


# Oxidative Stress, Glutathione System Activity, and Zinc/Selenium Imbalance in Adult Measles of Varying Severity According to Vaccination Status

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**Background:** Adult measles is increasingly associated with severe clinical manifestations, particularly among unvaccinated individuals. Oxidative stress and micronutrient depletion may contribute to disease severity; however, integrated data evaluating oxidative protein damage, glutathione system activity, and zinc/selenium status in adult measles remain limited. This study assessed oxidative stress markers, glutathione-dependent enzymes, and trace element levels according to vaccination status.

**Methods:** Eighty adults with laboratory-confirmed measles were stratified into vaccinated (n=40) and unvaccinated (n=40) groups. Oxidative protein modification was quantified spectrophotometrically at 356, 370, 430, and 530 nm. GPx and GR activities were measured using standard assays. Serum zinc and selenium concentrations were determined by atomic absorption spectrophotometry. Statistical analyses included distribution testing, group comparisons with Holm correction, and standardized effect size estimation.

**Results:** Unvaccinated patients demonstrated higher protein carbonyl levels at 356 nm ( $1.474 \pm 0.148$  vs  $1.266 \pm 0.041$ ;  $p=0.005$ ) and 370 nm ( $p<0.01$ ), along with lower GR activity ( $0.048 \pm 0.007$  vs  $0.061 \pm 0.003$ ;  $p=0.035$ ). Effect size analysis showed a large between-group difference for GR activity (Hedges  $g \approx 0.89$ ) and moderate effects for oxidative indices. Zinc levels were reduced by 24% in unvaccinated and 13% in vaccinated patients ( $78.7 \pm 0.72$  vs  $89.5 \pm 0.78$   $\mu\text{g/dL}$ ;  $p<0.001$ ). Selenium levels were decreased by 55% and 49%, respectively ( $61.3 \pm 0.49$  vs  $69.8 \pm 0.56$   $\mu\text{g/L}$ ;  $p<0.001$ ).

**Conclusion:** Adult measles was associated with oxidative protein modification, impaired glutathione system activity, and reduced zinc and selenium levels, particularly in unvaccinated patients. These findings are associative and require confirmation in prospective longitudinal studies.

**Plain Language Summary:** Measles remains a clinically significant viral infection in adults and can lead to severe complications, particularly in individuals who have not been vaccinated. In addition to its well-known symptoms, measles can disrupt the body's antioxidant defenses and alter the balance of essential trace elements in the blood.

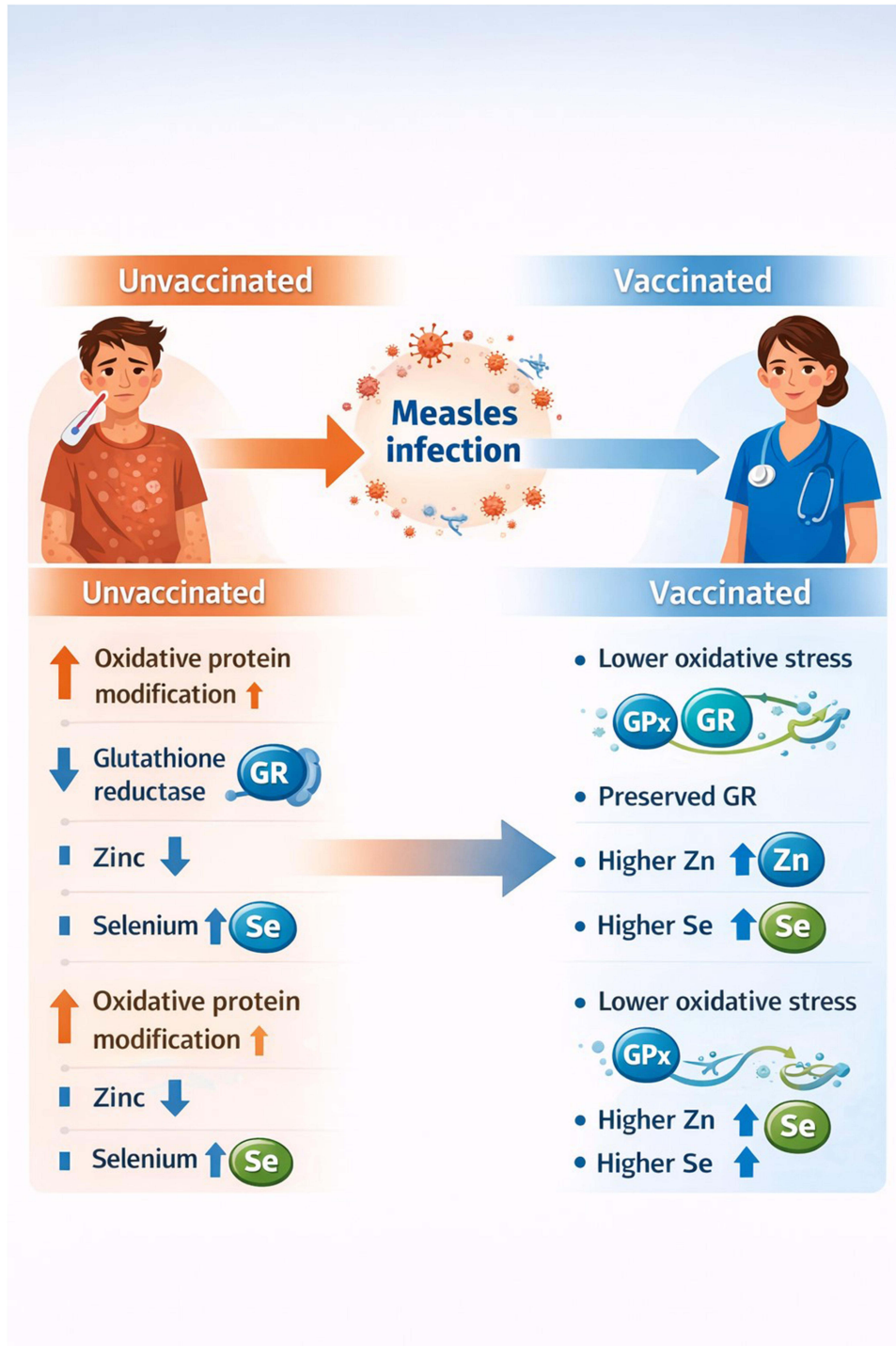
In this study, we compared vaccinated and unvaccinated adults hospitalized with measles. We examined laboratory markers of oxidative stress, including protein damage caused by excessive oxidative reactions, the activity of key antioxidant enzymes, and blood levels of zinc and selenium—two trace elements important for immune function.

