Measles Vaccine Failure in 9-month-old Infants

Sıddika Songül Yalçın[1], Defne Engür Karasımav[2], Kadriye Yurdakök[1]
[1]Department of Child Health and Diseases Social Pediatrics Unit, Hacettepe University School of Medicine, *Ankara, Turkey*
[2]Neonatal and Intensive Care Unit, İzmir Tepecik Training and Research Hospital, *İzmir, Turkey*

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 nonseroconverted 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. *(J Pediatr Inf 2015; 9: 153-60)*

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

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

Received: 20.08.2015
Accepted: 27.11.2015

Correspondence Address:
Sıddika Songül Yalçın
E-mail:
siyalcin@hacettepe.edu.tr

This study was presented at the 2nd International Symposium of Probiotics Prebiotics in Pediatrics, 7-9 March 2014, Antalya, Turkey.

DOI: 10.5152/ced.2015.2195

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 diary 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; Marseile Cedex, France) according to the manufacture'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 Kolmogrov–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 infection 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].

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≥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, µg/L	58.2±10.1	57.7±10.5	0.787
Levels<50 µg/L, n (%)	9 (25.5)	19 (22.6)	0.778
Serum zinc levels			
Available sample, n	33	58	
Mean levels, µg/dL	102.3±31.6	105.1±30.3	0.677
Levels<65 µg/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

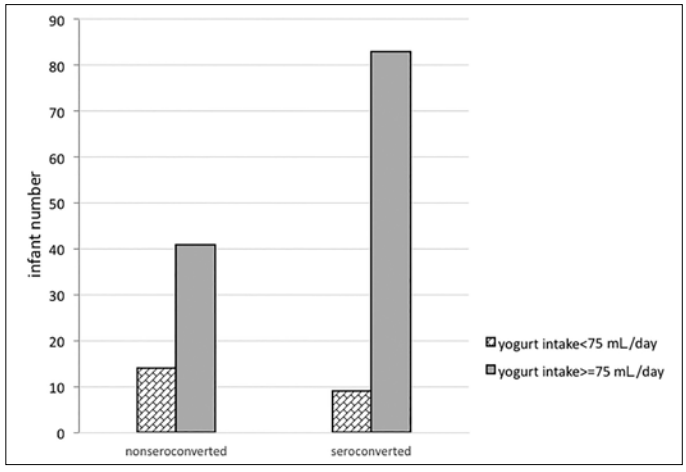

Figure 1. Vaccine response according to yogurt consumption (p=0.018)

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.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.S.Y., D.K.; Design - S.S.Y., DK; Supervision - S.S.Y., K.Y.; Data Collection and/or Processing - D.K.; Analysis and/or Interpretation - S.S.Y., D.K.; Literature Review - S.S.Y., D.K.; Writing - S.S.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: Supported by Hacettepe University Scientific Research Unit (Project no: 05 T02 101 001/05 D01 101 001).

References

1. Centers for Disease Control and Prevention. Prevention of Measles, Rubella, Congenital Rubella Syndrome, and Mumps, 2013. MMWR 2013; 62(No. RR-4): 1-33.
2. Leuridan E, Sabbe M, Van Damme P. Measles outbreak in Europe: susceptibility of infants too young to be immunized. Vaccine 2012; 30: 5905-13. [CrossRef]
3. Takashima Y, Schluter WW, Mariano KML, et al. Progress toward measles elimination - Philippines, 1998-2014. MMWR Morb Mortal Wkly Rep 2015; 64: 357-62.
4. Gans HA. The status of live viral vaccination in early life. Vaccine 2013; 31: 2531-7. [CrossRef]
5. World Health Organization. WHO position on measles vaccines. Vaccine 2009; 27: 7219-21. [CrossRef]
6. Gans H, Yasukawa L, Rinki M, et al. Immune responses to measles and mumps vaccination of infants at 6, 9, and 12 months. J Infect Dis 2001; 184: 817-26. [CrossRef]
7. Halsey NA, Boulos R, Mode F, et al. Response to measles vaccine in Haitian infants 6 to 12 months old. Influence of maternal antibodies, malnutrition, and concurrent illnesses. N Engl J Med 1985; 313: 544-9. [CrossRef]
8. Krober MS, Stracener CE, Bass JW. Decreased measles antibody response after measles-mumps-rubella vaccine in infants with colds. JAMA 1991; 265: 2095-6. [CrossRef]
9. Fowotade A, Okonko IO, Nwabuisi C, et al. Measles vaccine potency and sero-conversion rates among infants receiving measles immunization in Ilorin, Kwara State, Nigeria. J Immunoassay Immunochem 2015; 36: 195-209. [CrossRef]
10. 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. [CrossRef]
11. Yalcin SS, Yurdakök K, Özalp I, et al. The effect of live measles vaccines on serum vitamin A levels in healthy children. Acta Paediatr Jpn 1998; 40: 345-9. [CrossRef]
12. Chandra RK. Reduced secretory antibody response to live attenuated measles and poliovirus vaccines in malnourished children. Br Med J 1975; 2: 583-5. [CrossRef]
13. Cilla G, Peña B, Marimón JM, et al. Serologic response to measles-mumps-rubella vaccine among children with upper respiratory tract infection. Vaccine 1996; 14: 492-4. [CrossRef]
14. 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. [CrossRef]
15. Moore SE, Goldblatt D, Bates CJ, et al. Impact of nutritional status on antibody responses to different vaccines in undernourished Gambian children. Acta Paediatr 2003; 92: 170-6. [CrossRef]
16. Broome CS, McArdle F, Kyle JA, et al. An increase in selenium intake improves immune function and poliovirus handling in adults with marginal selenium status. Am J Clin Nutr 2004; 80: 154-62.

