



Hematological and Biochemical Assessment of Children Infected with Measles Virus: 2022 Outbreak in Pakistan

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Abstract: Measles is a contagious disease caused by an RNA virus. Resurgence of measles after Covid-19 and its severity among children has led to many speculations about the Measles vaccination coverage and its efficacy. In this study, the clinical data of children <9 years (n=19) admitted at the Pakistan Institute of Medical Sciences (PIMS) in the measles ward was analyzed. The blood samples were processed for hematology and routine biochemistry tests. The results obtained were statistically analyzed on SPSS-21 software by using One-Way ANOVA for Complete Parameters (CP), Kruskal Wallis, and Mann-Whitney test for Differential leucocyte count (DLC) and Biochemical parameters. A $p < 0.05$ was considered significant. The results suggest no significant difference in Complete blood parameters (CP) among non-vaccinated, partially vaccinated and fully vaccinated patients. Among DLC Basophils level was significantly different ($p=0.024$), being lower in partially vaccinated than non-vaccinated patients. Biochemical parameters showed that serum urea level was significantly different ($p=0.013$), showing a decline in fully vaccinated patients as compared to non-vaccinated patients. Moreover, a significantly higher level of Alkaline phosphatase as compared to the normal range was observed in fully vaccinated patients. However, lower levels of MCH, MCV, MCHC, RBC, Hb, eosinophils, and a higher level of RDW-CV were observed overall as compared to the normal range (healthy individuals). The results suggest improvements are needed in vaccination strategies for effectively controlling the disease. Anemic conditions in overall measles patients indicate poor health conditions. This study contains a limited sample size, further research on measles virus (MeV) mutations, and vaccine optimization could be helpful for the complete eradication of measles from Pakistan.

Keywords: Measles, Hematology, Biochemical parameters, Measles vaccination, Measles in children.

1. INTRODUCTION

Measles virus (MeV) is a very contagious virus that had been a cause of high fatality rates throughout the world before the advent of the Measles vaccine [1]. Measles virus is a single-stranded negative-sense RNA virus belonging to the family Paramyxoviridae and genus Morbillivirus [2]. There are other five genera belonging to this family including Rinderpest virus (RPV), Peste des Petitis Ruminant's Virus (PPRV), Canine Distemper Virus (CDV), Phocine Distemper Virus (PDV), Cetacean Morbillivirus (CeMV) that cause similar infectious diseases in Cattle, sheep and goats, Carnivores, seals and dolphins respectively [3].

The only reservoir of the measles virus is

human beings. The transmission of MeV takes place via respiratory aerosols as it is an airborne virus. Moreover, it can also be transmitted via direct contact with the surface containing respiratory secretions from the infected person [2]. Measles virus has a high infectivity rate as one infected person can infect more than 12 persons on average [4]. As the virus makes its way to the human body the prodromal phase spans over 7-10 days and then MeV manifests itself in the form of cough, coryza, and fever followed by a rash on the face and the other parts of the body. These symptoms disappear usually with a decrease in viral load conferring lifetime immunity. However, in children with an underdeveloped immune system, it can take severe form developing pneumonia, otitis

Received: December 2022; Accepted: January 2023

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media, encephalitis, blindness, and other secondary bacterial and viral infections [5]. Sometimes if the virus persists in the nervous system, it can cause severe neurodegenerative diseases including subacute sclerosing panencephalitis (SSPE) measles inclusion-body encephalitis (MIBE). These complications have been reported to be associated with mutations in the viral F protein [6].

Measles has caused huge mortality globally before the availability of vaccines in 1963. Approximately 30 million cases were reported and greater than 2 million deaths annually. But with the advent of industrialization, improved lifestyle & nutrition, and the introduction of one dose of vaccine during the 1st year of life, the mortality rate has declined greatly. Also, better healthcare facilities and antibiotic therapies for measles-associated infections contributed to decreased death rates [2,7]. Measles virus is relatively stable as compared to the other viruses of this family as it is considered monotypic having a single serotype. It has been divided into eight clades from A to H based on different variable regions of the MeV genome and 24 genotypes [8].

