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# Impact of vitamin D and zinc sufficiency on immune responses following COVID-19 vaccinations among healthcare workers

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**Introduction:** Vitamin D and zinc sufficiency are theoretically acclaimed to influence immune-boosting potentials following various immunizations. Herein, we explored the impact of these micronutrients on immune responses following Oxford-AstraZeneca coronavirus disease 2019 (COVID-19) vaccination among Nigerians.

**Methods:** Two hundred healthcare workers (HCs) who presented at the Rivers State University Teaching Hospital were recruited during the first dose and followed up 4 weeks post-first and post-second doses. Data (serum vitamin D/zinc, COVID-19 anti-spike immunoglobulin G [ASIgG]) were determined on the day of the first dose and repeated 4 weeks post-first dose and 4 weeks post-second dose. Vitamin D (VitD) status, assessed using serum 25(OH)D, was categorized as sufficient (≥50 nmol/L) or insufficient/deficient (<50 nmol/L) while zinc status was categorized as sufficient (≥11.3 μmol/L) or insufficient (<11.3 μmol/L). Post-second dose ASIgG titer status was categorized as optimal (>7,352 AU/mL) or sub-optimal (<7,352 AU/mL) as defined by the World Health Organization. Statistical significance was defined as $p<0.05$.

**Results:** HCs with both VitD and zinc sufficiency (n=97) had higher ASIgG titer levels (4 weeks post-first dose=15,977±367.88 AU/mL; 4 weeks post-second dose=22,603±451.18 AU/mL) after the first and second doses compared to only the VitD sufficient (n=58) cohorts (4 weeks post-first dose=4,680±154.77 AU/mL; 4 weeks post-second dose=7,850±200.60 AU/mL) and the zinc-sufficient (n=63) cohorts (4 weeks post-first dose=5,770±160.41 AU/mL; 4 weeks post-second dose=8,100±206.91 AU/mL) ($p<0.05$). The VitD and zinc-sufficient HCs were also more likely to achieve optimal ASIgG titer levels (odds ratio, 2.97; 95% confidence interval, 2.11–4.123; $p<0.001$) 4 weeks post-second dose following adjustment for confounders.

**Conclusion:** VitD and zinc sufficiency had a positive impact on immune responses following AstraZeneca COVID-19 vaccination.

**Keywords:** COVID-19; COVID-19 vaccination; Vitamin D; Zinc; Immune responses

## INTRODUCTION

Several vital micronutrients play major actions in conserving the cohesion and functional potentials of the human immune systems, presenting concerted interactions in varied steps that tend to determine immunologic responses [1]. Among these vital micronutrients, vitamin D (VitD) and zinc stand out for having important immunomodulatory functions in human immunologic systems [2-8]. In addition, several observational and experimental studies have also documented the influence of VitD and zinc to boost the immunogenicity and efficacy of several vaccines including the coronavirus disease 2019 (COVID-19) vaccines [7,8]. Serum zinc status, in its free form, has been reported in associated with vaccination response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [7]. VitD has also been characterized as a potential adjuvant agent for COVID-19 vaccines in recent reports [8]. However, deficiencies of both zinc and VitD in the general global population have been described as a global health concern as recently documented by the World Health Organization (WHO) and various other professional bodies [9,10]. Available records also show that billions of the global population irrespective of gender, age, geographical location, and economic status have been documented to have VitD and zinc deficient status [9,10]. Published studies on the immune responses to COVID-19 vaccines about zinc and VitD status are limited at present within the existing literature and have not been described among native Nigerians [3-5]. Given this link between VitD/zinc status and immune responses to vaccines and the widespread deficiencies of these two micronutrients, this study is set forth to evaluate the impact of VitD and zinc sufficiency on immune responses following COVID-19 vaccinations among Nigerian healthcare workers (HCs).

## MATERIALS AND METHODS

### Study design, site, and setting

The study was designed as a prospective case-controlled study conducted at the Rivers State University Teaching Hospital (RSUTH) in Rivers State, Southern Nigeria. RSUTH is one of the hospitals designated for COVID-19 vaccination using various vaccines during the peak of the COVID-19 pandemic. The hospital also has several clinical departments including chemical pathology and a well-equipped molecular laboratory where reverse transcriptase polymerase chain reaction (RT-PCR) tests are carried out to confirm COVID-19 among the suspected cases. The Department of Chemical Pathology of the hospital is well-equipped with several biochemical analyzers for routine/complex biochemical investigations by experienced analysts.

