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Evaluation of Humoral Immunity Induced by Commonly Administered COVID-19 Vaccines in Middle-aged Iranians

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Abstract

Background: Using a comparative analysis and assessment approach on a number of vaccine under investigation in a specific group is pertinent to local health policy and to our scientific understanding of vaccine responses.

Objectives: In this double-blind, cross-sectional study, the efficacy of two platforms inactivated COVID-19 vaccines (CO-Iran Barekat and Sinopharm) and adenoviral-vector COVID-19 vaccines (AstraZeneca and Sputnik V) most commonly used in the Iranian population was evaluated. The target population was 40 - 60 years old. Humoral immune response evaluated by the production of virus-neutralizing antibodies and immunoglobulin G binding to the receptor-binding domain (RBD).

Methods: Four hundred twenty volunteers aged 40 - 60 years were vaccinated with the COVID-19 vaccines including CO-Iran Barekat, Sinopharm, AstraZeneca and Sputnik. After receiving the second dose, the humoral immune response was assessed using a conventional neutralizing antibody assay and IgG ELISA.

Results: Recipients of the Barekat and Sinopharm vaccines had negative IgG responses of ~15.3% and ~32.97% respectively, while a negative IgG response in the Sputnik V vaccine group showed 10.58%. No negative IgG response was noted with the AstraZeneca group. In the neutralizing antibody assay against SARS-CoV-2, AstraZeneca, Sputnik V, COV-Iran Barekat and Sinopharm showed effective protection in 87.73%, 59.61%, 54.23% and 35.16% respectively. The S1-IgG and SARS-CoV-2 neutralization responses found with Sinopharm and COV-Iran Barekat were similar to those seen vaccinated individuals. In contrast, the conventional live-virus neutralization titer (cVNT50) in SARS-CoV-2-AstraZeneca vaccines was much higher than any of the other three groups. Also data analysis of adverse vaccine event revealed that injection site pain is the most common adverse event in the four groups.

Conclusions: The highest levels of neutralizing antibodies were found with AstraZeneca that further support its higher effective potential for protection to SARS-CoV-2. Antibody levels were measured with ELISA IgG Kits and a conventional neutralizing antibody assay technique.

Keywords: cVNT, SARS-CoV-2, Vaccine, AstraZeneca, Sputnik V, Sinopharm, COV-Iran Barekat

1. Introduction

COVID-19 has been spreading globally, with increases seen as new versions develop. COVID-19 is still spreading over the world, with numerous nations lately reporting a surge in transmission. The development of new variations has added to these oscillations. WHO designated several variations as variations of Interest (VOIs) (1) owing to their potential elevated risk to public health. Methods are being developed to quantify COVID-19 activity levels. After mass vaccination during the pandemic, COVID-19 activity in Iran has generally stabilized, although, like other members of the common cold virus family, an annual baseline increase

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in cases or hospitalizations due to virus circulation is expected. In Iran, since the early days of pandemic in April 2019, COVID-19 vaccine immunity testing and monitoring of vaccine adverse events have primarily been conducted in symptomatic adults within hospital settings for the clinical management (2-7).

Regarding the changes in the pandemic situation, and the non-seasonal nature of SARS-CoV-2 circulation, with multiple waves of virus activity per year and significant baseline activity, it was difficult to quantify the circulating activity of virus and its long-term immunity level compared to other respiratory viruses, such as influenza (8-9).

Other respiratory viruses' activity levels (common cold, influenza, RSV) have traditionally been tracked seasonally owing to the availability of national and reference labs and consistent historical data for at least the previous five seasons. While this is not possible for COVID-19 because of virus's novelty, and the lack of a clear seasonal pattern so far, given the frequency of viral evolution (i.e., variants), changes in testing protocols, and waning immunity in the population following vaccination campaigns.

During an epidemic or pandemic, when new and re-emerging diseases arise, and in the absence of a therapeutic drug against a virus, the preventive vaccines are the best and only tool to combat the disease, prevent its spread and circulation, and limit the number of viral mutations in terms of their ability to induce protective immunity. Even if there are multiple vaccine platforms that can stop the spread of the SARS-CoV-2 virus, their usage in different vaccinated groups may lead to variable levels of immunogenicity and safety, even when makers say they are of good quality. For instance, the fact that there have been significant waves of sickness, a lot of fatalities, and a lot of hospitalizations following vaccination, as well as the virus's stealthy spread over the globe for more than four years, shows this.

