Detection of Neutralizing Antibodies Among Health Care Workers and Staff Fully-vaccinated Against COVID-19 in a Baguio City Tertiary Hospital: A Cross-Sectional Study

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Abstract

Background. Coronavirus disease 2019, otherwise known as COVID-19 is caused by the novel coronavirus. The WHO stated that as of April 24, 2020, no study has evaluated if the antibodies against COVID-19 confer immunity. The aim therefore of this research is to determine the presence of neutralizing antibodies among fully vaccinated Health Care workers and staff of Notre Dame de Chartres Hospital

Methods. This study is a single-center, cross-sectional study conducted at Notre Dame de Chartres Hospital in Baguio City. This study was designed to determine the presence of neutralizing antibodies 6 months after the 2nd dose of COVID-19 vaccine, either with Sinovac (CoronaVac®), an inactivated virus, or Oxford AstraZeneca, a non-replicating viral vector. The study was approved by the Ethics Review Board of the Baguio General Hospital Medical Center. A total of 206 participants enrolled voluntarily in the study. Descriptive statistics such as frequency and percentage were used to determine the baseline characteristics of the research participants. The mean amounts of antibodies after vaccination against COVID-19 were determined. Independent-sample *t-test* was utilized to determine if there was a significant difference in antibody production when comparing the two brands of vaccine, according to sex, employee status, presence of at least one comorbidity, and history of COVID-19 vaccination. One-way analysis of variance (ANOVA) was used for the variable age. All statistical tests were conducted at $p<0.05$ level of significance. Computations were done using SPSS version 22.0.

Results. A total of 236 healthcare workers and staff of Notre Dame de Chartres Hospital were included in the study. Among the study participants given either Sinovac or AstraZeneca, 52.97% belong to the 20-30 years old age group. Most of them were females (69.92%). For employment status, healthcare workers comprised the majority of the study population at 71.61% while the rest (28.36%) were hospital staff. Most did not have any comorbidities, while 26.27% reported having comorbidities, with hypertension and asthma identified as the predominant diseases at 9.75% and 9.32%, respectively; followed by allergic rhinitis (5.32%) and diabetes mellitus (2.97%). Among the participants, 74.6% were never diagnosed with COVID-19, while 25.4% reported to have been infected, with 16.5% having only mild symptoms. Most of the study participants (67.4%) were inoculated with Sinovac® while the rest (32.6%) received AstraZeneca.

Conclusion. There was no significant difference in the mean amount of antibodies when grouped according to each of the following variables: age, sex, employee status, and comorbidities. These results apply to both SINOVAC and AstraZeneca groups. There was a significantly higher mean amount of antibodies in those who had previously contracted COVID-19 than in those who never had a previous infection. On the other hand, comparing the mean amount of antibodies between the two brands of vaccines, Sinovac™ and AstraZeneca™, those who were vaccinated with AstraZeneca™ developed higher amounts of antibodies than those who were vaccinated with Sinovac™.

Keywords Neutralizing antibodies, COVID-19 vaccine, healthcare workers

Introduction

Coronavirus disease 2019, (COVID-19) is caused by the novel coronavirus which was responsible for the Pandemic declared by the World Health Organization (WHO) last March 11, 2020.[1] There is a wide range of signs and symptoms with 80% presenting with mild symptoms, others are oxygen requiring while 5% are critical requiring mechanical ventilation.[2] The incubation period for COVID-19 is approximately 1-12.5 days, extending to up to 14 days. In a study done in China with 44,000 confirmed cases of COVID-19, there was an increase in case fatality rate as age advances, making age a strong risk factor for illness severity, and high risk for complications and death. Among patients older than 80 years, mortality was higher at 14.8% as compared with patients younger than 40 years at 0.2%. Also noted was an increase in case fatality rate in patients with

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comorbidities with a majority having cardiac conditions, diabetes, chronic respiratory diseases, and cancer at 10.5%, 7.3%, 6.3%, and 5.6%, respectively.[3]

