Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2021 Oct 07; 9(B):1219-1223.
https://doi.org/10.3889/oamjms.2021.6685
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Infective Diseases*

OPEN ACCESS

The Role of Sex, Ethnicity, Age, and Nutritional Status in the Seropositivity of the Measles Vaccine

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Edited by: Ksenija Bogoeva-Kostovska
Citation: Nurlatifah HRT, Barlianto W, Wiyasa IWA, Kusuma HMSC, Sari TL, Bachtiar NS. The Role of Sex, Ethnicity, Age and Nutritional Status in the Seropositivity of the Measles Vaccine. Open Access Maced J Med Sci. 2021 Oct 07; 9(B):1219-1223. https://doi.org/10.3889/oamjms.2021.6685
Keywords: Antibody; Determinant factors; Immunization; Measles; Seroconversion
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E-mail: nhr6008@gmail.com
Received: 21-Jun-2021
Revised: 24-Sep-2021
Accepted: 27-Sep-2021

Funding: This study was supported by the Ministry of Research, Technology, and Higher Education, Republic of Indonesia (grant no. 055/SP2H/LT/DRPM/2019)
Competing Interests: The authors have declared that no competing interests exist

Abstract

AIM: This study investigates the relationship between sex, ethnicity, age, nutritional status with the seropositivity of the Edmonston-Zagreb vaccine in children.

METHODS: A cross sectional, observational study was conducted. A total of 45 children were differentiated based on sex, ethnicity, age, and nutritional status when they received the Edmonston-Zagreb measle vaccine for the first time. Flow cytometry was used to look at differences in antibody status as well as populations of CD-4 and CD-8 cells that release IFN- γ.

RESULTS: We found no significant differences in antibody levels or CD-4 and CD-8 cell populations that secrete IFN- γ between boys and girls ($p > 0.05$). Besides, similar results were also confirmed in comparisons between Javanese and Sundanese ethnic groups, 9 months versus more than 9 months of age, or normal versus low body mass index ($p > 0.05$).

CONCLUSIONS: We conclude that sex, race, age, and nutritional status had no effect on immune response to vaccination. As a result, there was no barrier to seroconversion and optimal immunological performance in the children in this trial who received the Edmonston-Zagreb measles vaccination.

Introduction

The measles virus is a single-stranded RNA paramyxovirus that enters the body and circulates systemically to suppress the body's immune response [1], [2], [3]. Measles complications include otitis media, pneumonia, and acute encephalitis [4]. Vaccination, herd immunity, and infection with wild-type viruses are three steps that can be taken to prevent measles infection [5]. Becaues the effect is extremely lethal on children, the World Health Organization (WHO) has designated elimination as its top priority. Measles elimination is achieved when no measles virus transmission is detected in a given area over a 12-month period under the supervision of an adequate surveillance system [6], [7].

In Indonesia, only 80% of people have been immunized against measles. The number of reported cases has increased since 2014 [8], [9]. In 45 percent of these cases, the first dose of vaccination had been administered [10]. Vaccination can prevent 92 percent of infections with a single dose and more than 99 percent with multiple doses [11], [12]. This is particularly intriguing given that a previous study has shown that changing the antigenic structure of the measles virus does not allow the virus to escape the body's immune response. One of the reasons for the emergence of the outbreak case was a drop in antibody levels caused by the passage of time in areas where measles had been eradicated. In other words, wild-type viruses provide no stimulus for antibody induction [13], [14].

According to various studies, the immunity obtained as a result of vaccine administration is influenced by both stable and dynamic factors. Sex, ethnic, and age are examples of static and uncontrollable factors. Age, exposure to environmental antigens, prior infection and maternal passive immunity are some of the associated dynamic factors [15], [16], [17]. The effect of sex and ethnic on vaccine immune response

is still unknown. A previous study found no association between biological sex and cellular and humoral response factors. Regarding racial differences, it comes to racial differences, African-American races have more antibodies and cell-mediated immunity responses than Caucasian races [18]. Vaccination failure was higher at 8 months of age compared to 9–11 months of age [19]. Mothers who acquired natural infection, on the other hand, had higher antibody levels than vaccinated mothers, suggesting a higher potential for maternal transmission [20]. As far as we know, no study has been conducted in Indonesia to evaluate the factors of immunological response in measles vaccination. In Indonesia, research is focusing on the determinants of vaccine coverage and its dynamics [21], [22], [23]. As a result, the goal of this study is to investigate the immune response determinants in measles vaccination in Indonesia.

Materials and Methods

Subjects

The children in this study were vaccinated against measles at the Plumbon Health Center in Cirebon, West Java, Indonesia. The inclusion criteria for this trial were children in good health, no history of past infection, and parents agreeing to participate in the study. Children who were sick had a history of previous infections, or whose parents refused to participate in the study were all excluded from the study.