### Ethical considerations

Approval for the study was granted by the Health Research Ethics Committee of the RSUTH with approval reference RSUTH/REC/2021073. All study populations agreed to participate and subsequently provided written/signed informed consent. The study was conducted with strict adherence to the Rivers State Hospital Management Board-recommended guidelines and the principles embodied and laid down in the Helsinki Declarations of 1964, and as revised in 2013.

### Study tools and population

The study population consisted of eligible HCs who presented consecutively for the first and second doses of Oxford-AstraZeneca vaccination at RSUTH between 2021 and 2023.

### Sample size determination

The calculated minimum sample size required for this study is approximately 200. The sample size was determined using a sample size mathematical formula for case-control studies for characteristics in a given population >10,000 using a type 1 error rate of 5% (0.05), study power (1-β) of 80% (0.8), case/control ratio of 1, and 20% prevalence of COVID-19 vaccination acceptance rate in Nigeria [11,12]. Though the result from the sample size calculation was 156 each per case/control, we enrolled 200 HCs for each study group to improve the power of the study and to account for at least a 10% drop-out rate.

### Eligibility criteria

Criteria for inclusion are adult (aged ≥18 but ≤44 years) HCs without prior history of COVID-19 infection, COVID-19 anti-spike immunoglobin G (ASIgG) level <50.0 AU/mL, and RT-PCR negative status for COVID-19. Criteria for exclusion are age <18 or >44 years, prior history of COVID-19 vaccination, COVID-19 infection, malnourished status, post-menopausal, hypogonadism, hypopituitarism, thyroid disorders, pregnancy, and past/pre-existing comorbidities (cardiovascular disease, hypertension, chronic lung disease, asthma, sickle cell disease, human immunodeficiency virus/acquired immunodeficiency syndrome, diabetes, cancer, obesity, acute/chronic kidney disease, chronic liver disease, previous/current cigarette smoker, organ transplant recipient, and receiving immunosuppressive therapy) including recent history of medications known to influence zinc or VitD such as supplements. For each of the eligible HCs

recruited, an age and sex-matched control was recruited for comparison.

### Sampling method

A simple random sampling technique was employed as a sampling method for the recruitment of the study participants.

### Data collection

The study populations were recruited upon presentation to the designated COVID-19 vaccination unit in RSUTH. Upon presentation before getting the first vaccine jab, HCs were informed of the study to obtain informed consent. Thereafter, a semi-structured questionnaire was used to obtain baseline socio-demographic, anthropometric, and other clinical data.

Following the determination of eligibility status, first dose pre-vaccination blood specimen acquisition was done to determine baseline laboratory parameters before the first vaccination jab. After the first jab, recruited HCs were monitored weekly via physical and telephone calls until 4 weeks later, when they presented for the second jab (first cycle). At presentation for the second jab, no second dose pre-vaccination blood specimen was obtained, but the HCs were subsequently monitored until another 4 weeks later, when another second post-vaccination blood specimen was repeated (second cycle). Hence, serum specimens were collected at 3-time points: at baseline (T1, before vaccination among the potential vaccinees [cases] and non-vaccinees [controls]), at 4 weeks post-first dose from the vaccinated (T2), and 4 post-second doses from the vaccinated (T3) after the second dose.

### Specimen management

Non-fasting whole blood acquisition into plain specimen tubes and laboratory analysis were done following standardized protocols. The acquired specimen was allowed to clot undisturbed at room temperature and centrifuged afterward at 1,500 g for 10 minutes. The serum supernatant was thereafter transferred with Pasteur's pipette into plain tubes until analyzed. Processed serum was analyzed for VitD and ASIgG levels on an automated immunoassay analyzer (Architect i2000; Abbott Laboratories, Abbott Park, IL, USA). The analytic measurement range is reported to span 4.2–50,000.0 AU/mL (with a clinical reportable range of up to 200,000 AU/mL), with readings above 50.0 AU/mL (positive detection threshold) indicating seropositivity, according to the manufacturer. Specimens exceeding the measurable range were diluted 2- to 16-fold with the supplied dilution buffer, and then corrected by the dilution factor to determine the initial concentration. Serum zinc was determined via the flame atomic absorption spectrophotometric (Hitachi Model A-1800) methodology using the direct method described by Smith and associates [13].

