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[Omer Okuyan](#) , Seyma Dumur , [Yusuf Elgormus](#) , [Uğurcan Sayılı](#) , [Hafize Uzun](#) *

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Article

The Effect of Meningococcal Vaccines on New Generation of Systemic Inflammatory Markers in Children

Omer Okuyan ¹, Seyma Dumur ², Yusuf Elgormus ¹, Ugurcan Sayili ³ and Hafize Uzun ^{2,*}

¹ Istanbul Atlas University, Faculty of Medicine, Medicine Hospital, Department of Pediatrics, Istanbul, Turkey

² Istanbul Atlas University, Faculty of Medicine, Department of Medical Biochemistry, Istanbul, Turkey

³ Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Public Health, Istanbul, Turkey

* Correspondence: huzun59@hotmail.com

Abstract: Objective: Meningococcal meningitis (MM) is an acute, severe respiratory infectious disease caused by *Neisseria meningitidis* and remains an important cause of morbidity/mortality in children. Immunization with meningococcal vaccine (MV) is the most effective measure to control and prevent the transmission of MM. In this study, in order to support the appropriate use of various MVs in the prevention of MM, the effects of MVs, especially single-dose and inter-booster administered, on inflammatory parameters in <5-year-old children were investigated. **Methods:** A total of 464 healthy children were included in this study. The data of those who received the first 2 doses at 2-month intervals and the next dose between 8-12 months were included. Nimenrix (Pfizer) administered as a single dose to children from 12 months of age. Bexsero (GSK) was administered as 2+1 doses under 2 years of age and 2 doses 2 months apart over 2 years of age. Neutrophil, lymphocyte, monocyte, platelet counts, C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), derived NLR (dNLR), platelet-to-lymphocyte ratio (PLR), systemic inflammation response index (SIR-I) and systemic immune inflammation index (SII) were evaluated. **Result:** Of the 464 participants, 58.2% were male, with a mean age of 3.81 years, and both sex ratios and ages were similar across the Nimenrix and Bexsero groups. The laboratory and inflammatory parameters of the two vaccine groups were similar. In both vaccine groups, changes in laboratory parameters before and after vaccination were similar. The changes in laboratory parameters over time between vaccine groups and their interactions were not significant. **Conclusion:** The new generation of systemic inflammatory index as NLR, derived NLR (dNLR), PLR, SIR-I and SII are useful biomarkers indicating the inflammatory response of Nimenrix and Bexsero vaccines. Local and systemic adverse events were not observed in children followed up 3 months after vaccination. However, further studies involving larger patient cohorts as well as detailed laboratory data on specific markers of inflammation are needed to draw comprehensive conclusions regarding the inflammatory response following vaccination.

Keywords: Meningococcal vaccine; Nimenrix; Bexsero; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; systemic inflammation response index; systemic immune inflammation index

Introduction

Meningococcal diseases are one of the major causes of mortality and morbidity worldwide. The disease is clinically rapid and aggressive due to the difficulty in controlling endotoxin-associated vascular damage caused by the causative microorganism [1]. Worldwide, an estimated 1.2 million meningococcal infections occur annually and 135,000 of these cases result in death [2]. Looking at the death statistics of the Turkish Statistical Institute after 2009, the number of deaths related to meningococcal disease was reported as 154. Serious sequelae such as deafness, convulsions, limb amputation and mental retardation are observed in 5-30% of survivors [3].

Vaccination is the best way to protect the patient against this aggressive disease that leaves little time for intervention after the onset of symptoms [4]. Since the vast majority of invasive meningococcal are encapsulated and most diseases are caused by several serogroups, vaccine studies have targeted capsular polysaccharides of meningococci. There are two types of meningococcal vaccines (MVs): polysaccharide and conjugate [5]. Since most of the disease occurs in previously healthy individuals with no risk factors, vaccination is important in these age groups [6,7]. Blood samples including complete blood count, coagulation parameters, biochemistry, inflammatory markers such as C-reactive protein (CRP), procalcitonin and blood culture should be obtained quickly [8,9].