Development of immunity to a pathogen via natural infection occurs after one to two weeks persisting for three months before subsequently declining. As of April 24, 2020, WHO stated that no study has evaluated if the antibodies against COVID-19 confer immunity against the virus.[4] According to Dan et. al., substantial immune memory, which helps determine protection against reinfection and vaccine efficacy, occurred after infection with COVID-19. Approximately 95% of participants had immune memory six months post-infection.[5]

After infection with, or vaccination against COVID-19, an immune response is mounted against the virus via antibody production and the binding of these antibodies to the antigen strengthens over time in a process called affinity maturation. This then results in neutralization by recognizing and binding the receptor binding domain (RBD). This RBD is the target of the COVID-19 vaccines.[6]

There are four types of COVID-19 vaccines, namely, the whole virus, the protein subunit, nucleic acid, and the viral vector.[7] Sinovac *Biotech*™, an inactivated virus, has varying efficacy rates as reported in Brazil, Indonesia, and Turkey with 50.38%, 65%, and 91.25% efficacy, respectively. This vaccine has a 50.4% efficacy in preventing symptomatic infections. AstraZeneca™, an adenovirus-based vaccine, has a 90% efficacy according to the trials done in both the United Kingdom and Brazil. AstraZeneca was noted to be effective in preventing COVID-19 infection without hospitalizations or severe cases.[8]

Following infection, there is an activation of the immune system via antibody production targeting the specific proteins in the viral antigen (spike protein/S, envelope/E, membrane/M, or nucleocapsid/N). It is important to differentiate if antibody production was via natural infection or vaccination and is usually done via serological testing. According to the Centers for Disease Control, unvaccinated individuals with prior infection will test positive for an antibody either against the N or S protein, while individuals with vaccine-induced antibodies will test positive only for the S protein. Testing positive for the N protein, therefore, indicates a resolving or resolved infection. Anti-SARS-CoV-2 S assay, an immunoassay that quantitatively determines neutralizing antibodies against S protein RBD with a level of > 0.8 U/ml indicates a positive result.[9] However, the exact titer of these antibodies that will indicate the durability of immunity is still under investigation.

COVID-19 is a worldwide problem. Vaccination against this disease is necessary in the hopes of ending this pandemic. The study's primary outcome is to determine the presence of neutralizing antibodies six months post-vaccination with the COVID-19 vaccine, as this will help address this pandemic through the determination of durability of these antibodies which can be attributable to immunity.

General Objective. To determine the presence of neutralizing antibodies among fully vaccinated Health Care workers and staff of Notre Dame de Chartres Hospital

Specific Objectives.

1 To determine the baseline characteristics of healthcare personnel and staff of NDCH included in the study
2 To determine the presence of neutralizing antibodies 6 months after receiving the 2nd dose of the COVID-19 vaccine
3 To determine the significant difference in antibody production in terms of:
   a. Brand of vaccine injected
   b. Age
   c. Sex
   d. Presence of at least one comorbidity
   e. History of COVID-19 infection

Methods

Study design, Setting, and Participants. This research study is a single-center, cross-sectional study designed to determine the presence of neutralizing antibodies six months after the 2nd dose of a COVID-19 vaccine, either with *Sinovac*™ or AstraZeneca™. The study was approved by the Ethics Review Board of Baguio General Hospital Medical Center. A total of 236 participants have enrolled voluntarily in the study. Participants were provided with informed consent before data and specimen collection. Participants received the first dose of the vaccine in March or April 2021 and the second dose was received in April or May 2021. Each participant was assigned a specific code and was scheduled for blood extraction which was done by a registered Medical Technologist in the laboratory of the said institution. Blood samples were run by batch on the same day. Using the code assigned to each participant, results were released on the same day as well.

Inclusion Criteria.

1 >19 years old
2 Healthcare workers of Notre Dame de Chartres Hospital
3 Staff of Notre Dame de Chartres Hospital
4 Should have completed the two doses of the COVID-19 vaccine, either Sinovac™ or AstraZeneca

Exclusion Criteria.

1 Healthcare workers and staff who were not able to complete the two doses of the COVID-19 vaccine
2 Healthcare workers and staff who received a different brand of vaccine
3 Those who fulfilled the inclusion criteria but did not consent to be included in the study
4 Those who were not within the sixth month period from the second dose of the vaccine when the study was conducted

Conceptual Framework. The conceptual framework for this study is depicted in *Figure 1*.