### Quality assurance

The utilized study questionnaire was explored for reliability and validity using appropriate methodologies. All necessary precautions were taken to prevent environmental zinc contamination of blood specimens, reagents, and equipment as recommended by the International Zinc Nutrition Consultative Group (IZiNCG) [14]. All specimens for VitD analyses were obtained during the same Nigerian climate season (December to March) to obviate the seasonal differences of dermal VitD synthesis due to ultraviolet rays. Two levels of supplied commercial control sera were used to monitor intra-assay and inter-assay analytic precision, and at all times, the intra- and inter-assay coefficients of variation were below 5% and 10%, respectively.

### Infection prevention and control measures

Adequate infection prevention and control measures as recommended by the Nigeria Center for Disease Control were strictly adhered to during the data acquisition, specimen collection, and laboratory analysis [15].

### Variable definitions/stratifications

- Serum VitD categories: VitD status, assessed using serum 25(OH)D, was categorized as sufficient (≥50 nmol/L) or insufficient/deficient (<50 nmol/L) as defined by the National Academy of Medicine [16].
- Serum zinc categories: Zinc status was dichotomized as sufficient (≥11.3 μmol/L) or insufficient (<11.3 μmol/L) based on the IZiNCG recommendations [14].
- Body mass index (BMI) categories: BMI was categorized as underweight (<18.5 kg/m$^2$), normal weight (18.5–24.9 kg/m$^2$), overweight (25.0–29.9 kg/m$^2$), and obese (≥30 kg/m$^2$) [17].
- Post-second optimal ASIgG antibody titer status: Post-second dose ASIgG titer status was categorized as optimal (>7,352 AU/mL) or sub-optimal (<7,352 AU/mL) as defined by the WHO [18-20].

### Data management

Data management and analyses were done using SPSS software for Windows version 25 (IBM Corp., Armonk, NY, USA). The continuous data were initially evaluated for conformity to a normal distribution pattern using the Shapiro-Wilk tests. The continuous data violating the normal distribution patterns were log-transformed before analysis, expressed using

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means ± standard deviations, and compared by independent Student's t-test or analysis of variance, as appropriate. The categorical data were reported as counts/percentages and compared with the $\chi^2$ or Fisher's exact tests, as appropriate. Logistic regression analysis was used to evaluate associations between dependent and independent variables at 95% confidence intervals (CIs). A p-value <0.05 was deemed statistically significant.

## RESULTS

**Table 1** depicts the pre-vaccination baseline demographic, laboratory, and clinical data of studied populations. From the table, no statistical difference was noted in any of the pre-vaccination baseline demographic, laboratory, and clinical data between the recruited potential vaccinees before their vaccination and the recruited age and sex-matched control subjects (p>0.05) (**Table 1**).

**Table 2** depicts the dynamics of serum ASIgG concentrations by VitD and zinc status from baseline (before vaccination) to 4 weeks post-first week dose and 4 weeks later post-vaccination dose. In **Table 2**, there was a progressive dynamic increase of serum ASIgG concentration from baseline through to the 4 weeks first/second post-vaccination periods among the different VitD and zinc categories (p<0.001).

However, those HCs with both VitD and zinc sufficiency status (n=97) had higher ASIgG titer levels (4 weeks post-first dose=15,977±367.88 AU/mL; 4 weeks post-second dose=22,603±451.18 AU/mL) after the first and second doses compared to only the VitD sufficient (n=58) cohorts (4 weeks post-first dose=4,680±154.77 AU/mL; 4 weeks post-second dose=7,850±200.60 AU/mL) and the zinc-sufficient (n=63) cohorts (4 weeks post-first dose=5,770±160.41 AU/mL; 4 weeks post-second dose=8,100±206.91 AU/mL) (p<0.05) (**Table 2**).

As shown in **Table 3**, The HCs with both VitD and zinc sufficient status were likely to achieve optimal ASIgG titer levels (≥7,354 AU/mL) (odds ratio, 2.970; 95% CI, 2.11–4.123; p<0.001) 4 weeks post-second dose following adjustment for age and gender compared to those with isolated VitD and zinc sufficient status (**Table 3**).

