenuated measles vaccine (EU 2415, Edmonston-Zagreb strain, Serum Institute of India, Hadapsar, India) was subcutaneously administered in a volume of 0.5 mL in the left upper arm. Follow-up forms, including temperature record, any event, and yogurt consumption, were

provided to parents. Daily yogurt consumption was measured using a glass (200 mL).

Day 0–15: Safety and reactogenicity were assessed for 15 days with daily completion of the follow-up forms by parents/guardians. Subjects were monitored for immediate reactions in the first 30 min following vaccine injection. Parents/guardians recorded the occurrence, intensity, and duration of solicited injection site (tenderness, redness, and swelling) for the first 4 days post-vaccination and the systemic (fever, vomiting, drowsiness, appetite lost, irritability, rash, coryza, diarrhea) reactions occurring on the day of vaccination and after 15 days. The presence of fever was confirmed by an axillary temperature reading. Intensity of solicited local reactions and fever was graded on a 0–3 scale. Ratings were given as follows: for tenderness, grade 1 (injection site pain), 2 (painful on moving), and 3 (spontaneously painful and/or preventing normal activity); for redness/swelling, grade 1 (diameter, <20 mm), 2 (diameter, 20–50 mm), and 3 (diameter, >50 mm); and for fever, grade 1 (37.5–38°C), 2 (38–39°C), and 3 (>39°C). The occurrence of any other unsolicited event was noted. Additionally, they were asked to record any events and intercurrent illness, which required medical attention, occurring up to 30 days post-vaccination. Information was recorded in the follow-up forms for each subject.

Post-vaccination visit: Infants were controlled on Day 42 post-vaccination. Dietary intake of daily yogurt, breastfeeding status, and any history of infectious diseases were recorded since Day 0. Weight and height were measured again, and the second set of blood samples was collected.

Anthropometric measurement: The percentiles of the median of weight-for-age, weight-for-height, and height-for-age were calculated from the World Health Organization Multicentre Growth Reference Study (35).

Yogurt intake: Infants can be administered yogurt from 6 months of age as a part of complementary food. Stomach size of a 9-month-old infant is 150–200 mL, and an infant should consume a meal containing dairy products, vegetable, meat, and cereals at the same time (36). A portion of dairy may be a pot or 150 g of yogurt. Therefore, half the portion was taken as the cutoff point.

Serological assessment and methods: Blood samples for serological assessment were collected from all subjects before vaccination (Day 0) and 42 days post-vaccination (Day 42). Pre-vaccination blood samples were collected for determining complete blood count and

serum zinc, selenium, and anti-measles IgG levels. Post-vaccination blood samples were collected for determining TNF- α and anti-measles IgG levels on Day 42. Complete blood count [hemoglobin (Hb) level, mean corpuscular volume (MCV), red cell distribution width (RDW), and leucocyte counts] was measured using a cell counter (CoulterSTKS, Lion) from EDTA-containing tubes. Other blood samples were centrifuged, and serum samples were separated and stored at -20°C until measurement. Zinc levels were determined using the atomic absorption spectrophotometer Varian Techtron model 1200 (Varian Techtron, Melbourne, Vic., Australia), and selenium levels were analyzed using the fluorometric procedure that was defined by Lalonde et al. (37). Measles-specific IgG antibody levels in both samples were measured by enzyme-linked immunosorbent assay (ELISA) using a quantitative commercial kit (Euroimmun Anti-measles ELISA IgG; Luebeck, Germany) according to the manufacturer's protocol. Seroconversion was defined as the appearance of detectable antibody levels in the serum of subjects who were seronegative before vaccination. Seroboosting was defined as a four-fold increase in ELISA titers of individuals who were seropositive before vaccination. Serum TNF- α level was measured with a TNF- α ELISA kit (TNF- α ELISA IM1121 Immunotech, Beckman Coulter Company; Marseille Cedex, France) according to the manufacturer's protocol at the Hospital of Hacettepe University, Laboratory of Biochemistry.

Statistical analysis

Statistical analysis was performed using IBM® SPSS® Statistics for Windows 21.0 (SPSS Inc.; Chicago, IL, USA). The normality of data distribution was checked using the Kolmogorov–Smirnov test. The independent samples t test or Mann-Whitney U test for skewed data was used to compare the differences between nonseroconverted group (NSG) and seroconverted group (SG). Categorical analysis was performed by the χ^2 or Fisher's exact test, as appropriate. Multiple logistic regression analysis (method=backward stepwise) was used to determine independent predictors of seroconversion. Hosmer–Lemeshow goodness of fit statistics was used to assess the model fit. A p value of <0.05 was considered to be statistically significant result.

Results

The persistence of passive antibodies was detected in three (2.0%) cases on Day 0. Of these three cases, one case had a similar antibody titer in the second sera, and two cases had an antibody titer below the detectable value. Of all cases, 62.6% of infants were seroconverted on Day 42; there were 55 infants in the NSG group and 92 infants in the SG group.

