Evaluation of the Effectiveness of COVID-19 Vaccination on Serum IgG, and IgM Levels in Saudi Arabia

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ABSTRACT

Three types of COVID-19 vaccines have FDA approval and are used worldwide; their immune response sturdiness is limited, and the level of serum IgG and IgM will help in determining the effectiveness of the vaccines against COVID-19 viruses. The point of this study was to look into the humoral immune response to SARS-Cov-2 by checking the levels of IgG and IgM in the serum of people who had been vaccinated. The study also includes a comparison between two authorized vaccines used at the beginning of the pandemic, BNT162b2 and AZD1222. Methods: A total of 88 samples were collected 3-4 weeks after vaccination from different groups of confirmed COVID-19 vaccinated to evaluate the concentrations of IgG and IgM using ELISA, groups including control subjects who did not receive any vaccine, vaccinated pre-COVID-19 infection, vaccinated post-COVID-19 infection, healthy vaccinated one dose, and healthy vaccinated two doses. Results: vaccinated pre-COVID-19 infection groups showed a significant increase in IgG and IgM compared to control, additionally, healthy vaccinated groups (with one or two doses) showed a significant increase in IgG. However, post-COVID-19 infection vaccination showed no significant difference. Conclusion: IgG and IgM concentrations increased as a response to the vaccine, and vaccination with a booster dose showed a higher elevation. Moreover, vaccination prior to infection may mitigate the severity of symptoms after infection. Finally, both BNT162b2 and AZD1222 are effective in boosting immunity, and their side effects need further studies in the long term.

Key words: COVID-19, SARS-CoV-2, Immunoglobulins, IgG, IgM, vaccines.

INTRODUCTION

Almost a year after the COVID-19 pandemic started, much research was completed successfully and developed vaccines against SARS-CoV-2. The immediate establishment of massive vaccination programs held promise for a successful battle against the virus. As of 4 September 2023, approximately 13.5 billion vaccine doses have been administered globally [1]. Pfizer-BioNTech has approved numerous COVID-19 vaccines, including mRNA vaccines. COVID-19 vaccine recognized as Comirnaty and Moderna COVID-19 vaccine recognized as Spikevax) were leaders in the candidates, then a viral vector vaccine recognized as AstraZeneca COVID-19 vaccine has been approved [2].

COVID-19 characteristics and outcomes are highly variable, ranging from asymptomatic or mild symptoms such as fever, cough, and fatigue to more severe symptoms with serious complications including multiple organ failure, acute respiratory distress syndrome, and even death [3,4]. Many factors may affect the overall response to the infection, such as age, sex, and health conditions [5-7]. Studies demonstrated that females were less susceptible to infections than males due to biological gender differences in the immune system and receptors. This might be related to sex hormones (including estrogens, progesterone, and androgens) and immune-regulatory genes on the X-chromosome. Furthermore, studies suggest that these differences influence the outcomes of infections in terms of infection severity, viral load, and other comorbidities [8,9]. The vaccination can lead to a decline in the severity of these symptoms.

The immune system responds to the SARS-Cov-2 infection by activating innate and adaptive immunity, as well as its cellular and humoral components. B cells, CD8+, CD4+ T cells (cytotoxic T cells and helper T cells), and CD38+ are important parts of adaptive immunity. They work with innate immunity to fight viral infections by working together [10,11]. B cells are very important because they make antibodies that attack viruses and infected cells. These antibodies protect against infection in a number of ways, such as through neutralization, complement activation, antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent phagocytosis (ADP) [12]. B cells are additionally the key component in the management of COVID-19 spread, as they are the main target of vaccine development. Activated B cells secrete different types of immunoglobulins, including IgM, IgG, IgA, IgD, and IgE [13].

