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# Humoral anti-SARS-CoV-2 immune response for different strains after Sinovac-CoronaVac and Oxford/AstraZeneca (ChAdOx1-S) full vaccination on a healthcare population in Brazil

## Resposta imune humoral anti-SARS-CoV-2 para diferentes cepas virais após vacinação completa com Sinovac-CoronaVac e Oxford/AstraZeneca (ChAdOx1-S) em uma população de trabalhadores da saúde no Brasil

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**ABSTRACT**

COVID-19, caused by the SARS-CoV-2 virus, is a global respiratory syndrome with high mortality rates. Vaccination is currently the only proven method to prevent the disease, although the role of lab data in assessing efficacy remains uncertain. This study aimed to assess spike-binding and neutralizing antibody levels following full vaccination with Oxford/AstraZeneca (ChAdOx1 nCoV-19) or CoronaVac in healthcare workers in southeastern Brazil. ChAdOx1 nCoV-19 and CoronaVac induced IgG antibodies against trimeric spike glycoproteins in 99.5% and 80.9% of individuals, respectively. Neutralizing antibodies were produced against two viral strains groups: variants group 1 (Wuhan-Hu-1, Alpha) and variants group 2 (Beta, Gamma) with neutralization rates of 88.3% and 78.2% for ChAdOx1 nCoV-19, and 68.1% and 48.9% for CoronaVac. No associations were found between neutralizing levels and comorbidities, age, or side effects. A positive correlation was observed between IgG antibody concentrations against trimeric spike glycoproteins and neutralizing levels for both vaccines and variants. These findings indicate that both vaccines induced reasonable levels of neutralizing antibodies against variants group 1, but only ChAdOx1 nCoV-19 maintained acceptable levels against a variant strain. The study suggests that evaluating vaccine responses to different pathogen strains can aid in managing healthcare workforce concerns and improve vaccine selection, thereby enhancing overall vaccination strategies.

**Keywords**: ChAdOx1 nCoV-19. CoronaVac. COVID-19 Vaccines. Neutralizing antibodies. SARS-CoV-2.

**RESUMO**

A Covid-19, causada pelo vírus SARS-CoV-2, é uma síndrome respiratória global com altas taxas de mortalidade. A vacinação é atualmente o único método comprovado para prevenir a doença, embora o papel dos dados laboratoriais na avaliação da eficácia ainda seja incerto. Este estudo teve como objetivo avaliar os níveis de anticorpos anti-spike e anticorpos neutralizantes após a vacinação completa com Oxford/AstraZeneca (ChAdOx1 nCoV-19) ou CoronaVac em profissionais de saúde no sudeste do Brasil. ChAdOx1 nCoV-19 e CoronaVac induziram anticorpos IgG contra glicoproteína spike (S) em 99,5% e 80,9% dos indivíduos, respectivamente. Anticorpos neutralizantes foram produzidos contra dois grupos de cepas virais: grupo de variantes 1 (Wuhan-Hu-1, Alfa) e grupo de variantes 2 (Beta, Gama), com taxas de neutralização de 88,3% e de 78,2% para ChAdOx1 nCoV-19, de 68,1% e de 48,9% para CoronaVac. Não foram encontradas associações entre os níveis de neutralização e de comorbidades, de idade ou de efeitos colaterais. Observou-se correlação positiva entre as concentrações de anticorpos IgG contra glicoproteínas spike (S) e os níveis de neutralização para ambas as vacinas e as variantes. Estes resultados indicam que ambas as vacinas induziram níveis razoáveis de anticorpos neutralizantes contra variantes do grupo 1, mas apenas ChAdOx1 nCoV-19 manteve níveis aceitáveis contra uma cepa variante. O estudo sugere que a avaliação das respostas vacinais a diferentes cepas patogênicas pode auxiliar no gerenciamento das preocupações da força de trabalho em saúde e melhorar a seleção de vacinas para pacientes específicos, melhorando, assim, as estratégias gerais de vacinação.

**Palavras-chave**: Anticorpos neutralizantes. ChAdOx1 nCoV-19. CoronaVac. SARS-CoV-2. Vacinas contra Covid-19.

## INTRODUCTION

Coronaviruses are important human and animal pathogens (Swelum et al., 2020). In late 2019, a new coronavirus was identified as the cause of several cases of pneumonia in Wuhan, China (She et al., 2020). Since then, the virus spread rapidly, resulting in an epidemic across China, followed by a global pandemic. In February 2020, the World Health Organization named the disease as COVID-19, which means "coronavirus disease 2019". Recent epidemiological (December 2023) data show that there have been 773,819,856 confirmed cases of COVID-19 with 7,010,568 deaths worldwide (World Health Organization [WHO], 2023b).

Coronaviruses are a family of enveloped positive-sense single-stranded RNA viruses. Complete genome sequencing and phylogenetic analysis indicated that the coronavirus causing COVID-19 is a beta coronavirus of the same subgenus of severe acute respiratory syndrome (SARS) virus (Hu, Guo, Zhou & Shi, 2021). Subsequently, the Coronavirus Study Group of the International Committee on Taxonomy of Viruses proposed that this virus should be designated as coronavirus of severe acute respiratory syndrome 2 (SARS-CoV-2) (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses et al., 2020).

Currently, in addition to behavioral measures, which consist of wearing masks, social distancing, and hand hygiene, the only pharmacological option available to prevent SARS-CoV-2 infection is through vaccination (Scarabel, Guardascione, Dal Bo & Toffoli, 2021). Indeed, the number of confirmed cases, hospitalization, and deaths associated to COVID-19 have dropped since the first vaccines were launched (Li et al., 2021; Haas et al., 2022; Kayano et al., 2022; Shoukat et al., 2022).

