ORIGINAL RESEARCH

The Influence of Two Priming Doses of Different Anti-COVID-19 Vaccines on the Production of Anti-SARS-CoV-2 Antibodies After the Administration of the Pfizer/BioNTech Booster

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Introduction: A global vaccination program was implemented in late 2020 to end the pandemic caused by the SARS-CoV-2 virus. However, the immune response elicited by the vaccines proved to be insufficient due to the rapid emergence of new viral mutations. Therefore, the factors influencing cellular and humoral immune responses after the administration of different vaccines against SARS-CoV2 need to be identified.

Materials: In the present study, anti-SARS-CoV-2 antibody titers were analyzed 20 to 50 days after the administration of a third (booster) dose of the BNT162b2 vaccine in 192 residents of the city of Olsztyn (Poland) primed with two AstraZeneca or Pfizer/BioNTech vaccines.

Methods: Antibody titers were determined in venous blood serum in the ECLIA test using the Cobas e411 Roche analyzer.

Results: The study revealed that persons who received three doses of the Pfizer/BioNTech vaccine had significantly higher antibody titers than those who received two doses of AstraZeneca and a booster dose of Pfizer/BioNTech.

Keywords: vaccination, COVID-19, BNT162b2, ChAdOx1, anti-SARS-CoV-2

Introduction

According to the latest available data (late July 2022), the severe acute respiratory syndrome coronavirus (SARS-CoV-2) caused more than 572 million confirmed cases of COVID-19 and caused more than 6.39 million deaths around the world.[1] The virus is known to be acquired from zoonotic source and mainly spreads airborne through direct and contact transmission.[2] Since the beginning of the pandemic, SARS-CoV-2 has undergone numerous genetic and antigen mutations. The most prevalent and best researched mutations include the Alpha (B. 1. 1. 7/20I/N501Y. V1), Beta (B. 1. 351/20H/N501Y. V2), Gamma (B. 1. 1. 28. P1/P. 1/20J/N501Y. V3), Delta (B. 1. 617. 2/21A), and Omicron (B. 1. 1. 529/21K/BA. 1) variants. Several vaccines have been developed to protect against COVID-19 and decrease the risk of severe illness and death.[3] The vaccines manufactured by Oxford/AstraZeneca (ChAdOx1) and Pfizer–BioNTech (BNT162b2) were most popular in Europe. In early studies evaluating the efficacy of these vaccine brands, the BNT162b2 mRNA vaccine demonstrated >90% efficacy, whereas the AstraZeneca AZD1222 vaccine containing the adenovirus vector demonstrated 60–70% efficacy against symptomatic infections.[4–7]

Clinical study reports have shown that both vaccines were characterized by high safety and high immunogenicity. However, very few studies have directly compared the efficacy of these vaccines. According to many authors, the effectiveness of immunization is determined not only by vaccine type but also by the patient's age and gender.[8] A number of studies

performed on the elderly population, which is at highest risk of serious complications from COVID-19, revealed that vaccine-induced immunity is insufficient to confer full protection against infections caused by SARS-CoV-2.[4,9] Studies show that older people and women comply more closely with the pandemic guidelines.[10] The protective effect of certain medicinal products (including statins) should be considered in high-risk patients.[11]

Numerous studies have confirmed that the protection conferred by two doses of the vaccine against COVID-19 (symptomatic and asymptomatic infections) wanes over time. Despite the above, two vaccine doses still effectively protect against severe COVID-19 infections and death all over the world.[8,9,12] In Poland, the booster dose campaign began in September 2021 to maintain a high level of protection in the population at the greatest risk of severe complications from COVID-19 (elderly persons, persons with comorbidities, health care employees), and the booster dose became available to the general population in November 2021.[13] Only Pfizer/BioNTech and Moderna vaccines were authorized for use as boosters. A booster dose of the AstraZeneca vaccine was not available.