Although the biological characteristics of pandemic virus, which are completely different and unique to each person, differ from those of its family members and are unpredictable, they are another reason for the spread of disease in the population (10).

In this article, to assess and interpret the immunity level of individuals vaccinated with the four most commonly used vaccines in Iran, we conducted this evaluation by measuring humoral immunity (immunoglobulin G and neutralizing antibodies). We obtained serum from recipients of the four predominant COVID-19 vaccines in the Iranian population at least 130 days post-second dose. Following testing, we analyzed the data for each vaccine platform by initially calculating the mean and standard deviation (SD) within each vaccine group, and subsequently employing various statistical methods.

It is perhaps safe to say that there is still a lack of real-world data regarding risk groups, the comparisons of different vaccines and vaccination regimens, and simultaneous evaluation of various humoral and cellular immunity parameters. Despite numerous limitations and shortcomings for several reasons, the present study provided the first data on SARS-CoV-2 immunogenicity induced by vaccines widely used in the Iranian population.

This study compared the protective effects of four different vaccine platforms used in various regions of the Iranian population in terms of humoral and cellular immunogenicity, and safety against the Wuhan strain, which was the dominant circulating variant during the past two years of pandemic. The study was conducted on older age groups (between 40 - 60 years) who were immunized with four mentioned vaccines, 110 - 130 days after receiving the second dose. The methodology involved measuring humoral immune activity by assessing the production of virus-neutralizing antibodies (VNA) and immunoglobulin G (IgG) binding to the receptor-binding domain (RBD).

2. Methods

2.1. Study Design and Data Collection

This double-blind laboratory-based cross-sectional cohort study was approved by the Ethics Committee (Ethics Code: IR. TUMS.MEDICINE.REC. 1400.558 and Registered Proposal Code: 4 - 18 - 18 - 060 - 001018). Serum samples were previously collected to study the side effects of four vaccines under study with all necessary demographic data. Among them, samples from individuals between 40 and 60 years old were separated, coded, and sent to the laboratory. Participants had no interaction with our research team regarding vaccine selection, and their responses could not be influenced by vaccine identity. Laboratories who performed assays were fully blinded to the vaccine group assignment. Vaccine type was revealed only after completion of data analysis. The first blood sample for assessing serum antibodies, was obtained between the 21st and 31st days after the second vaccine dose. The immunogenicity of each vaccine based on IgG and nAb measurement was determined.

2.2. Subjects and Exclusion Criteria

The study population consisted of healthy adult volunteers seeking either Sputnik V or AstraZeneca, Sinopharm or Iran-Co Barekat COVID-19 vaccination, confirmed by negative rapid PCR COVID-19 on the day of immunization. Participants were geographically diverse, with an equal distribution of individuals above and below the age of 50, and a balanced gender ratio. Exclusion criteria included uncontrolled comorbidities, immunodeficiency, pregnancy, and a positive COVID-19 PCR test at the time of blood sampling.

2.3. Enzyme-Linked Immunosorbent Assay for the Detection of SARS-CoV-2-Specific Immunoglobulin G

To determine the IgG titer of SARS-CoV-2, 100 serum samples were selected from each vaccine group. To conduct the work and obtain the results, two commercial ELISA kits (RAZIAnti-RBD-SARS-CoV-2 Virus/IgG) (Iran), and Euroimmune Anti-SARS-CoV-2 Virus/IgG (Germany) were selected. Each sample was evaluated by three operators using distinct codes with both kits. Each sample was tested six times to reduce operator error and its influence on the interpretation of the data. The testing procedure was conducted in accordance with the manufacturer's guidelines for the kit. The outcomes of the IgG ELISA experiment were represented as optical density (OD). Based on the instructions provided by the kit and also through validation process of our negative serum, cut-off values were defined as following: less than or equal to 1.1 was considered negative, between 1.1 and 2.8 as very weak, greater than 2.8 to 4.2 as weak, greater than 4.2 to 8.5 as moderate and titers greater than or equal to 8.5 as strong antibody response were classified.