17. Hoffmann PR, Berry MJ. The influence of selenium on immune responses. Mol Nutr Food Res 2008; 52: 1273-480. [CrossRef]
18. Kreft B, Fischer A, Kruger S, et al. The impaired immune response to diphtheria vaccination in elderly chronic hemodialysis patients is related to zinc deficiency. Biogerontology 2000; 1: 61-6. [CrossRef]
19. Isolauri E, Joensuu J, Suomalainen H, et al. Improved immunogenicity of oral D x RRV reassortant rotavirus vaccine by Lactobacillus casei GG. Vaccine 1995; 13: 310-2. [CrossRef]
20. Kukkonen K, Nieminen T, Poussa T, et al. Effect of probiotics on vaccine antibody responses in infancy--a randomized placebo-controlled double-blind trial. Pediatr Allergy Immunol 2006; 17: 416-21. [CrossRef]
21. Soh SE, Ong DQ, Gerez I, et al. Effect of probiotic supplementation in the first 6 months of life on specific antibody responses to infant Hepatitis B vaccination. Vaccine 2010; 28: 2577-9. [CrossRef]
22. West CE, Gothefors L, Granström M, et al. Effects of feeding probiotics during weaning on infections and antibody responses to diphtheria, tetanus and Hib vaccines. Pediatr Allergy Immunol 2008; 19: 53-60. [CrossRef]
23. Youngster I, Kozer E, Lazarovitch Z, et al. Probiotics and the immunological response to infant vaccinations: a prospective, placebo controlled pilot study. Arch Dis Child 2011; 96: 345-9. [CrossRef]
24. de Vrese M, Rautenberg P, Laue C, et al. Probiotic bacteria stimulate virus-specific neutralizing antibodies following a booster polio vaccination Eur J Nutr 2005; 44: 406-13. [CrossRef]
25. Link-Amster H, Rochat F, Saudan KY, et al. Modulation of a specific humoral immune response and changes in intestinal flora mediated through fermented milk intake. FEMS Immunol Med Microbiol 1994; 10: 55-63. [CrossRef]
26. Olivares M, Díaz-Ropero MP, Sierra S, et al. Oral intake of Lactobacillus fermentum CECT5716 enhances the effects of influenza vaccination. Nutrition 2007; 23: 254-60. [CrossRef]
27. Paineau D, Carcano D, Leyer G, et al. Effects of seven potential probiotic strains on specific immune responses in healthy adults: a double-blind, randomized, controlled trial. FEMS Immunol Med Microbiol 2008; 53: 107-13. [CrossRef]
28. Rizzardini G, Eskesen D, Calder PC, et al. Evaluation of the immune benefits of two probiotic strains Bifidobacterium animalis ssp. lactis, BB-12® and Lactobacillus paracasei ssp. paracasei, L. casei 431® in an influenza vaccination model: a randomised, double-blind, placebo-controlled study. Br J Nutr 2012; 107: 876-84. [CrossRef]
29. Boge T, Rémigy M, Vaudaine S, et al. A probiotic fermented dairy drink improves antibody response to influenza vaccination in the elderly in two randomized controlled trials. Vaccine 2009; 27: 5677-84. [CrossRef]
30. Bunout D, Hirsch S, Pía de la Maza M, et al. Effects of prebiotics on the immune response to vaccination in the elderly. JPEN J Parenter Enteral Nutr 2002; 26: 372-6. [CrossRef]