A cost-effective live attenuated vaccine of measles is available and is usually given in two doses, the first dose at the 9th month and the second dose in the second year of life. Often the measles vaccine is incorporated into the mumps and rubella vaccine (MMR), and it is equally effective. Most of the countries have met WHO targets of measles complete immunization and have successfully eradicated measles but it still prevails in some African and Asian countries. Pakistan is also among those countries where there are still a significant number of measles cases [9]. B3 genotype has been reported in Pakistan previously from different areas including Sindh, Islamabad, and Khyber Pakhtunkhwa [10-12].

A recent spike in measles cases has been witnessed in Pakistan after Covid-19 pandemic in 2022. Several factors have been speculated for this re-emergence of measles. Despite complete vaccination of some patients, they still developed symptoms of measles. Our research analyzes the hematological and biochemical parameters of measles patients admitted at the Pakistan institute of medical sciences (PIMS) Islamabad to investigate the efficacy of MMR vaccination and

the correlation of measles severity with different hematological and biochemical parameters.

2. MATERIALS AND METHODS

2.1 Inclusion/Exclusion Criteria

A Measles patients included in this study were 19 aged below 9 years admitted at the Pakistan Institute of Medical Sciences (PIMS) children's measles ward and were recruited for blood sampling. Only the patients whose vaccination status was known were included in this study and the rest of them were excluded. Written informed consent was obtained from the parents/guardians of young Children for the collection of clinical samples.

2.2 Clinical Specimen Collection

Children aged 1 month to 9 years having laboratory-confirmed measles and showing mild to severe symptoms of measles were enrolled in the current study. The data set of measles patients was divided into three subgroups based on their vaccination status including three Not vaccinated, eight partially vaccinated, and eight fully vaccinated. Patients who did not receive any dose of MMR vaccine at the time of admission at PIMS were considered as not vaccinated (n=3), and those who received one dose of vaccine at the time of admission at the hospital were assigned as partially vaccinated status (n=8) and the patients who had received two doses of MMR vaccine were considered fully vaccinated (n=8). Gender was also recorded but not used for analysis due to the limited number of samples (n=19).

Venous blood sample was successfully collected from all the patients in a 5 ml heparin vacutainer tube by the medical practitioner. Blood samples were processed for analyzing hematological parameters (CP, DLC) and routine biochemistry tests (BSR, total bilirubin, serum creatinine, SGPT (ALT), alkaline phosphatase, serum urea, calcium, potassium, sodium). The overall flow chart of the research has been shown in (Figure 1).

2.3 Blood Sample Processing

2.3.1 Hematological parameters

Blood was taken intravenously (1.5 ml) from the

measles patients into 5 ml EDTA tubes. The tubes were placed on the rotor to maintain the homogeneity of blood samples. The blood sample was fed to the probe of the TOSOH automated hematology analyzer and the results of CP (TLC, Platelets count, MHC, MCV, MCHC, RBC, Hb, PCV, RDW-CV, Platelet distribution width, mean platelet volume) and DLC (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, NRBC_per 100WBCs, Immature granulocytes) were recorded.

2.3.2 Biochemical parameters

Whole blood sample (2 ml) was taken from measles patients intravenously into a yellow top 5 ml glass tube. The blood was allowed to clot by setting it aside for 15-20 minutes. When the blood is fully clotted the tubes were centrifuged at 1000-2000 g

for 10 minutes (Thermo-scientific LABOFUGE 200, Sweden). After centrifugation, the tubes were gently taken out and serum was obtained. The gel settled above the blood clot and the serum was separated into clear test tubes labeled with the patient's ID. The samples were placed in TOSOH G11 HPLC Analyzer, Japan and the report generated for the study parameters was recorded.

2.4 Statistical Analysis

Statistical analysis was performed on data sets obtained from laboratory tests. One-Way ANOVA was performed for comparing variations of TLC, Platelets count MCH, MCV, MCHC, RBC, Hb, PCV, RDW-CV, Platelets distribution width, and Mean platelet volume between three patients' groups. A p-value below 0.05 was considered