Brazil had one of the highest incidence and mortality rates worldwide since the beginning of the pandemic, but this picture has changed dramatically after massive vaccination campaigns have taken place in January 2021 (Ferreira et al., 2023). One year later, in January 2022, Brazil reached the mark of 330 million doses administered, which resulted in a fall of the number of cases and deaths associated with COVID-19 (Ministério da Saúde, 2022). So far, over 515 million doses have been administered in the country and, currently (November 26, 2023), Brazil has 172 million persons vaccinated with a complete

primary series (World Health Organization [WHO], 2023a).

At first, the strategy of vaccination in Brazil prioritized the elderly and healthcare workers, given that such groups are more likely to be exposed and thus are more vulnerable. As healthcare workers were the first population to be vaccinated, most of them were immunized with either CoronaVac or ChAdOx1 nCoV-19, the first and second vaccines approved for use in the country (Moreira et al., 2022).

Fabrication methods of CoronaVac and ChAdOx1 nCoV-19 vaccines are different and thus may elicit different immunological responses in vaccinated individuals. The vaccine developed by the University of Oxford and AstraZeneca, ChAdOx1 nCoV-19 (AZD1222), consists of a replication-deficient adenoviral vector encoding the spike (S) glycoprotein of SARS-CoV-2, based on the full-length sequence of the original strain (SARS-CoV-2, Wuhan-1) (Van Doremalen et al., 2022). On the other hand, CoronaVac, which is the vaccine produced by the Butantan Institute (IB)/Sinovac Biotech, contains inactivated SARS CoV-2 viruses from the original strain (Instituto Butantan, 2022; Jin, Li, Zhang, Li & Zhu, 2022).

In general, vaccine efficacy is evaluated according to endpoints routinely used on clinical trials, such as disease severity, mortality, infection, and transmission (Mohammed et al., 2022). Additionally, the effectiveness of a vaccine can be also assessed by evaluating its capability in generating a particular immune response: for instance, immunoglobulin G (IgG) levels can indicate developed immunity due to previous SARS-CoV-2 infection (Vangelista & Secchi, 2020). However, other studies have suggested that the presence of antibodies alone is not enough to determine the readiness of immune responses against SARS-CoV-2 infection (Carrillo et al., 2021; Dolscheid-Pommerich et al., 2022), making it necessary to evaluate the ability of generated antibodies to neutralize the virus.

In this sense, recent studies suggest that the presence of neutralizing antibodies above 20.2% confers 50% protection against symptomatic infections caused by the SARS-CoV-2 (Khoury et al., 2021). However, the true value of antibody thresholds to indicate protection is under debate. Therefore, further studies are necessary to better understand the correlation between the development of antibodies and protective immunity against SARS-CoV-2.

This study was designed to assess the production of spike-binding antibodies and neutralizing antibodies induced by ChAdOx1 nCoV-19 or CoronaVac vaccines against the original SARS-CoV-2 strain and the Alpha variant (var. 1) and against the second batch of variants Beta and Gamma (var. 2) in a population of healthcare workers of a diagnostic service in Brazil. Herein, we have shown that both vaccines induced IgG and neutralizing antibody production in response to var. 1 at reasonable levels, but the immune response against var. 2 was markedly impaired. We have also observed that IgG and neutralizing antibody production were highly co-related.

## MATERIALS AND METHODS

### Study design and serological assay tests

This retrospective study was conducted at the Diagnostic Institute of Sorocaba (IDS) in collaboration with the University of Sorocaba – UNISO, located in the state of Sao Paulo, Southeastern Brazil. The present work was approved by the Ethic's review board of the University of Sorocaba (47300621.0.0000.5500). We evaluated the immune response of a group of healthcare workers after complete vaccination with either ChAdOx1 nCoV-19 or CoronaVac during the period ranging from March 2021 to July 2021.

Healthcare workers were first informed of the study and signed a form attesting their participation was of free will. Participating individuals were initially asked to report having any side effects after vaccination and also whether they suffered from any co-morbidities. Individuals who had been previously diagnosed with SARS-CoV-2 infection (as detected by RT-PCR or serology tests) were excluded from the study. A final number of 235 individuals were deemed eligible for this research.

Individuals had their blood collected by venous puncture 60 days after being fully vaccinated. The samples were centrifuged at 1500 rpm for 15 minutes for separation of serum, which was kept at -20 °C until further analysis. For assessment of IgG antibodies anti-trimeric spike glycoprotein levels, the Liaison SARS-CoV-2 TrimericS IgG kit 311510 (DiaSorin®, Stillwater, USA) was used according to manufacturer instructions. Briefly, the Liaison SARS-CoV-2 TrimericS IgG kit consists of an indirect chemiluminescence test, in which magnetic particles coated with recombinant SARS-CoV-2 bind to IgG antibodies anti-trimeric spike glycoprotein found in serum or plasma samples, which are then bound to isoluminol-bound anti-human IgG. The limit of quantification of this kit is 4.24 AU/mL (antibody units per milliliter) and levels of IgG antibodies anti-trimeric spike glycoprotein are considered positive when above 33.8 AU/mL.

For analysis of neutralizing antibody activity, the ECO F COVID nAb kit 80954880157 (ECO Diagnóstica®, Nova Lima, Brazil) was used according to manufacturer instructions. All assessments of IgG and neutralizing levels were carried out after the second dose of the vaccine had been administered to the enrolled subjects. The ECO F COVID nAb kit consists of a capillarity-based assay where neutralizing antibodies found in a serum or plasma sample bind to biotin-coated SARS-CoV-2 spike proteins, which then bind to a streptavidin-coated solid phase, generating a fluorescent signal. Levels of neutralizing antibodies are considered "reagent" when above a threshold of 20%. Of note, this kit provides results for two variant groups, namely var. 1 (Original strain Wuhan-Hu-1, Alpha variant) and var. 2 (Beta, Gamma) within the same sample.