We found that unvaccinated patients showed higher levels of oxidative stress and lower concentrations of zinc, selenium, and glutathione reductase activity than vaccinated patients. These biochemical changes were associated with a more severe course of the disease. Vaccinated individuals demonstrated a milder biochemical response, suggesting partial protection not only against infection but also against harmful oxidative processes.

These findings may contribute to understanding biochemical mechanisms linked to disease severity and suggest that certain laboratory markers could assist in early clinical assessment. Further prospective studies are needed to confirm these observations and clarify their potential clinical implications.

**Keywords:** measles, adults, vaccination status, oxidative stress, micronutrient imbalance, zinc, selenium, glutathione system

**Graphical Abstract**



## Introduction

Over the past decade, measles incidence has increased both globally and in Ukraine, affecting not only children but also a growing proportion of adults, largely due to declining vaccination coverage.<sup>1–6</sup> Adult measles is frequently associated with a more severe clinical course, higher complication rates, and prolonged hospitalization, underscoring the need to identify early biochemical predictors of disease severity that may support clinical risk stratification and management.<sup>1–6</sup>

One of the key processes associated with viral infections is oxidative stress (OS), which arises from the excessive production of reactive oxygen species (ROS) during viral replication and inflammatory immune responses.<sup>7,8</sup> When antioxidant defense mechanisms are overwhelmed, ROS contribute to cellular damage, activation of inflammatory cascades, and induction of apoptosis, thereby aggravating tissue injury and disease progression.<sup>7–9</sup> Oxidative stress plays a central role in the pathogenesis of multiple viral infections, including influenza, COVID-19, respiratory syncytial virus infection, and other acute respiratory viral diseases.<sup>9–14</sup> However, the contribution of oxidative imbalance to the clinical course of measles, particularly in adults, remains insufficiently studied.<sup>9</sup> However, integrated data simultaneously evaluating oxidative protein modification, glutathione system activity, and trace element status in adult measles, particularly in relation to vaccination status, are lacking.

Protein oxidative modification is considered an early and sensitive marker of oxidative stress. Carbonyl derivatives formed during oxidative protein damage reflect irreversible structural changes that impair enzymatic activity, receptor function, and membrane integrity, ultimately affecting cellular metabolism and organ function.<sup>15–23</sup> Monitoring oxidative protein modification, therefore, provides valuable insight into the severity of inflammatory and infectious processes and has been proposed as a laboratory indicator of tissue injury in critical conditions.<sup>17–22</sup>

In parallel, the acute phase response is associated with pronounced alterations in trace element metabolism. Zinc (Zn) and selenium (Se) play essential roles in immune regulation and antioxidant defense, serving as cofactors for enzymes of the glutathione system and other redox-regulating pathways.<sup>24–28</sup> During systemic inflammation, redistribution of Zn and Se results in decreased serum concentrations, which may exacerbate oxidative stress, impair immune responses, and contribute to adverse clinical outcomes in infectious and critical illnesses.<sup>29–37</sup>

The Ivano-Frankivsk region belongs to a biogeochemical zone characterized by chronic deficiencies of several trace elements, including zinc and selenium, due to soil and water composition.<sup>38</sup> Notably, this region experienced a high burden of measles during recent outbreaks, raising the possibility that pre-existing micronutrient imbalance may influence disease severity in adult patients.<sup>1–6,38</sup> Despite accumulating evidence linking Zn and Se status to outcomes in acute infectious and inflammatory conditions, data specifically addressing their role in adult measles—particularly in relation to vaccination status—remain limited.<sup>29,30</sup>

Importantly, trace element deficiencies are not limited to specific regions but represent a global public health concern, particularly in populations with suboptimal nutritional status, which increases the broader relevance of these findings.

Vaccination against measles is well established as an effective measure for preventing infection and reducing disease severity.<sup>29</sup> Beyond its role in adaptive immune protection, vaccination may also modulate the intensity of systemic inflammation and oxidative stress during infection, thereby influencing metabolic and redox homeostasis.<sup>29,37</sup> However, the extent to which vaccination history affects oxidative stress markers, glutathione system activity, and trace element status in adults with measles has not been sufficiently explored.

Therefore, this study addresses an important gap by providing an integrated assessment of oxidative protein damage, glutathione system function, and micronutrient balance in adult measles patients stratified by vaccination status.

A graphical abstract summarizing the proposed pathogenic model of oxidative stress, glutathione system impairment, and Zn/Se imbalance in adult measles patients depending on vaccination status is provided in the [Supplementary Materials](#).

## Aim

This study aimed to assess the degree of oxidative protein modification, glutathione system activity, and zinc and selenium status in adult patients with measles, and to evaluate their association with disease severity according to vaccination history.

## Materials and Methods

### Study Design and Participants

This observational study included 80 adult patients with laboratory-confirmed measles who were hospitalized at the Center for Infectious Diseases of the Ivano-Frankivsk Regional Council, Ukraine. Patients were enrolled during the acute phase of the disease and stratified into two groups according to vaccination history: vaccinated (n=40) and unvaccinated (n=40). Vaccination status was confirmed by official immunization records (preventive vaccination cards, form No. 063/o). Patients with an undocumented vaccination history were classified as unvaccinated.

The study groups were comparable in terms of age, sex, and presence of comorbid conditions. All laboratory parameters were compared with internationally accepted reference values. Medical and diagnostic procedures were performed after obtaining written informed consent from all participants.

All biochemical measurements were performed according to standardized laboratory protocols routinely used in clinical biochemical research. Commercially available reagents and assay kits were used for all analyses in accordance with manufacturers' instructions.

Serum zinc and selenium concentrations were determined by flame atomic absorption spectrophotometry using a Shimadzu AA-7000 series atomic absorption spectrophotometer (Model GFA-7000A; Shimadzu Corporation, Kyoto, Japan).

Calibration was performed for each analytical session using certified reference standard solutions within the working concentration range (0–20 ppb). Multi-point calibration curves were generated prior to sample analysis and verified for linearity before measurement.

For selenium, the calibration curve was constructed using linear regression analysis according to the equation:  $A = 0.00264 \times C - 0.00446$  ( $R^2 = 0.965$ ).