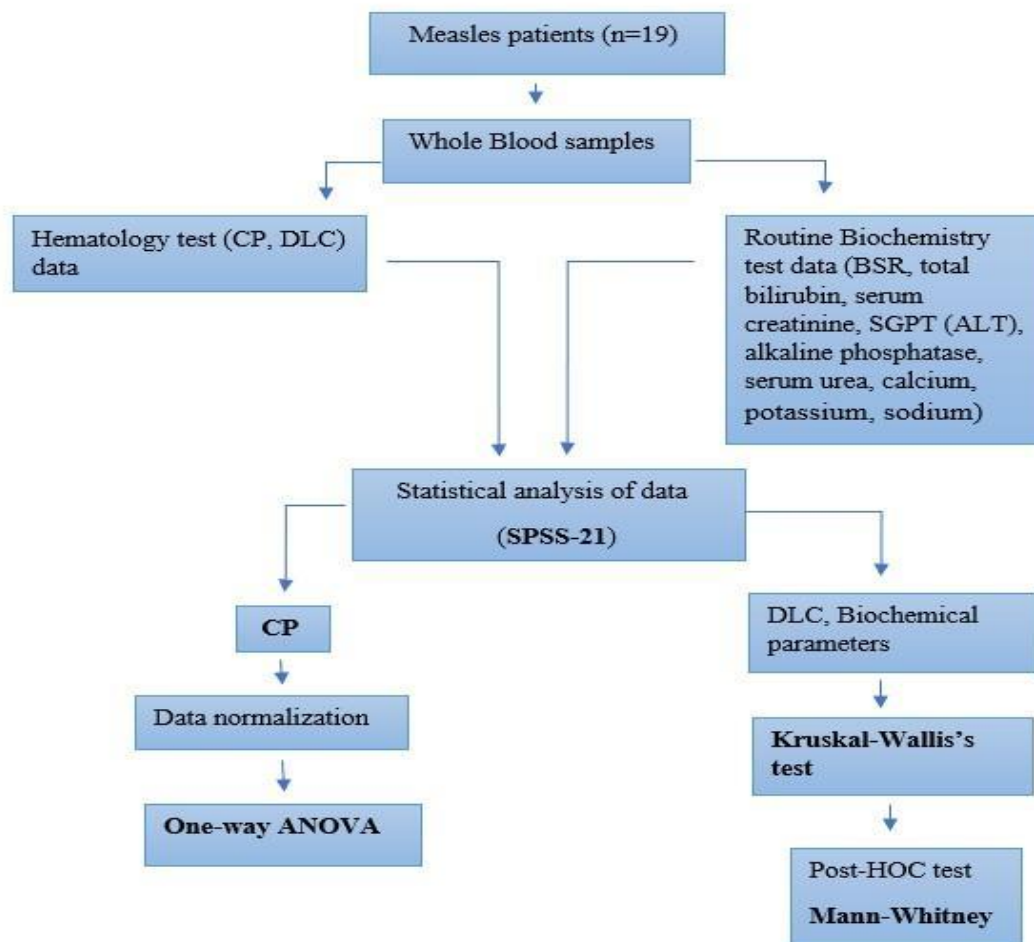


Fig. 1. Consort Diagram. Whole blood samples from nineteen patients were taken and processed for Haematology (Complete blood test, CBC) and routine biochemistry tests. The data obtained from the test results were analyzed in SPSS-21 software. Complete parameter (CP) data were analyzed by One-way ANOVA. Differential leucocyte count (DLC) and biochemical parameters were analyzed by the Kruskal-Wallis test and by the Mann-Whitney test.

significant. Non-parametric tests (Kruskal-Wallis, Mann-Whitney) were performed for DLC and Biochemical parameters.

3. RESULTS

The total number of measles patients recruited in the current study are 19 including six female and thirteen male patients from one month to nine years old children. Their vaccination status has been shown in Figure 2.

3.1 Hematological Parameters

3.1.1 Complete Blood Parameters (CP)

Our results showed that there was no significant

difference between not vaccinated, partially-vaccinated and fully-vaccinated patients for TLC [F (2, 16)=0.284, p=0.756], Platelets count [F (2, 16)=2.172, p=0.146], MCH, [F(2, 16)=1.451, p=0.264], MCV [F(2, 16)=1.174, p=0.335], MCHC [F(2, 16)=1.575, p =0.237], RBC [F(2, 16)=2.077, p=0.158], Hb [F(2, 16)=0.27, p=0.974], PCV [F(2, 16)=0.150, p=0.862], RDW-CV, [F(2, 16)=3.257, p =0.065], Platelets distribution width [F(2, 16) =1.139, p=0.345], and Mean platelet vol. [F(2, 16) =0.260, p=0.774]. Lower levels of MCH, MCV, MCHC, RBC, and Hb (as compared to the normal range in healthy subjects) were observed in all three groups of measles patients. Moreover, there was a very high RDW-CV in all the groups as compared to the normal range (Table 1).