As a response to the SARS-CoV-2, specific antibodies against spike protein (S) and nucleocapsid (N) are produced. They play a special role by neutralizing and inhibiting the entry of the virus into the cells, as well as blocking the binding of the receptor-binding domain (RBD) with angiotensin-converting enzyme-2 (ACE2) [14,15]. IgM is the first antibody to be produced after pathogen invasion, and its concentration declines earlier than IgG which is the most abundant antibody response for long-term immunity in viral infection. For several weeks after infection, the serum IgG concentration remains high [16,17]. Therefore, their serum levels play a crucial role in evaluating the effectiveness of the vaccine against COVID-19 infection.

In this study, the aim was to measure the serum levels of IgM and IgG in different groups of COVID-19-vaccinated subjects to evaluate the effectiveness of vaccination against SARS-CoV-2 viruses. Additionally, a comparison of the two authorized and used vaccines is Saudi Arabia at the start of the pandemic regarding serum levels of the chosen antibodies examined.

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MATERIALS AND METHODS

Study design and procedures

This is a prospective study that was conducted at King Abdulaziz Hospital in Jeddah, Saudi Arabia, in March 2021. Prior to the specimen collection, we notified patients or their guardians and gave them the opportunity to give informed consent. We obtained blood samples from the King Abdulaziz Hospital in Jeddah, Saudi Arabia. We aliquoted the samples and maintained them at (-80) throughout the experiment. Real-time reverse transcriptase polymerase chain reaction (RT-PCR) confirmed the clinical and radiological diagnoses of COVID-19 in each patient. The National Health Commission of China used the New Clinical Classification System for patient classification.

Vaccinated groups were divided as follows:

Group 1 (Controls): included healthy individuals of similar age and sex, who had not been immunized with any dose of vaccine.

Group 2 (vaccinated pre-COVID-19 infection): included patients who had been immunized with one dose of the vaccine before being infected by the COVID-19 virus.

Group 3 (vaccinated post-COVID-19 infection): included vaccinated individuals with one dose who had been already infected by COVID-19.

Group 4 (Healthy vaccinated with one dose): included healthy individuals who had been immunized with one dose of the vaccine.

Group 5 (Healthy vaccinated with two doses): included healthy individuals who had been immunized with two doses of the vaccine.

Blood samples from vaccinated were collected 3-4 weeks after vaccination.

Exclusion criteria: Immunological problems, people who had received chemotherapy or immunosuppressive medicines, chronic infections, hematological disorders, and any other laboratory or clinical indications of further infections were disqualified.

Measurement of IgG, and IgM

A total of 88 blood samples were collected in a serum separator (SST) tube (3ml) and classified into 5 groups as illustrated in the patients' section (group 1 (n=18), group 2 (n=18), group 3 (n=20), group 4 (n=21), group 5 (n=11)), as the most the population were recovered or currently infected with COVID-19 the size of group 5 were limited. After that serum IgG and IgM levels were measured by using Human SARS-CoV-2 spike IgG and IgM ELISA kits (Thermo Fisher, Cat#: BMS2325, BMS2324 respectively) following the manufacturer's instructions. The concentrations were determined by reading optical density at 450 using The BioTek 800 TS absorbance reader.

Statistical Analysis

Using Prism GraphPad software version 9.5.0, the results of statistical investigations were presented as the mean standard error of the mean (SEM) as the data was normally distributed. The Kruskal-Wallis test and post hoc test are used in trials with more than two groups. The one-way ANOVA test was used to assess differences between normally distributed variables, Dunn's multiple comparison test was used for parameters that are not normally distributed, and Tukey's multiple comparison test was used to find significant differences across groups. When there were just two groups in an experiment, Mann-Whitney tests or unpaired t-tests were utilized. A P-value of 0.05 or less was considered statistically significant.

Ethical approval

The Institutional Review Board (IRB) of the Research and Studies Department—Jeddah Health Affairs, registration number KACST, KSA: H-02-J-002 research number 1373 was obtained.