31. Matsuda F, Chowdhury MI, Saha A, et al. Evaluation of a probiotics, Bifidobacterium breve BBG-01, for enhancement of immunogenicity of an oral inactivated cholera vaccine and safety: a randomized, double-blind, placebo-controlled trial in Bangladeshi children under 5 years of age. Vaccine 2011; 29: 1855-8. [CrossRef]
32. Yalçın SS, Yalçın S. Probiotic food (Probiyotik gıdalar). In: Kara A, Coşkun T. Prebiotics and Probiotics from Theory to Clinics (Teoriden Kliniğe Prebiyotikler Probiyotikler). Akademi Uluslararası Yayıncılık San ve Tic Ltd Şti. İstanbul. 2014; 405-32 [In Turkish].
33. Meyer AL, Micksche M, Herbacek I, et al. Daily intake of probiotic as well as conventional yogurt has a stimulating effect on cellular immunity in young healthy women. Ann Nutr Metab 2006; 50: 282-9. [CrossRef]
34. Elmadfa I, Klein P, Meyer AL. Immune-stimulating effects of lactic acid bacteria in vivo and in vitro. Proc Nutr Soc 2010; 69: 416-20. [CrossRef]
35. Centers for Disease Control and Prevention. WHO Growth Standards Are Recommended for Use in the U.S. for Infants and Children 0 to 2 Years of Age. Available at http://www.cdc.gov/growthcharts/who_charts.htm Accessed July 1, 2015.
36. Yalçın SS. Tamamlayıcı beslenmeye geçiş. In: Türkiye Milli Pediatri Derneği Sosyal Pediatri Derneği Ortak Kılavuzu 2014; 40-7. http://www.millipediatri.org/UserFiles/kilavuzlar/kilavuz-2.pdf
37. Lalonde L, Jean Y, Roberts KD, et al. Fluorometry of selenium in serum or urine. Clin Chem 1982; 28: 172-4.
38. Ceyhan M, Kanra G, Erdem G, et al. Immunogenicity and efficacy of one dose MMR vaccine at twelve months of age as compared to monovalent measles vaccination at nine months followed by MMR revaccination at fifteen months of age. Vaccine 2001; 19: 4473-8. [CrossRef]
39. Evliyaoglu N, Altintas D, Kilic NB, et al. Measles antibody response in vaccinated children. Turk J Pediatr 1996; 38: 315-21.
40. Işık N, Uzel N, Gökçay G, et al. Seroconversion after measles vaccination at nine and fifteen months of age. Pediatr Infect Dis J 2003; 22: 691-5. [CrossRef]
41. Redd SC, King GE, Heath JL, et al. Comparison of vaccination with measles-mumps-rubella vaccine at 9, 12, and 15 months of age. J Infect Dis 2004; 189: 116-22. [CrossRef]
42. Techasena W, Sriprasert P, Pattamadilok S, et al. Measles antibody in mothers and infants 0-2 years and response to measles vaccine at the age of 9 and 18 months. J Med Assoc Thai 2007; 90: 106-12.
43. Savy M, Edmond K, Fine PE, et al. Landscape analysis of interactions between nutrition and vaccine responses in children. J Nutr 2009; 139: 2154-218. [CrossRef]
44. Borchers AT, Keen CI, Gershwin ME. The influence of yogurt/ lactobacillus on the innate and acquired immune response. Clin Rev Allerg Immunol 2002; 22: 207-30. [CrossRef]

45. Pérez N, Iannicelli JC, Girard-Bosch C, et al. Effect of probiotic supplementation on immunoglobulins, isoagglutinins and antibody response in children of low socio-economic status. Eur J Nutr 2010; 49: 173-9. **[CrossRef]**

46. Jacobson RM, Ovsyannikova IG, Vierkant RA, et al. Independence of measles-specific humoral and cellular immune responses to vaccination. Hum Immunol 2012; 73: 474-9. **[CrossRef]**