Neutrophils, lymphocytes and platelets are involved in the control of inflammation and systemic inflammation is associated with changes in the quantity and composition of circulating blood cells such as neutrophilia, lymphopenia and thrombocytosis [10]. Mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have recently been investigated as novel inflammatory markers in many diseases [11]. MPV is a potential marker of platelet count and activity and correlates with inflammation and inflammation severity [12]. NLR may be useful for predicting the activity of autoimmune and inflammatory diseases [13]. PLR is used as an index for the inflammatory state in various diseases. It is suggested that these markers can be used in various clinical situations to identify patients and the prognosis of the disease or to predict health status [14,15].

In the literature review, there is no study suitable for our purpose. In this study, in order to support the appropriate use of various MVs in the prevention of Meningococcal meningitis (MM), the inflammatory effects of MVs, especially single-dose and inter-booster administered, on inflammatory parameters in 5-year-old children were investigated.

Materials and Methods

Ethical approval of this study was obtained by the Non-Interventional Ethics Committee of the Medical Faculty of Istanbul Atlas University (04.03.2024; No: E-22686390-050.99-40431). The study was performed in accordance with the Helsinki Declaration, and informed consent was obtained from the families of all patients prior to their inclusion in the study.

The presenting complaints, clinical and laboratory findings, treatment and follow-up of patients admitted to the Pediatric Outpatient Clinic between 2018 and 2024 within the scope of meningococcal routine vaccination were evaluated retrospectively. A flow chart of the selection of cases is shown in Figure 1.

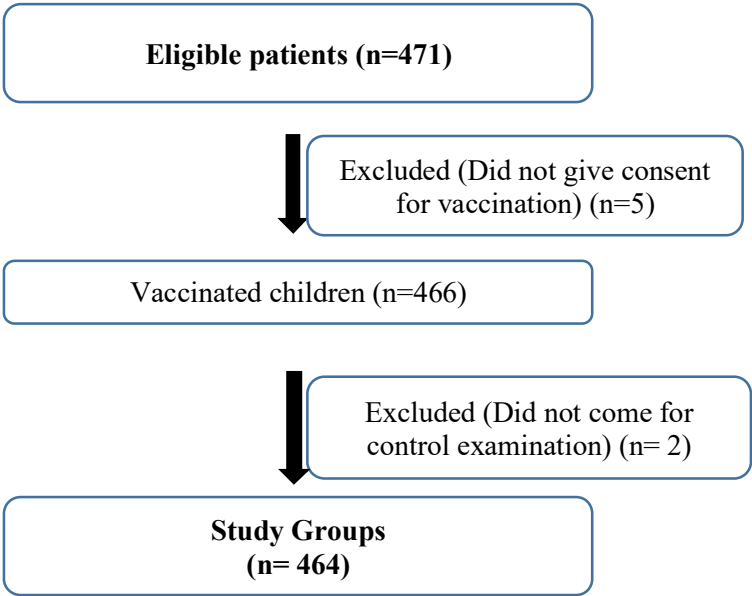


Figure 1. A flow chart of the selection of cases.

The data of those who received the first 2 doses at 2-month intervals and the next dose between 8-12 months were included. The MenACWY-TT conjugate vaccine (Nimenrix®, Pfizer) administered as a single dose to children from 12 months of age. The 4-component meningococcal serogroup B vaccine (4CMenB, Bexsero®, GSK) was administered as 2+1 doses under 2 years of age and 2 doses 2 months apart over 2 years of age. No one in our hospital had a febrile convulsion after vaccination in our hospital.

Inclusion Criteria

Four hundred and sixty-four healthy children aged 3.81 ± 1.48 years who applied for routine vaccination were included in the study.