The entire world is still experiencing the COVID-19 pandemic, which is why the efficacy of anti-SARS-CoV-2 vaccines should be monitored in patients with a history of COVID-19 as well as in individuals who received different vaccines. Anti-SARS-CoV-2 antibody titers are a reliable indicator of vaccine efficacy.[14] In this study, anti-SARS-CoV-2 antibody titers were evaluated after the administration of the BNT162b2 booster dose in individuals who had been primed with different vaccines and differed in age, gender, BMI, comorbidities, and history of COVID-19.

Materials and Methods
Study Population
The study involved 192 residents of the city of Olsztyn (Poland) aged 23–77, of both sexes. The inclusion criterion was vaccination with two doses of BNT162B2 or ChAdOx1-S in the second quarter of 2021, followed by a booster dose of BNT162b2 between 15 December 2021 and 15 January 2022. The exclusion criterion was vaccination at least one dose outside the stated period. The studied population was divided into two groups: persons who were primed with two doses of BNT162B2 and persons who were primed with two doses of ChAdOx1-S.

All participants provided the following information in the survey questionnaire: the date of second and the third vaccine dose, side effects after vaccination, and comorbidities. Then, the two groups were divided into subgroups based on gender (male, female), age (≤50, >50 years), BMI (≤24.9, >24.9 kg/m^2), comorbidities (absent, present), and side effects after vaccination (side effects, no side effects). All participants gave their written consent to participate in the study and have blood samples taken.

Blood samples for analyses of antibody titers were collected between 1 and 4 February 2022, ie, 20 to 50 days after the administration of the BNT162B2 booster. Blood was collected into Vacutainer tubes for serum separation by centrifugation (red stopper). Blood was centrifuged for 10 minutes at 2000 × g at room temperature. The serum was separated and stored at −2°C to −8°C until analysis.

Method of Determining Antibody Levels
The Elecsys anti-SARS-CoV-2 S test (Roche S-RBD tAb) was used to assess total anti-SARS-CoV-2 S antibody levels. This test is based on the electrochemiluminescence immunoassay (ECLIA) which is used for in vitro quantitative determination of total antibodies (IgG/IgA/IgM) against the SARS-CoV-2 S-RBD protein in the human serum. The assay was conducted with the use of the fully automated Roche Cobas E411 analyzer (Roche Diagnostics). The ECLIA test is a three-step procedure that uses a recombinant protein representing the receptor binding domain (RBD) of the S antigen in a double-antigen assay format and favors the detection of high-affinity antibodies against SARS-CoV-2. Serum samples are incubated with a mix of biotinylated and ruthenylated RBD antigens to produce double antigen immune-complexes. Streptavidin-coated microparticles are then added, and DAGS complexes bind to the solid phase. The reagent mixture is transferred to the measuring cell where the microparticles are magnetically captured. Electrochemiluminescence is initiated by applying voltage, and it is measured with a photomultiplier. Signal yield increases with the antibody titer. The test has a measuring range of 0.40–250 U/mL (up to 25,000 U/mL in a 1:100 dilution), and concentrations below 0.80 U/mL are regarded as negative, whereas concentrations of ≥0.80 U/mL are regarded as positive.[15]

Statistical Analysis

Data were processed statistically in GraphPad Prism 8.4.3 for Windows (GraphPad Software, La Jolla, USA). The distribution of results was analyzed by the Shapiro–Wilk test. Student's *t*-test was used to determine the normality of distribution, and the Mann–Whitney *U*-test was used to compare data without normal distribution. The results were presented as median values (minimum – maximum). Statistical significance was established at $p < 0.05$. Spearman correlation coefficient was used to evaluate the relationships between total anti-SARS-CoV-2 S antibodies levels and clinical-demographic parameters describing the study group.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Warmian-Masurian Medical Chamber in Olsztyn (protocol code 36/2021/VIII; 8 November 2021).

Results

Characteristics of the Study Group

The study involved 192 people who received three doses of the anti-SARS-CoV-2 vaccine. The evaluated population was divided into two groups: persons who received three doses of the Pfizer vaccine (59%) and persons who received two doses of the AstraZeneca vaccine and a Pfizer booster dose (41%). In both groups, most participants were women (84%, 57%), persons older than 50 years (66%, 51%), and persons with history of COVID-19 (60%, 57%). Detailed characteristics of both study groups are presented in Table 1.