Vaccine

The vaccine used is the Serum Institute India's Edmonston-Zagreb measles vaccine (Pune, India). This vaccine is a combination of the MR vaccine and another vaccine. The vaccine given is the first dose as part of an Indonesian vaccination program (Batch Number 0128W0780 and 0128W0800).

Analysis of demographic factors

Sex, ethnicity, and age are among the demographic factors examined. When administering the first dose of vaccination, demographic factor analysis was performed.

Nutritional factor analysis

Among the nutritional parameters investigated were body weight, height, mass index (BMI). Nutritional variables were assessed concurrently with the delivery of the first dose of immunization.

Measles-specific neutralizing antibody assay

According to prior research, this antibody assay was assessed utilizing a plaque-reduction microneutralization technique and a recombinant measles virus strain [24]. Seropositivity was defined as an antibody level of 120 mIU/ml (disease protection was assumed) [25]. The minimum detectable antibody concentration in our analysis was 106.95 mIU/ml.

Flow cytometry

The determination of measles-specific T cells producing IFN-γ was performed according to a previous studies [24], [26]. Surface antibodies against CD8 (PE/Cy5 Anti-human CD8a Antibody, Biolegend, cat.no. 300910) and CD4 (FITC Anti-human CD4 Antibody, Biolegend, cat.no. 317408) were used to label cell suspensions. We used anti-IFN-γ antibody (Biolegend, USA, cat.no. 502509) for intracellular cytokine staining. The flow cytometry acquisition and analysis software FACScalibur (Becton Dickinson, USA) was used.

Statistical analysis

The mean ± standard deviation was used to present all data. For comparison, the student's t-test or Mann-Whitney test were applied. For each of the markers, linear regression was used to perform the association between the determinants. All analysis was conducted by SPSS software (IBM Corporation, New York City, USA). p-values of < 0.05 were considered significant.

Results

Table 1 shows the 45 infants aged 9-11 months who got the Edmonston-Zagreb measles vaccine. There were only two ethnic variations among all subjects based on self-declared ethnicity. There were 37.1% of subjects who were Javanese and 62.9% of

Table 1: Subject characteristics according to demographic, anthropometric, and nutritional status

Variable	Categories	Value or frequency (%)
Age of child (months)		9.83 ± 0.86
Sex of child	Female	16 (45.71)
	Male	19 (54.29)
Age at vaccination	9 months	17 (48.57)
	>9 months	18 (51.43)
Ethnicity	Javanese	13 (37.14)
	Sundanese	22 (62.86)
Anthropometric	Weight (kg)	8.26 ± 1.05
	Height (cm)	68.67 ± 3.00
	BMI (kg/m^2)	17.52 ± 1.69
Nutritional status (BMI for age)	Normal (−2-+2 SD)	32 (91.42)
	Undernourished (< -2 SD)	3 (8.58)

BMI: Body mass index; SD: Standard of deviation. Value are presented as mean ± standard of deviation, frequency are presented as percentage.

Table 2: Specific antibody and cellular immunity according to subject's demographic and nutritional status

Variable	Categories	Antibody (mIU/mL)	P-value[a]	CD4 T cells secreting IFN-γ (%)	P-value[b]	CD8 T cells secreting IFN-γ (%)	P-value[b]
Sex of child	Female	453.57 ± 386.10	0.140	7.81 ± 3.84	0.445	5.19 ± 3.53	0.990
	Male	259.42 ± 160.30		6.83 ± 3.62		5.20 ± 3.43	
Age at vaccination	9 months	369.12 ± 363.05	0.493	7.86 ± 3.17	0.423	6.02 ± 3.05	0.143
	> 9 months	371.44 ± 272.72		6.89 ± 4.27		4.30 ± 3.21	
Ethnicity	Javanese	460.17 ± 394.50	0.226	7.20 ± 3.26	0.842	4.28 ± 2.35	0.232
	Sundanese	317.11 ± 257.83		7.46 ± 4.04		5.73 ± 3.88	
Nutritional status	Normal	383.73 ± 329.24	0.811	7.30 ± 3.77	0.750	5.29 ± 3.50	0.602
	Undernourished	240.95 ± 88.10		8.04 ± 3.70		4.18 ± 2.88	

Value is presented as mean ± standard of deviation; frequency are presented as percentage; [a]Mann-Whitney test; [b]Independent t-test; *P*<0.05 was considered significant statistically, IFN-γ: Interferon-γ.

Sundanese. From anthropometric measurement, the mean weight of the subjects was 8.26 1.05 kg, while the mean length and mean body mass index were 68.67 3.00 cm and 17.52 1.69 kg/m2 respectively. There were three subjects classified as undernourished based on the BMI for age in the WHO growth chart. All of the study participants were in healthy condition and had never had a measles vaccination before nor had a measles natural infection.