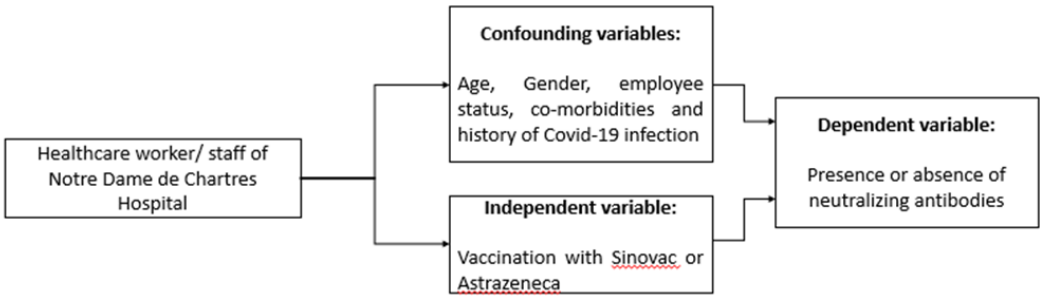

Figure 1. Conceptual Framework of the Study

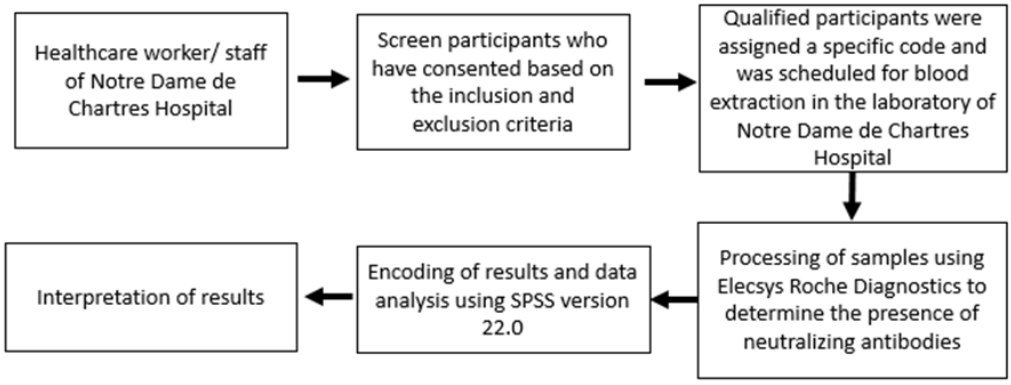

Figure 2. Schematic Diagram of Study Procedures

Sample Size. This study included vaccinated healthcare workers and staff of Notre Dame de Chartres Hospital with a population size of 531. Using *Open-epi* online sample size calculator, with a 95% confidence level, the computed sample is 236.

The initially computed sample size was n=224. Anticipating a 5% non-response or non-participation, the researchers considered a sample size of 236.

Methods

The research study is a cross-sectional study design. The procedures followed are depicted in *Figure 2*. Informed consent was secured and participants were asked to fill up a questionnaire. The screening was done based on the inclusion and exclusion criteria. Qualified participants were assigned a specific code and were scheduled for blood extraction which was done by a registered medical technologist. Blood samples were processed in the laboratory of Notre Dame de Chartres Hospital using the *Elecsys Roche Diagnostics* with a positivity cut-off of 0.8 U/ml, indicating the presence of neutralizing antibodies.

Outcome Measures. The primary outcome measure was the determination of the presence or absence of neutralizing antibodies six months after vaccination with two doses of either Sinovac™ or AstraZeneca™ in healthcare workers and staff of Notre Dame de Chartres Hospital.

Statistical Analysis. Descriptive statistics such as frequency and percentage were used to determine the baseline characteristics of the research participants. To determine the presence and amount of antibodies post-vaccination with the COVID-19 vaccine, the mean was used. Independent-samples *t-test* was utilized to determine if there was a significant difference in the antibody production when comparing according to the brand of vaccine, sex, employee status, presence of at least one comorbidity, and history of COVID-19 vaccine; while one-way analysis of variance (ANOVA) was used for the variable age. All statistical tests were conducted at $p<0.05$ level of significance. Computations were done using *SPSS version 22.0*

Terminologies.