Exclusion Criteria

Patients with chronic disease, chronic diarrhea, heart disease, malnutrition, central nervous system infection, respiratory system infection, patients who had used antibiotics in the last month or patients who had been treated in any center before admission were excluded from the study. At the same time, those who had had an allergic reaction to meningococcal or a similar vaccine and those with known allergies to any substance in the vaccine were excluded from the study.

In our hospital, vaccinated children are routinely followed up and side effects of vaccines are evaluated after 3 months. The effects of vaccines on inflammatory parameters were evaluated with CRP and new generation inflammatory biomarkers.

Laboratory Assessments

Venous blood samples were taken from all patients at the time of admission. For CBC, 0.5–2 mL of blood was drawn into purple capped ethylenediaminetetraacetic acid (EDTA) tubes and measured in an automatic blood count device (Sysmex XN 1000, Roche Diagnostics GmbH, Mannheim, Germany) within 1 h at the latest.

The derived NLR (dNLR) was calculated as follows: Neutrophil count / (White cell count – Neutrophil count).

The NLR was calculated as follows: Neutrophil count / Lymphocyte count

The PLR was calculated as follows: Platelet count / Lymphocyte count

The SII was calculated with formula as follows: (Neutrophil count x Platelet count) / Lymphocyte count.

The systemic inflammation response index (SIR-I) was calculated with formula as follows: (Neutrophil count x Monocyte count)/Lymphocyte count.

The serum CRP levels were measured using the nephelometric method (Immage 800 Beckman Coulter, CA 92821, USA).

Statistical Methods

IBM SPSS (The Statistical Package for the Social Sciences) version 21.0 software was used for the evaluation and analysis of the data. Descriptive statistics were expressed as frequencies (n) and percentages (%) for categorical variables and means $\pm$ standard deviations or medians (25th percentile - 75th percentile) for numerical variables. The normality of continuous variables was assessed using histograms and Q-Q plots. Furthermore, hypothesis tests were conducted to determine the relationships between variables. The chi-square test was used to compare categorical variables. Independent samples t tests or Wilcoxon tests were applied to compare continuous variables between two independent groups. Paired samples t tests or Wilcoxon tests were applied to compare continuous variables between two dependent groups. Finally, two-way repeated-measures ANOVA was used to examine interactions between groups. A p value < 0.05 was considered to indicate statistical significance.

Results

Of the 464 participants, 58.2% were male, and the sex ratio was similar between the vaccine groups (Nimenrix: 55.5% male/44.5% female vs. Bexsero: 60.9% male/39.1% female; p=0.239). The

mean age of the participants was 3.81±1.48 years, and the ages were similar between the vaccine groups (Nimenrix: 3.77±1.46 years vs. Bexsero: 3.85±1.51 years; p=0.570).

None of the patients had fever, cough, wheezing, rhinorrhea, shortness of breath, history of previous the Paediatric and Neonatal Intensive Care Unit (PICU/NICU) and hospitalisation before vaccination. While 11.9% of the Bexsero group had fever after vaccination, none of the Nimenrix group had fever. Three months after vaccination, none of the patients in both groups had cough, wheezing, rhinorrhea, shortness of breath, history of previous NICU/PICU and hospitalization.

There were no statistically significant differences between the Nimenrix and Bexsero groups in any of the laboratory parameters before and after vaccination. All inflammatory parameters were similar between the two groups (Table 1).

Table 1. Comparison of laboratory parameters between vaccine types.

