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ORIGINAL ARTICLE

FREQUENCY OF DEVELOPMENT OF NEUTRALIZING ANTIBODIES FOR SARS COV-2 VIRUS AFTER SINOPHARM VACCINATION - A SINGLE-CENTRE STUDY FROM ISLAMABAD, PAKISTAN

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ABSTRACT

Background: The COVID-19 pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has led to high morbidity and mortality worldwide. The Sinopharm vaccine was first to be rolled out in Pakistan for mass vaccination of population at risk. The objective of this study was to determine the frequency of development of Neutralizing antibodies for SARS CoV-2 virus after Sinopharm vaccination.

Materials & Methods: It was a cross-sectional observational study conducted at the Department of Pathology of Pakistan Atomic Energy Commission General Hospital H/11 Islamabad from 2nd April 2021 to 18th May 2021. Blood samples of 114 persons of both genders who had received Sinopharm vaccination and at least three weeks had elapsed after last dose of vaccination were taken. Tests for measuring neutralizing spike antibody were performed using Roche analyser Cobas 6000. Antibodies value greater than 0.8U/ml was taken as positive antibody titre.

Results: Positive neutralizing antibody was observed in 111 (97.37%) persons while negative antibody titre was observed in 3 persons (2.63%). Of the persons who developed antibodies,74(66.67%) were males while 37 (33.33%) were females. High variability and low antibody titers were observed in age group 60 years and above and between 40 to 49 years. Gender of the subjects had no effect on antibody titre level.

Conclusion: Neutralizing antibodies to spike proteins of SARS-CoV2 after Sinopharm vaccination developed in 97.37%. High variability and low antibody titers were observed in age group 60 years and above and between 40 to 49 years.

KEY WORDS: Antibodies; Corona; Immune system Vaccination; Virus.

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INTRODUCTION

The COVID-19 pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has led to high morbidity and mortality worldwide. Globally, as of 11:08am CEST 20th May, 2021, 164,409,804 confirmed cases of SARS-CoV-2 infection have been reported, resulting in 3,409,220 deaths.[1] In Pakistan the numbers of positive cases as of 20th May 2021 is 890,391 with 19,987 deaths with death and recovery rate of 2.2% and 90.3% respectively.[2] Physical distancing, quarantine, and isolation are effective in limiting the spread of disease but asymptomatic carriers have potential to spread disease and hence to further waves of SARS-CoV-2 infection.[3,4] There is no effective treatment for COVID-19 infections and some population groups like health-care workers, older people (aged >70 years), and those with underlying health conditions are at particularly at high risk.[5,6] Also SARS CoV-2 virus has high rate of transmission.[7] All these factors combined have led to parallel efforts to develop effective vaccine against the disease.

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Vaccines are designed mainly through three approaches differentiated using a full virus or bacterium, the triggering of the immune system due to a partial germ, or the making of unique proteins based on the instruction of only genetic material. The first approach to vaccine making is to apply chemicals, radiation, or heat to kill or inactivate the virus or the bacterium carrying the disease. Numerous studies proved the efficacy of chemical and radiation injections in eliminating or resisting diseases among people, such as polio and flu vaccines.[8] According to the WHO report (January 5th, 2021), in total, there are 63 candidate vaccines under human clinical trial and more than 172 candidates in preclinical development worldwide.[9] The development of the Sinopharm vaccine involves dousing a significant stock of corona viruses with beta-propiolactone, which results in defusing the coronavirus. Interestingly, the diffusion of coronavirus halts the replication process; however, the proteins, including spike, remain composed. Moreover, when a small quantity of adjuvant, an aluminum-based compound, is mixed with diffused viruses, the immune system stimulates a response to the vaccine.[10] The Sinopharm vaccine injects neutralised coronavirus into human arms. On exposure to the human body inside, the dead coronavirus is absorbed by an immune cell called an antigen-presenting cell, which destroys the coronavirus with some remains on the surface. These remains are identified by helper T cells, and if they fit into surface proteins, the T cells activate and trigger other immune cells to respond to the vaccine. Likewise, B-type immune cells, which carry various shapes of surface protein, may also reel upon the dead coronavirus if matched. On locking the virus, the B-cell absorbs either all or part of the virus and displays the remains on its surface. The B-cell triggers as the activated helping T-cell latches onto the surface.[11] This accelerates the generation of antibodies in similar shape to the surface proteins. In short, the invader is countered by the antibodies generated by B cells. The immune system responds to live coronavirus if injected with BBIBP-CorV.[12]

Sinopharm began developing an inactivated vaccine against the Corona virus in January 2020. In June 2020, promising results were reported in a clinical trial on monkeys. The second phase of the trial on humans reported the generation of antibodies against the coronavirus with no serious side effects. The third phase was conducted across the countries of the UAE, Morocco, and Peru, with similar findings. In November 2020, the China-based Sinopharm Chairman announced the injection of a million people with the Sinopharm vaccine. Onward, the UAE government approved BBIBP-CorV for vaccinating its people against COVID and reported an efficacy rate of 86 percent. On December 30th, 2020, the Chinese government approved it after reporting an efficacy rate of 79.34 percent.[13,14] Government of Pakistan approved Emergency use of Sinopharm vaccine on 10th March 2021 for use in persons above 60 years of age group. This vaccine was first to be rolled out in Pakistan for mass vaccination of population at risk. However, data regarding effectiveness of this vaccine in respect of developing neutralizing antibodies in Pakistani population is limited. Thereof this study was designed to determine frequency of development of neutralizing antibody after Sinopharm vaccination.

