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MOLECULAR AND EXPERIMENTAL BIOLOGY IN MEDICINE

ORIGINAL ARTICLE

COMPARISON BETWEEN THE HOMOLOGOUS BNT162b2 AND THE HETEROLOGOUS Gam-COVID-Vac/BNT162b2 VACCINE REGIMEN IN REPUBLIC OF NORTH MACEDONIA

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Abstract: The medical and socio-economic consequences that stemmed from the COVID-19 pandemic, forced the healthcare policymakers in Republic of North Macedonia to rely on five different vaccines against the SARS-CoV-2 virus, in order to reach a satisfactory level of herd immunity. It is here where we got the idea to compare the heterologous Gam-COVID-Vac/BNT162b2 regimen to the homologous BNT162b2 regimen, with our main focus being the immunogenicity differences between the two of them. Additionally, we researched the variation in humoral immune response relative to age strata; the reactogenicity differences; and discrepancies in SARS-CoV-2 infection incidence between the two regimens. To achieve this, antibody titers in sera samples from fifty-three (53) healthcare workers, divided in heterologous and homologous group, were analysed at six different time checkpoints. Our results showed robust immunogenic response after the administration of the booster dose (4. 2-fold increase in antibody titers), followed by a slower-waning humoral immune protection in the heterologous regimen, compared to the homologous BNT162b2 schedule, furthermore confirmed by non-inferiority testing (Geometric Mean Ratio=0,98) at the final checkpoint. That, coupled with the similar reactogenicity (p=0,767) of both regimens, imply that the Gam-COVID-Vac/BNT162b2 combination might be a feasible approach in the effort to contain the COVID-19 pandemic.

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Submitted: November, 2022
Accepted: December, 2022

Key words: SARS-CoV-2, COVID-19, heterologous vaccination, "mix-and-match" principle, Gam-COVID-Vac, BNT162b2

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogen responsible for the Coronavirus Disease 2019 (COVID-19) pandemic, that has resulted in more than 636 million cases and over 6.6 million deaths globally (until the day of writing, 25.11.2022).[1] The SARS-CoV-2 is a positive-sense, single-strand RNA virus that has four structural proteins: the spike (S), envelope (E), membrane (M), and nucleocapsid (N) protein. The spike (S) glycoprotein is a class I fusion protein that has two regions: S1 and S2. The S1 subunit contains the Receptor Binding Domain (RBD) that binds to the Angiotensin-Converting Enzyme 2 (ACE-2) molecule on the host's cell, while the S2 subunit contains the fusion peptide.[2] The S-protein is highly immunogenic, instigating a robust immune response in the event of a viral infection in an individual. The humoral aspect of this response is in part, characterized by the production of neutralizing antibodies that prevent viral entrance in the host's cells. Hence, eliciting high titers of neutralizing antibodies by means of active immunization is the aim of different vaccine development strategies.[3] Furthermore, analysis of these RBD-specific antibody titers is a method of assessing the humoral immune response.[4]

Human-to-human transmission through respiratory droplets has enabled this virus to cause the largest pandemic in the last century. That, coupled with the economic difficulties that followed the nation-wide lockdowns, put the world's research capacities in a race to create a safe and effective vaccine as a mean of prevention. At the end of 2020, the Pfizer-BioNTech

BNT162b2 vaccine received the first authorization for emergency use from the Food and Drug Administration (FDA).[5] Today, out of the several dozens of vaccines against the SARS-CoV-2, developed with different platforms, North Macedonia is using five of them, described in detail in Table 1. Health officials who faced delays and unpredictability of vaccine supplies throughout last year, advocated for using the vaccine that was available at a given period, instead of waiting for enough supplies of one vaccine type, which could postpone the achievement of herd immunity.