	Vaccine Type					
	Nimenrix		Bexsero			
	Mean±Std	Median(25p-75p)	Mean±Std	Median(25p-75p)	p value	
Before Vaccination	WBC (10 ³ /μL)	7918±1401	8030(6820-9000)	7970±1445	8080(6910-9200)	0,565*
	HGB (g/dL)	11.58±1.83	11.1(10.6-12.2)	11.45±1.81	11.1(10.5-12.2)	0,530*
	HCT (%)	34.4±4.64	33.3(31.8-35.9)	33.88±4.72	33.1(31.2-35.3)	0,223*
	PLT (10 ³ /μL)	316721±5940 4	318000(271000-363000)	316836±6553 9	318000(267000-361000)	0.984†
	LYM (10 ³ /μL)	4.67±1.38	4.86(3.5-5.64)	4.7±1.52	4.65(3.65-5.48)	0.833†
	NEUTROPHIL (10 ³ /μL)	2.55±1.1	2.34(1.75-3.2)	2.63±1.22	2.43(1.7-3.32)	0.477†
	MONOCYTE (10 ³ /μL)	0.99±0.32	0.96(0.73-1.25)	0.99±0.42	0.9(0.65-1.25)	0,298*
	PLR	74.09±28.03	69.01(54.78-84.47)	74.67±31.55	68.46(54.41-84.35)	0,855*
	NLR	0.63±0.39	0.55(0.33-0.82)	0.63±0.4	0.57(0.33-0.83)	0,801*
	SII	196.68±124.7 5	171.28(107.19-245.07)	197.62±128.2	173.71(108.16-251.85)	0,938*
	dNLR	0.56±0.43	0.48(0.28-0.67)	0.61±0.53	0.47(0.28-0.7)	0,893*
	SIR-I	0.57±0.33	0.48(0.34-0.74)	0.63±0.5	0.47(0.29-0.84)	0,761*
	CRP (mg/L)	1.85±1.37	1.25(0.76-2.76)	1.81±1.28	1.25(0.85-2.55)	0,955*
	WBC (10 ³ /μL)	7775±1298	7680(6720-8830)	7800±1423	7880(6590-8920)	0,804*
	HGB (g/dL)	11.53±1.21	11.4(10.8-12.2)	11.52±1.13	11.4(10.8-12.2)	0,858*
HCT (%)	34.41±3.03	34.1(32.5-36.3)	34.32±2.99	34(32.4-36.3)	0,998*	
After Vaccination	PLT (10 ³ /μL)	312886±6294 8	306000(272000-361000)	309030±6732 9	299000(262000-355000)	0.524†
	LYM (10 ³ /μL)	4.52±1.26	4.46(3.53-5.31)	4.64±1.65	4.51(3.34-5.73)	0.366†
	NEUTROPHIL (10 ³ /μL)	2.67±1.09	2.4(1.86-3.38)	2.51±1.04	2.39(1.68-3.28)	0.122†
	MONOCYTE (10 ³ /μL)	0.94±0.47	0.76(0.62-1.09)	0.95±0.43	0.81(0.63-1.25)	0,387*
	PLR	73.41±21.03	69.57(57.12-83.53)	74.63±30.49	69.17(53.87-86.06)	0,522*
	NLR	0.66±0.39	0.57(0.36-0.81)	0.64±0.44	0.52(0.34-0.74)	0,162*
	SII	201.47±112.9 7	178.07(116.04-269.14)	192.51±129	154.93(103.77-256.46)	0,106*
	dNLR	0.6±0.4	0.5(0.34-0.75)	0.57±0.44	0.43(0.29-0.73)	0,095*
	SIR-I	0.63±0.46	0.52(0.26-0.9)	0.63±0.52	0.47(0.23-0.9)	0,538*
	CRP (mg/L)	1.69±1.03	1.35(0.95-2.35)	1.88±1.25	1.45(0.95-2.61)	0,264*

Abbreviations: WBC: White blood cell; HGB: hemoglobin; HCT: hematocrit; PLT: platelet; LYM: lymphocyte; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; SII: systemic immune-inflammatory index; dNLR: derived neutrophil-to-lymphocyte ratio; SIR-I: neutrophil count × monocyte count / lymphocyte count ; CRP: C reactive protein. †: Independent samples t test; *: Mann-Whitney U test.