### Data and statistical analysis

Demographic and SARS-CoV-2 screening data of all 235 enrolled individuals were obtained from the diagnostics institute employee registry. Contingency tables categorizing data were analyzed using Fisher exact tests or Chi-square tests. Odds-ratio values were considered significant when $p<0.05$. Absolute IgM and IgG values were non-normally distributed as assessed by D'Agostino-Pearson normality tests. Comparisons were thus made using either Mann-Whitney or Kruskal-Wallis tests followed by Dunn's post hoc test while correlations between absolute IgG values and neutralizing antibody levels were carried out using Spearman's correlation tests. P values were considered significant when <0.05. Results were expressed as median alongside respective confidence intervals. All analyses were carried out using GraphPad Prism 9® (GraphPad, San Diego, CA, USA).

## RESULTS AND DISCUSSION

A total of 235 individuals were eligible to participate in the study. Of these, 32 were male (13.6%) and 203 were female (86.4%). Most of them were less than 40 years old (187 individuals - 74.3%), while the remaining were more than 40 years old (48 individuals - 29.8%).

With regard to comorbidities, there were 41 individuals who have suffered from them (17.4%), and 34 have taken any kind of medication regularly (14.5%). The number of individuals

reporting adverse effects after taking their first and second doses was 102 (43.4%) and 110 (46.8%). Individuals surpassing threshold concentrations of IgG and neutralizing levels for both var. 1 and var. 2 were, respectively, 225 (95.7%), 198 (84.3%) and 170 (72.3%).

All these data comprise subjects who had taken either CoronaVac or ChAdOx1 nCoV-19. The number of individuals who had taken CoronaVac was lower than the number of individuals who had taken ChAdOx1 nCoV-19, which amounted to 47 (20%) and 188 (80%). These data are summarized in Table 1.

**Table 1**
Overall description of subject data.

| Parameter | Total sample N (%) | CoronaVac N (%) | ChAdOx1 nCoV-19 N (%) |
|---|---|---|---|
| Sex | | | |
| Male. | 32 (13.6) | 15 (31.9) | 17 (9.0) |
| Female. | 203 (86.4) | 32 (68.1) | 171 (91.0) |
| Age | | | |
| <40 years old. | 187 (74.3) | 33 (70.2) | 154 (81.9) |
| >40 years old. | 48 (25.6) | 14 (29.8) | 34 (18.1) |
| Comorbidities | | | |
| Yes. | 41 (17.4) | 11 (23.4) | 30 (16.0) |
| No. | 194 (82.6) | 36 (76.6) | 158 (84.0) |
| Use of medication | | | |
| Yes. | 34 (14.5) | 9 (19.1) | 25 (13.3) |
| No. | 200 (85.1) | 38 (80.9) | 162 (86.2) |
| Adverse effects (1st dose) | | | |
| Yes. | 102 (43.4) | 6 (12.8) | 96 (51.1) |
| No. | 133 (56.6) | 41 (87.2) | 92 (48.9) |
| Adverse effects (2nd dose) | | | |
| Yes. | 110 (46.8) | 4 (8.5) | 105 (55.9) |
| No. | 125 (53.2) | 43 (91.5) | 82 (43.6) |
| IgG | | | |
| Reagent. | 225 (95.7) | 38 (80.9) | 187 (99.5) |
| Non-reagent. | 10 (4.3) | 9 (19.1) | 1 (0.5) |
| Neutralizing antibody (Var. 1) | | | |
| Reagent. | 198 (84.3) | 32 (68.1) | 166 (88.3) |
| Non-reagent. | 37 (15.7) | 15 (31.9) | 22 (11.7) |
| Neutralizing antibody (Var. 2) | | | |
| Reagent. | 170 (72.3) | 23 (48.9) | 147 (78.2) |
| Non-reagent. | 65 (27.7) | 24 (51.1) | 41 (21.8) |
| Vaccine Taken | | | |
| CoronaVac. | 47 (20.0) | | |
| ChAdOx1 nCoV-19. | 188 (80.0) | | |

Source: The authors.
*Notes*. Summarized data for all subjects enrolled in the study according to sex, age, comorbidities, use of medication, adverse effects (at the moment of taking both first and second doses) and whether IgG levels and neutralizing levels for both var. 1 (Original strain Wuhan-Hu-1, Alpha variant) and var. 2 (Beta, Gamma) reached thresholds considered significant. No discrimination was made based on which vaccine was taken. N = number of assessed subjects.

In order to compare responses elicited by CoronaVac and ChAdOx1 nCoV-19, Fisher exact tests were performed using the type of vaccine as the independent variable, in order to analyze IgG and neutralizing levels alongside occurrence of adverse effects at the time both first and second doses were taken.

In comparison to CoronaVac, ChAdOx1 nCoV-19 had 44.29 more chances to induce IgG levels above a threshold considered reagent, 3.357 more chances to lead to neutralizing levels against var. 1 above a threshold considered reagent, 3.741 more chances to lead to neutralizing levels against var. 2 above a threshold considered reagent, 7.130 more chances to cause adverse effects at the first shot and 8.750 more chances to cause adverse effects at the second shot. All of these odds-ratio values were considerably significant ($p<0.01$ in all instances). These data are summarized in Table 2.