2.4. Neutralizing Antibody Level

Neutralizing antibody titers were determined by the dilution that resulted in 50% neutralization as our previous article (11). An antibody titer of less than 1:8 was regarded as negative.

2.5. Statistical Analysis

2.3. Statistical Analysis Statistical analysis will be conducted using SPSS version 21.0 (Armonk, New York, USA). Descriptive statistics will be presented as mean ± SD for normally distributed variables, and as median (minimum/maximum) for non-normally distributed variables. Two multiple regression analyses designed to explore the relationships among different factors (such as age, gender, BMI, previous infection, Vitamin D levels, and corticosteroid use) different vaccine groups.

3. Results

A total of 418 serum samples from participants, equally divided between two age groups of over 50 and under 50 years, were selected and analyzed. The descriptive statistics of participants' age stratified by vaccine type are presented in Table 1 . The Sputnik V and Sinopharm group exhibited the higher mean age than Iran Co Barekat. AstraZeneca group demonstrated the lowest mean age. It is important to note that the data indicate a substantial degree of variation in the mean age of vaccine platforms Gender distribution across vaccine groups is summarized in Table 2 . Males constituted a higher proportion among Sputnik V and AstraZeneca recipients. In contrast, females were more prevalent among Barekat recipients. The Sinopharm group exhibited a relatively balanced gender distribution. Overall, the study population showed a nearly equal distribution of females and males. The average interval between sampling and administration of the second vaccine dose is presented in Table 3 . Sputnik V recipients had the longest mean interval followed by Sinopharm. Substantially shorter intervals were observed for AstraZeneca and Barekat. The corresponding 95% confidence intervals indicated limited variability within each vaccine group.

The comprehensive comparison of IgG and neutralizing antibody (nAb) responses presented in Table 4 . Distribution of IgG responses markedly varied across vaccines. While Sputnik V recipients showed a balanced distribution across categories, Sinopharm showed a notable prevalence of negative and very weak responses in vaccine recipients. AstraZeneca group demonstrated robust immunogenicity, with a high percentage of strong and moderate response.

Barekat displayed a mixed profile, with the highest proportion in the moderate range.

Overall between group, moderate IgG titers were the most frequently observed category followed by strong and very weak responses. Negative IgG titers accounted for 14.09% of participants.

In this Table 4 . Neutralizing antibody responses also showed variation across vaccine platforms. Among Sputnik V recipients, 52.88% were classified as nAb positive, while 40.38% were negative and 6.73% exhibited weakly positive responses. In the Sinopharm group, negative nAb responses were most prevalent (64.83%), whereas 25.27% of participants were classified as positive and 9.89% as weakly positive. Participants vaccinated with AstraZeneca (AZD1222) demonstrated the highest proportion of positive nAb responses, with 75.47% classified as positive, 12.26% as negative, and 12.26% as weakly positive. In the Barekat vaccine groups, positive nAb responses were observed in 48.73% of participants,

while 46.21% were negative and 5.04% were weakly positive. Across the entire study population (N = 420), more than half of participants (51.43%) exhibited positive neutralizing antibody responses, while 40.24% were negative and 8.33% were weakly positive. Table 5 presents the association of positive response of IgG and nAbs with other independent variables in multiple negative binomial regression models. Using incidence rate ratios (IRR) with corresponding 95% confidence intervals and statistical significance values the results demonstrated significant heterogeneity in immune responses based on vaccine platform and prior infection status.

In this analysis, there was no significant correlation between antibody responses and demographic factors, such as age and sex. The interval between testing and vaccination did not exhibit a measurable effect on immunological outcomes in the same way. These results indicate that the vaccine platform and prior infection status are more significant determinants of the serological response within the studied population than these host characteristics. We performed a multivariate analysis for the association between host and vaccine-related factors with two key immunological outcomes: the development of moderate-to-strong IgG antibody levels and production of neutralizing antibodies (nAbs). The finding in Table 5 supported the concept of hybrid immunity, where natural infection combined with vaccination yields superior serological responses compared to vaccination alone.