In the Nimenrix group, only the monocyte count decreased significantly after vaccination (0.96 (0.73-1.25) vs. 0.76 (0.62-1.09); p=0.004). Changes in all other parameters before and after vaccination

were not statistically significant. In the Bexsero group, there was a significant increase in hemoglobin (11.1 (10.5-12.2) vs. 11.4 (10.8-12.2); p=0.015) and hematocrit (33.1 (31.2-35.3) vs. 34 (32.4-36.3)) levels, while changes in other parameters were not significant. Changes in inflammatory parameters were not significant in either group. (Table 2).

Table 2. Comparison of pre- and post-vaccination laboratory parameters within vaccine types and over time.

		Vaccine Type						Two-way repeated measures ANOVA p value		
		Nimenrix			Bexsero			Time	Vaccine Type	Time*Vaccine Type
		Before Vaccination	After Vaccination	p value	Before Vaccination	After Vaccination	p value			
WBC (10 ³ /μL)	Mean±Std	7918±1401	7775±1298	0.186*	7970±1445	7800±1423	0.102*	0,091	0,671	0,88
	Median(25p-75p)	8030(6820-9000)	7680(6720-8830)		8080(6910-9200)	7880(6590-8920)				
HGB (g/dL)	Mean±Std	11.58±1.83	11.53±1.21	0.113*	11.45±1.81	11.52±1.13	0.015*	0,951	0,47	0,54
	Median(25p-75p)	11.1(10.6-12.2)	11.4(10.8-12.2)		11.1(10.5-12.2)	11.4(10.8-12.2)				
HCT (%)	Mean±Std	34.4±4.64	34.41±3.03	0.058*	33.88±4.72	34.32±2.99	0.001*	0,374	0,248	0,389
	Median(25p-75p)	33.3(31.8-35.9)	34.1(32.5-36.3)		33.1(31.2-35.3)	34(32.4-36.3)				
PLT (10 ³ /μL)	Mean±Std	316721±59404	312886±62948	0.478†	316836±65539	309030±67329	0.186†	0,146	0,67	0,619
	Median(25p-75p)	318000(271000-363000)	306000(272000-361000)		318000(267000-361000)	299000(262000-355000)				
LYM (10 ³ /μL)	Mean±Std	4.67±1.38	4.52±1.26	0.156†	4.7±1.52	4.64±1.65	0.680†	0,24	0,448	0,607
	Median(25p-75p)	4.86(3.5-5.64)	4.46(3.53-5.31)		4.65(3.65-5.48)	4.51(3.34-5.73)				
NEUTROP HIL (10 ³ /μL)	Mean±Std	2.55±1.1	2.67±1.09	0.290†	2.63±1.22	2.51±1.04	0.263†	0,973	0,592	0,124
	Median(25p-75p)	2.34(1.75-3.2)	2.4(1.86-3.38)		2.43(1.7-3.32)	2.39(1.68-3.28)				
MONOCYTE (103/μL)	Mean±Std	0.99±0.32	0.94±0.47	0.004*	0.99±0.42	0.95±0.43	0.17*	0,067	0,859	0,796
	Median(25p-75p)	0.96(0.73-1.25)	0.76(0.62-1.09)		0.9(0.65-1.25)	0.81(0.63-1.25)				
PLR	Mean±Std	74.09±28.03	73.41±21.03	0.672*	74.67±31.55	74.63±30.49	0.862*	0,847	0,627	0,864
	Median(25p-75p)	69.01(54.78-84.47)	69.57(57.12-83.53)		68.46(54.41-84.35)	69.17(53.87-86.06)				
NLR	Mean±Std	0.63±0.39	0.66±0.39	0.374*	0.63±0.4	0.64±0.44	0.739*	0,479	0,705	0,567
	Median(25p-75p)	0.55(0.33-0.82)	0.57(0.36-0.81)		0.57(0.33-0.83)	0.52(0.34-0.74)				
SII	Mean±Std	196.68±124.75	201.47±112.97	0.403*	197.62±128.2	192.51±129	0.405*	0,985	0,616	0,551
	Median(25p-75p)	171.28(107.19-245.07)	178.07(116.04-269.14)		173.71(108.16-251.85)	154.93(103.77-256.46)				
dNLR	Mean±Std	0.56±0.43	0.6±0.4	0.118*	0.61±0.53	0.57±0.44	0.748*	0,94	0,769	0,215
	Median(25p-75p)	0.48(0.28-0.67)	0.5(0.34-0.75)		0.47(0.28-0.7)	0.43(0.29-0.73)				
SIR-I	Mean±Std	0.57±0.33	0.63±0.46	0.244*	0.63±0.5	0.63±0.52	0.859*	0,32	0,295	0,4
	Median(25p-75p)	0.48(0.34-0.74)	0.52(0.26-0.9)		0.47(0.29-0.84)	0.47(0.23-0.9)				
CRP (mg/L)	Mean±Std	1.85±1.37	1.69±1.03	0.297*	1.81±1.28	1.88±1.25	0.458*	0,566	0,353	0,135
	Median(25p-75p)	1.25(0.76-2.76)	1.35(0.95-2.35)		1.25(0.85-2.55)	1.45(0.95-2.61)				