RESULTS

We collected a total of 88 serum samples, as shown in Table 1. as their average age was 40.26 11.01, with 26 of them being male (29.54%) and 62 being female (70.46%). We divided the participants into five distinct groups: Healthy controls made up of group 1 (n = 18), and group 2 (n = 18) included vaccinated pre-COVID-19 patients with one dose of the vaccine (5 clinically severe and 13 mild cases), group 3 (n=20) included vaccinated post-COVID-19 COVID-19 with one dose of the vaccine, group 4 (n=21) included healthy participants with one dose of the vaccine, and group 5 (n=11) included healthy participants with two doses of the vaccine.

Table 1. Demographic data of participants.

		Age		Gender	
	n	Mean ± SD	Range	Male	Female
Group 1	18	40.56 ± 11.00	21 - 65	5 (27.8%)	13 (72.2%)
Group 2	18	48.17 ± 13.91	32 - 87	12 (66.7%)	6 (33.3%)
Group 3	20	41.6 ± 6.32	28 - 52	3 (15%)	17 (85%)
Group 4	21	38 ± 8.54	26 – 53	4 (19%)	17 (81%)
Group 5	11	28.73 ± 4.92	23 - 37	2 (18.2%)	9 (81.8%)

Comparison of IgG and IgM levels pre and post COVID-19 vaccination:

In the study, there was an interest to examine levels of IgG and IgM in patients who received one dose of the vaccine before the onset of infection (group 2) or after they had been infected (group 3). As the pandemic spread, the government employed vaccination as a strategy to control COVID-19, aiming to vaccinate as many members of the community as possible. As people got the vaccine under different conditions (pre or post) infection, it was interesting to examine and compare levels of antibodies in people's serum. Looking at Figure 1. both IgG and IgM showed the same results, as there was a highly significant difference between the healthy control and group 2 vaccinated pre-COVID-19 group as $p \leq 0.0001$ and ≤ 0.01, respectively. In addition, a highly significant difference was recorded between pre- and post-COVID-19 vaccinated patients' groups 2 and 3 as $p \leq 0.0001$ for both IgG and IgM concentrations. Moreover, no significance was recorded between control and group 3 pointing to the effectiveness of the vaccine before infection on the levels of IgG and IgM.

Comparison IgG and IgM concentrations in healthy subjects receiving one and two doses vaccination:

The COVID-19 vaccination serves as a booster shot to ensure ongoing immunity for individuals. We examined the levels of IgG and IgM in the serum of healthy volunteers who received one or two doses, as shown in Figure 2. We collected the samples after 3 to 4 weeks of vaccination. IgG showed a highly significant difference between groups 4 and 5 ($p \leq 0.0001$) as individuals who received two doses showed higher levels of IgG compared to one dose group. On the other hand, there was no significant difference in the level of IgM between both groups.