MATERIALS & METHODS

This was a cross-sectional observational study carried out in Department of Pathology of P.A.E.C General Hospital H/11 Islamabad from 2nd April 2021 to 18th May 2021. Local ethics committee permission was taken (IRB/1102:1.03.2021). Informed consent from persons was obtained before inclusion in the study. A data collection Performa was designed for the study which included demographic detail as well as timing of vaccination and previous Covid status of participants. 114 persons of both genders who had received Sinopharm vaccination and at least three weeks had elapsed after last dose of vaccination to assess antibody response were included. Persons who had received said vaccination included 2 categories; persons who never had had Covid -19 viral infection (PCR and/or antigen Negative) and had received 2 doses of sinopharm vaccine 3 weeks apart and persons who have had covid -19 infection, both symptomatic and asymptomatic (PCR and/or antigen Positive) and received either one or two doses of sinopharm vaccine. Persons in whom 3 weeks had not elapsed after sinopharm vaccination, those who didn't receive sinopharm vaccination and persons who got Covid-19 infection during post three weeks of vaccination were excluded from the study. Those persons who fulfilled inclusion criteria, their blood samples were taken in after filling the data form designed for the study. Blood samples were centrifuged to separate serum. Tests for measuring neutralizing spike antibody were performed using Roche analyser Cobas 6000. Anti-SARS-CoV-2 S is an immunoassay and determines in vitro quantity of antibodies (including IgG) to the SARS-CoV-2 spike (S) protein receptor binding domain (RBD) in human serum and plasma. Value greater than 0.8U/ml was taken as positive antibody titre. Results were analyzed using SPSS version 21. Age gender, profession and frequency of development of neutralizing antibodies were quantitative variables and expressed as frequency, percentage mean and standard deviation. The Kruskal-Wallis H test was used to determine if there was statistically significant difference between antibody titre levels of different age groups and among male and females.

RESULTS

A total of 114 persons were included in the study with 76 (66.67%) males and 38 (33.33%) females, male to female ratio being 1: 0.5. Mean age of population

included in the study was 45 ±12.23 years ranging from 22-77 years. Age and gender distribution of population under study and antibody titres is shown in Table 1

Table 1: Age and gender distribution of population under study and antibody titres

Variables		Count	Antibody titers
Age	Less than 30	14	197.82±77.53
	30-39	25	197.62 ±80.06
	40-49	36	154.51±102.26
	50-59	23	193.45.45±92.95
	60 and above	16	104.58±92.32
Gender	Male	76	165.83±96.69
	Female	38	178.73±94.47

Positive neutralising antibody was observed in 111(97.37%) persons while negative antibody titre was observed in 3 persons (2.63 %). Of the persons who developed antibodies 74 (66.67 %) were males while 37 (33.33 %) were females, male to female ratio 1: 0.5.

Box plot showing high variability and low antibody titers in age group 60 years and above and between 40 to 49 years is shown in Fig. 1 (Kruskal-Walis H P value 013, at least one group mean is significantly different)

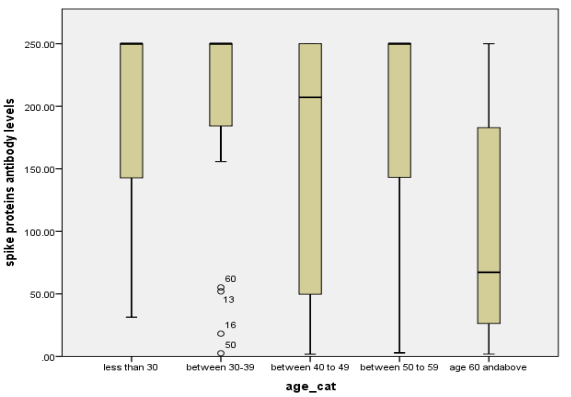

Figure 1 Age group-wise distribution of spike protein antibody levels

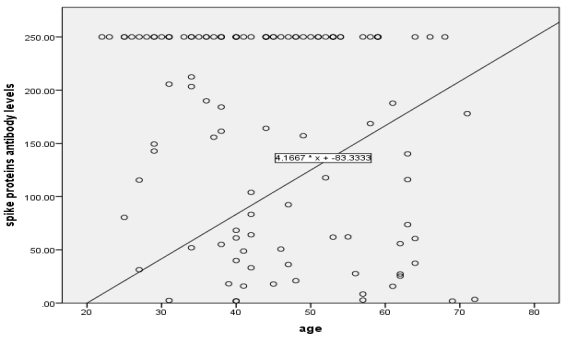

Figure 2 Scatterplot showing comparison of age with spike protein antibody levels

As the age increases antibodies levels declines. Linear regression coefficient, -1.663, 95% confidence level -3.098 to -0.229 p value 0.23. Implying one year increase in age results in decline of 1.663 units of antibodies levels. Breakup of patient who developed antibodies is shown in table 2.