For zinc, the corresponding regression equation was:  $A = 0.00479 \times C - 0.00016$  ( $R^2 = 0.990$ ) where A represents absorbance and C represents element concentration (ppb). Sample concentrations were calculated by back-calculation from the respective regression equations. Instrument performance and analytical stability were monitored using internal quality control samples analyzed within each batch.

All biochemical assays were performed as single measurements in accordance with standardized protocols. Laboratory personnel conducting the biochemical analyses were blinded to patients' vaccination status in order to minimize potential analytical bias.

### Diagnostic Criteria

The diagnosis of measles was established based on epidemiological history, characteristic clinical manifestations, and laboratory confirmation. Specific IgM antibodies to measles virus were detected in serum samples using an enzyme-linked immunosorbent assay (ELISA). Diagnostic results were documented in standardized hospital medical records (form No. 003/o).

### Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki (1964–2013), International Council for Harmonisation Good Clinical Practice (ICH GCP, 1996), EEC Directive No. 609/86 (24 November 1986), and Order No. 690 of the Ministry of Health of Ukraine (23 September 2009). The study protocol was approved by the Local Ethics Committee of Ivano-Frankivsk National Medical University. All participants provided written informed consent before inclusion in the study.

### Assessment of Oxidative Protein Modification

Oxidative modification of plasma proteins was assessed using spectrophotometric analysis based on the detection of carbonyl derivatives formed during oxidative damage. Protein carbonyl groups were quantified following derivatization with 2,4-dinitrophenylhydrazine (DNPH). Absorbance of the resulting hydrazones was measured at wavelengths of 356, 370, 430, and 530 nm, corresponding to early and late products of oxidative protein degradation. Oxidative protein modification was assessed spectrophotometrically by determining protein carbonyl derivatives at wavelengths of 356, 370, 430, and 530 nm using established methods.

The intensity of oxidative protein modification was expressed as optical density units per gram of protein or per milliliter of serum. Blood samples (0.05–0.1 mL) were centrifuged at 1500 rpm for 10 minutes to obtain serum. Serum samples were stored at  $-20^{\circ}\text{C}$  and were not subjected to repeated freeze–thaw cycles. Sample transportation and storage conditions complied with standard laboratory requirements.<sup>39</sup>

## Assessment of Glutathione System Enzyme Activity

Glutathione reductase (GR) activity (nmol/min·mg protein) was determined by measuring the rate of NADPH oxidation spectrophotometrically at 340 nm. Glutathione peroxidase (GPx) activity ( $\mu\text{mol}/\text{min}\cdot\text{mg}$  protein) was assessed by monitoring the rate of reduced glutathione (GSH) oxidation, based on changes in optical density at 270 nm during the enzymatic reaction.

## Determination of Zinc and Selenium Concentrations

Serum zinc and selenium concentrations were determined by flame atomic absorption spectrophotometry using a Shimadzu AA-7000 series atomic absorption spectrophotometer (Model GFA-7000A; Shimadzu Corporation, Kyoto, Japan).

Calibration was performed for each analytical session using certified reference standard solutions. Multi-point calibration curves were generated prior to sample analysis within the working concentration range (0–20 ppb), and linearity was verified before measurements.

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For zinc, the corresponding regression equation was:  $A = 0.00479 \times C - 0.00016$  ( $R^2 = 0.990$ ) where A represents absorbance and C represents element concentration (ppb). Sample concentrations were calculated by back-calculation from the respective regression equations.

All measurements were performed under optimized analytical conditions according to the manufacturer's technical specifications for each element (including wavelength, slit width, lamp current, and flame parameters). Instrument stability and analytical accuracy were monitored using internal quality control samples analyzed within each batch.

Laboratory personnel conducting biochemical analyses were blinded to patients' vaccination status to minimize potential analytical bias.

## Inclusion and Exclusion Criteria

Inclusion criteria were: age  $\geq 18$  years; clinical signs consistent with measles (fever, cough, coryza, conjunctivitis, oral enanthema, and characteristic exanthema); hospitalization within 1–5 days of disease onset; moderate or severe disease course; positive ELISA IgM test for measles virus; and absence of concurrent acute viral infections of other etiology.

Exclusion criteria included: hospitalization later than 6 days after disease onset; mild measles; negative ELISA results; and intake of dietary supplements or multivitamin preparations containing zinc or selenium within 3 months prior to enrollment.

## Statistical Analysis

All data were recorded in standardized individual case report forms. Statistical analysis was performed using IBM SPSS Statistics software (version 28). Data distribution was assessed using the Shapiro–Wilk test. Normally distributed variables were compared using Welch's *t*-test, while non-normally distributed data were analyzed using the Mann–Whitney *U*-test. Multiple comparisons were adjusted using Holm's correction. Correlation analyses were conducted using Pearson's or Spearman's coefficients, as appropriate. A *p*-value  $< 0.05$  was considered statistically significant.

A sensitivity analysis was additionally performed to estimate the minimal detectable effect size given the study sample. With 40 participants per group, the study had 80% power to detect a standardized between-group difference of approximately Cohen's  $d=0.63$  at a two-sided  $\alpha=0.05$ . Therefore, the study was adequately powered to detect moderate-to-large effects but may have been underpowered for small effect sizes. Standardized effect sizes (Hedges *g* with 95% confidence intervals) were calculated for all primary between-group comparisons.

## Results

### Clinical Characteristics of the Study Population

Patients were admitted to the Center for Infectious Diseases at a mean of  $3.77 \pm 0.11$  days after disease onset. The age of enrolled participants ranged from 18 to 61 years, with a mean age of  $27.59 \pm 0.40$  years. Overall, 54 patients (67.5%) were admitted by emergency medical services due to moderate or severe clinical conditions at presentation. A history of contact with individuals presenting catarrhal symptoms 10–14 days before disease onset was reported by 56 patients (70.0%).

In the vaccinated group (Group I), the mean age was  $31.9 \pm 2.02$  years; 23 patients (57.5%) were male and 17 (42.5%) were female. Severe disease was documented in 2 patients (5.0%), moderate disease with complications in 25 patients (62.5%), and moderate disease without complications in 13 patients (32.5%). The most frequent complications included acute catarrhal non-obstructive bronchitis (62.5%) and reactive hepatitis (47.5%). Less frequent complications were viral-bacterial community-acquired pneumonia (2.5%), mild iron-deficiency anemia (7.5%), and bacterial conjunctivitis (5.0%). The mean length of hospital stay in this group was  $8.74 \pm 0.51$  days.

