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]. Because 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 outbreaks occur. 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

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

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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 measles 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 secrete IFN-γ. The authors have declared that no competing interests exist.

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.

Keywords: Antibody; Determinant factors; Immunization; Measles; Seroconversion

Editorial

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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/m²) | 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.
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 2: Specific antibody and cellular immunity according to subject's demographic and nutritional status

| Variable                  | Categories | Antibody (mIU/mL) | P-value<sup>a</sup> | CD4 T cells secreting IFN-γ (%) | P-value<sup>b</sup> | CD8 T cells secreting IFN-γ (%) | P-value<sup>b</sup> |
|---------------------------|------------|-------------------|---------------------|---------------------------------|---------------------|---------------------------------|---------------------|
| Sex of child              | Female     | 453.57 ± 386.10   | 0.140               | 7.81 ± 3.84                     | 0.449               | 5.19 ± 3.53                     | 0.990               |
|                           | Male       | 258.42 ± 160.30   | 0.445               | 6.83 ± 3.62                     | 0.493               | 5.20 ± 3.43                     | 0.423               |
| Age at vaccination         | 9 months   | 389.12 ± 363.05   | 0.493               | 7.86 ± 3.17                     | 0.423               | 6.02 ± 3.05                     | 0.143               |
|                           | > 9 months | 371.44 ± 272.72   | 0.842               | 6.89 ± 4.27                     | 0.232               | 4.28 ± 2.35                     | 0.053               |
| Ethnicity                 | Javanese   | 460.17 ± 394.50   | 0.226               | 7.20 ± 3.26                     | 0.750               | 5.29 ± 3.77                     | 0.602               |
|                           | Sundanese  | 371.11 ± 207.83   | 0.842               | 7.46 ± 4.04                     | 0.232               | 4.16 ± 2.88                     | 0.053               |
| 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 | 0.053               | 8.04 ± 3.70                     | 0.493               | 4.28 ± 2.78                     | 0.053               |

<sup>a</sup> Value is presented as mean ± standard deviation; 
<sup>b</sup> P<0.05 was considered significant statistically; 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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