Comparison of Total Anti-SARS-CoV-2 Antibodies Level Depending on the Sex, Age, BMI, Coexisting Diseases, Post-Vaccination Symptoms and History of COVID-19 in Group of People Who Were Primed with Two Doses of BNT162B2 or ChAdOx1-S

In both groups, total anti-SARS-CoV-2 antibody levels were higher in patients who received Pfizer than AstraZeneca vaccines. Total anti-SARS-CoV-2 antibody titers were higher in women who received Pfizer vaccines than in women

Table 1 Characteristics of Study Group

Parameter	Number of Persons (%) Who Were Primed with Two Doses of BNT162B2 (n=114)	Number of Persons (%) Who Were Primed with Two Doses of ChAdOx1-S (n=78)
Age, years		
≤50	48 (42%)	27 (31%)
>50	66 (58%)	51 (69%)
Sex		
Female	84 (74%)	57 (73%)
Male	30 (26%)	21(27%)
History of COVID-19		
Present	60 (53%)	57 (73%)
Absent	54 (47%)	21(27%)
BMI, kg/m^2		
≤ 24.9	66 (58%)	30 (38%)
>24.9	48 (42%)	48 (62%)

(*Continued*)

Table 1 (Continued).

Parameter	Number of Persons (%) Who Were Primed with Two Doses of BNT162B2 (n=114)	Number of Persons (%) Who Were Primed with Two Doses of ChAdOx1-S (n=78)
Other diseases		
Present	69 (60%)	48 (62%)
Absent	45 (40%)	30 (38%)
Post-vaccination symptoms		
Present	57 (50%)	51 (65%)
Absent	57 (50%)	27 (35%)

who received AstraZeneca vaccines (p=0.0111). In patients both younger (p=0.0189) and older than 50 years, anti-SARS-CoV-2 antibody titers were higher (p=0.0495) after Pfizer than AstraZeneca vaccination. Total anti-SARS-CoV-2 antibody levels were significantly higher in patients with normal BMI after Pfizer than AstraZeneca vaccination (p=0.0375). Patients with side effects from vaccination (p=0.0434) and a history of COVID-19 (p=0.0400) had much higher total anti-SARS-CoV-2 antibody titers after receiving the Pfizer vaccine than the AstraZeneca vaccine. In patients with comorbidities, total anti-SARS-CoV-2 antibody levels were significantly after Pfizer vaccination than AstraZeneca vaccination (p=0.0059). All results are shown in Table 2 and Figure 1.

Table 2 Comparisions of Results Anti-SARS-CoV-2S Antibodies Concentration in Both Group of Residents with p value

Parameter	Persons Who Were Primed with Two Doses of BNT162B2 (n=114)			Persons Who Were Primed with Two Doses of ChAdOx1-S (n=78)			p value
	Median	Q1	Q3	Median	Q1	Q3	
Age, years							
≤50	14,795	11,231	19,656	10,368	8501	13,047	0.0189
>50	17,278	11,384	24,791	11,325	8659	18,983	0.0495
Sex							
Female	17,154	11,605	23,436	11,305	9434	18,983	0.0111
Male	12,946	10,195	18,891	12,986	4035	18,965	0.8868
History of COVID-19							
Present	14,415	11,126	23,436	11,117	7568	14,644	0.0400
Absent	17,154	12,620	22,284	17,712	11,325	23,879	0.8476
BMI, kg/m^2							
≤24.9	17,154	12,620	24,639	13,047	8968	19,146	0.0375
>24.9	14,415	10,467	19,656	11,216	9086	16,591	0.5455
Other diseases							
Present	16,710	11,461	24,639	10,840	8035	16,146	0.0059

(*Continued*)

Table 2 (Continued).