1 Neutralizing antibody - an antibody that is responsible for defending cells from pathogens, which are organisms that cause disease. They are produced naturally by the body as part of its immune response, and their production is triggered by both infections and vaccinations against infections

Table I: Demographic Data and characteristics of fully vaccinated health workers and staff in the Notre Dame de Chartres Hospital (n=236)

VARIABLE	SINOVAC™		ASTRAZENECA™		TOTAL	
	n	%	n	%	n	%
Age						
20-30 years old	91	38.56%	34	14.41%	125	52.97%
31-40 years old	36	15.25%	25	10.59%	61	25.85%
41-50 years old	26	11.02%	10	4.24%	36	15.25%
51-60 years old	6	2.54%	4	1.69%	10	4.24%
>60 years old	0	0.00%	4	1.69%	4	1.69%
Sex						
Male	47	19.92%	24	10.17%	71	30.08%
Female	112	47.46%	53	22.46%	165	69.92%
Employee status						
Healthcare worker	123	52.12%	46	19.49%	169	71.61%
Hospital staff	36	15.25%	31	13.14%	67	28.39%
Comorbidities						
Without	114	48.31%	60	25.42%	174	73.73%
With	45	19.07%	17	7.20%	62	26.27%
Comorbidities						
Hypertension	15	6.36%	8	3.39%	23	9.75%
Diabetes Mellitus	5	2.12%	2	0.85%	7	2.97%
Valvular Heart Disease	0	0.00%	1	0.42%	1	0.42%
Chronic Kidney Disease	1	0.42%	0	0.00%	1	0.42%
Asthma	19	8.05%	3	1.27%	22	9.32%
Allergic Rhinitis	11	4.66%	1	0.42%	12	5.08%
Hyperthyroidism	2	0.85%	0	0.00%	2	0.85%
Thyroid Cancer	1	0.42%	0	0.00%	1	0.42%
Gout	2	0.85%	0	0.00%	2	0.85%
CAD	2	0.85%	0	0.00%	2	0.85%
Thalassemia	2	0.85%	0	0.00%	2	0.85%
Rheumatic Fever	1	0.42%	0	0.00%	1	0.42%
Myocarditis	2	0.85%	0	0.00%	2	0.85%
MVP	1	0.42%	0	0.00%	1	0.42%
Fibroadenoma of the Breast	0	0.00%	1	0.42%	1	0.42%
Endometriosis	0	0.00%	1	0.42%	1	0.42%
TIA, HTN, PreDM, Dyslipidemia	0	0.00%	1	0.42%	1	0.42%
SLE	0	0.00%	1	0.42%	1	0.42%
Combination	18	7.63%	4	1.69%	22	9.32%
Total	91	38.56%	34	14.41%	125	52.97%

2 Health care workers (HCW) - refers to persons serving in health care settings who have direct exposure to patients or infectious materials

3 Staff – people employed by an organization. In this study, the word staff is used to refer other employees other than healthcare workers.

4 Receptor Binding Domain (RBD) - part of a virus located on the spike domain that allows it to bind to body receptors to gain entry into cells and leads to infection.

Ethical Considerations. The paper was approved by the Ethics Review Board of Baguio General Hospital Medical Center. A specific code was assigned to each participant and no names were disclosed, to maintain the confidentiality and anonymity of the patients who fulfilled the inclusion criteria of this study. Research participants were not subjected to harm and all blood extractions were done by a registered and trained Medical Technologist in the laboratory. Participants were allowed to withdraw at any given time. The data collection form used a specific code for each participant and was used for data analysis. A password-protected laptop and application were used as well. The study was funded by the primary investigator. There was no conflict of interest in performing this study.