Antibody responses to the different vaccine brands were analyzed using multiple negative binomial regression models, with the effects of other variables being adjusted. AZD1222 exhibited higher incidence rates for moderate and strong IgG levels, as well as for a positive response of neutralizing antibodies, in comparison to Sinopharm and Sputnik V (P-values < 0.05). Both IgG and neutralizing antibody responses after Barekat vaccination were comparable to those after Sinopharm vaccination. Although the point estimates of incidence-rate ratios (IRR) for AZD1222 were higher than for Sputnik V in both outcomes, the overlapping confidence intervals indicate that the difference among the point estimates is not statistically significant.

4. Discussion

Adenoviral vector vaccines and inactivated vaccines offer diverse mechanisms and strategies for inducing immune responses. Adenoviral vector vaccines leverage live, but non-replicating viruses to produce robust cellular, and humoral immunity, predominantly requiring fewer doses. Conversely, inactivated vaccines focus on safety and widespread immunity via non-viable pathogens, although often necessitating multiple doses to achieve sufficient immune protection. Both vaccines play vital roles in the contemporary vaccination strategies, particularly against emergent pathogens like SARS-CoV-2. AZD-1222 (ChadOx1 nCoV-19) consists of replication-deficient simian adenovirus vector (ChAdOx1) with replication deficiency. This non-replicating virus carries the optimal codon sequence for spike protein. Studies showed that the vaccine is better tolerated in the elderly than in the young, and after a booster dose, develops similar immunogenicity in all age groups (12-14). Sputnik V vaccine (rAd26-S and rAD5-S), made by a Russian company, contains the glycoprotein S gene of the SARS-CoV-2 virus. The first and second doses of this vaccine are based on two different types of adenoviruses. Phase 1/2 studies indicated that both formulations of this vaccine (rAd26-S and rAD5-S) were safe. Sinopharm (BBIP) is an inactivated entire virion produced by a Chinese company and manufactured with alum adsorption. This vaccine was developed using an isolated strain (Wuhan) obtained from a COVID-19 patient in China. Research indicates that this vaccine induces both humoral and cellular responses (15-16). COV-Iran Barekat (BIV1-CovIran) is an inactivated whole virus particle vaccine manufactured by Shifa Pharmed Industrial Group a subsidiary of Barkat Pharmaceutical Group. The harvested virus were inactivated with β-propiolactone. After purification, the inactivated virus particles were sterilized with filtration, and formulated with Alhydrogel as an adjuvant (17-18).Adaptive response to SARS-CoV-2 relies on two components: virus-neutralizing antibodies (NAbs) preventing the attachment of free virions to ACE2 receptor-expressing host cells, and effector CD8+ and CD4+ T lymphocytes eliminating infected cells by direct or by cytokine-mediated cytotoxicity (19-20).Furthermore, long-living memory T and B cells are produced, which, in the event of re-infection, resume the creation of effector T cells and antibodies, as well as regulatory T subsets that guard against the harmful consequences of nonspecific activation (Inoue and Kurosaki 2024).Protective humoral and cellular immunity to SARS-CoV-2 was shown both in animal models and in human (21) also it determined in the patients with inborn errors of immunity (11). Recently, SARS-CoV-2-specific bone marrow plasma cells, and persistent germinal center B cell response were reported after recovery from COVID-19, in favor of long-lived humoral immune memory (22-23).

This study aimed to analyze the SARS-CoV-2 virus Humoral antibody titer, after 2nd dose vaccination in Iran by, Sinopharm, AZD1222, Sputnik V and IranCo-

Table 1. Description of Age in Participants [a, b, c, d, e]

Vaccine Code/Age	Mean	SE	95% CI
Sputnik V	58.12019	1.468354	55.23389 - 61.00649
Sinopharm	55.20769	2.064078	51.1504 - 59.26499
AstraZeneca	42.10613	1.302381	39.54608 - 44.66618
Barekat	47.8153	1.303278	45.25349 - 50.37711
Total number of observations	418		

[a] Mean age estimation for 418 participants over vaccine platform (V Code).