Parameter	Persons Who Were Primed with Two Doses of BNT162B2 (n=114)			Persons Who Were Primed with Two Doses of ChAdOx1-S (n=78)			p value
	Median	**Q1**	**Q3**	**Median**	**Q1**	**Q3**	
Absent	16,676	10,504	21,786	13,936	10,510	19,745	0.9012
Post-vaccination symptoms							
Present	15,637	12,038	21,499	11,325	9147	16,805	0.0434
Absent	16,923	11,151	23,986	11,305	6591	19,309	0.1683

Correlation of Total Anti-SARS-CoV2 Antibodies in Patients After Pfizer Vaccination with Chosen Clinical Parameters

A positive correlation was also observed between total anti-SARS-CoV2 antibody levels and the patients' age (p=0.012) Figure 2.

Correlation of Total Anti-SARS-CoV2 Antibodies After AstraZeneca Vaccination with Chosen Clinical Parameters

A negative correlation was noted between total anti-SARS-CoV2 antibody levels and a history of COVID-19 (p = 0.031) Figure 3.

Multiple Regression Analysis

In order to find a relationship between level of anti-SARS-CoV-2S antibodies to the patient's age, gender and the presence of coexistence diseases we developed multiple linear regression models. Multiple regression analysis showed that the kind of vaccine was associated with the higher level of antibodies (p < 0.001). Moreover, we did not observe association between age (p = 0.5405), gender (p=0.4286) and coexistence diseases (p = 0.9588) to the concentration of antibodies (Table 3).

Discussion

The role of anti-SARS-CoV-2 antibody levels changed since the beginning of the COVID-19 pandemic. At present, antibody titers are not only regarded as indicators of humoral immunity but also used to diagnose infections and perform epidemiological evaluations.[16] Antibody levels in the blood provide information about the immune response to stimulation with the pathogenic antigen both during infection and after vaccination. After vaccination or infection, antibody levels may wane over time, but the number of memory cells that rapidly induce the production of antibodies after repeated contact with the pathogen remains unchanged.[17] Research into the immune response to the SARS-CoV-2 infection has demonstrated that antibodies targeting the spike (S) protein of SARS-CoV-2 play a key role in protection against the virus.[18] In patients with a history of COVID-19, those antibodies persist in the blood for longer than antibodies targeting the nucleocapsid (N) protein of SARS-CoV-2. It should be noted that all vaccines authorized for use in Europe (Pfizer/BioNTech, Moderna, AstraZeneca) rely on the S protein of SARS-CoV-2.[19]