Results

A total of 236 healthcare workers and staff from the Notre Dame de Chartres Hospital were included in the study. *Table I* describes the demographics and characteristics of the study population. Among the study participants both given Sinovac and AstraZeneca 52.97% belonged to the 20 to 30 age group. Most of them were females (69.92%) while the rest are males. For the employment category, healthcare workers comprised the majority of the study population (71.61%) while the rest (28.36%) were hospital staff. Though most reported no comorbidities, 26.27% reported having comorbidities, with hypertension and asthma identified as the predominant diseases at 9.75% and 9.32%, respectively, followed by allergic rhinitis (5.32%) and diabetes mellitus (2.97%).

Table II. Clinical data (History of COVID-19 Infection and vaccination received by health workers and staff in the Notre Dame de Chartres Hospital (n=236)

Variable	N	Percentage
History of COVID-19 infection	176	74.6%
I was never diagnosed with COVID-19	60	25.4%
Infected with COVID-19		
Asymptomatic	4	1.7%
Mild	39	16.5%
Moderate	5	2.1%
Severe	2	0.8%
Brand of vaccine injected		
Sinovac™	160	67.8%
AstraZeneca™	76	32.2%

Table III. Antibodies (Anti-SARS-Cov2S) Across the Different Variables

VARIABLE	SINOVAC™		ASTRAZENECA™	
	Mean (U/mL)	p-value	Mean (U/mL)	p-value
Age		0.189		0.340
20-30 years old	83.9216		172.6403	
31-40 years old	118.2636		209.3365	
41-50 years old	87.2012		261.9240	
51-60 years old	21.9820-		159.1375	
>60 years old			101.3275	
Sex		0.395		0.899
Male	79.0896		188.1409	
Female	95.2441		193.0535	
Employee Category		0.254		0.017
Healthcare worker	95.6874		158.1271	
Hospital staff	71.8106		243.3534	
No comorbidities	81.0577	0.084	194.4137	0.767
At least 1 comorbidity	114.1436		181.8465	
History of COVID-19 infection		<0.001*		0.029*
Never Infected	56.0968		170.5663	
Infected	182.8760		261.8053	

*Significant at $p < 0.05$

Table IV. Overall comparison on the production of neutralizing antibodies after vaccination with 2 doses of SINOVAC and ASTRAZENECA (Anti-SARS-Cov2S)

Brand of Vaccine	Mean Number of Units (Anti-SARS-Cov2S, U/mL)	p-value
SINOVAC™	90.4499	*<0.001*
ASTRAZENECA™	191.5266	

*Significant at $p < 0.05$

Table II lists the pertinent COVID-19 history and vaccination of the study sample. Among the participants, 74.6% were never diagnosed with COVID-19, while 25.4% reported to have been infected, with 16.5% having only mild symptoms. Most of the study participants (67.4%) were inoculated with Sinovac™ while the rest (32.6%) received AstraZeneca™.

Table III shows antibodies across the different variables, including age, sex and comorbidities and history of COVID-19 infection. There was no significant difference in the mean amount of antibodies when grouped according to each of the variables. The variable for employee status showed an elevated mean value for hospital staff in comparison with healthcare workers, revealing statistically significant results in the AstraZeneca™ group compared with the Sinovac™ group. For the history of COVID-19 infection, there is a significantly higher mean amount of antibodies in participants who previously contracted COVID-19 than those who never had a previous infection. These results apply to both Sinovac and AstraZeneca™ groups.

Table IV shows the overall comparison of the production of neutralizing antibodies after vaccination with Sinovac™ or AstraZeneca™. The mean number of units for Sinovac™ and AstraZeneca™ 90.44 U/ml and 191.5 U/ml, respectively, showing a significant difference in the mean amount of antibodies when the two brands of vaccine were compared. Those who were vaccinated with AstraZeneca™ developed a higher amount of antibodies than those who were vaccinated with Sinovac™.

Discussion

Vaccination is one of the key hopes for containing the COVID-19 pandemic.[10] To sustain the health care services, healthcare workers should be protected from infection or reinfection from the said virus.

Our study had 236 participants, with the majority in the ages 20 to 30 years old (52.97%), females (69.92%), and healthcare workers (71.6%). Most had no comorbidities; however of those with comorbidities, 9.75% and 9.32% had hypertension and asthma, respectively.