**Table 2**
Contingency tables comparing CoronaVac and ChAdOx1 nCoV-19.

| Dependent variable | Outcome | CoronaVac | ChAdOx1 nCoV-19 | p-value | Reciprocal of Odds-ratio | Confidence interval |
|---|---|---|---|---|---|---|
| IgG | Reagent. | 38 | 187 | <0.0001 | 44.29 | 6.732 to 487.9 |
| | Non-reagent. | 9 | 1 | | | |
| Neutralizing Ab. Var. 1 | Reagent. | 32 | 166 | 0.0015 | 3.537 | 1.593 to 7.373 |
| | Non-reagent. | 15 | 22 | | | |
| Neutralizing Ab. Var. 2 | Reagent. | 23 | 147 | 0.0002 | 3.741 | 1.955 to 7.183 |
| | Non-reagent. | 24 | 41 | | | |
| Adverse effects (1st dose) | Reported any. | 6 | 96 | <0.0001 | 7.130 | 2.880 to 16.51 |
| | Absent. | 41 | 92 | | | |
| Adverse effects (2nd dose) | Reported any. | 6 | 105 | <0.0001 | 8.750 | 3.525 to 20.27 |
| | Absent. | 41 | 82 | | | |

Source: The authors.
*Notes*. Fisher exact tests were carried out to compare variables between both vaccines assessed. P-values were considered significant when <0.05, and are highlighted in bold letters. Reciprocal of Odds-ratios were shown for ease of understanding. Fisher exact tests were performed using the type of vaccine as the independent variable.

As to further assess differences between CoronaVac and ChAdOx1 nCoV-19, IgG and neutralizing raw values were compared, rather than the number of individuals exceeding a threshold level considered reagent. Individuals who had taken ChAdOx1 nCoV-19 showed IgG levels considerably higher than individuals who had taken CoronaVac (Fig. 1A), and the same applies to neutralizing levels for both var. 1 (Fig. 1B) and var. 2 (Fig. 1C).

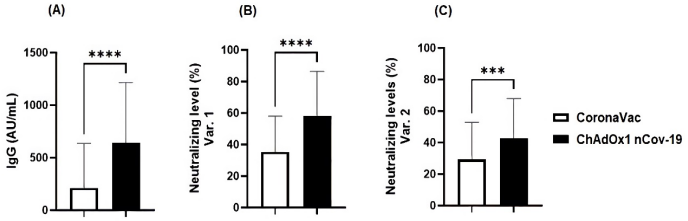
In addition, for both vaccines, we decided to determine whether factors such as age and sex, among others, could influence number of individuals reaching threshold neutralizing levels considered reagent. First, Fisher exact tests were performed assuming reagent neutralizing levels for either var. 1 or var. 2 as the independent variable. All other parameters (sex, age, comorbidities, use of medication, adverse effects at the first shot and adverse effects at the second shot) were assumed as dependent variables. As summarized in Tables 3 and 4, the factors assessed had no influence on the outcomes of the tests for either variant.

Moreover, we compared the influence of the same factors mentioned above on the neutralizing levels for both var. 1 (Original strain Wuhan-Hu-1, Alpha variant) and var. 2 (Beta, Gamma variants) as exerted by CoronaVac (Fig. 2A - 2F, 2G - 2L). No significant differences were observed in any instance. We also compared neutralizing levels exerted by CoronaVac between both variants, but no significant differences were found (Fig. 3A). Finally, we correlated IgG concentrations with neutralizing levels for both variants tested, considering only individuals who had

taken CoronaVac. Significant positive correlations were found between IgG concentrations and neutralizing levels for both variant groups (Fig. 3B and 3C).

**Figure 1**

Efficacy comparison between CoronaVac and ChAdOx1 nCoV-19.




Source: The authors.

*Notes*. Mann-Whitney tests were carried out to compare IgG concentrations (A) and neutralizing levels for var. 1 (B) and var. 2 (C), as shown by subjects, between CoronaVac and ChAdOx1 nCoV-19. Results shown as median alongside confidence interval of the median. ***, **** p-value <0.001, 0.0001.

**Table 3**

Contingency tables comparing influence of variables on reagent neutralizing levels exerted by CoronaVac (Variant 1).

| Dependent Variable | Outcome | Reagent | Non-reagent | p-value | Odds-ratio | Confidence interval |
|---|---|---|---|---|---|---|
| Sex | Male. | 13 | 2 | 0.0944 | 4.447 | 0.9168 to 21.86 |
| | Female. | 19 | 13 | | | |
| Age | <40 years old. | 22 | 11 | >0.9999 | 0.800 | 0.2354 to 3.057 |
| | >40 years old. | 10 | 4 | | | |
| Comorbidities | Reported any. | 9 | 2 | 0.4614 | 2.543 | 0.4704 to 12.93 |
| | Absent. | 23 | 13 | | | |
| Use of medication | Reported any. | 8 | 1 | 0.2363 | 3.354 | 0.5256 to 21.40 |
| | Absent. | 24 | 14 | | | |
| Adverse effects (1st dose) | Reported any. | 4 | 2 | >0.9999 | 0.8526 | 0.1595 to 4.557 |
| | Absent. | 28 | 13 | | | |
| Adverse effects (2nd dose) | Reported any. | 2 | 2 | 0.5829 | 0.4426 | 0.06846 to 2.862 |
| | Absent. | 30 | 13 | | | |

Source: The authors.

*Notes*. Fisher exact tests were carried out to compare neutralizing levels deemed reagent and non-reagent. P-values were considered significant when <0.05, and are highlighted in bold letters.

The same way we assessed the influence of several factors on CoronaVac efficacy, we did the same for ChAdOx1 nCoV-19. We analyzed whether age and gender, among other parameters, could influence number of individuals reaching threshold neutralizing levels considered reagent. Similarly to the results found for CoronaVac, the factors assessed did not influence the outcomes of the tests carried out for ChAdOx1 nCoV-19, for either variant. These data are summarized in Tables 5 and 6.

We then assessed the influence of the same factors on the neutralizing levels exerted by ChAdOx1 nCoV-19 for both variants (Fig. 4A – 4F, 4G – 4L). For ChAdOx1 nCoV-19, individuals aged older than 40 years had higher neutralizing levels for var. 1 than younger individuals (Fig. 4B). Neutralizing levels for var. 1 were lower in individuals suffering from co-morbidities, albeit in non-significant manner (p=0.0952) (Fig. 4C).