[b] The Sputnik V group exhibited the highest mean age at 58.12 years (standard error [SE] = 1.47), with a 95% confidence interval (CI) ranging from 55.23 to 61.01 years.

[c] Participants vaccinated with Sinopharm had a mean age of 55.21 years (SE = 2.06), and the 95% CI spanned 51.15 to 59.26 years.

[d] The AstraZeneca group demonstrated the lowest mean age at 42.11 years (SE = 1.30), with a narrower 95% CI of 39.55 to 44.67 years.

[e] The Barekat Vaccine recipients had a mean age of 47.82 years (SE = 1.30), with a 95% CI of 45.25 to 50.38 years.

Table 2. A Comprehensive Analysis of Gender Distribution Among Participants Vaccinated with Four Distinct COVID-19 Vaccines [a, b, c]

Vaccine Code	Female	Male	Total
Sputnik V	44 (42.31)	60 (57.69)	104 (100.00)
Sinopharm	50 (54.95)	41 (45.05)	91 (100.00)
AstraZeneca	42 (39.62)	64 (60.38)	106 (100.00)
Barekat	71 (60.68)	46 (39.32)	117 (100.00)
Total	207 (49.52)	211 (50.48)	418 (100.00)

[a] Values are expressed as No. (%).

[b] The data delineate both the numerical count and proportional representation of female and male participants for each vaccine, alongside aggregated totals.

[c] Across all vaccines, the total sample size was 418 participants, with a nearly balanced gender distribution: 49.52% female (n = 207) and 50.48% male (n = 211).

Table 3. Average in Dosing Intervals Between Sampling and Receiving the Second Dose of Vaccine [a, b, c, d]

Vaccine Code	Mean	SE	95% CI
Sputnik V	130.6699	1.5685	127.5867 - 133.7531c
Sinopharm	124.1429	1.247569	121.6905 - 126.5952
AstraZeneca	83.31132	0.3934238	82.53797 - 84.08467
Barekat	75.66667	0.8300998	74.03495 - 77.29838
Total number of observations	418		

[a] Sputnik V vaccinee exhibited the longest, meanwhile for AstraZeneca and Barekat participant's lower mean intervals were observed.

[b] Dosing interval Sputnik V group, resulted a mean of 130.67 units of time (SE = 1.57 and 95% confidence interval, ranged from 127.59 to 133.75, indicating a relatively consistent interval duration among recipients.

[c] The Sinopharm group showed a shorter average interval, with a mean of 124.14 (SE = 1.25) and a 95% confidence interval between 121.69 and 126.60.

[d] AstraZeneca recipients had a mean interval of 83.31 and (SE = 0.39), with a narrow 95% confidence interval ranging from 82.54 to 84.08. Similarly, the Barekat vaccine group demonstrated the shortest average interval, with a mean of 75.67 (SE = 0.83) and a 95% confidence interval between 74.03 and 77.30.

Barekat. The findings indicated that the positive responses for IgG and neutralizing antibodies after vaccination with AZD1222 were superior to those of Sputnik V, Sinopharm, and Barekat, whereas the immunogenicity of Barekat and Sinopharm was comparable.

The results indicated that, when considering Sinopharm as the reference vaccine, Sputnik V and AZD1222 exhibited elevated incidence rates for moderate and strong IgG levels, together with a positive response of neutralizing antibodies (P-values < 0.05). The IgG and neutralizing antibody responses after immunization with Barekat were comparable to those elicited by Sinopharm. Although the point estimates of incidence-rate ratios (IRR) for AZD1222 were higher than Sputnik V in both outcomes, but is not statistically significant.