The Elecsys test quantifies antibodies targeting the S protein of SARS-CoV-2 which are able to neutralize the virus.[15] Research has demonstrated that a positive result of the antibody test was correlated with a positive result of a microneutralization assay which assesses the immune response, ie, the extent to which antibodies are able to neutralize the virus.[20,21] In the literature, post-vaccination antibody responses were compared after the administration of one dose and two doses of different vaccines against SARS-CoV-2 (AstraZeneca, Pfizer/BioNTech, Moderna). However, very few studies have analyzed differences in anti-SARS-CoV-2 antibody levels after the administration of three doses of different
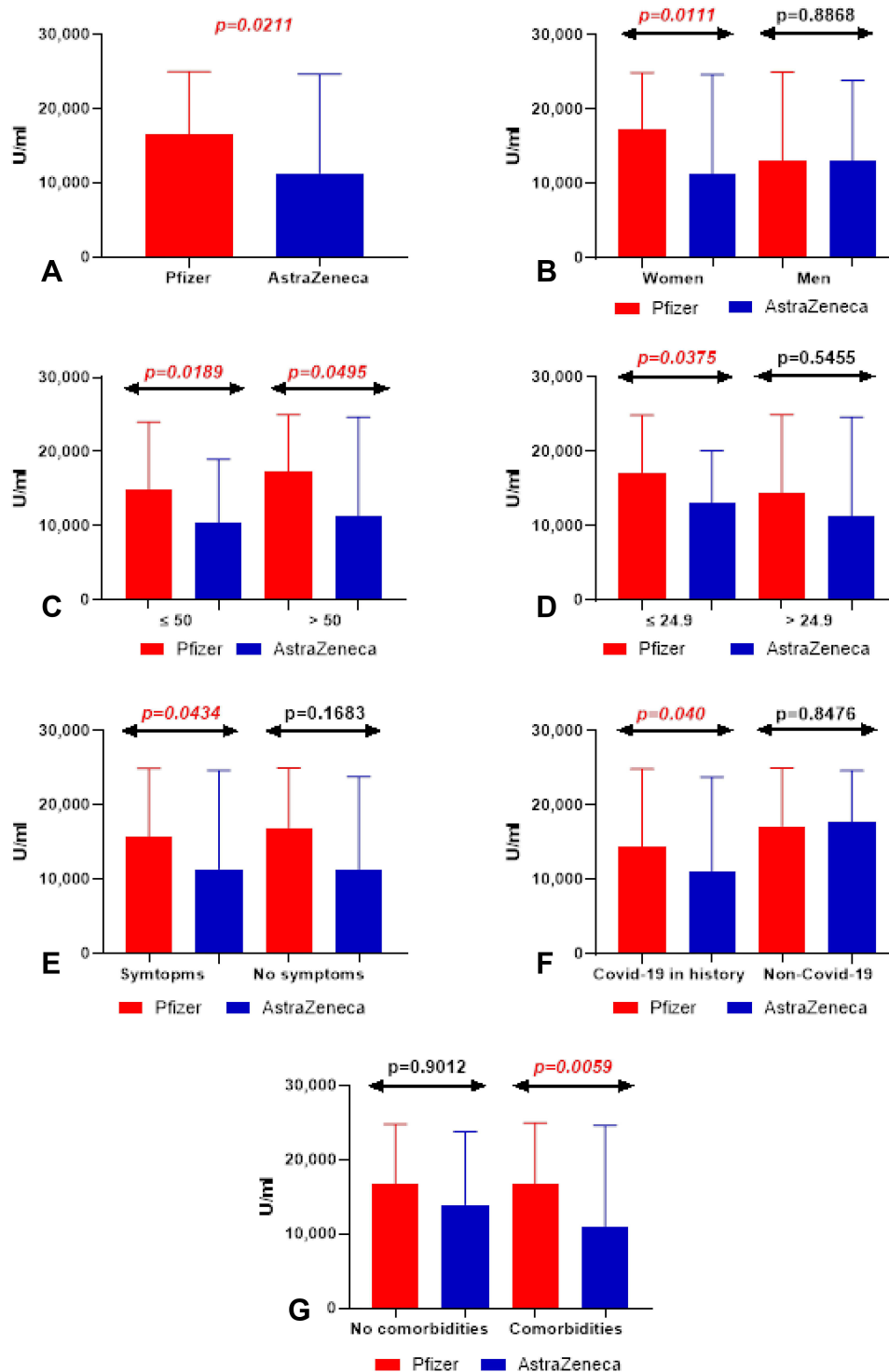
Figure 1 (**A**) Comparison of total anti-SARS-CoV-2 antibodies level between patients after Pfizer and AstraZeneca vaccination. The data are presented as median (minimum - maximum). (**B**) Comparison of total anti-SARS-CoV-2 antibodies level in groups of women and men after Pfizer and AstraZeneca vaccination. The data are presented as median (minimum - maximum). (**C**) Comparison of total anti-SARS-CoV-2 antibodies level in