**Table 4**

Contingency tables comparing influence of variables on reagent neutralizing levels exerted by CoronaVac (Variant 2).

| Dependent Variable | Outcome | Reagent | Non-reagent | p-value | Odds-ratio | Confidence interval |
|---|---|---|---|---|---|---|
| Sex | Male. | 9 | 6 | 0.3587 | 1.929 | 0.5931 to 6.179 |
| | Female. | 14 | 18 | | | |
| Age | <40 years old. | 14 | 19 | 0.2124 | 0.4094 | 0.1187 to 1.410 |
| | >40 years old. | 9 | 5 | | | |
| Comorbidities | Reported any. | 8 | 3 | 0.0933 | 3.733 | 0.8327 to 14.13 |
| | Absent. | 15 | 21 | | | |
| Use of medication | Reported any. | 6 | 3 | 0.2865 | 2.471 | 0.6076 to 9.879 |
| | Absent. | 17 | 21 | | | |
| Adverse effects (1st dose) | Reported any. | 4 | 2 | 0.4158 | 2.316 | 0.4844 to 13.00 |
| | Absent. | 19 | 22 | | | |
| Adverse effects (2nd dose) | Reported any. | 1 | 3 | 0.6085 | 0.3182 | 0.02358 to 2.330 |
| | Absent. | 22 | 21 | | | |

Source: The authors.

*Notes*. Fisher exact tests were carried out to compare neutralizing levels deemed reagent and non-reagent. P-values were considered significant when <0.05, and are highlighted in bold letters.

However, neutralizing levels for var. 2 were indeed lower in a significant manner in these individuals (Fig. 4I). We screened patient story of the enrolled subjects who had taken ChAdOx1 nCoV-19 and reported co-morbidities and found that 42% of these individuals suffered from respiratory diseases (such as asthma or severe coughs). We carried further tests comparing neutralizing levels between subjects grouped according to having respiratory diseases or not, but found no relevant differences (data not shown).

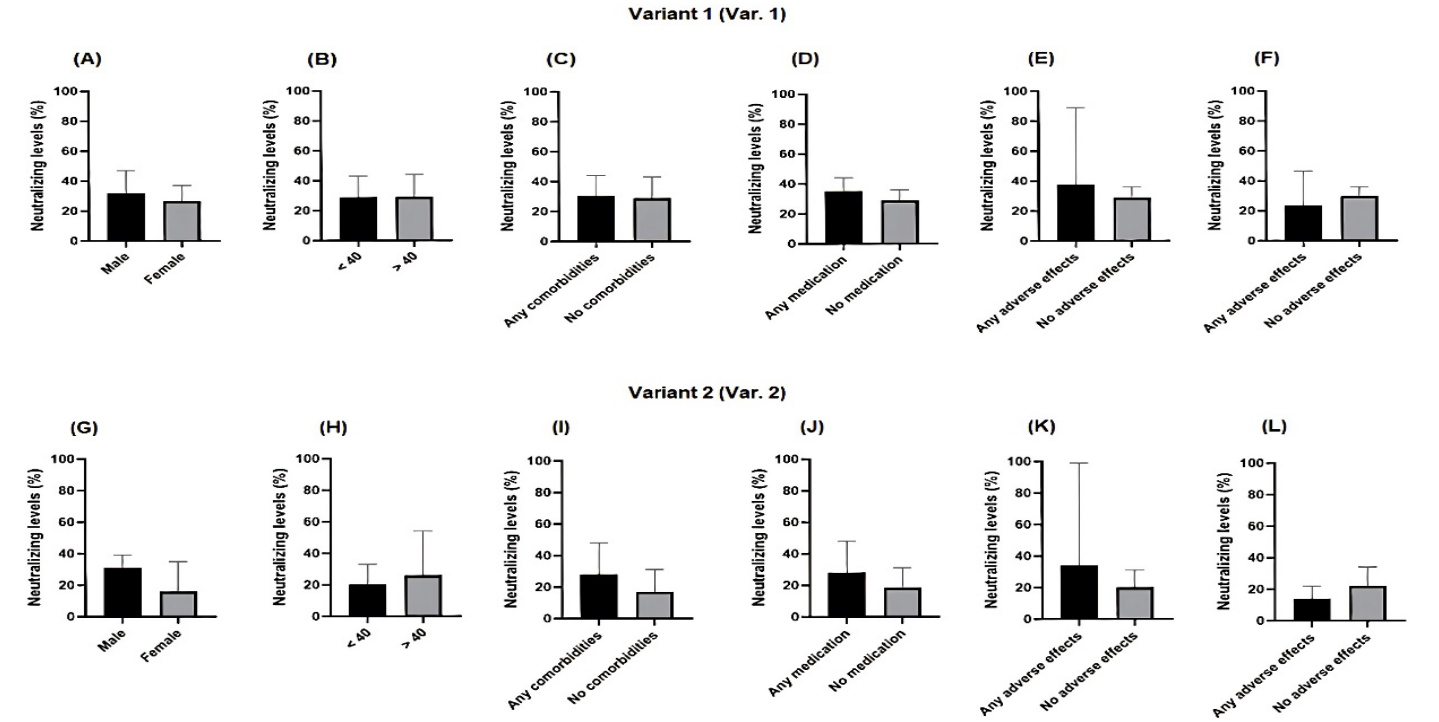
We also compared neutralizing levels exerted by ChAdOx1 nCoV-19 between both variants, which were found to be significantly higher for var. 1 in comparison to var. 2 (Fig. 5A). Next, we correlated IgG levels with neutralizing levels for both variants, for individuals who had taken ChAdOx1 nCoV-19 only. In the same vein as found for CoronaVac, for both variants, significant positive correlations were found between IgG concentrations and neutralizing levels (Fig. 5B and 5C).