Table 4. Presents Both Numerical Counts and Percentages for Titer of IgG and Neutralizing Antibody According to Reference Range [a, b, c, d, e, f]

Variables	Weakly Positive			Positive		
	Negative	Very weak	Weak	Moderate	Strong	Total
Titer of IgG after vaccination						
Sputnik V	11 (10.58)	29 (27.88)	11 (10.58)	30 (28.85)	22 (22.12)	104 (100)
Sinopharm	30 (32.97)	24 (26.37)	10 (10.99)	16 (17.58)	11 (12.09)	91 (100)
AZD1222	0 (0.00)	3 (2.83)	7 (6.60)	53 (50.00)	43 (40.57)	106 (100)
Barekat	18 (15.3)	33 (27.73)	13 (10.92)	43 (36.13)	12 (10.08)	119 (100)
Total	59 (14.09)	89 (21.19)	41 (9.76)	142 (33.81)	89 (21.19)	420 (100)
Titer of nAbs after vaccination						
Sputnik V	42 (40.38)	7 (6.73)		55 (52.88)		104 (100)
Sinopharm	59 (64.83)	9 (9.89)		23 (25.27)		91 (100)
AZD1222	13 (12.26)	13 (12.26)		80 (75.47)		106 (100)
Barekat	55 (46.21)	6 (5.04)		58 (48.73)		119 (100)
Total	169 (40.24)	35 (8.33)		216 (51.43)		420 (100)

[a] Values are expressed as No. (%).

[b] Neutralizing Antibody titre categorized as negative, weakly positive, and positive.

[c] AstraZeneca recipients showed (75.47%) positive nAb responses, followed by Sputnik V (52.88%) and Barekat (49.15%). Sinopharm recipients showed lowest, (25.27%) positive, while AstraZeneca recipient had the lowest (12.26%) negative. Weakly positive responses ranging from 5.08% (Barekat) to 12.26% (AstraZeneca), were relatively uncommon across all vaccines.

[d] IgG responses into five different tiers: Negative, very weak, weak, moderate, and high.

[e] AstraZeneca recipients, showed the most robust IgG responses by, 50.00% moderate and 40.57% strong antibody titers and no negative (0.00%) responses. In contrast, Sinopharm vaccinees exhibited (32.97%) negative results, and limited strong responses (12.09%). Sputnik V showing (28.85%) moderate, 22.12% strong. Barekat participants having predominant moderate responses (35.23%) but strong responses accounted for 10.08%, while negative and weak titers were observed in 15.13% and 10.92% of participants, respectively.

[f] Overall, across all participants (N = 420), moderate IgG titers were the most common (33.81%), followed by strong and very weak responses (each 21.19%). Negative IgG titers accounted for 14.09% of the total sample.

Table 5. The Association of Positive Response of IgG and nAbs with Other Independent Variables in Multiple Negative Binomial Regression Models [a, b, c, d]

Independent Variables	Moderate and Strong IgG Level		Positive Neutralizing Antibodies	
	IRR (95% CI)	P-Value	IRR (95% CI)	P-Value
Age (y)	1.00 (0.99 - 1.01)	0.566	1.00 (0.99 - 0.01)	0.943
Female sex	1.12 (0.86 - 1.46)	0.412	1.02 (0.79 - 1.32)	0.863
Prior COVID-19	1.46 (1.05 - 2.03)	0.024	1.48 (1.07 - 2.04)	0.018
Test to vaccination interval (day)	0.99 (0.98 - 1.01)	0.441	1.00 (0.99 - 1.01)	0.989
Vaccines				
Sinopharm	Reference	-	Reference	-
Sputnik V	1.65 (1.03 - 2.65)	0.039	1.61 (1.04 - 2.49)	0.033
AZD1222	2.30 (1.15 - 4.62)	0.019	2.29 (1.21 - 4.33)	0.011
Barekat	1.20 (0.54 - 2.49)	0.658	1.50 (0.73 - 3.10)	0.274

Abbreviations: IRR, incidence-rate ratio; CI, confidence intervals

[a] The result performed a multivariate analysis for the association between host and vaccine-related factors with two key immunological outcomes: Development of moderate-to-strong IgG antibody levels and production of neutralizing antibodies (nAbs).

[b] The analysis of (IRR) and CI (95%) and P-value revealed, age, female sex and interval between testing and vaccination had no statistically significant relationship with moderate-to-strong IgG levels or positive nAb responses. In contrast prior COVID-19 effect statistically significant relationship (IRR = 1.46, 95% CI: 1.05 - 2.03; P = 0.024) for moderate-to-strong IgG responses as well as positive neutralizing antibody responses (IRR = 1.48, 95% 1.07 - 2.04; P = 0.018).