In the study of Trieu, M.C. et.al., healthcare workers with direct contact with COVID-19 patients had higher infection rates at 2.4%., compared to those without any exposure which was at 1.4%.[11] In the same study, nurses ages 23 to 31 years old had the highest risk. Our study showed no significant difference in the amount of antibodies produced based on employee category in terms of the brand of vaccine administered.

In a study by Zhang et.al., with 206 patients, participants in the 18 to 40 years age range had significantly higher titers of neutralizing antibodies at 95.14% compared to

the 40 to 60 age group at 78.43%.[12] Collier et.al have demonstrated sera from participants above 80 years old had lower neutralization potency.[13] In our study, the mean value of neutralizing antibodies was higher in the 30 - 50 age range. In the Sinovac™ group, the highest mean value was in the 31 – 40 years age range at 118.2 U/ml while in the AstraZeneca™ group, the highest was seen in the 41 - 50 age range with a mean value of 261.9 U/ml. However, despite the difference in the mean amount of neutralizing antibodies in each age group, it was not statistically significant.

Our study showed that for both brands of vaccines, females compared to males had a higher mean value of neutralizing antibodies. However, this was not statistically significant reflecting similar results to a study done by Zhang et.al.[14]

In our study, the presence of comorbidities was not statistically different. This is similar to the results reported by Ali et al.[15]

In a study by Edara et.al. with 102 residents, 60 had no prior infection while 36 had a positive RT-PCR result and a median level of S-protein IgG antibody titer of 48 U/ml for those without COVID-19 and 40,000 U/mL for those with COVID-19.[16] In a study by Havervall et.al., the median levels of neutralizing antibody were also higher in previously infected BNT162b2 (Pfizer) vaccinated individuals than COVID-19 naïve BNT162b2 (Pfizer) vaccinated participants.[17] This indicates that participants with prior COVID-19 infection had higher levels of antibodies. The same results were also seen in our study wherein those with prior infection had a higher mean value of antibodies for both Sinovac™ and AstraZeneca™ and was noted to be statistically significant.

A study by Yu S. et.al. showed that Sinovac Biotech™ developed vaccine-induced specific SARS-CoV-2 neutralizing antibodies in mice, rats, and primates starting Day 4 after the initial vaccination and 100% seroconversion at Day 42. On the other hand, the chimpanzee adenovirus vector that encodes the spike protein of the virus has the advantage of producing a more persistent cellular immunity.[18]

In our study, the mean number of units for Sinovac™ and AstraZeneca™ are 90.44% and 191.5%, respectively. The results showed a significant difference in the mean amount of antibodies when the two brands of vaccines were compared, with AstraZeneca™ having a higher amount of antibodies than Sinovac™.

The exact level of antibody and the protection it confers is still under investigation. A study by Khoury et.al. suggested that neutralization titers will be an important predictor of vaccine efficacy in the future as new vaccines emerge. It also predicts that a decline in neutralization titer may mean a waning of immune protection from infection, hence booster immunization may be required within a year.[19]

Conclusion

There's no significant difference in the mean amount of antibodies when grouped according to each of the following variables: age, sex, and comorbidities and these results apply to both Sinovac™ and AstraZeneca™ groups. Taking into consideration the employee category, there was no significant difference between healthcare workers and staff in the Sinovac™ group, however with an elevated mean value of neutralizing antibodies in hospital staff compared with the healthcare workers in the AstraZeneca™ group which showed a statistically significant difference. When comparing the mean amount of antibodies, those who were vaccinated with AstraZeneca™ developed a higher amount of antibodies than those who were vaccinated with Sinovac™.

Limitations and Recommendations

The study had a total number of 236 participants, meeting the exact target sample size for the study. A larger sample size would have had a better outcome, however, due to limited financial resources the exact sample size was utilized.

AstraZeneca™ and Sinovac™ were the only two vaccines available to the population at the time of the study, hence were the brand of vaccines considered.

We recommend conducting a prospective type of this research involving the population who had booster(s) for the COVID-19 vaccines.

Conflict of Interest. The authors declare that there is no conflict of interest.

Funding. This study was funded by the primary investigator

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