Table 2 shows comparison between antibody immune titers, CD4 T or CD8 T cells that produce IFN-γ according to demographic factors. Boys had higher immune titers to antibodies than girls, but it was not statistically significant (p > 0.05). In terms of CD4 or CD8 T cells that produce IFN-γ, there was no significant difference between both subjects (p > 0.05). The Javanese have higher antibody immune titers than the Sundanese but the difference is insignificant (p > 0.05). This insignificant finding was also observed in IFN-γ producing CD4 or CD8 T cells between Javanese and Sundanese, (p > 0.05). There was no difference in post-immunization immune response (p > 0.05) between groups that received the vaccine at 9 months and groups that received the vaccine after 9 months. The normal BMI group had greater antibody immune titers than the low BMI group, although the difference was not statistically significant (p > 0.05).

Table 3 depicts the relationship between demographic factors and post-immunization immune responses. Measles-specific antibody levels were not associated with sex, age, or ethnicity (p > 0.05). There was no correlation (p > 0.05) between measles-specific antibody levels and body weight, height, or BMI. Anthropometric indices were also unassociated with measles-specific T cells producing IFN-γ (p > 0.05). The findings of this study did not show an association between demographic, anthropometric characteristics, and humoral/cellular immune responses to measles vaccine.

Table 3: Associations between demographic and anthropometric on specific antibody and celular immunity

Variable	Antibody	CD4 T cells secreting IFN-γ	CD8 T cells secreting IFN-γ
Sex of child	0.057	0.445	0.990
Age at vaccination	0.491	0.617	0.601
Ethnicity	0.202	0.842	0.232
Body weight	0.051	0.766	0.320
Body length	0.427	0.190	0.900
BMI	0.053	0.976	0.787

Value is presented as *P* value from linear regression test; *P*<0.05 was considered significant statistically; BMI: Body mass index, IFN-γ: Interferon-γ.

Discussion

Seropositive control and low vaccine efficiency are multifaceted and depend on the vaccination program's capability, vaccine potency, and host characteristics (particularly the immune system as a consequence of age and nutritional status) [27]. Vaccination rates were higher in boys than in girls, but not by a significant statistically. This suggests that sex has no effect on the development of post-vaccination immune responses. This finding contradicts previous study which found that after receiving the Edmonston-Zagreb vaccine, girls' antibodies were higher than boys' [28].

In this study, there was no difference in post-immunization immune response between immunizations given at 9 months of age versus vaccines given after 9 months of age. This finding suggests that the age of the immunization vaccine is not a factor in the development of an adequate immune response. This finding is consistent with previous study, which found that age at first vaccine administration had no effect on seroconversion or long-term seropositivity to measles [4]. There was also no significant difference between the Javanese and the Sundanese in this study. This finding suggests that ethnic factors have no effect on immune response, especially in ethnic groups from Indonesia. When it comes to racial differences, African-American races have more antibodies and cell-mediated immunity responses than Caucasian races [18].

Poor nutritional status suppresses cell-mediated immunity and contributes to the emergence of vaccine-induced complications [29], [30], [31]. There were no significant variations in antibody titers or CD4 or CD8 T cells secreting IFN-γ between the low BMI and normal BMI groups, according to this study. This shows that an adequate immune response can be achieved in both good and poor nutritional conditions. This finding agrees with previous findings [32], but contradicts other studies that show a reduced immune response in children with poor nutritional status [33].

Overall, the study's weaknesses include the small number of samples, fact that it was only conducted at one center rather than a multi-center study, and the involvement of only two tribes. The next study will focus on a larger sample size, multiple centers, and various ethnic in Indonesia.

Conclusions

It was determined that sex, ethnicity, age, and nutritional state had no effect on immunological response to measles vaccination. As a result, there is no barrier to seroconversion and optimal immunological accomplishment when the children in this trial get the Edmonston-Zagreb measles vaccination. In other words, these factors have no effect on the effectiveness of measles vaccination-induced immunity.

Recommendations

The administration of the Edmonston-Zagreb measles vaccine to the children in this study presents no barriers to seroconversion and optimal immune achievement, indicating that this vaccine is feasible and effective for children in Indonesia.

Ethical Approval

The Health Research Ethics Committee, Faculty of Medicine, Brawijaya University, Malang, East Java, Indonesia, approved this study (No:250/EC/KEPK-S3/09/2019). The subject's parents were informed and signed informed consent forms.

Authors Contributions

TNHR, WB, IWAW, HMSCK, NSB conceived and designed the experiments; TNHR, TLS performed the experiments; TNHR, TLS analyzed and interpreted the data; TNHR, WB, NSB contributed reagents, materials, analysis tools or data; TNHR, WB, TLS wrote the paper. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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