groups of patients before and after the age of 50 after Pfizer and AstraZeneca vaccination. The data are presented as median (minimum - maximum). (**D**) Comparison of total anti-SARS-CoV-2 antibodies level in groups of patients with normal and increased BMI after Pfizer and AstraZeneca vaccination. The data are presented as median (minimum - maximum). (**E**) Comparison of total anti-SARS-CoV-2 antibodies level in groups of patients with and no post-vaccination symptoms after Pfizer and AstraZeneca vaccination. The data are presented as median (minimum - maximum). (**F**) Comparison of total anti-SARS-CoV-2 antibodies level in groups of patients with and without history of COVID 19 after Pfizer and AstraZeneca vaccination. The data are presented as median (minimum - maximum). (**G**) Comparison of total anti-SARS-CoV-2 antibodies level in groups of patients with and without coexisting diseases after Pfizer and AstraZeneca vaccination. The data are presented as median (minimum - maximum).
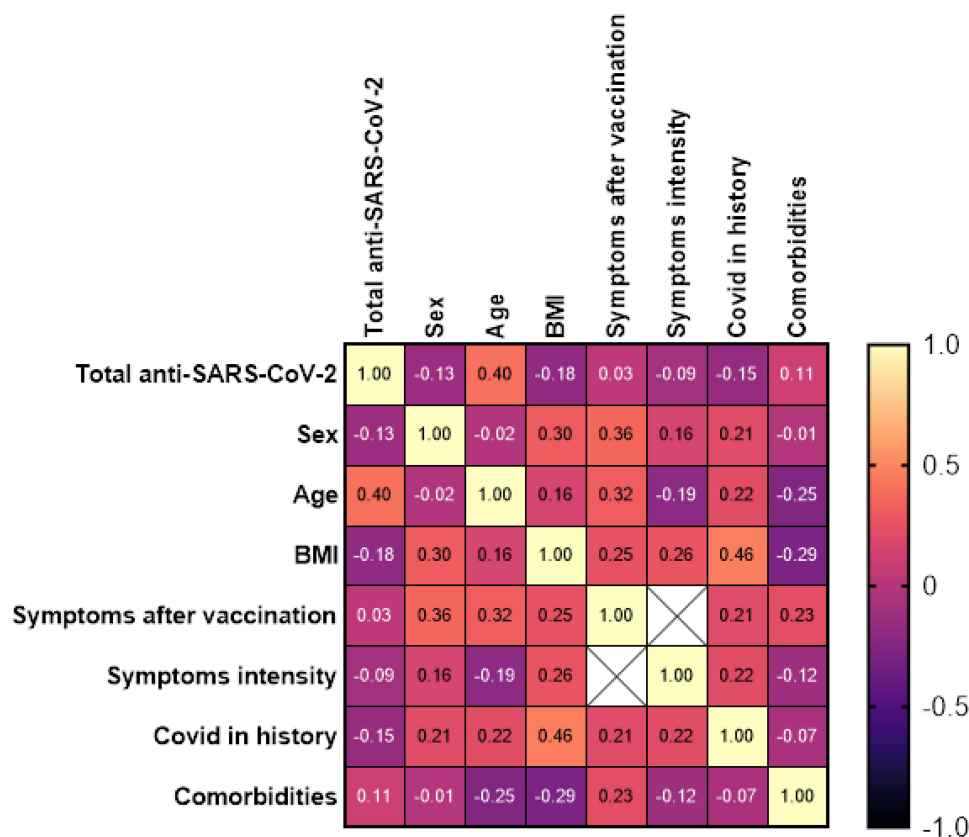
Figure 2 Heat map of correlation of total anti-SARS-CoV2 antibodies in patients after Pfizer vaccination with chosen clinical parameters.