There was no difference in birth weight between the groups (3093±648 g in NSG, 3216±591 g for SG; $p=0.242$). The two groups were similar for maternal history of measles vaccination and illness, infant sex, low birth weight, breastfeeding status (exclusive breastfeeding duration and current breastfeeding status), infant's history for infectious diseases, and anthropometric measurement (Table 1). The frequencies of malnourished cases according to height-for-age and weight-for-age

were similar between the groups. There were no cases with <75% of the median weight-for-age.

Hb level, leucocyte count, and serum zinc and selenium levels did not differ between the groups. There were no differences in the frequencies of anemia ($Hb<11$ g/dL) and low selenium and zinc levels between the groups (Table 2).

The frequencies of antipyretic use, local tenderness, irritability, fever, coryza, and rashes between Days 0 and 15 were similar between the groups (Table 3). Post-vaccination, 10 infants had upper respiratory tract infec-

Table 1. Baseline characteristics of cases according to vaccine response, n (%)

	Non seroconverted	Seroconverted	p
n	55	92	
Maternal history for measles vaccination	31 (56.4)	50 (54.3)	0.812
Maternal history for measles infection	27 (49.0)	39 (42.3)	0.429
Infant Characteristics			
Sex, Male	33 (60.0)	49 (53.3)	0.426
Gestational age <37 week	7 (12.7)	10 (10.9)	0.733
Birth weight <2500 g	8 (14.5)	8 (8.1)	0.270
Exclusive breastfed ≥ 6 mo	29 (52.7)	47 (50.1)	0.847
Breastfeeding at 9 mo	43 (78.2)	64 (69.6)	0.256
History of infectious diseases during last month before vaccination	12 (21.8)	23 (25.0)	0.661
Height at 9 mo, cm*	72.3±3.0	72.5±2.6	0.770
<90% of the median height for age, n (%)	3 (5.5)	3 (3.3)	0.672
Weight at 9 mo, g*	9038±1029	9162±1077	0.495
<90% of the median weight for age, n (%)	6 (10.9)	11 (12.0)	0.848
*mean±SD			
SD: standard deviation			

Table 2. Blood parameters of infants on Day 0 according to vaccine response, mean±SD

	Non seroconverted	Seroconverted	p
Blood count			
Available sample, n	53	88	
Hemoglobin, g/dL	11.0±0.8	11.1±1.0	0.808
Hemoglobin<11 g/dL, n (%)	21 (39.6)	32 (36.3)	0.699
MCV<70 fL, n (%)	5 (9.4)	14 (15.9)	0.275
RDW $\geq 14.5\%$, n (%)	17 (32.1)	34(38.6)	0.432
Leucocytes/mm ³	10766±2591	11242±3078	0.348
Serum selenium levels			
Available sample, n	44	84	
Mean levels, $\mu\text{g/L}$	58.2±10.1	57.7±10.5	0.787
Levels<50 $\mu\text{g/L}$, n (%)	9 (25.5)	19 (22.6)	0.778
Serum zinc levels			
Available sample, n	33	58	
Mean levels, $\mu\text{g/dL}$	102.3±31.6	105.1±30.3	0.677
Levels<65 $\mu\text{g/dL}$, n (%)	2 (6.1)	6 (10.3)	0.488
SD: standard deviation			

Table 3. Vaccine side effects and any infectious diseases following vaccination, n (%)

	Non seroconverted	Seroconverted	p
Vaccine side effects			
Local tenderness, Days 0–3	0 (0.0)	2 (2.2)	0.528
Fever, Days 5–15	10 (18.2)	7 (7.6)	0.052
Irritability, Days 5–15	23 (41.8)	26 (28.8)	0.092
Coryza, Days 5–15	12 (21.8)	14 (15.2)	0.310
Rash, Days 5–15	3 (5.5)	9 (9.8)	0.536
Any infectious disease post-vaccination	3 (5.5)	11 (12)	0.194

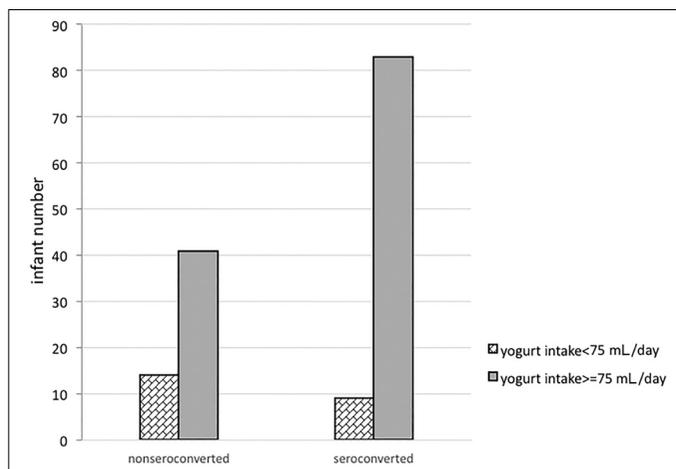


Figure 1. Vaccine response according to yogurt consumption (p=0.018)

tion and four had acute gastroenteritis; there were no differences in the frequencies of infectious disease between the groups.