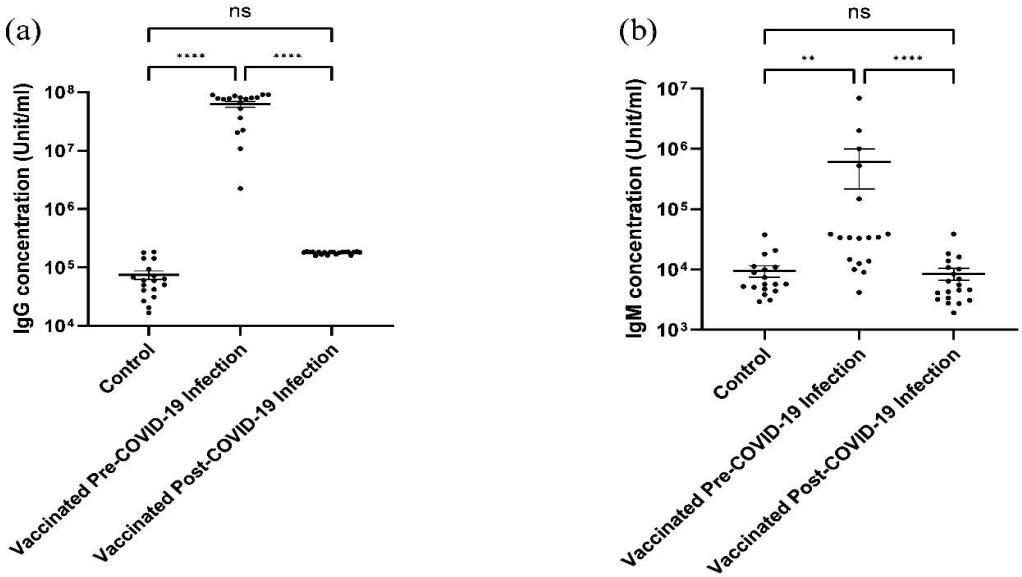

Figure 1. Comparison of IgG and IgM concentrations pre and post-infection. a) IgG levels compared between control (group 1), one dose vaccinated pre-COVID-19 infection (group 2), and one dose vaccinated post-COVID-19 infection (group 3). b) IgM levels compared between control (group 1), pre-COVID-19 one dose vaccinated (group 2), and post-COVID-19 one dose vaccinated (group 3). Data represent mean and SEM. * P-value < 0.05 is considered significant, ** P-value < 0.01 is considered very significant, *** P-value < 0.001, and **** P-value < 0.0001 are considered extremely significant.

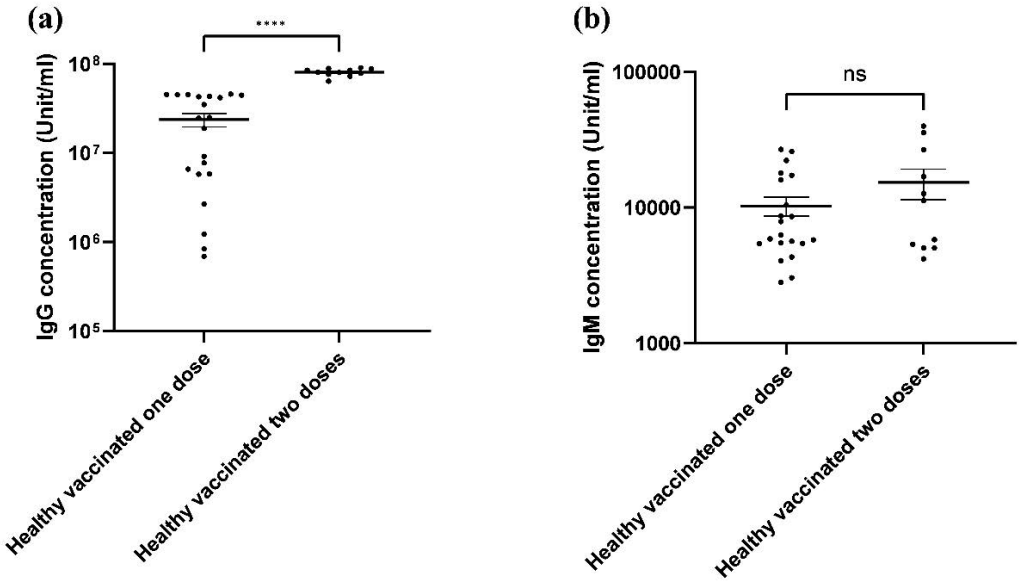

Figure 2 Comparison of IgG and IgM concentrations in healthy individuals receiving different vaccine doses. a) IgG levels compared between healthy vaccinated with one dose (group 4) and healthy vaccinated with two doses (group 5). b) IgM levels compared between healthy one dose vaccine (group 4) and healthy two doses vaccine (group 5). Data represent mean and SEM. * P-value < 0.05 is considered significant, ** P-value < 0.01 is considered very significant, *** P-value < 0.001, and **** P-value < 0.0001 are considered extremely significant.