Abbreviations: WBC: White blood cell; HGB: hemoglobin; HCT: hematocrit; PLT: platelet; LYM: lymphocyte; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; SII: systemic immune-inflammatory index; dNLR: derived neutrophil-to-lymphocyte ratio; SIR-I: neutrophil count × monocyte count / lymphocyte count; CRP: C reactive protein. †: Paired samples t test; *: Wilcoxon test.

Additionally, two-way repeated-measures ANOVA was performed to evaluate the interactions between temporal changes in laboratory parameters and vaccine type. The results showed that temporal changes in all evaluated hemogram parameters and inflammatory markers were not significant; there were no differences between the vaccine groups, and there was no time-vaccine interaction. (Table 2).

Discussion

Vaccination recommendations against *N.meningitidis*, which can cause epidemics all over the world, have started to be included in many guidelines, especially in Europe and America [16–20]. Although effective protection has been achieved with 4CMenB [21] and MenACWY-TT [22], their effects on clinical protection are not clearly known. In the current study, the most common local and systemic adverse events in children administered Nimenrix and Bexsero were tenderness and redness (erythema) at the vaccination site. While 11.9% of the Bexsero group had fever after vaccination, none of the Nimenrix group had fever. Three months after vaccination, none of the patients in both groups had cough, wheezing, rhinorrhea, shortness of breath, history of previous NICU/PICU and hospitalization. Changes in inflammatory parameters were not significant in either group. Although MVs is not included in the routine vaccination schedule in Turkey and some other countries, according to the results of the study, it is recommended that it be included in the routine vaccination schedule as soon as possible.

The most common local and systemic side effects in infants and children are vaccination site tenderness and erythema, fever and sensitization, while in adolescents and adults, vaccination site pain, malaise and headache are the most common. In addition, it has been reported that fever is observed at a higher rate in infants when administered together with other routine vaccines [23–25]. McQuaid et al [25] reported that the 4CMenB vaccine is immunogenic and was fairly well tolerated by 5-year-old children, although injection-site pain was noteworthy. In the current study, the most common local and systemic adverse events in children administered 4CMenB and MenACWY-TT were tenderness and redness (erythema) at the vaccination site. While 11.9% of the Bexsero group had fever after vaccination, none of the Nimenrix group had fever. Although side effects (fever and local reactions) are observed more frequently in 4CMenB compared to MenACWY-TT vaccines, they are within acceptable limits. Our results confirms existing evidence regarding the safety of 4CMenB vaccination in babies under 2 years of age [26,27]. Prophylactic paracetamol administration could represent a protective factor against fever, especially during the first 24 h after vaccination [26]. Fever reaction was higher in 4CMenB administration with routine infant vaccines and a significant decrease in fever reaction was observed with prophylactic paracetamol administration [28]. However, further studies directly comparing this age group and the issue of prevention for high-risk infants are needed to confirm this difference.