vaccines. A cohort study conducted by Munro et al produced highly important findings. The cited authors analyzed seven different vaccines that have been authorized for use as boosters after two priming doses of BNT162b2 or ChAdOx1. Each booster produced a satisfactory humoral immune response, and the noted differences were not significant.[22] Most researchers evaluated changes in antibody levels after the administration of the same vaccine, and a similar analysis was conducted in our previous studies.[23,24]

Hillus et al compared immune responses after the administration of two doses of the AstraZeneca vaccine, two doses of the Pfizer/BioNTech vaccine, and a mixed AstraZeneca and Pfizer/BioNTech vaccine schedule. They found that heterologous immunization produced a stronger humoral immune response, expressed by higher antibody titers, than homologous immunization.[25] Similar observations were made by Groß et al[26] and Rose et al[27] who reported higher humoral immune responses after mixed vaccine regimens than those noted in this study. However, the cited authors evaluated patients who received two, rather than three doses of the vaccine, as in the present study. Soytas et al demonstrated that a BNT162b2 booster after two priming doses of ChAdOx1 elicited a stronger humoral immune response than three doses of ChAdOx1.[28] Keskin et al recommended BNT162b2 as a booster after two priming doses of CoronaVac.[29]

Atmar et al compared immune responses after mRNA-1273 (Moderna), Ad26.COV2.S (Johnson & Johnson–Janssen), and BNT162b2 (Pfizer/BioNTech) boosters administered in various combinations after two priming doses of the same vaccine brands. They found that heterologous boosters were more effective than homologous boosters.[30] However, the cited authors did not evaluate the AstraZeneca vaccine which was compared with the Pfizer/BioNTech vaccine in the current study. Faustini et al found that immunity against SARS-CoV-2 is determined not only by the type of vaccine but also by viral mutations. The group administered BNT162b2 as a booster following two priming doses of the same vaccine had a stronger immune response against the Omicron variant that persons who received two doses of AstraZeneca, followed by a Pfizer/BioNTech booster. In turn, three doses of Pfizer/BioNTech were less effective against the Delta variant that two doses of AstraZeneca, followed by a Pfizer/BioNTech booster.[31]
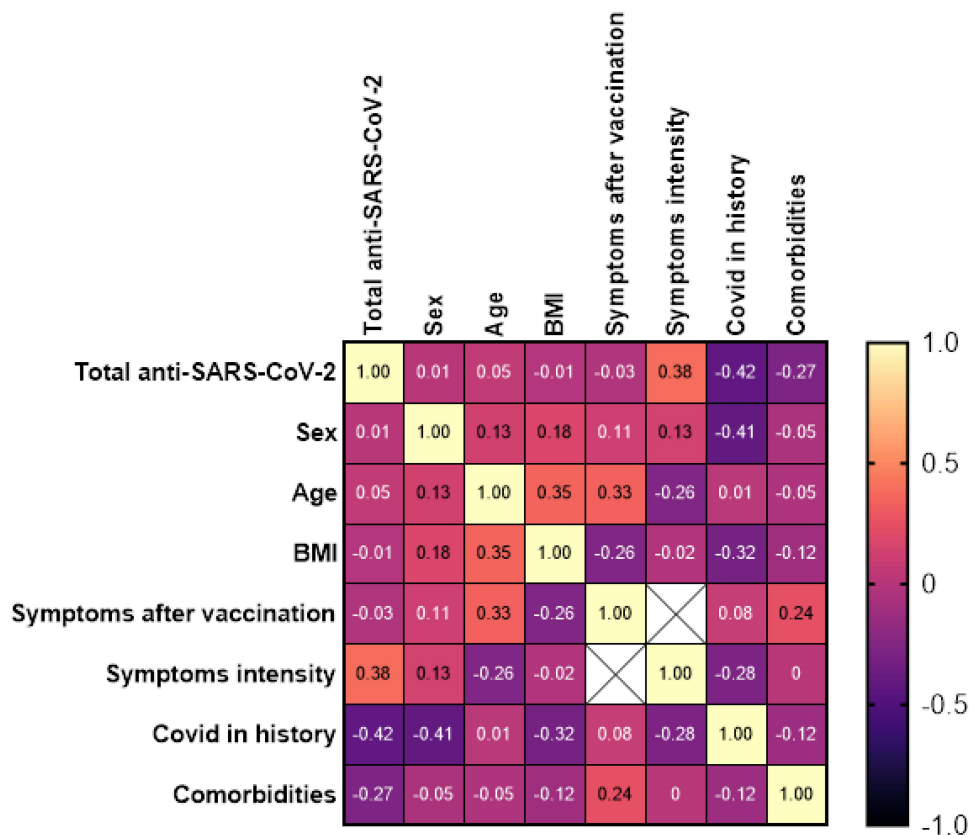
Figure 3 Heat map of correlation of total anti-SARS-CoV2 antibodies after AstraZeneca vaccination with chosen clinical parameters.