Comparison of of IgG and IgM concentrations after receiving (BNT162b2) and (AZD1222) vaccines:

With the emergence of the COVID-19 infection, pharmacological companies raced to develop a vaccine and released it as an emergency solution passing all required trial phases for approval as the only solution available at the time. Both (BNT162b2) and (AZD1222) vaccines were the first vaccines approved and used in Saudi Arabia to minimize the spread of the viral infection. Levels of both IgG and IgM in different individuals received these two types of vaccine were examined in the current study. Among those vaccinated, 58.57% (n=41) received the mRNA vaccine (Pfizer BioNTech, BNT162b2), and 41.43% (n=29) obtained viral vector vaccine (Oxford–AstraZeneca, AZD1222) (Table 2).

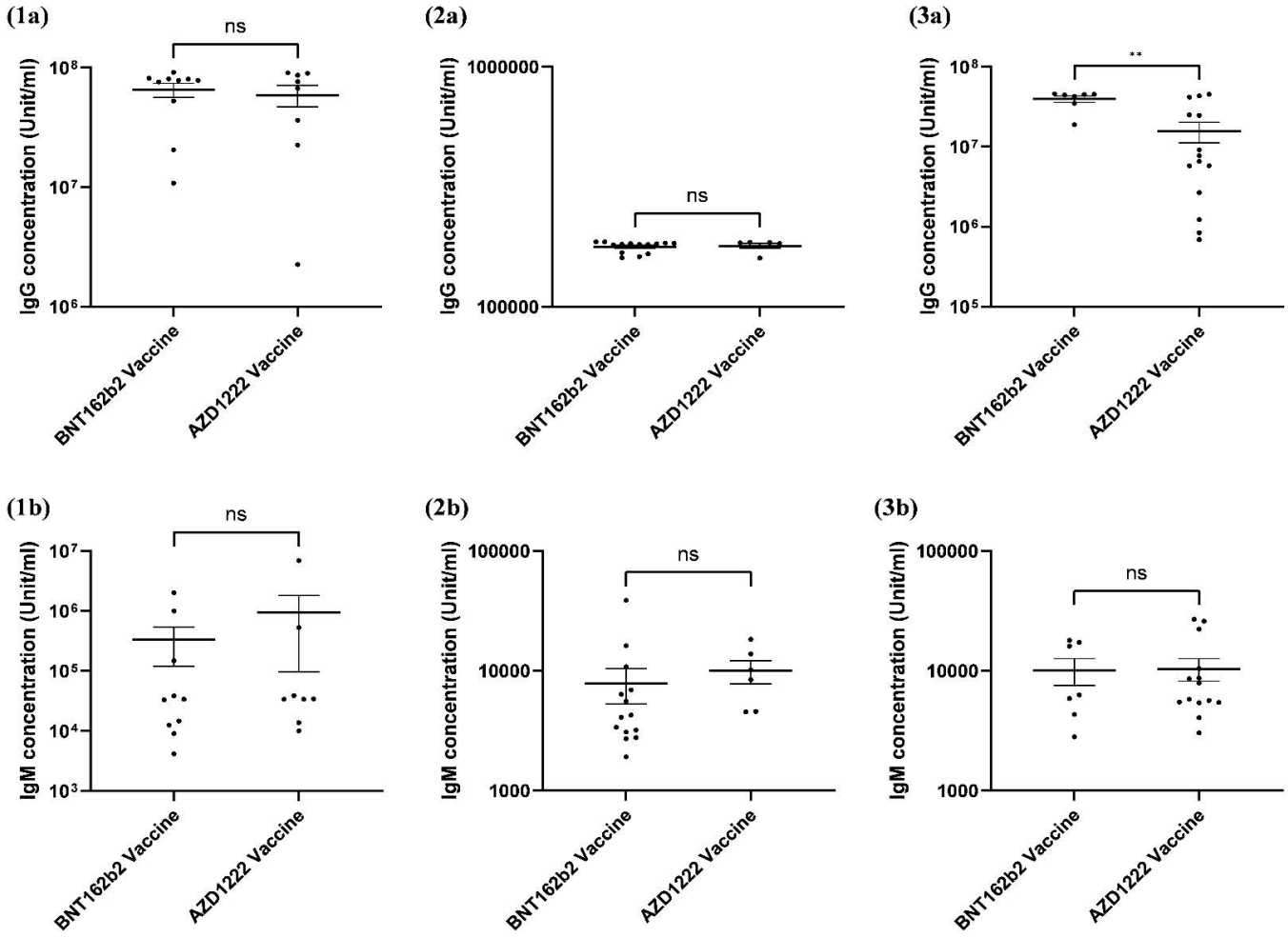

Figure 3. **Comparison of IgG and IgM levels in individuals received (BNT162b2) or (AZD1222) vaccines.** a) comparison of IgG levels after receiving BNT162b2 or AZD1222 vaccines in: (1a) vaccinated pre-COVID-19 infection (group2), (2a) vaccinated post-COVID-19 infection (group 3), and (3a) healthy one dose vaccinated (group 4). b) comparison of IgM levels after receiving BNT162b2 or AZD1222 vaccines in: (1b) vaccinated pre-COVID-19 infection (group 2), (2b) vaccinated post-COVID-19 infection (group 3), and (3b) healthy one dose vaccinated (group 4). Data represent mean and SEM. * P-value < 0.05 is considered significant, ** P-value < 0.01 is considered very significant, *** P-value < 0.001, and **** P-value < 0.0001 are considered extremely significant.

Table 2. Comparison of demographic data between two types of vaccine

	mRNA vaccine (BNT162b2)			Viral vector vaccine (AZD1222)		
	n	Age (Mean ± SD)	Gender	*n*	Age (Mean ± SD)	Gender
Group 2	10	48.30 ± 18.07	M=7, F=3	8	48 ± 7.05	M=5, F=3
Group 3	14	41.43 ± 6.32	M=3, F=11	6	42 ± 6.9	F=6
Group 4	7	35.57 ± 7.25	F =7	14	39.21 ± 9.13	M=4, F=10
Group 5	10	28.6 ± 5.17	M=2, F=8	1	30 ± 00	F=1

Looking into Figure 3. below, both IgG and IgM levels were compared in each group (group 2, group 3 and group 4) dividing the individuals as either BNT162b2 vaccinated or AZD1222 vaccinated. Healthy one dose vaccinated group showed significant difference as BNT162b2 group had higher IgG level compared to AZD1222. No differences were recorded to the other groups or in IgM concentration indicating that both vaccines were effective and increase the expression of measured antibodies to the same concentrations. Group 5 healthy two doses vaccinated data are not presented due to limited data availability.