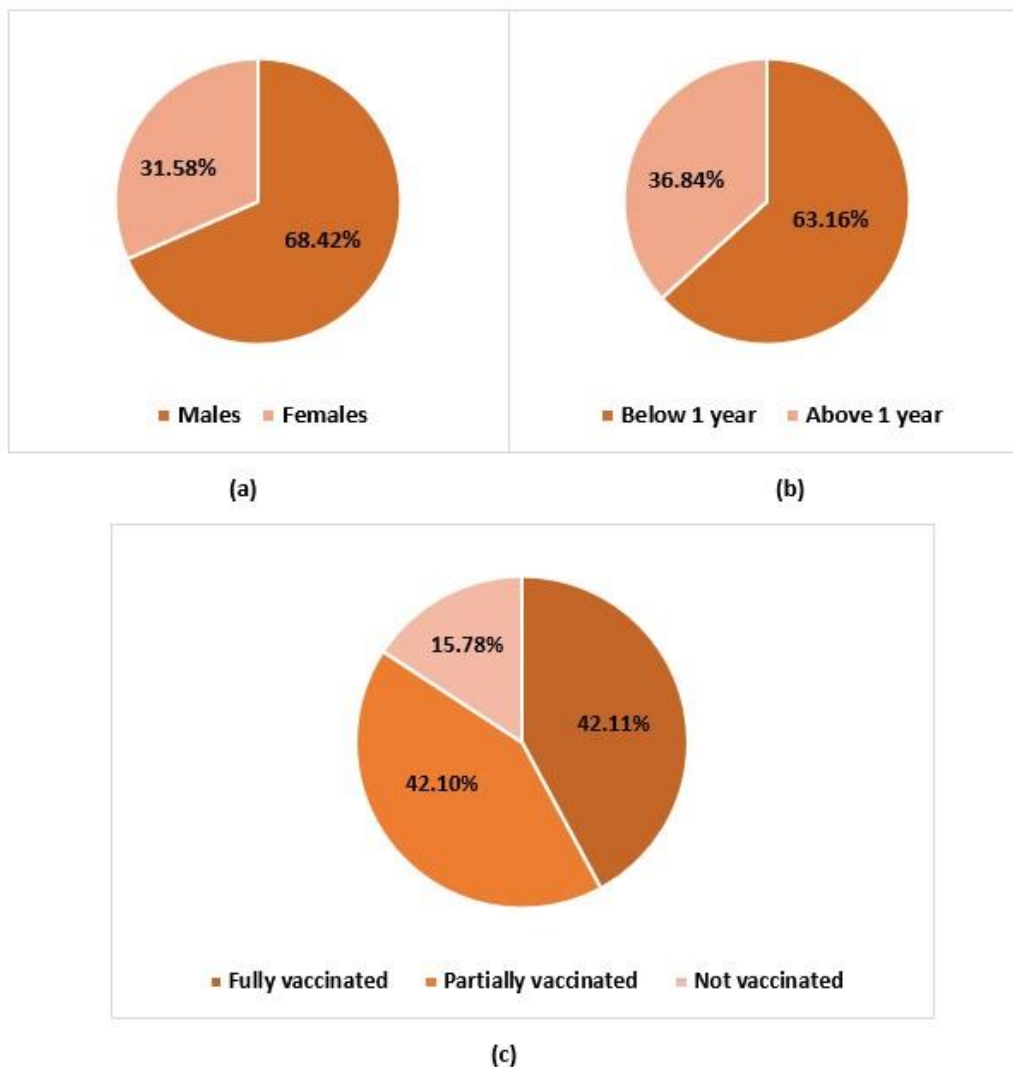


Fig. 2. (a) Gender ratio of measles patients, (b) The age ratio (upto-9 years), (c) The ratio of the vaccination status of measles patients. (No dose=not vaccinated, 1 dose=partially vaccinated, 2 doses=fully vaccinated).

3.1.2 Differential Leucocyte Count

There was no significant difference ($p>0.05$) between neutrophils, lymphocytes, monocytes, eosinophils, NRBC_per100WBCs, immature granulocytes among not vaccinated, partially vaccinated, and fully vaccinated measles patients, except for Basophils ($p=0.024$) that was significantly different between non vaccinated and partially vaccinated patients (Figure 3) Moreover, a lower level of Eosinophils as compared to the normal range in healthy subjects prevailed in all the three patient groups (Table 2).