In the unvaccinated group (Group II), the mean age was  $28.6 \pm 1.38$  years; 21 patients (52.5%) were male, and 19 (47.5%) were female. Severe disease was observed in 9 patients (22.5%), while moderate disease with complications was recorded in 31 patients (77.5%). Complications were more frequent and included acute catarrhal non-obstructive bronchitis (60.0%), reactive hepatitis (65.0%), viral-bacterial community-acquired pneumonia (40.0%), mild to moderate iron-deficiency anemia (32.5%), otitis media (5.0%), pleurisy (5.0%), and bacterial conjunctivitis (15.0%). The mean duration of hospitalization in this group was longer than in vaccinated patients.

### Oxidative Modification of Proteins

At the time of hospital admission, statistically significant differences in oxidative protein modification were observed between vaccinated and unvaccinated patients (Table 1 and Table 2). For all analyzed spectral ranges (356, 370, 430, and

**Table 1** Levels of Oxidative Protein Modification in Adult Patients with Measles at the Time of Hospital Admission ( $M \pm SEM$ ) (Arbitrary Units of Optical Density per mL of Serum)

Wavelength (nm)	Reference Values	Group II (Unvaccinated) (n = 40)	Group I (Vaccinated) (n = 40)
356	$0.826 \pm 0.046$	$1.474 \pm 0.148$	$1.266 \pm 0.041$
370	$0.864 \pm 0.051$	$1.392 \pm 0.152$	$1.082 \pm 0.015$
430	$0.444 \pm 0.019$	$0.653 \pm 0.089$	$0.504 \pm 0.008$
530	$0.176 \pm 0.007$	$0.113 \pm 0.007$	$0.104 \pm 0.003$

**Notes:** Values are presented as mean  $\pm$  standard error of the mean (SEM). Group I — vaccinated patients; Group II — unvaccinated patients. Oxidative protein modification was assessed spectrophotometrically using the DNPH method.

**Table 2** Statistical Significance of Differences in Oxidative Protein Modification Parameters Between Study Groups ( $p$ -values for Intergroup and Reference Comparisons)

Wavelength (nm)	$p$ (Group II vs Reference)	Significance	$p$ (Group I vs Reference)	Significance	$p$ (Group II vs Group I)	Significance
356	0.000077	<0.001	0.000034	<0.001	0.005386	<0.01
370	0.015087	<0.05	0.421046	NS	0.000357	<0.01
430	0.024328	<0.05	0.054633	NS (borderline)	0.006672	<0.01
530	<0.000001	<0.001	<0.000001	<0.001	0.218911	NS

**Notes:** Group I—vaccinated patients; Group II — unvaccinated patients. NS — not significant ( $p \geq 0.05$ ).  $P$ -values indicate the statistical significance of differences between groups and relative to reference values.

530 nm), unvaccinated patients demonstrated higher levels of oxidative modification of proteins compared with reference values.

At 356 nm, which reflects early products of oxidative protein damage, unvaccinated patients exhibited significantly higher values compared with both reference values ( $p < 0.001$ ) and vaccinated patients ( $p < 0.01$ ). At 370 nm, oxidative modification indices were also significantly increased in unvaccinated individuals relative to reference data ( $p < 0.01$ ), whereas vaccinated patients demonstrated values close to the reference range.

At 430 nm, unvaccinated patients showed significantly elevated protein carbonyl levels compared with both reference values ( $p < 0.05$ ) and vaccinated patients ( $p < 0.01$ ). At 530 nm, oxidative modification indices in unvaccinated patients remained significantly higher than reference values ( $p < 0.001$ ); however, no statistically significant difference was observed between vaccinated and unvaccinated groups at this wavelength ( $p > 0.2$ ).

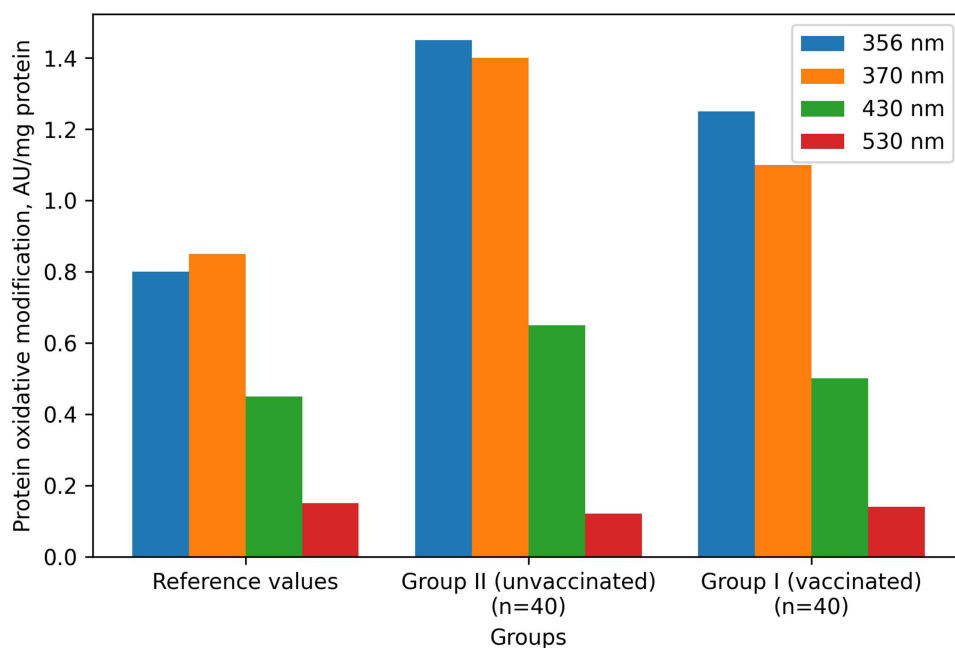
Overall, higher levels of oxidative protein modification at 356, 370, and 430 nm were consistently observed in unvaccinated patients at hospital admission (Figure 1).

## Activity of Glutathione System Enzymes

Analysis of antioxidant enzyme activity revealed no statistically significant differences in glutathione peroxidase (GPx) activity between vaccinated and unvaccinated patients; values in both groups remained within the reference range (Table 3 and Table 4).