DISCUSSION

Vaccination is one of the most effective ways to control pandemics and reduce complications. Knowledge around the antibody titer after vaccine doses can be used as an important indicator to evaluate the effectiveness of the vaccination in fighting infection [2]. SARS-Cov-2 spike proteins (S1and S2) reported to be the most subunits induced by the production of neutralizing antibodies, S2 is more conserved across coronaviruses, while S1 especially the receptor-binding domain (RBD) is less conserved [18]. In our study, we evaluated the titers of anti S1-IgG and IgM in sera from different vaccinated groups.

The presented results demonstrated that IgG and IgM were generally increased in vaccinated groups in comparison to healthy controls; these findings are in agreement with previous studies [19-21]. Antibody titer was high in one dose vaccinated pre-COVID-19 infection compared to vaccinated post-COVID-19 infection. During COVID-19 infection,

specific anti S1-IgG and IgM produced directly against the virus. High titers of antibodies in COVID-19 patients were found in previous studies [20,22,23]. In the current study, the lowest antibody titer was found in vaccinated post COVID-19 infection, which is contrasting others' findings. Tretyn et al. (2021) found that the titer of IgG after one dose of vaccine was higher in recovered COVID-19 individuals than those who had never been infected, thus suggesting that the first dose in this case has a similar effect of the boost dose [24]. This heterogeneity in antibody response might be relying on the long duration between recovery and receiving the vaccine, this may result in a defect in generating long-term protection during the previous infection due to the failure formation of germinal center (GC) as a result of the significant decrease in the T follicular helper cells (Th), thus a robust extrafollicular response rather than GC response, which is responsible for activating and developing long-lived memory and plasma B cells [13].