3.2 Biochemical Parameters

Statistical analysis of biochemical parameters including Blood Sugar Random (BSR), total bilirubin, serum creatinine, SGPT (ALT), alkaline phosphatase, serum urea, calcium, potassium, and sodium of three groups of measles patients showed no significant difference ($p>0.05$) among all the parameters except significantly different serum urea ($p=0.013$) between not vaccinated and vaccinated group. Moreover, a significantly higher level of Alkaline phosphatase as compared to the normal range was observed in fully vaccinated patients.

4. DISCUSSION

The symptoms and clinical manifestation of measles can vary in different patients depending on their age, nutritional status, and immunocompetency. The analysis of clinical data of measles patients ($n=19$) suggested that most of the measles patients were anemic with a lower level of MCH, MCV, MCHC, RBCs, and hemoglobin and a very high ratio of RDW-CV than the normal range among the healthy subjects (Table 1). The anemic condition ($Hb<11$) prevailed among all the patients irrespective of their vaccination status.

Our study is comparable with previous studies involving viral infections including dengue, hepatitis, HIV and Covid-19 led to a decrease in hemoglobin hence causing anemia in the infected patients [13-16]. Hemoglobin contains iron that carries oxygen to different organs of the body and when the concentration of hemoglobin decreases it causes hypoxia which could ultimately lead to organ dysfunction specifically targeting respiratory organs. Anemic conditions might have aggravated

the respiratory problems in hospitalized measles patients, [17] as many of them ($n=7$) were put on ventilators for proper breathing. The genetic factor of the infected host can play a role in the viral induction of anemia [18]. The nutritional status and composition of the diet can also contribute towards anemia [19]. Some studies also suggest that the antiviral therapy or administration of antiviral drugs during treatment might induce anemia, by hemolysis or other related mechanisms [14]. Among all patient groups, there was no significant difference in hemoglobin level and other indicators of anemia, so we might infer that the vaccination did not affect the hemoglobin level, there might be some other reason including the viral induction of hemolysis, the poor nutritional status of children or the genetic factor of infected patients.

Measles vaccine in combination with other vaccines could be associated with mild adverse effects following the immunization (AEFI). Studies have reported the incidence of fever, neurological symptoms, agitation, nervousness, gastrointestinal diseases, thrombocytopenia, redness, swelling, local pain, lymphadenitis, etc [20]. Our results indicate a lower level of eosinophils in the patients (Table 2) that were partially vaccinated (one dose of vaccination). Some of these patients also showed symptoms of hyperpyrexia, skin rash, and excessive crying that are comparable with already reported studies [20].

The paradigm of eosinophils includes the destructive and inflammatory functions in cells. They are recruited because of T helper cells Th2 type reactions releasing cytotoxic granule proteins, different lipid mediators, and cytokines that promote parasite destruction, inflammation, and tissue damage. Under baseline conditions, eosinophils perform homeostatic, protective, and immunoregulatory functions in different organs of the body including the gastrointestinal tract, lungs, thymus mammary glands, and adipose tissues [21]. Eosinophils showed a decline (0.09 %) in partially vaccinated patients as compared to non-vaccinated (0.43 %) and then gradually increased (0.72 %) in fully vaccinated patients. With this transition in eosinophil levels, we can speculate that the previous history of administration of the MMR vaccine 1st dose could be associated with altered levels of eosinophils in measles patients that

Table 1. Comparison of complete blood parameters of not vaccinated, partially-vaccinated, and fully-vaccinated measles patients as compared to the normal range.