In contrast, glutathione reductase (GR) activity was significantly reduced in both groups compared with reference values, with a more pronounced decrease observed in unvaccinated patients. GR activity was significantly lower in Group II compared with Group I ( $p < 0.05$ ), indicating a greater degree of impairment of glutathione regeneration in unvaccinated individuals (Figure 2).

Effect size analysis demonstrated a large between-group difference in GR activity (Hedges  $g = -0.89$ ), a small-to-negligible effect for GPx activity ( $g = 0.11$ ), and moderate effects for selected oxidative protein modification indices ( $g$  ranging from  $-0.38$  to  $-0.59$ ). Effect size estimates for all between-group comparisons are presented in Supplementary Table S1. GR



**Figure 1** Level of oxidative modification of proteins in adult patients with measles at hospital admission depending on vaccination status (mean  $\pm$  SEM). Protein oxidative modification was assessed at wavelengths of 356 nm, 370 nm, 430 nm, and 530 nm. Data are shown for reference values, unvaccinated patients (Group II,  $n=40$ ), and vaccinated patients (Group I,  $n=40$ ).

**Table 3** Activity of Antioxidant Enzymes in Adult Patients with Measles ( $M \pm SEM$ ) ( $\mu\text{mol/Min mg Protein}$  for GPx;  $\text{nmol/Min mg Protein}$  for GR)

Antioxidant Enzyme	Reference Values	Group II (Unvaccinated) (n = 40)	Group I (Vaccinated) (n = 40)
Glutathione peroxidase (GPx)	$0.16 \pm 0.08$	$0.140 \pm 0.015$	$0.148 \pm 0.004$
Glutathione reductase (GR)	$0.19 \pm 0.05$	$0.048 \pm 0.007$	$0.062 \pm 0.003$

**Notes:** Values are presented as mean  $\pm$  standard error of the mean (SEM). Group I – vaccinated patients; Group II – unvaccinated patients.

**Abbreviations:** GPx, glutathione peroxidase; GR, glutathione reductase.

**Table 4** Statistical Comparison of Antioxidant Enzyme Activity Between Study Groups and Reference Values

Enzyme/Comparison	Student's t-Test (p)	Mann-Whitney U-Test (p)	Interpretation
<b>Glutathione peroxidase (GPx)</b>			
Reference vs Group II	0.731	0.557	No significant difference
Reference vs Group I	0.535	0.224	No significant difference
Group II vs Group I	0.131	0.186	No significant difference
<b>Glutathione reductase (GR)</b>			
Reference vs Group II	0.0077	<0.001	Significant difference
Reference vs Group I	0.0148	<0.001	Significant difference
Group II vs Group I	0.035	$\leq 0.05$	Borderline significance

**Notes:** Group I – vaccinated patients; Group II – unvaccinated patients. Reference – normative reference range.  $p < 0.05$  was considered statistically significant.

activity demonstrated a large effect size, whereas GPx showed a negligible effect. Oxidative protein modification indices demonstrated small-to-moderate effects.

## Serum Zinc and Selenium Levels

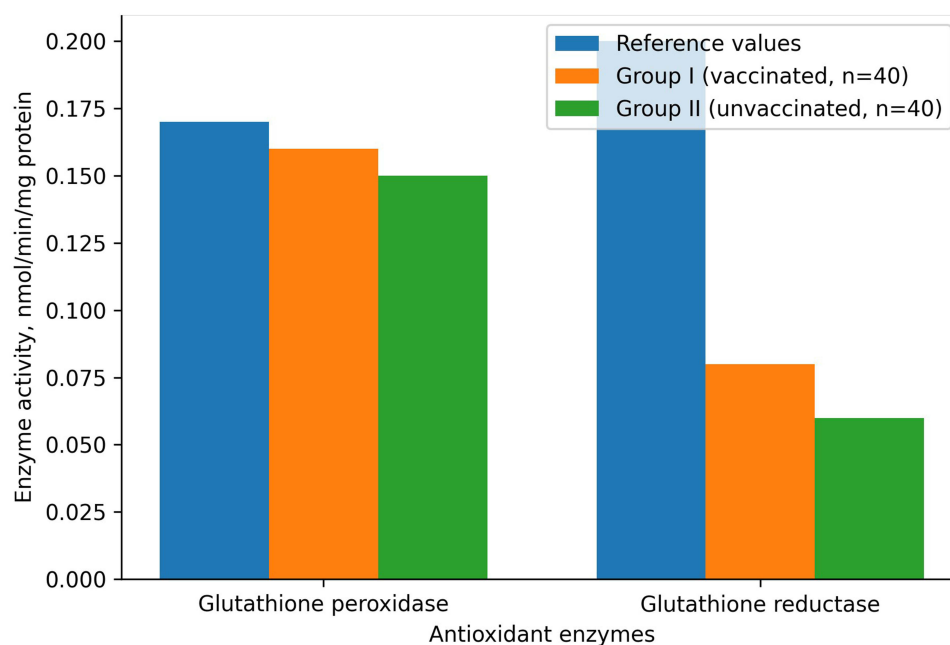
Serum zinc concentrations were significantly lower in both vaccinated and unvaccinated patients compared with reference values (Table 5). A clear gradient was observed, with the lowest zinc levels detected in unvaccinated patients (Figure 3). Zinc concentrations in vaccinated patients were approximately 13% lower than reference values, whereas unvaccinated patients demonstrated a reduction of approximately 24%. The difference between the two groups was statistically significant ( $p < 0.001$ ) (Table 6).

Similarly, serum selenium concentrations were significantly reduced in both groups relative to reference values. Vaccinated patients exhibited a decrease of approximately 49%, while unvaccinated patients showed a reduction of approximately 55% (Figure 3). Selenium levels were significantly lower in unvaccinated patients compared with vaccinated individuals ( $p < 0.001$ ) (Table 5 and Table 6).

Across all comparisons, differences in zinc and selenium concentrations between vaccinated and unvaccinated patients remained statistically significant after adjustment for multiple testing (Table 7).

## Discussion

This study provides a comprehensive biochemical characterization of adult measles, demonstrating that disease severity is closely associated with the intensity of oxidative stress, dysfunction of the glutathione antioxidant system, and



**Figure 2** Activity of antioxidant defense enzymes in adult patients with measles at hospital admission. Glutathione peroxidase and glutathione reductase activities are shown for reference values, vaccinated patients (Group I, n=40), and unvaccinated patients (Group II, n=40). Data are presented as mean  $\pm$  SEM.

disturbances in zinc and selenium homeostasis. Importantly, these alterations were consistently more pronounced in unvaccinated patients, indicating that vaccination status modifies not only the clinical course of measles but also the underlying biochemical response to infection (Conceptual schematic model Figure 4).