[c] Sinopharm as the reference category, vaccine type showed differential associations with immunological outcomes.

[d] Receiving the Sputnik V and AstraZeneca vaccines was significantly associated with higher rates of moderate to strong IgG responses and positive nAb responses. In contrast, no statistically significant associations were observed for the Barekat vaccine with either moderate-to-strong IgG responses (IRR = 1.20, 95% CI: 0.54 - 2.49; P = 0.658) or positive nAb responses (IRR = 1.50, 95% CI: 0.73 - 3.10; P = 0.274).

Statistical evaluations shows difference in the humoral antibody response titer among the recipients of Sputnik vaccine, and Iran Co Barekat is not significant (P-values < 0.05), considering to comparison the two different

platforms, we would expect a higher humoral response from the Sputnik V than Iran Co Barekat vaccine. Because unlike inactivated vaccines, adenovirus vectors can express viral antigens in the body, leading to more complete activation of the immune system. The immunogenicity of the Sinopharm vaccine was reported in several studies in the world. Vályi-Nagy et al. compared humoral and T cell mediated immune responses elicited by BBIBP-CorV and BNT162b2 (22-23). RBD-specific antibody responses after two doses of BBIBP-CorV was shown by Ferenci et al. (24). Matula et al. evaluated the antibody and T Cell Responses against SARS-CoV-2 induced after third dose of Sinopharm and BNT162b2 (22). In contrast with our results, Tamás Ferenci and Balázs Sarkadi reported the detectable level of antibody after two doses was positive in 90 % of Sinopharm vaccine recipients below the age of 50 (24).In contrast, our analysis of the results indicated that nAbs were negative in 64.83% of participants and positive in only 35.16% of those who received two dosages of Sinopharm. It is possible that the extended sampling interval in comparison to AZD1222 was the reason for the decrease in neutralizing antibodies in individuals who received Sinopharm and Sputnik vaccines. This spike-antibody waning after the second dose of COVID-19 vaccines has also been reported in other vaccines, such as BNT162b2 or ChAdOx1 (25).

2021).Moreover, a study which conducted in Sri Lanka suggested the vaccine efficacy of AZD1222 was 90% against 79.34% for Sinopharm (26). However, our data showed anti-SARS-CoV-2 neutralizing antibodies were positive in 87% of AZD1222 vaccine recipients, and 58.61% and 53.16% for Sputnik V and Sinopharm. In a study conducted in Mongolian vaccine recipients showed that antibody levels of AZD1222 is more than Sputnik V and Sinopharm. Similar to this study, our data analysis indicated a significant increase in anti-SARS-CoV-2 antibody titer in AZD1222 vaccine recipients compared to Sputnik V and Sinopharm (27). According to the findings of a comparative pilot clinical study on the immunogenicity and safety of Sinopharm BBIBP-CorV and Sputnik V in the Republic of Belarus, the majority of Sinopharm (BBIBP-CorV)-vaccinated patients had levels below 150 BAU/ml after 6 months and ≤500 BAU/ml after 42 days, while the Sputnik V vaccine group had IgG levels above 500 BAU/ml at the 42nd day and 6 months following the first dose of the vaccine (28). In agreement with our findings, the serum concentration of IgG in vaccinated participants with Sputnik V was significantly higher than inactivated vaccine: Sinopharm, and Iran Co Barekat. In another study, the seropositive rate for AZD1222 vaccine recipients was reported 80% compared to Sinopharm (16.7%) in the individuals three months post-vaccination in Sri Lanka (29). The effectiveness, immunogenicity, and adverse effects of COVID vaccination in the Iranian population has been the subject of several published studies. The side effects and effectiveness of four COVID-19 vaccines, Sputnik V, Sinopharm (BBIBP-CorV), COVIran Barekat, and AZD1222, were evaluated in some studies (30-31). The study found that while all four vaccines offered comparable protection against hospitalization and death 14 days after the second dose, the AZD1222 vaccine demonstrated superior protection after only one dose. The outcomes are in line with the current article in this respect. Moreover, the findings of Zare et al. were similar to our results, but their participants were healthcare workers and the sampling interval differed from our study (32).