Parameters	Not vaccinated	Partially vaccinated	Fully vaccinated	Normal range
	(n=3)	(n=8)	(n=8)	
	Mean \pm SD	Mean \pm SD	Mean \pm SD	
TLC ($\times 10^9/L$)	12.8 \pm 4.2	10.2 \pm 1.9	9.4 \pm 2.3	6-18
Platelet count ($\times 1000/\mu l$)	399 \pm 73.5	442.3 \pm 58.9	292.6 \pm 44.7	200-550
MCH (pg)	18.3 \pm 2.7	21.5 \pm 1.3	22.1 \pm 0.8	25-29
MCV (fl)	60 \pm 8.3	68 \pm 3.6	69.8 \pm 2.3	72-84
MCHC (g/dL)	30.5 \pm 0.5	31.5 \pm 0.4	31.6 \pm 0.3	32-36
RBC (million/ μl)	5.6 \pm 0.3	4.9 \pm 0.4	4.6 \pm 0.1	6-18
Hb (g/dL)	10.2 \pm 1.4	10.3 \pm 0.4	10.1 \pm 0.3	11-15.5
PCV	33.4 \pm 4.1	32.6 \pm 1.4	31.9 \pm 0.9	30-38
RDW-CV (%)	20.8 \pm 1.7	17.4 \pm 0.8	16.7 \pm 0.8	10-15
Platelets distribution width (%)	15.1 \pm 0.3	15.5 \pm 0.2	15.5 \pm 0.12	15-17
Mean platelet vol.	8.6 \pm 0.30	8.4 \pm 0.4	8.2 \pm 0.3	6.5-12

Abbreviations: TLC= total leucocyte count, MCH= mean corpuscular hemoglobin, MCV= mean corpuscular volume, MCHC= mean corpuscular hemoglobin concentrations, PCV=packed cell volume, RDW-CV= red cell distribution width-coefficient of variation.

Table 2. Comparison of differential leucocyte count in not vaccinated, partially-vaccinated, and fully-vaccinated measles patients as compared to the normal range.

Differential Leucocyte Count (DLC) %	Not vaccinated		Partially vaccinated		Fully vaccinated		Normal range
	(n=3)		(n=8)		(n=8)		
	Mean	SE	Mean	SE	Mean	SE	
Neutrophils	56.6	11.6	54.9	6.3	48.8	7.9	30-60
Lymphocytes	34.1	12.2	38.5	6.0	43.1	6.8	25-55
Monocytes	8.5	0.9	6.4	1	7.2	2.5	2-10
Eosinophils	0.43	0.3	0.09	0.1	0.72	0.5	1-6
Basophils	0.3	0.1	0.1	0.03	0.2	0.03	0.0-2.0
NRBC_per100WBCs	0.6	0.6	0.07	0.05	0.00	0.0	0.00-2
Immature granulocytes	0.5	0.1	0.3	0.1	0.4	0.10	0.0-100

gradually recovered in fully vaccinated patients. The manifestation of allergy, inflammation, and breathing issues in partially vaccinated patients could be possibly related to AEFI.

Some other significant variations among the clinical data of measles patients were observed in the level of Alkaline phosphatase which was slightly higher than the normal range in fully vaccinated patients, and the level of serum-urea that remarkably declined from non-vaccinated toward fully vaccinated measles patients. Although

the later one was found to be in the normal range in all the measles patients as compared to the healthy subjects. (Table 3) There is no direct evidence for the influence of MMR vaccination history on biochemical parameters in measles patients. But viral infections including hepatitis B and C have been reported to cause an increase in the level of serum Alkaline phosphatase (ALP) [22]. Alkaline phosphatase level in not vaccinated and partially-vaccinated patients lies under the normal range but are higher in fully-vaccinated patients as compared to the normal subjects. We can infer that vaccination

Table 3. Statistics for the comparison of biochemical parameters among three measles patients' groups as compared to the normal range.

Biochemical parameters	Not vaccinated (n=3)	Partially vaccinated (n=8)	Fully vaccinated (n=8)	Reference range
	Mean± SD	Mean± SD	Mean ± SD	
BSR (mg/dL)	124 ± 19.7	102.9 ± 7.8	121.6 ± 17.5	80-160
Total bilirubin (mg/dL)	0.4 ± 0.03	0.3 ± 0.02	0.4 ± 0.02	Upto-1.0
Serum creatinine (mg/dL)	0.3 ± 0.01	0.3 ± 0.03	0.3 ± 0.6	Upto-1.2
SGPT (ALT) (U/L)	25.7 ± 6.8	43.1 ± 11.2	40.5 ± 10.4	Upto-42
Alkaline phosphatase (U/L)	119.3 ± 0.7	123.9 ± 8.1	137.8 ± 22.7	Upto-135
Serum urea (mg/dL)	23.7 ± 2.7	27.6 ± 2.9	15.4 ± 1.5	12-50
Calcium (mg/dL)	9.3 ± 0.4	9.1 ± 0.2	8.7 ± 0.2	8.5-10.5
Potassium (m.mol/L)	4.2 ± 0.1	4.5 ± 0.1	4.3 ± 0.2	3.5-5
Sodium (m.mol/L)	133.6 ± 2.8	133.4 ± 2.2	135.5 ± 0.8	135-145