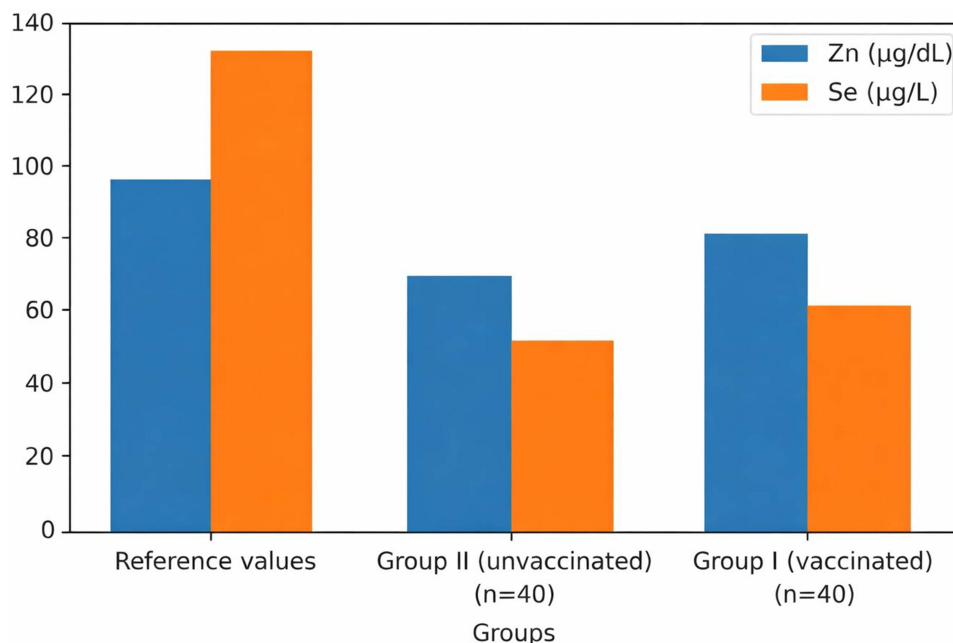
The present analysis was based on biochemical assessments performed at a single time point during the acute phase of measles at hospital admission. Some oxidative modification indices demonstrated distributional asymmetry and variability differences between groups; therefore, effect estimates should be interpreted with caution and confirmed in larger cohorts. While this approach is appropriate for capturing early oxidative and micronutrient-related alterations associated with disease severity, it does not allow evaluation of temporal dynamics, recovery patterns, or causal relationships, which would require longitudinal follow-up.

Oxidative modification of proteins represents an early and irreversible consequence of excessive reactive oxygen species generation during viral infection. Elevated levels of protein carbonyl derivatives reflect structural damage to proteins, leading to impaired enzymatic activity, altered receptor signaling, and compromised membrane integrity.<sup>15–23</sup> In the present study, unvaccinated patients exhibited significantly higher protein carbonyl levels, particularly at wavelengths corresponding to early oxidative damage (356 and 370 nm), indicating more intense oxidative protein degradation at the time of hospitalization. It should be noted that the assessment of protein carbonyl derivatives using the 2,4-dinitrophenylhydrazine (DNPH) method has certain methodological limitations. Classical acid-based protocols may overestimate carbonyl content due to incomplete removal of excess DNPH and potential interference, whereas modified neutral pH

**Table 5** Serum Zinc and Selenium Levels in Adult Patients with Measles at the Time of Hospital Admission (M  $\pm$  SEM)

Trace Element	Reference Values	Group II (Unvaccinated) (n = 40)	Group I (Vaccinated) (n = 40)
Zinc (Zn), $\mu\text{g/dL}$	103.21 $\pm$ 0.90	78.69 $\pm$ 0.72	89.54 $\pm$ 0.78
Selenium (Se), $\mu\text{g/L}$	137.58 $\pm$ 0.50	61.35 $\pm$ 0.49	69.87 $\pm$ 0.56

**Notes:** Values are presented as mean  $\pm$  standard error of the mean (SEM). Group I – vaccinated patients; Group II – unvaccinated patients.



**Figure 3** Serum zinc (Zn) and selenium (Se) levels in adult patients with measles at hospital admission. Data are shown for reference values, unvaccinated patients (Group II, n=40), and vaccinated patients (Group I, n=40). Values are expressed in µg/L and presented as mean ± SEM.

protocols improve the specificity and reproducibility of measurements.<sup>40–43</sup> Similar mechanisms of oxidative injury have been described in other viral infections, including influenza, COVID-19, and respiratory syncytial virus infection.<sup>9–14</sup> Our findings extend these observations to adult measles and highlight vaccination status as an important modifier of oxidative stress intensity.

The glutathione system is a central component of cellular antioxidant defense. While glutathione peroxidase activity remained largely preserved in both study groups during early hospitalization, glutathione reductase activity was significantly reduced, especially in unvaccinated patients. Glutathione reductase is essential for maintaining adequate levels of reduced glutathione, and its suppression limits the capacity of cells to neutralize reactive oxygen species, thereby amplifying oxidative stress.<sup>17,18,34</sup> The observed pattern—preserved GPx activity with reduced GR activity—suggests early depletion of glutathione regeneration rather than primary failure of peroxide detoxification, a phenomenon previously described in systemic inflammatory and septic conditions.<sup>17,19–21</sup>

Trace element redistribution during acute infection represents a key component of the inflammatory response. In this study, both zinc and selenium concentrations were significantly reduced in adult patients with measles, with a clear gradient favoring vaccinated individuals. Hypozincemia during acute inflammation is largely mediated by interleukin-6–dependent upregulation of

**Table 6** Differences in Serum Zinc and Selenium Levels Between Study Groups and Reference Values

Parameter	Comparison	Mean Difference (Δ)	95% CI	Hedges g	p (Welch)	p (Mann–Whitney)
Zinc (µg/dL)	Reference vs Group II	24.52	22.20–26.84	2.35	<0.001	<0.001
Zinc (µg/dL)	Reference vs Group I	13.67	11.27–16.07	1.48	<0.001	<0.001
Zinc (µg/dL)	Group II vs Group I	–10.85	–12.96 to –8.74	1.32	<0.001	<0.001
Selenium (µg/L)	Reference vs Group II	76.23	74.82–77.64	3.90	<0.001	<0.001
Selenium (µg/L)	Reference vs Group I	67.71	66.21–69.21	3.25	<0.001	<0.001
Selenium (µg/L)	Group II vs Group I	–8.52	–10.00 to –7.04	1.45	<0.001	<0.001

**Notes:** Group I – vaccinated patients; Group II – unvaccinated patients; CI – confidence interval. Effect sizes are presented as Hedges g. Parametric comparisons were performed using Welch's t-test; non-parametric comparisons using the Mann–Whitney U-test.