**Table 1.** Pre-vaccination baseline demographic, laboratory and clinical parameters of studied populations

| Variables | Potential vaccinees (cases) (n = 200) | Non-potential vaccinees (controls) (n = 200) | p-value |
|---|---|---|---|
| Age (yr) | 32.86±4.18 | 33.09±4.12 | 0.758 |
| Gender | | | NA |
| Males | 106 (53.0) | 106 (53.0) | |
| Females | 94 (47.0) | 94 (47.0) | |
| BMI (kg/m$^2$) | 26.77±3.40 | 27.10±3.14 | 0.676 |
| Serum VitD status (nmol/L) | 46.7±6.88 | 47.34±7.03 | 0.509 |
| Serum zinc status (μmol/L) | 13.4±2.13 | 12.93±2.34 | 0.442 |
| Serum ASIgG (AU/mL) | 22.11±2.16 | 23.22±2.02 | 0.577 |
| BMI status | | | 0.664 |
| Normal weight | 66 (33.0) | 70 (35.0) | |
| Overweight | 98 (49.0) | 90 (45.0) | |
| Obese | 36 (18.0) | 40 (20.0) | |
| VitD status | | | 0.187 |
| Sufficient (≥50 nmol/L) | 58 (29.0) | 61 (30.5) | |
| Insufficient (<50 nmol/L) | 142 (71.0) | 139 (69.5) | |
| Zinc status | | | 0.169 |
| Sufficient (≥11.3 μmol/L) | 63 (31.5) | 65 (32.5) | |
| Insufficient (<11.3 μmol/L) | 137 (68.5) | 135 (67. 5) | |
| VitD + zinc status | | | 0.340 |
| Sufficient | 97 (48.5) | 98 (49.0) | |
| Insufficient | 103 (51.5) | 102 (51.0) | |

Values are presented as mean ± standard deviation or number (%).
NA, not applicable; BMI, body mass index; VitD, vitamin D; ASIgG, anti-spike immunoglobulin G.

**Table 2.** Dynamics of ASIgG levels by VitD/zinc status among the vaccinated healthcare workers

| Parameters of variables | ASIgG concentration (AU/mL) | | | p-value |
|---|---|---|---|---|
| | Baseline (before vaccination) | Four weeks post-first dose | Four weeks post-second dose | |
| Panel A | | | | |
| Sufficient VitD status (≥50 nmol/L) | 25.34±2.63 | 4,680±154.77 | 7,850±200.60 | <0.001[a] |
| Sufficient zinc status (≥11.3 μmol/L) | 26.43±2.71 | 5,770±160.41 | 8,100±206.91 | <0.001[a] |
| Sufficient VitD + zinc status | 27.16±3.02 | 15,977±367.88 | 22,603±451.18 | <0.001[a] |
| p-value | 0.308 | <0.001[a] | <0.001[a] | |
| Panel B | | | | |
| Insufficient VitD status (<50 nmol/L) | 23.41±2.54 | 3,114.77±101.67 | 6,011.76±166.51 | <0.001[a] |
| Insufficient zinc status (<11.3 μmol/L) | 24.40±2.41 | 2,987.52±97.96 | 5,771.62±153.66 | <0.001[a] |
| Insufficient VitD + zinc status | 26.26±2.87 | 2,990.88±97.56 | 5,719.87±144.15 | <0.001[a] |
| p-value | 0.266 | 0.187 | 0.204 | |

ASIgG, anti-spike immunoglobulin G; VitD, vitamin D.
[a]Statistically significant.

**Table 3.** Likelihood of achieving serum optimal ASIgG titer levels by VitD/zinc sufficient status among the vaccinated healthcare workers

| Categories of variables | ASIgG concentration (≥7,354 AU/mL) | | |
|---|---|---|---|
| | Odd ratio[a] | 95% CI | p-value |
| Sufficient VitD status (≥50 nmol/L) | 1.210 | 1.033–1.402 | 0.074 |
| Sufficient zinc status (≥11.3 μmol/L) | 1.650 | 1.244–1.890 | 0.082 |
| Sufficient VitD + zinc status | 2.970 | 2.110–4.123 | <0.001[b] |

ASIgG, anti-spike immunoglobulin G; VitD, vitamin D; CI, confidence interval.
[a]Adjusted for sex/age; [b]Statistically significant.