Recently, the determination of systemic inflammation has been facilitated by the use of new biomarkers that can be easily calculated with whole blood parameters. NLR has also been shown to be important in determining the prognosis of infectious diseases including respiratory syncytial virus (RSV), COVID-19, bacteremia [29–32]. Mediu et al. [33] showed that there is no inflammation at 21 to 31 days post vaccination with Pfizer-BioNTech COVID-19 vaccine, regardless of age and gender, based on the hematological parameters. Wang et al. [34] demonstrated that, the prevalence of latent tuberculosis infection (LTBI) was as high as 18.8% in patients with end-stage kidney disease or kidney transplant. Bacillus Calmette-Guérin (BCG) vaccination and high NLR might have protective effects against LTBI in patients with renal failure or transplant. The present study demonstrated that, there is no significant difference in PLR, NLR and dNLR between Bexsero group and Nimenrix group 3 month post vaccination period following administration of vaccines. The results of the study suggest that the prediction of inflammatory status after MVs by these inexpensive and routinely monitored parameters may be of benefit to physicians working in countries with limited resources.

SIR-I and SII markers, which can be obtained by the ratio of simple hemogram parameters to each other, are the subject of research in many diseases associated with inflammation. Wang et al. [35] suggests that SII may be an effective indicator for predicting the severity of Mycoplasma pneumoniae pneumonia (MPP) in children. SII is more sensitive and specific than NLR, PLR, and SIR-I in evaluating the condition of MPP. In current study, SIR-I and SII levels, used as a combination of all these parameters, did not significantly differ between vaccine groups. The results of our

previous study [36] showed that breastfed and RSV vaccinated children were less prone to inflammation because their NLR, PLR, and SII ratios were lower. The vaccine does not prevent the disease 100%. However, it can prevent severe disease with exsiccation or death. The other inflammatory markers SIR-I and SII are similarly useful biomarkers.

CRP is widely measured clinically as an end-point marker of systemic inflammation that predicts elevated risk for incident various disease. To the best of our knowledge, this study is the first to document differences in CRP response to MV in relation to symptoms and baseline levels of CRP. In current changes in CRP levels were also not significant in either group. McDade et al. [37] reported that influenza vaccination produces a mild CRP response in the Philippines. Lower CRP at baseline was associated with larger CRP response to vaccination in the entire sample, and among participants without recent symptoms of infection.

This study has several limitations. i) As a retrospective study, the study only involved healthy individuals, so the conclusions cannot be employed for severe and critical cases. Obviously these indices are traditional markers, but they are cheap, convenient and perhaps a better choice. ii) Antibody response of vaccinated children could not be monitored after vaccination. iii) Limited by the sample size, differences between different vaccine doses have not been discussed and large clinical trials are needed to confirm the protective effect of different doses and types of vaccines.

The inclusion of Bexsero and Nimenrix vaccines in routine immunization programs in many countries provides an ideal opportunity to evaluate the impact of these vaccines in a real-world setting and our results will guide the assessment of inflammation in the administration of these vaccines. Fast, simple and convenient, these hematologic indices are markers that can be used to predict the severity of inflammation in vaccination. MM can also occur in children without additional risk factors. Predicting the inflammatory status even in children without an additional risk factor with NLO, dNLR, PLR, SIR-I and SII obtained from routine whole blood samples after vaccination is important in terms of patient approach. Local and systemic adverse events were not observed in children followed up 3 months after vaccination. Although meningococcal infections are one of the most feared infectious diseases due to their high mortality and epidemics, vaccination is not yet widely practiced. In MM, where serogroup changes continue dynamically, it will be possible to reduce mortality and morbidity with surveillance and immunization in accordance with surveillance. However, further studies involving larger patient cohorts as well as detailed laboratory data on specific markers of inflammation are needed to draw comprehensive conclusions regarding the inflammatory response following vaccination.

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