**Table 7** Normality Assessment and Statistical Testing of Oxidative Stress Markers, Antioxidant Enzymes, and Trace Elements

Parameter	Distribution Normality	Statistical Test	p-value (Raw)	p-value (Holm-Adjusted)	Conclusion
OPM 356 nm	Normal	Welch t-test	0.00537	0.0107	Significant
OPM 370 nm	Non-normal	Mann–Whitney U-test	0.000357	0.001	Significant
OPM 430 nm	Normal	Welch t-test	0.00667	0.013	Significant
OPM 530 nm	Normal	Student's t-test	0.2189	0.44	Not significant
Glutathione reductase (GR)	Non-normal	Mann–Whitney U-test	0.035	0.07	Trend
Zinc (Zn)	Normal	Welch t-test	$5.09 \times 10^{-16}$	<0.001	Significant
Selenium (Se)	Normal	Welch t-test	$2.87 \times 10^{-18}$	<0.001	Significant

**Notes:** Normality was assessed prior to hypothesis testing. Holm correction was applied to adjust for multiple comparisons. A p-value < 0.05 was considered statistically significant.

**Abbreviations:** OPM, oxidative protein modification; GR, glutathione reductase.

the hepatic ZIP14 transporter, resulting in rapid zinc sequestration in hepatocytes as part of the nutritional immunity response.<sup>29,31</sup> Selenium depletion reflects reduced synthesis and secretion of selenoprotein P during systemic inflammation, redistribution of selenium to target tissues, and impaired hepatic function.<sup>30,32,33</sup> These mechanisms are more pronounced in severe inflammatory states and have been associated with adverse outcomes in infectious and critical illnesses.<sup>33,34,44,45</sup>

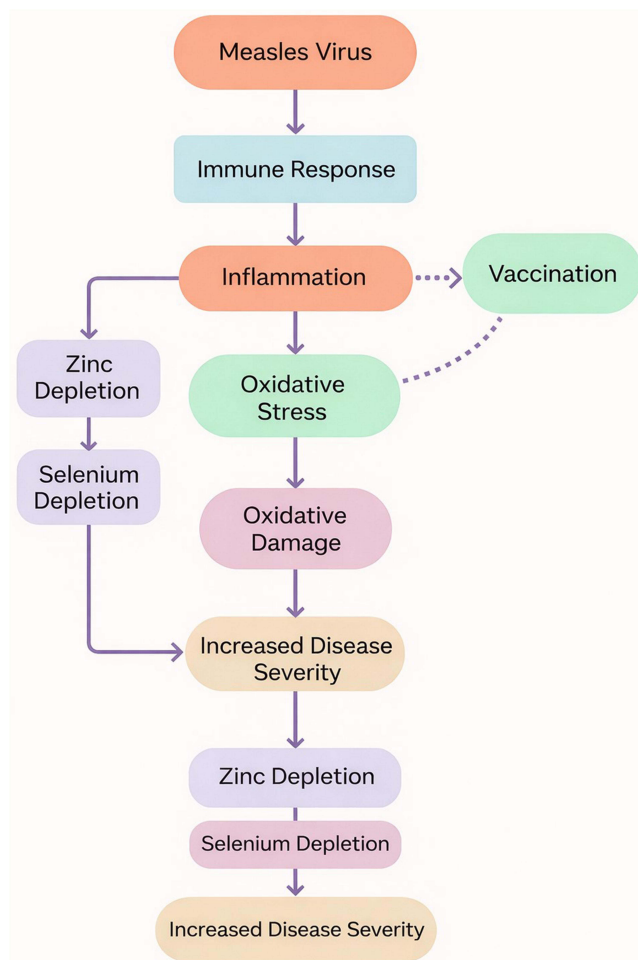
Importantly, the observed reductions in serum zinc and selenium levels should be interpreted with caution. Given the absence of baseline micronutrient assessment and the known regional prevalence of trace element deficiency, it is not possible to fully distinguish infection-related acute-phase redistribution from pre-existing deficiency.

Zinc and selenium play complementary roles in immune regulation and redox balance.<sup>40,43</sup> Zinc modulates innate and adaptive immune responses and regulates pro-inflammatory signaling pathways, including NF-κB activation.<sup>24,35–37</sup> Selenium is an essential cofactor for selenoproteins such as glutathione peroxidases, which protect cells from oxidative damage and regulate inflammatory responses.<sup>25–27,32–34</sup> The combined depletion of Zn and Se observed in unvaccinated patients may therefore exacerbate oxidative stress by simultaneously reducing antioxidant capacity and enhancing inflammatory signaling. This synergistic effect provides a plausible mechanistic explanation for the higher oxidative protein damage and more pronounced glutathione system impairment identified in this group.

The observed biochemical differences between vaccinated and unvaccinated patients expand the current understanding of the protective effects of measles vaccination. Beyond preventing infection or reducing viral replication, vaccination appears to attenuate the magnitude of systemic inflammation and oxidative stress, thereby limiting secondary metabolic and redox disturbances.<sup>29,37</sup> This observation is consistent with epidemiological data demonstrating reduced complication rates and improved outcomes among vaccinated individuals and adds a mechanistic dimension to the concept of vaccine-mediated protection.

From a clinical perspective, the combination of elevated protein carbonyl levels, reduced glutathione reductase activity, and decreased serum zinc and selenium concentrations constitutes a coherent panel of early biochemical markers associated with disease severity. These parameters are measurable using routine laboratory techniques and may support early risk stratification in hospitalized adult patients with measles, particularly among unvaccinated individuals who appear more vulnerable to rapid oxidative and metabolic deterioration.