The results of this study indicate that persons primed with AstraZeneca produced significantly fewer antibodies after a Pfizer/BioNTech booster than patients who received three Pfizer/BioNTech doses. Despite the fact that antibody levels were not assessed after two vaccine doses, our results seem to confirm the observations made by Aldridge et al[32] who found that two priming doses of Pfizer/BioNTech produced significantly more anti-SARS-CoV-2 antibodies than two priming doses of AstraZeneca 21 days (antibody levels were more than ninefold higher) and 3 months (antibody levels were more than fivefold higher) after vaccination. Other researchers also reported that Pfizer/BioNTech elicited a stronger humoral immune response than AstraZeneca on the same days post vaccination.[6,33–36]

The side effects of anti-SARS-CoV-2 vaccines were also described in the literature. The most common side effects include pain at the injection site, fever, and fatigue. In the current study, side effects were significantly more prevalent in patients subjected to the heterologous rather than the homologous vaccine schedule. The relevant results were reported by Shaw.[37]

Table 3 Multiple Regression Analysis of the Level of Anti-SARS-CoV-2S Antibodies

Parameter	Anti- SARS-CoV-2s Antibodies		
	Estimate	95% CI	P value
Sex	−1562	−5485 to 2362	0.4286
Age	1090	−2456 to 4636	0.5405
Coexistence diseases	94,92	−3574 to 3764	0.9588
Vaccine type	−3582	−7086 to −78,62	0.0452

Interesting observations were made by Munro[22] who compared the prevalence of side effects 7 days after the administration of different vaccines as boosters. Moderate or severe side effects were reported in patients who received the AstraZeneca booster after two doses of Pfizer/BioNTech, Moderna (m1273) or Curevac (CVn) boosters after two doses of AstraZeneca, and Pfizer/BioNTech after two doses of AstraZeneca. The last combination produced the same results to those noted in our study, and the results generated by the remaining schedules were similar to those reported by other researchers.[30,38–40]

The humoral immune response can also be affected by other factors, including age, gender, or history of COVID-19. In the present study, anti-SARS-CoV-2 antibody levels were higher in women than in men after the homologous regimen. Similar observations were made by other authors.[41,42] Our previous research revealed that antibody titers after two and three vaccines were higher in patients with a history of COVID-19,[23] and similar findings were reported by other authors.[31,43] However, in the present study, anti-SARS-CoV-2 antibody levels were higher in patients without a history of COVID-19 in both groups. These findings could be attributed to the fact that many individuals have asymptomatic infections and are unaware of their infection status. Our previous study analyzed health care employees who are more likely to undergo a test when they develop symptoms or after they had contact with an infected person, even if they are asymptomatic.

A quantitative anti-SARS-CoV-2 antibody test is a highly helpful in planning the anti-COVID-19 vaccine schedule. In addition to patient interviews, the results of an antibody test provide valuable information about factors that can confer protection against SARS-CoV-2. In view of the rapid emergence of new viral mutations, any information that can help contain COVID-19 is invaluable.

Conclusions

In conclusion, this study demonstrated that a homologous vaccine schedule comprising three Pfizer/BioNTech doses elicits a stronger humoral immune response than a mixed schedule composed of two AstraZeneca doses and a booster dose of Pfizer/BioNTech.

Data Sharing Statement

The full data presented in this study are available on request from the corresponding author.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Warmian-Masurian Medical Chamber in Olsztyn (protocol code 36/2021/VIII; 8 November 2021).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

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Author Contributions

Conceptualization, B.W.-B. and A.B.; methodology, B.W.-B.; software, G.B.; validation, B.W.-B., A.B. and J.D.; formal analysis, B.W.-B.; investigation, A.B.; resources, B.W.-B.; data curation, G.B.; writing—original draft preparation, B.W.-B.; writing—review and editing, B.W.-B. and J.D.; visualization, B.W.-B.; supervision, J.D.; project administration, E.S.-F.; funding acquisition, A.B. All authors have read and agreed to the published version of the manuscript.

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Disclosure
The authors declare no conflict of interest.

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