## DISCUSSION

In the current study, there was a significant progressive increase of serum ASIgG concentration from baseline through to the 4 weeks first/second post-vaccination periods among the different VitD and zinc categories. However, those HCs with both VitD/zinc sufficiency status had higher ASIgG titer levels following the first and second vaccination doses compared to only the isolated VitD-sufficient cohorts and those of isolated zinc-sufficient cohorts. Additionally, those studied HCs with both VitD/zinc sufficient status were also likely to achieve optimal ASIgG titer levels 4 weeks post-second dose following adjustment for age and sex compared to those with isolated VitD and zinc sufficient status.

Though data relating to this subject remains scarce within the pre-existing literature, the current findings align with previous similar studies [7,8]. In a cohort study conducted in Germany among adult HCs (n=126), the HCs received two doses of Pfizer BioNTech vaccine, provided up to 4 serum samples over a time course of 6 months, and the total SARS-CoV-2 IgG and neutralizing antibody potency was determined, along with total as well as free zinc concentrations [7]. The authors observed a positive correlation between free zinc concentrations and both the induced antibodies and neutralizing potency of the antibodies [7]. Though the COVID-19 vaccine deployed in this German study was not the type evaluated in this present study, the study findings seem to align with the current study findings and corroborats the role of zinc in vaccine immunogenicity and efficacy [7].

Consistent with the current findings, data from a longitudinal study of subjects (n=712) in Greece observed that sufficient VitD status was associated with higher antibody titers 3 months post-vaccination with Pfizer BioNTech vaccine [21].

Moreover, recently available data from Jolliffe and colleagues also showed an independent association between VitD supplement use and enhanced humoral responses to COVID-19 vaccination [22]. This study assayed ASIgG titer before and after administration of 2 doses of Oxford AstraZeneca or Pfizer BioNTech vaccine among adults (n=9,101) in a longitudinal study in the United Kingdom and evaluated 6-6 potential determinants of the antibody response for their possible association with seronegativity. In an adjusted multivariable analysis of the vaccine response, regular VitD supplementation was associated with a significantly lower risk of post-vaccination seronegativity. While no data was provided on dosage, frequency of intake, or serum VitD status, these data are consistent with the role of VitD in supporting vaccine responses, including COVID-19 vaccines.

Although several critical mechanisms have been adduced to the enhanced immune-boosting responses by several micronutrients including VitD and zinc in the literature, there is consensus that the basic underlying mechanism is the establishment of potent cellular and humoral immune homeostasis and plays vital immunomodulatory roles as recently described [23,24].

The findings here highlight the need to screen for COVID-19-associated metabolic bone perturbations during COVID-19 management. The genetic basis of COVID-19-induced metabolic bone perturbations should be an area of intense research.

The study was strongly strengthened by a well-designed vaccination program underlying this observational study and the standardized specimen management and analyses by experienced scientists blinded to any clinical information.

Yet, the study was limited by some factors which are potential areas for improvement in future studies. Among these limitations is the focus on only the humoral immune response without concomitant assessment of the cell-based immune responses. The observational study design also precludes conclusions on mechanisms and causality.

The time points of analysis were few, and a more frequent sampling scheme would have provided a more detailed picture of the dynamic alterations occurring in response to vaccination. The study considered only healthy adults, so the current data cannot be extrapolated to other groups of subjects including children, the elderly, etc. Finally, the study was a single-center study, so, its findings may not reflect the larger population within the studied region.

In the current study, there was a significant progressive increase of serum ASIgG concentration from baseline through to the 4 weeks first/second post-vaccination periods among the different VitD and zinc categories. Studied HCs with both VitD/zinc sufficiency status had higher ASIgG titer levels following the first and second vaccination doses

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compared to only the isolated VitD-sufficient cohorts and those of isolated zinc-sufficient cohorts. Additionally, HCs with both VitD/zinc sufficient status were also likely to achieve optimal ASIgG titer levels 4 weeks post-second dose following adjustment for age and sex compared to those with isolated VitD and zinc sufficient status.

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No potential conflict of interest relevant to this article was reported.

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