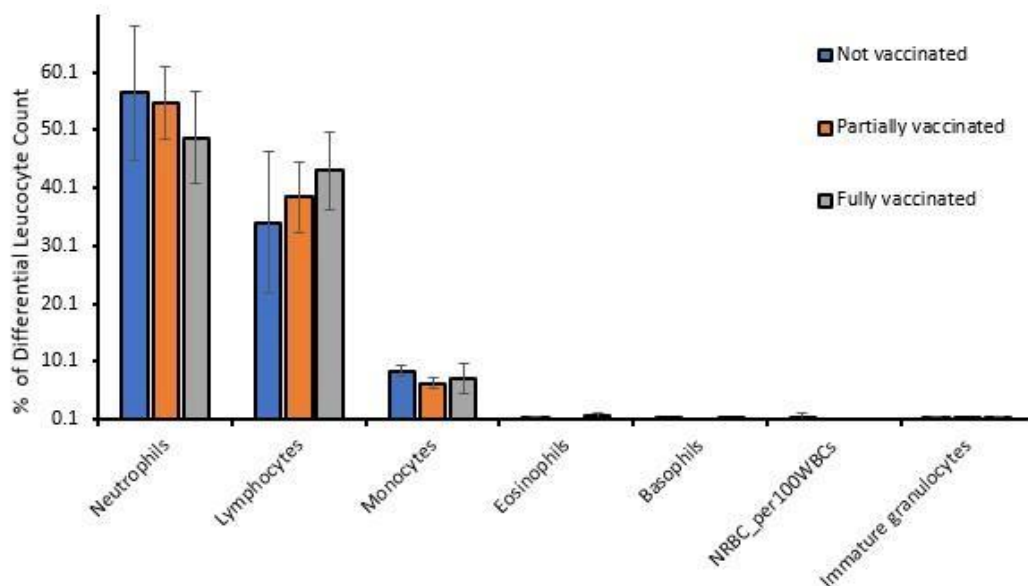


Fig. 3. Comparison of differential leucocyte count in not vaccinated, partially-vaccinated, and fully-vaccinated measles patients as compared to the normal range.

has somehow played a role in increasing ALP levels. ALP is a membrane-bound glycoprotein that promotes the hydrolysis of several kinds of phosphate monoesters. It is reported to be increased in patients with bone and liver diseases, but the level of ALP is slightly higher in infants and adolescents as compared to adults due to bone growth. A high level of ALP has been reported to be associated with respiratory infections [23]. In our case, complete MMR vaccination increases the level of ALP so we can say that the vaccination might have contributed to the aggravation of respiratory problems in measles patients despite curing the disease. Vaccination history affected the level of serum urea among measles patients by decreasing its level from non-vaccinated to completely vaccinated patients, but the fluctuation is under the normal range as compared to the healthy subjects, so we did not consider it under AEFI.

5. CONCLUSION

Despite the MMR vaccination administration/campaigns, still, measles cases are being reported in the country. Our study indicated the suboptimal immunization conferred by the MMR vaccination. There can be several possible reasons including poor storage conditions of vaccines. The other possible reason could be malnourishment among the affected children (measles patients) as all the participants included in this study were <9 years so they might not be immunocompetent. Another possible reason behind it can be the variation/evolution in the measles virus, as it is an RNA virus and these viruses usually have a relatively high rate of mutations. Further research could be conducted on a large set of measles patients with respect to their nutritional status, specific genetic factors, immunocompetency, and efficacy of MMR vaccination. The investigation for the optimization of immunization strategies and molecular characterization of the measles virus circulating among Pakistani patients could further highlight the unexplored aspects of measles prevalence, to meet the UN sustainable development goal of complete eradication of measles from developing countries such as Pakistan.

6 ACKNOWLEDGEMENTS

We acknowledge Ms. Naima Iram who helped with

organizing, editing, and analyzing of study data.

7. CONFLICT OF INTEREST

The authors declare no conflict of Interest.

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