In this study, we were able to assess the humoral response against SARS-CoV-2 in 235 health workers immunized with ChAdOx1 nCoV-19 and CoronaVac by measuring IgG and neutralizing antibodies. Our results have demonstrated that ChAdOx1 nCoV-19 was capable of inducing higher levels of both trimeric and neutralizing IgG antibodies against both variants assessed in this study in comparison to CoronaVac. This finding is aligned with other studies which have also reported ChAdOx1 nCoV-19 is more effective in inducing humoral responses than CoronaVac and even other vaccines, such as Ad26.COV2.S and mRNA-1237 (Rogliani, Chetta, Cazzola & Calzetta, 2021).

To date, several vaccines have been distributed (Basta & Moodie, 2022). However, many of already distributed vaccines were engineered utilizing the original Wuhan-Hu-1 strain while SARS-CoV-2 suffered a number of mutations leading to the appearance of new viral strains, to which such vaccines are less effective against (Chavda, Patel & Vaghasiya, 2022). In this study, we evidenced that for both assessed vaccines, ChAdOx1 nCoV-19 and CoronaVac, neutralizing antibody levels were lower for var. 2 in comparison

**Figure 2**

Influence of subject variables on neutralizing levels for var. 1 and var. 2 exerted by CoronaVac.

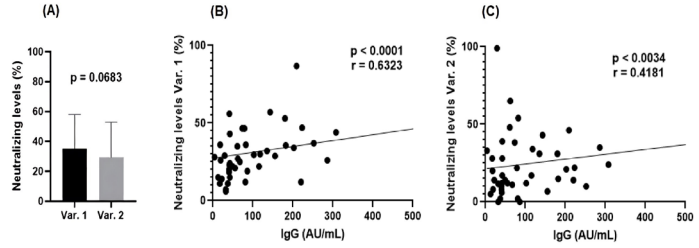



Source: The authors.

*Notes*. Mann-Whitney tests were carried out to compare neutralizing levels for var. 1 according to sex (A, G), age (B, H), comorbidities (C, I), medication (D, J), adverse effects at first dose (E, K) and adverse effects at second dose (F, L). Results shown as median alongside confidence interval of the median.

**Figure 3**

Comparison of neutralizing levels between variants for CoronaVac.




Source: The authors.

*Notes.* Mann-Whitney test was carried out to compare neutralizing levels between both variants assessed (A). Results shown as median alongside confidence interval of the median. Spearman tests were carried out to correlate IgG levels with neutralizing levels for var. 1 (B) and var. 2 (C). A total of 5 individuals were far off in the x axis and are thus not represented in these graphs.

to var. 1. As for CoronaVac, a number of studies have shown it has diminished effectiveness against SARS-CoV-2 variants Alpha, Beta, Gamma, Delta and Omicron (Vacharathit et al., 2021; Hadj Hassine, 2022; Ranzani et al., 2022; Wang et al., 2022).

As for ChAdOx1 nCoV-19, studies have shown it has significantly lower effectiveness against the Omicron variant (Dejnirattisai et al., 2022). Other studies suggest such reduction in effectiveness is due to selective pressure, increasing the virus adaptability to the host, improving "escape" mechanisms and boosting transmission. As the human population develops immunity either due to vaccination or to natural infection, so increases the pressure upon the SARS-CoV-2 virus to select more advantageous mutations, leading to new strains (Liu et al., 2021).

Even though the prevalence of SARS-CoV-2 infections is similar between sexes, males are more likely to show severe forms of disease (Del Sole et al., 2020; Jin et al., 2020; Booth et al., 2021; Fabião et al., 2022). Also, advanced age and presence of co-morbidities are significantly associated with disease severity (Fang et al., 2020).

Our data show that IgG levels and neutralizing antibody levels have not been influenced by factors such as age, sex and use of medication in either group of health workers assessed. However, neutralizing antibody levels in response to ChAdOx1 nCoV-19 against SARS-CoV-2 var. 2 were lower in individuals who reported suffering from some type of comorbidity.

**Table 5**

Contingency tables comparing influence of variables on reagent neutralizing levels exerted by ChAdOx1 nCoV-19 (Variant 1)**.**

| Dependent variable | Outcome | Reagent | Non-reagent | p-value | Odds-ratio | Confidence interval |
|---|---|---|---|---|---|---|
| Sex | Male. | 15 | 2 | >0.9999 | 0.9934 | 0.2285 to 4.646 |
| | Female. | 151 | 20 | | | |
| Age | <40 years old. | 136 | 18 | >0.9999 | 1.007 | 0.3487 to 3.039 |
| | >40 years old. | 30 | 4 | | | |
| Comorbidities | Reported any. | 25 | 5 | 0.3575 | 0.6028 | 0.2122 to 1.605 |
| | Absent. | 141 | 17 | | | |
| Use of medication | Reported any. | 20 | 5 | 0.1834 | 0.469 | 0.1578 to 1.268 |
| | Absent. | 145 | 17 | | | |
| Adverse effects (1st dose) | Reported any. | 85 | 11 | >0.9999 | 1.049 | 0.4432 to 2.484 |
| | Absent. | 81 | 11 | | | |
| Adverse effects (2nd dose) | Reported any. | 92 | 13 | 0.8225 | 0.8725 | 0.3669 to 2.098 |
| | Absent. | 73 | 9 | | | |