Healthy volunteers who received one or two doses of the available vaccines showed high levels of both IgG and IgM that increased with the second booster shot. Our findings are supported by those of Zurac et al. (2020) and Narasimhan et al. (2020) who showed a higher response in IgG and IgM after the booster dose than the first dose [21,25]. These findings suggested that two doses of the COVID-19 vaccine provide more effective protection against the infection than one dose. In addition, previous studies reported a decline in the IgG levels 6 months after the second dose of vaccinations, as the levels of IgG reached were like their levels 3 weeks after the first dose in participants with no prior COVID-19 infection [2,26]. Furthermore, Łysek et al. (2023) monitored IgG levels after the third dose, and they found that the levels of IgG were higher than 6 months after the second dose and last up to 6 months after the third dose [2]. These findings were in agreement with Cheng et al. (2022), Romero et al. (2021), and Zeng et al. These studies have shown that the third dose of the COVID-19 vaccine provides longer-lasting immune protection than the second dose [2,13,27,28].

The current study included 72.2% (n=13) of patients who had mild symptoms while 27.8% (n=5) were severe, which agrees with previous studies that showed proportions of hospitalization higher in unvaccinated patients than vaccinated with the Pfizer-BioNTech or Oxford-AstraZeneca COVID-19 vaccine [29,30]. Both types of vaccines proved to be effective in the same way regarding their effect on IgG and IgM concentrations. Studies have been visualizing the effect of different vaccines on immunity. One study, based on 365 vaccine recipients, demonstrated that the type of vaccine has a significant impact on post-vaccination anti-spike IgG responses. Moderna and BioNTech's mRNA vaccines produced the highest amount of spike-specific IgG and IgA antibodies, along with a high serum neutralization potential [31].

Comparatively, the DNA-vectored Sputnik-V and AstraZeneca vaccines generated comparable levels of SARS-CoV-2 specific IgG. Unexpectedly, the Sputnik-V group had more IgA expression than the AstraZeneca group did. However, both groups detected similar amounts of neutralizing antibodies. Sputnik-V and the AstraZeneca vaccination share significant conceptual and operational similarities, which can explain these results [31]. In addition, the antibodies produced by various people who get the Moderna (mRNA-1273) or Pfizer-BioNTech (BNT162b2) vaccinations are quite similar and closely comparable [32].

This is a single center study which restrict the generalizability of the study findings. The cross-sectional nature of the study design restricts the ability to examine causality among the study variables. Therefore, the study findings should be interpreted carefully.

Future longitudinal studies are required to assess the immune response across the time. Analysis of study samples in future studies is recommended to be conducted across different time points (1,3, and 6 months after vaccination).

CONCLUSION

This study provides valuable data on humoral immunity response to SARS-CoV-2. Both IgG and IgM concentrations increased as a response to the vaccine, and those vaccinated with a booster dose showed a higher elevation. Patients who had been vaccinated prior to COVID-19 had higher levels of antibodies and tended to have mild symptoms after infection. Although our study evaluating the IgG and IgM levels was limited to 3-4 weeks after the second dose, it interestingly showed that different vaccinated groups may have contributed to evaluating the effectiveness of the COVID-19 vaccine. Therefore, booster vaccinations appear to improve stimulation of the immune memory, and the IgG level increased dramatically after the second vaccination dose. Finally, both BNT162b2 and AZD1222 are effective in boosting immunity, but their side effects need more studies in the long term.

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Ethical approval and Informed Consent: The Institutional Review Board (IRB) of the Research and Studies Department—Jeddah Health Affairs, registration number KACST, KSA: H-02-J-002 research number 1373 was obtained. Informed consent was obtained from all subjects involved in the study.

Potential Conflict of Interest: None

Competing Interest: None

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