There were no differences between the groups with respect to weight gain between Days 0 and 42 (414±249 g for NSG and 345±252 g for SG, p=0.112).

Daily mean (±SD) yogurt consumption was 114±71 g for NSG and 125±49 g for SG (p=0.307). However, the frequency of yogurt consumption of ≥75 ml/day was less in the NSG group than in the SG group (74.5 % and 90.2%, respectively; p=0.018; Figure 1).

Serum TNF-α levels were similar in both the groups on Day 42 [median (25p–75p); 28.3 pg/mL (19.3–37.6) for NSG, 28.3 pg/mL (14.5–44.7) for SG; p=0.940].

To identify predictors of seroconversion, we performed backward stepwise logistic regression analysis. From the factors, including maternal history of measles disease and measles vaccination, gestational age (≥37 vs. <37 week), gender (female vs. male), birthweight (≥2500 vs. <2500 g), weight for age (≥90 vs. <90% of median weight for age), infectious disease during last month (yes vs. no), Hb level (≥11 vs. <11 g/dL), infectious disease post-vaccination (yes vs. no), infant yogurt intake (≥75 vs. <75 mL/day), and current breastfeeding at 9 months of age (yes vs. no), multiple logistic regression

analysis confirmed that the seroconversion rate was high in children with yogurt intake of ≥75 mL/day than in those with yogurt intake of <75 mL/day [OR:2.85 (95% CI:1.12–7.24), p=0.027].

Discussion

Primary vaccine failure at 9 months of age was 37.4%. Previous studies reported similar rates of 10%–39% (9-11, 38-42).

Macro- and micronutrient deficiencies, including iron, zinc, and selenium, were supposed to have a role in maintaining an optimal immune response; however, previous studies did not demonstrate any association between malnutrition and immune response to the measles vaccine (7, 15-18, 43). Similarly, no effects of nutritional status and serum zinc and selenium levels on seroconversion to measles vaccination were observed in this study.

In our study, seroconverted cases more frequently consumed yogurt. This might be explained by the potential immune response by yogurt (33, 34, 44). Some studies reported an immune-enhancing effect following oral attenuated *Salmonella typhi* Ty21a vaccine, oral attenuated poliomyelitis vaccine, oral cholera vaccine, and attenuated influenza vaccine in adults who were treated with probiotics (24-30). There are also previous studies reporting an enhanced antibody response in infants who were treated with probiotics following hepatitis B vaccinations and *Haemophilus influenzae* type b and oral rhesus-human re-assortant rotavirus vaccine (19-21). In contrast, Pérez et al. (45) recently demonstrated that probiotic supplementation has no effect on antibody responses following diphtheria, tetanus, pertussis, and *H. influenzae* type b and 23-valent pneumococcal vaccines in children of low socioeconomic status in Argentina. West et al. (22) reported some probiotic enhanced anti-diphtheria antibody titers only in infants who were breastfed for <6 months in that study when adjusted for breastfeeding duration. Recently, Youngster et al. (23) reported that there was no interference between probiotic supplementation and immune response of healthy infants to measles,

mumps, rubella, and varicella vaccination; however, a trend towards a better antibody responses in the probiotic treatment group, with more infants reaching protective titers at 3 months post-immunization. Overall, some studies in infants demonstrate an increase in vaccine response, but this is not entirely consistent. It is too early to draw any conclusions regarding the potential influence of probiotics on the response to vaccination. However, commercial yogurt consumption for infants might improve not only vaccine response but also nutritional status. Randomized controlled studies with yogurt supplementation are required.

Measles immunization activates memory T cells with CD4- and CD8-positive subsets that produce cytokines, which are critical in the development and regulation of the entire immune response. Cell signaling of the T-helper 1 type favors cytokine production that governs cellular immunity, such as TNF- α (46). However, we found no differences in serum TNF- α levels between seroconverted and nonconverted cases. Further studies are necessary to detect differences *in vitro* cytokine production.

There are some limitations for this study. The best markers for viral vaccine efficacy are unclear. Vaccine efficacy was based on the identification of humoral immunity, but recent data suggest that T-cell immunity may be equal or more important. This study included yogurt consumption and breastfeeding status; other foods were not analyzed. However, yogurt is the main fermented food consumed by infants.

Conclusion

In conclusion, more than one in three infants who were vaccinated at 9 months of age had primary vaccine failure. Nutritional status, including selenium and zinc levels, did not affect vaccine response. To the best of our knowledge, this is the first study to evaluate the possible role of yogurt on measles vaccine efficacy in infants aged 9 months. Yogurt consumption should be encouraged. In further studies, the effect of yogurt consumption on seroconversion could be investigated with other live vaccines.

Ethics Committee Approval: Ethics committee approval was received for this study from Hacettepe University Ethical Committee (LUT 05/21).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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- D.K.; Analysis and/or Interpretation - S.S.Y., D.K.; Literature Review - S.S.Y., D.K.; Writing - S.S.Y.

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