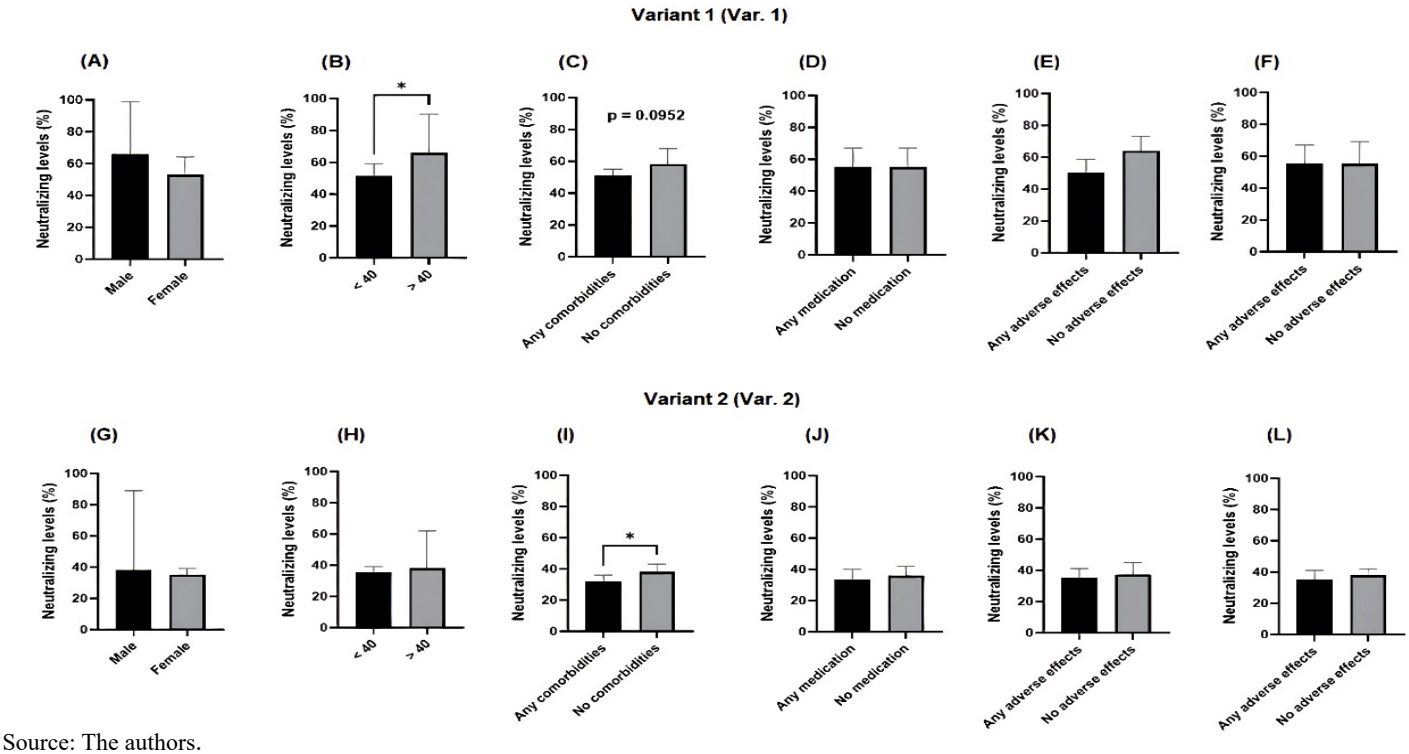
Source: The authors.

*Notes*. Fisher exact tests were carried out to compare neutralizing levels deemed reagent and non-reagent. P-values were considered significant when <0.05, and are highlighted in bold letters.

According to the literature, COVID-19 presents increased mortality risks particularly in the elderly, the obese and in individuals suffering from comorbidities, especially

**Figure 4**

Influence of subject variables on neutralizing levels for var. 1 and var. 2 exerted by ChAdOx1 nCoV-19.




Source: The authors.

*Notes*. Mann-Whitney tests were carried out to compare neutralizing levels for var. 1 according to sex (A, G), age (B, H), comorbidities (C, I), medication (D, J), adverse effects at first dose (E, K) and adverse effects at second dose (F, L). Results shown as median alongside confidence interval of the median. *p<0.05.

**Table 6**

Contingency tables comparing influence of variables on reagent neutralizing levels exerted by ChAdOx1 nCoV-19 (Variant 2).

| Dependent variable | Outcome | Reagent | Non-reagent | p-value | Odds-ratio | Confidence interval |
|---|---|---|---|---|---|---|
| Sex | Male. | 14 | 3 | >0.9999 | 1.333 | 0.4118 to 4.546 |
| | Female. | 133 | 38 | | | |
| Age | <40 years old. | 121 | 33 | 0.8196 | 1.128 | 0.4853 to 2.760 |
| | >40 years old. | 26 | 8 | | | |
| Comorbidities | Reported any. | 24 | 6 | >0.9999 | 1.138 | 0.4480 to 2.927 |
| | Absent. | 123 | 35 | | | |
| Use of medication | Reported any. | 20 | 5 | >0.9999 | 1.143 | 0.3984 to 2.947 |
| | Absent. | 126 | 36 | | | |
| Adverse effects (1st dose) | Reported any. | 75 | 21 | >0.9999 | 0.9921 | 0.4905 to 1.990 |
| | Absent. | 72 | 20 | | | |
| Adverse effects (2nd dose) | Reported any. | 80 | 25 | 0.5935 | 0.7758 | 0.3869 to 1.555 |
| | Absent. | 66 | 16 | | | |

Source: The authors.

*Notes*. Fisher exact tests were carried out to compare neutralizing levels deemed reagent and non-reagent. P-values were considered significant when <0.05, and are highlighted in bold letters

cardiovascular and metabolic disorders (Sanyaolu et al., 2020). It has also been reported that effectiveness of ChAdOx1 nCoV-19 tends to be lower in individuals suffering from co-morbidities, especially regarding severe COVID-19 symptoms, in accordance with our findings (Nordström, Ballin & Nordström, 2021)

While almost half of the individuals who reported comorbidities suffered from respiratory diseases, this has not played any role on the effectiveness of ChAdOx1 nCoV-19 among individuals suffering from comorbidities. Respiratory diseases such as asthma and COPD have surprisingly not been linked to increased hospitalization, likely due to the use of inhaled corticosteroids commonly used in these diseases, which reduce ACE2 levels and therefore reduce infections. Whether this can be linked or not to different humoral responses to SARS-CoV-2 antigens is unknown (Hahn, Nordmann-Kleiner, Trainotti, Hoffmann & Greve, 2020; Rogliani, Lauro, Di Daniele, Chetta & Calzetta, 2021; Wakabayashi, Pawankar, Narazaki, Ueda & Itabashi, 2021; Kow & Hasan, 2022; Lee et al., 2022).