A study of vaccinated and unvaccinated individuals conducted in Kerman showed that two-dose vaccination by vector vaccine reduced hospitalization by 67% compared with the inactivated virus vaccines, indicating stronger protection from the vector vaccine (33). It is important to note that the AstraZeneca vaccine demonstrated significantly different results than the inactivated vaccines of Sinopharm and Iran Co Barakat in our study. However, the difference between the inactivated and Sputnik vaccines was not statistically significant. Given the small sample size and limited vaccine diversity, these findings cannot be generalized, and further research is needed to highlight the role of vector platform-based vaccines in other populations (33).

The rates of immune responses induced in seronegative individuals vaccinated with Sinopharm and Oxford-AstraZeneca were reported to be 63.8% and 79.1%, respectively (34) which is in close agreement with the results obtained from our study. Another study that evaluated antibodies using IgG ELISA and neutralizing antibodies against SARS-CoV-2 reported that Oxford/AstraZeneca and Sputnik V had similar results in inducing high levels of anti-SARS-CoV-2 spike and neutralizing antibodies, which were higher than Sinopharm and Covaxin (35). These results contradict the findings of our investigation on the similarities in neutralizing antibody production between Sputnik and AstraZeneca. The results of this study are comparable to those of Enayat et al. (3), who showed increased levels of anti-(RBD) IgG after the first and second doses of AZD1222 compared to Sinopharm. However, that study included a small sample size of vaccinated healthy individuals. We observed that of individuals who received two doses of inactivated vaccine, Sinopharm and COVIran Barekat showed 51.80% and 53.77%

seropositive responses, respectively. The most common side effects of Sputnik V, AZD-1222, and inactivated vaccines among the Iranian population were injection site pain, muscle pain, fatigue, fever and chills, and headache. The findings were largely congruent with clinical trials conducted by vaccine producers. The occurrence of adverse effects was typically greater in females than in males, with a stronger association seen with Sputnik V. The incidence of side effects was inversely correlated with age, indicating that older individuals were less prone to post-vaccination problems. An "Umbrella Review." results on Effectiveness of COVID-19 Vaccines (36) showed that various factors, including geographic, and pandemic-related considerations, significantly influenced vaccine effectiveness. Further research is needed to strengthen public confidence in the vaccine and better understand the possible long-term immunity and side effects in different populations on approved COVID-19 vaccines. In recent years, the relentless efforts of various organizations around the world to develop an effective COVID-19 vaccine reduced the spread of the disease and improved the health of the community. So far, numerous scientific studies were conducted on the effectiveness and safety of different vaccine platforms. However, four years after the start of SARS-CoV-2 pandemic, concerning variants continue to emerge. Consequently, it can be inferred that we are not yet entirely liberated from this regrettable occurrence that has inflicted substantial damage upon us. The disease can be more severe and affect various age groups differently due to the fact that new variants of COVID-19 can spread more readily and may elude immunity from previous infection or vaccination, as well as reduce the efficacy of existing treatments and preventive measures. This calls for updating and further studies on the long-term effectiveness of vaccines used. Fortunately, the reports so far indicated a decrease in hospitalizations and that the situation is under control. It is hoped that the global community will be better prepared to face and manage similar public health emergencies in the future.

Footnotes

AI Use Disclosure The authors declare that no generative AI tools were used in the creation of this article.

Authors' Contribution A.M. designed the study, the methodology. R.G. and M.H.A. contributed to sample and data collection. R.S developed and operated the methodology, and collected the test data. B.A. contributed the methodology, collecting the data and analyzed the data. R.G. contributed in initial draft of the manuscript. A.M. wrote the initial and final manuscript.

Conflict of Interests Statement The authors declare no conflicts of interest.

Data Availability The data presented in this study are uploaded during submission and are openly available for readers upon request.

Ethical Approval This study was approved by the Ethics Committee of Tehran University of Medical Sciences (ethics code: IR.TUMS.MEDICINE.REC.1400.558).

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