Several limitations of this study should be acknowledged. The single-center design and assessment of biochemical parameters at a single time point limit the evaluation of dynamic changes during disease progression and recovery. Cytokine profiling was not performed, which would have provided additional insight into inflammatory drivers of micronutrient redistribution and oxidative stress. In addition, baseline nutritional status was not assessed and may have influenced trace element levels. Nevertheless, the consistency and statistical robustness of the observed intergroup differences support the validity and clinical relevance of the findings.



**Figure 4** Conceptual model of oxidative stress and micronutrient imbalance in adult measles according to vaccination status. This schematic presents a conceptual model of the potential interactions between measles infection, inflammatory response, oxidative stress, zinc and selenium depletion, and clinical severity. The relationships shown are based on observed biochemical associations in the present study and existing literature and should be interpreted as hypothesis-generating rather than causal.

These interpretations should be considered in light of the study limitations, including the observational design, absence of baseline micronutrient data, and lack of longitudinal follow-up.

## Limitations

This study has several limitations that should be considered when interpreting the findings. First, the single-center, observational design limits the generalizability of the results to populations with different epidemiological, nutritional, or healthcare settings and precludes causal inference.

Second, baseline zinc and selenium status prior to measles infection was not assessed. Given the regional prevalence of micronutrient deficiencies, it is not possible to fully distinguish infection-related acute-phase redistribution from pre-existing deficiency.

Third, potential confounding factors such as detailed dietary intake, inflammatory cytokine profiles, and antioxidant supplementation history beyond predefined exclusion criteria were not systematically evaluated.

Finally, biochemical parameters were assessed at a single time point during the acute phase of disease, which does not allow evaluation of temporal dynamics, recovery patterns, or long-term associations. Longitudinal studies are required to confirm the persistence and clinical relevance of the observed biochemical alterations.

No formal a priori power calculation was performed, as the study was designed as an exploratory observational analysis. However, sensitivity analysis indicated adequate power to detect moderate-to-large between-group effects,

whereas small effect sizes may have remained undetected. Nevertheless, the sample size was sufficient to detect moderate between-group differences across multiple independent biochemical parameters. These findings should be interpreted within the context of the study design and warrant confirmation in larger, prospective studies.

## Conclusions

In conclusion, adult measles was associated with pronounced oxidative protein modification, impaired glutathione system activity, and reduced serum zinc and selenium levels, particularly among unvaccinated patients. Vaccination status was associated with a more favorable oxidative and micronutrient profile at hospital admission.

These biochemical alterations may reflect early pathophysiological processes related to disease severity; however, given the observational design and the absence of baseline and longitudinal data, causal inferences cannot be made. The identified markers should therefore be considered hypothesis-generating and warrant further investigation in larger, prospective studies with longitudinal follow-up.

The combined assessment of oxidative stress markers and micronutrient status may contribute to improved understanding of disease severity patterns and could potentially inform future risk stratification approaches pending further confirmation.

## Novelty Statement

For the first time in Ukraine, a comprehensive clinical and laboratory study of adult patients with measles was conducted, comparing the degrees of oxidative stress, the intensity of oxidative modification of proteins, the activity of glutathione system enzymes, and the microelement balance (Zn, Se) depending on the vaccination status of patients. Our data show that vaccination against measles not only modifies the clinical course of the disease but also has a pronounced protective effect on the intensity of oxidative imbalance, reducing the levels of protein modification and the degree of depletion of antioxidant systems. The identified biochemical markers (Zn↓, Se↓, OMP↑, GR↓) form a new diagnostic panel for early prediction of the severity of measles and can be used in personalised approaches to patient management.

## Clinical Implications

The results obtained indicate that simultaneous assessment of Zn and Se levels, protein oxidative modification indicators, and glutathione reductase activity at the time of hospitalisation may be useful for:

- Early risk stratification in adult patients with measles;
- Identifying patients who are at increased risk of complications and severe disease;
- Identifying a group of patients who require enhanced monitoring or correction of micronutrient imbalance;
- Developing personalised treatment strategies, especially in unvaccinated patients;
- Optimising the management of measles outbreaks among the adult population.

Zn, Se, GR and OMP markers can be considered as accessible early biomarkers of severity, which adds practical value to the study.

## Strengths and Limitations

### Strengths of the Study

1. Comprehensive biochemical analysis covering several levels of oxidative stress: protein carbonylation, the enzymatic link of the glutathione system, and micronutrient status.
2. Comparison by vaccination status, which allowed us to assess the protective effect of vaccination on the course of measles.
3. Use of standardised methods of spectrophotometry and atomic absorption analysis.
4. Clear inclusion/exclusion criteria, which reduces the risk of confounding factors.
5. Homogeneity of the cohort in terms of age and comorbidities.

## Limitations

1. Lack of data on the dynamics of indicators at different stages (only the initial hospitalisation point).
2. The study was conducted in a single centre, which may limit the generalisability of the results.
3. Cytokine levels (IL-6, TNF- $\alpha$ ) were not studied, which could further confirm the mechanisms of micronutrient redistribution.
4. No analysis of nutritional status and past nutritional deficiencies.
5. Some of the 2,4-DNFG methods have potential variability characteristic of the classic protocol.

## Data Sharing Statement

All data used in this study are stored on secure servers at Ivano-Frankivsk National Medical University. A set of anonymised data is available upon reasonable request to the corresponding author for scientific or educational use. The data are not publicly available due to confidentiality and medical privacy requirements.

## Ethical Approval Statement

The study was conducted in accordance with the Helsinki Declaration (1964–2013), ICH GCP (1996), EEC Directive No. 609/86, and Order No. 690 of the Ministry of Health of Ukraine dated 23 September 2009.

The study protocol was reviewed and approved by the Local Ethics Committee of Ivano-Frankivsk National Medical University (protocol No. 111/19 dated 19 November 2019). All patients provided written informed consent to participate in the study and to the processing of their personal data.

## Author Contributions

All authors made a substantial contribution to the work; participated in drafting or critically revising the article; approved the final version for publication; agreed on the journal to which the manuscript was submitted; and accept responsibility for all aspects of the work.

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The research was conducted without external funding. Laboratory analyses were performed at Ivano-Frankivsk National Medical University, the Centre for Bioelementology of IFNMU, and the Centre for Infectious Diseases as part of routine medical and diagnostic work.

## Disclosure

The authors declare that there is no conflicts of interest regarding the materials presented in the article.

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