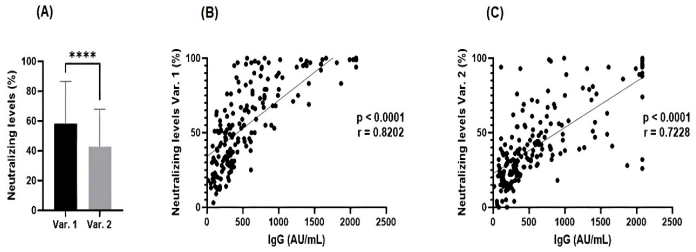
Regardless, our findings evidence comorbidities in general as responsible for reducing the overall effectiveness of ChAdOx1 nCoV-19. It is worth noting that CoronaVac does not show any differences on antibody levels depending on comorbidities, in accordance with WHO reports, which state that the vaccine is equally effective in both scenarios (World Health Organization [WHO], 2021).

Lastly, we have identified a positive correlation between IgG levels and neutralizing antibody levels for both vaccines, for each variant assessed. These findings are supported by other studies who reported similar results (Dolscheid-Pommerich et al., 2022; Manenti et al., 2022; Takheaw et al., 2022). Antibody detection assays against SARS-CoV-2 are useful tools to assess the immunological picture of an individual, however, only neutralizing activity measures in a reliable manner the actual protection conferred by the generated antibodies, and the search for neutralizing activity tests in clinical settings has increased largely worldwide (Khoury et al., 2021).

Our findings suggest that it is possible to infer neutralizing antibody levels for SARS-CoV-2 out of simpler IgG detection tests, which are cheaper, faster and more accessible in comparison to gold-standard cell culture methods (Theel et al., 2020). However, it should be noted that the assay used to detect neutralizing antibodies indicates only antibodies which react with the SARS-CoV-2 antigen. Furthermore, this work does not

present virus-containing assays for comparison. Therefore, more studies are required to confirm any assumptions about the correlation with protection or possible replacement of viral neutralization tests (VNT) by these commercial systems.

**Figure 5**
Comparison of neutralizing levels between variants for ChAdOx1 nCoV-19.




Source: The authors.
*Notes*. Mann-Whitney test was carried out to compare neutralizing levels between both variants assessed (A). Results shown as median alongside confidence interval of the median. Spearman tests were carried out to correlate IgG antibodies anti-trimeric spike glycoprotein levels with neutralizing levels for var. 1 (B) and var. 2 (C). ****p<0.0001.

In underdeveloped countries, immunological screening becomes easier and more reliable due to the possibility of assessing both seroprevalence and protection conferred from a single test. It must be pointed out that the results here reported should not be limited to SARS-CoV-2, given that several emerging and reemerging diseases (such as poliomyelitis in Brazil), as well as other prevalent diseases such as HIV, hepatitis, multiple sclerosis, among others, are always a threat to public health (Sok & Burton, 2018; Colbert et al., 2019; Dunn, Fogdell-Hahn, Hillert & Spelman, 2020).

Limitations of the study include the fact that results were obtained from health workers and thus represent only a fraction of the Brazilian population. In addition, the number of CoronaVac recipients was far less than ChAdOx1 nCoV-19 and this may influence the interpretation of the result. Even so, most of the individuals were female vaccinated with ChAdOx1 nCoV-19, which made statistical analyses within this group more reliable than analyses among individuals having received CoronaVac.

Still, health workers as a group are in constant danger to being exposed to SARS-CoV-2. Even though our results were limited to ChAdOx1 nCoV-19 and CoronaVac, these were the two major vaccines that have been distributed in Brazil, especially to health workers.

## CONCLUSION

Our findings suggest that both vaccines were effective against var. 1, but less so against var. 2, with CoronaVac, in which CoronaVac neutralizing antibody levels dropped drastically for var. 2. Additionally, the ChAdOx1 nCoV-19 vaccine induced the production of antibodies with a significantly higher chance than the CoronaVac vaccine, indicating enhanced efficacy at the expense of increased chances of adverse effects. This information is relevant when choosing vaccines for specific patients, considering susceptibility to adverse effects, in order to seek an appropriate balance between efficacy and potential risks.

This way, we evidence that evaluation of neutralizing levels against different viral strains can aid managing occupational matters of groups of health workers and better selecting of patients for vaccination. Also, our data supports the notion that IgG tests could be carried instead of tests assessing neutralizing antibodies, as both parameters were reported to be correlated. This is of use for underdeveloped countries or poorer communities as IgG tests are cheaper and more accessible.

Finally, our findings could be extrapolated to vaccines directed against other emerging pathogens, where policy makers, diagnostics laboratories and health agencies could better employ and/or develop better-directed IgG detection tests.

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## ETHICAL APPROVAL

The study was approved by the Ethic's review board of the University of Sorocaba (47300621.0.0000.5500).

## COMPETING INTERESTS

Beatriz Birelli do Nascimento reports equipment, drugs, or supplies were provided by DiaSorin Inc. Beatriz Birelli do Nascimento reports equipment, drugs, or supplies were provided by ECO Diagnóstica. Beatriz Birelli do Nascimento reports a relationship with IDS - Instituto de Diagnóstico Sorocaba that includes: board membership, employment, and equity or stocks.

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The authors declare that they have no financial interests.

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## PEER REVIEW

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