DISCUSSION

Protective effects of vaccines at mass population level are affected by many factors. These include intrinsic host factors (such as age, sex, genetics, and comorbidities), perinatal factors (such as gestational age, birth weight, feeding method, and maternal factors), and extrinsic factors (such as preexisting immunity, microbiota, infections, and antibiotics). Further, environmental factors (such as geographic location, season, family size, and toxins), behavioral factors (such as smoking, alcohol consumption, exercise, and sleep), and nutritional factors (such as body mass index, micronutrients, and enteropathy) also influence how individuals respond to vaccines. Moreover, vaccine factors (such as vaccine type, product, adjuvant, and dose) and administration factors (schedule, site, route, time of vaccination, and co-administered vaccines and other drugs) are also important. Therefore, results of vaccine effectiveness vary among populations.[15]Also measuring vaccine response in real world also takes into account logistical factors involved in mass vaccination processes like transport and storage of vaccines and other cold chain requirements.[16]

Table 2: Breakup of patients who developed antibodies

Category of persons	No. who developed antibody		No. who did not developed antibody		Total
	Male	Female	Male	Female	
Never had had covid-19 viral infection (PCR and/or antigen Negative) and had received 2 doses of Sinopharm vaccine 3 weeks apart	32	17	2	0	51
Have had covid-19 infection, both symptomatic and asymptomatic (PCR and/or antigen Positive)) and received one dose of sinopharm vaccine as booster	42	20	0	1	63
Total	74	37	2	1	114

Sinopharm vaccine is first vaccine to be used for mass vaccination of Pakistani population. As it requires two doses to be administered at least three weeks apart and another three weeks to attain antibody levels, therefore, now data is being generated about effectiveness of this vaccine in developing neutralizing antibodies to spike protein in our population. Very limited data is available regarding effectiveness of Sinopharm Vaccine. In a study conducted in China on subjects receiving Sinopharm vaccine, the mean of subjects in phase I & II trials was age was 41.2±9.6 years and 43.5±9.1 years respectively. Mean age of our study population was 45±12.23 years. While men constituted 66.67% of our study population, females were in greater representation in Chinese population i.e. 58 women (60.4%) in phase 1 and 142 women (63.4%) in phase 2. In our study, though greater number of subjects have had covid 19 infection i.e. 63 and but 51 subjects had no history and laboratory of evidence of having covid-19 infection; therefore, humoral immune response in this group was generated by the vaccine and not through natural infections which is possibility in individuals who had history and laboratory of evidence of having covid-19 infection. Only two males out of 51 subjects constituting 3.93% did not develop antibody while rest 49 (96.07%) showed seroconversion. Overall seropositivity rate for spike antibody test was 97.37%. Interim results of Sinopharm Vaccine in Chinese population observed an efficacy of 79.4 % and 72.5 %. In another study on sinopharm, more than 95% of individuals seroconverted with detectable neutralizing antibody in the two different trials.[17,18,19]

There is very limited data at this point in time about rest of population in the world. Researchers in Brazil initially said it was 78% effective in their clinical trials, but in January 2021 revised that figure to 50.4% after including more data in their calculations. However, the United Arab Emirates, which approved a Sinopharm vaccine earlier this month, said the vaccine was 86% effective, according to interim results of its phase III trial.[13,14] Another important observation in study was that high variability and low antibody titers were observed in age group of 60 years and above and decreasing antibody levels with advancing age. Studies regarding effect of age on humoral immune responses to vaccination suggest that age is an important determinant of humoral immunity.[20] This finding is important in deciding use of Sinopharm vaccine in this age group which is also high risk specially keeping in view other vaccine options now available.

Limitation of study: The study design was cross-sectional so antibody levels at one time was analyzed which may not be predictor of future protection. Also, as there are many mutant strains of SARS CoV 2 virus and study did not include study of the strains; therefore, antibody development to specific strain cannot be determined.

CONCLUSION

Neutralizing antibodies to spike proteins of SARS-CoV2 after Sinopharm vaccination developed in 97.37%. High variability and low antibody titers were observed in age group 60 years and above and between 40 to 49 years, and decreasing antibody levels with advancing age.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	HAS, SA
Acquisition, Analysis or Interpretation of Data:	HAS, SA, QA, SA, ZRK
Manuscript Writing & Approval:	HAS, SA, QA, SA, STA

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.