Using many vaccines, developed with different technologies, has presented us the unique opportunity to apply the "mix-and-match" principle in the immunization against the SARS-CoV-2. This concept, also known as a heterologous vaccination, can be defined as immunization with two doses of different vaccines or different prime-boost schedules.[6] It has previously been used in pre-clinical and clinical trials of vaccination strategies against several pathogens: Ebola virus, Human immunodeficiency virus, malaria, tuberculosis, influenza and hepatitis B.[7] The disparity in vaccine equity and the delay in supplies regarding the vaccines against SARS-CoV-2, has again put the 'mix-and-match' principle in the focus of researchers and governing bodies alike. Another possible indication for the heterologous vaccine regimen is observed on an individual level: after a serious adverse reaction, like anaphylaxis, is reported following the primary immunization, the boosting should be conducted using a different vaccine. In the case of COVID-19, reports linked the adenoviral vector vaccines ChAdOx1[8] and Ad26.COV2.S[9] to the rare vaccine-induced thrombotic thrombocytopenia (VITT) and subsequently, even cerebral venous sinus thrombosis. Regulatory officials proposed raising the age limit for the administration of these vaccines and advised those who already completed the primary immunization schedule, to receive a different type of vaccine as a booster.[10] Therefore, most of the studies in the literature analyzing the 'mix-and-match' principle in COVID-19 vaccination are focusing on the ChAdOx1/BNT162b2 schedule. Articles researching regimens combining other vaccines are scarcer, but systematic reviews of most of the studies available are reaching similar conclusions.[7, 11-13] Immunogenicity of the heterologous regimens are comparable or even more robust than the homologous; and while the reactogenicity can be stronger, it is still well-tolerated; in addition, the flexibility of the heterologous regimens mitigates the logistical challenges that make the homologous vaccine schedules more fluctuating. To our knowledge, there have been little to no studies, whose focus is the Gam-COVID-Vac/BNT162b2 vaccine regimen and there have not been studies analysing the 'mix-and-match' principle in COVID-19 immunization in North Macedonia.

In this study, the primary aim was to compare the titers of neutralizing antibodies against the receptor-binding domain of SARS-CoV-2, elicited after the application of the heterologous Gam-COVID-Vac/BNT162b2 versus the homologous BNT162b2 vaccine regimen. The secondary objective was to assess immunogenicity in different age strata from our cohort. Furthermore, we defined two exploratory objectives: to estimate the frequency of possible side effects after both regimens and to establish potential differences in the incidence of SARS-CoV-2 infection between both vaccine schedules.

Table 1. Vaccines approved and used in Republic of North Macedonia

Name of vaccine	Type of vaccine	Manufacturer	Recommended age	Dosage
BNT162b2	mRNA	Pfizer-BionTech	>12 years	two doses, 21 days between
Gam-COVID-Vac	Adeno-viral vector	Gamelaya	>18 years	two doses, 21 days between
ChAdOx1	Adeno-viral vector	Oxford-AstraZeneca	>18 years	two doses, 4-12 weeks
CoronaVac	Inactivated virus	Sinovac	>18 years	two doses, 14-28 days
BBIBP-CorV	Inactivated virus	Sinopharm	>18 years	two doses, 21-28 days

Legend: In addition to the vaccine's name, type and manufacturer, the recommended age and dosage as per the Ministry of Health of North Macedonia are provided.

MATERIAL AND METHODS

We conducted a single-center, open-label, prospective cohort study, consisting of fifty-three (53) healthcare workers, who had received a booster dose in the period between October and December 2021. Our study took part from March 2021 to July 2022.

Patients

The cohort was divided into two groups. The first group, hereon after referred to as the "heterologous" group (n=21), consisted of vaccinees that had received the Gam-COVID-Vac vaccine (Gamaleya, Moscow, Russia) as primary vaccination (the first and the second dose were Gam-COVID-Vac, administered with 21 days

interval between them). The second group, hereon after referred to as the "homologous" group (n=32), consisted of vaccinees that had received the BNT162b2 vaccine (Pfizer-BioNTech, Mainz, Germany) as primary vaccination (the first and the second dose were BNT162b2, administered with 21 days interval between them). Both of these groups received the BNT162b2 vaccine as a third, heterologous or homologous booster dose, six to eight months after the primary immunization.

Sera samples were collected at six time points: two weeks after the first dose of the primary immunization (n=48), one to three weeks after the second dose of the primary immunization (n=49), three months after the primary immunization (n=48), six months after the primary immunization (n=53), one week to one month after the BNT162b2 vaccine as a heterologous or homologous booster dose (n=53), and six to eight months after the third, boosting dose (n=28).

A COVID-19 questionnaire was utilized to gather information about possible side-effects after the vaccination; whether the participants were infected with the virus and if that infection was confirmed by a polymerase chain reaction (PCR) or a rapid antigen test; and the vaccinees' general health status and possible comorbidities. The self-reported side-effects were characterized by their duration (three levels, depending on whether they lasted less than a day, between one and three days, or more than three days) and, some of them, by intensity as well (three levels for pain). Each occurring adverse reaction, its duration and intensity (where applicable) were graded with one point for each level, and the sum of all points resulted in a cumulative adverse reaction score (cARS) for one vaccinee.

Every participant was familiarized with the aim and the methods of this study and gave their written informed consent for participation. This study has been reviewed and approved by the Ethical Committee from the Faculty of Medicine in Skopje.

We excluded potential participants who lacked the "after booster dose" testing time point, even though they had antibody titers' results from the other testing checkpoints.

Methods

Serological testing was performed by means of a chemiluminescence immunoassay for quantitative analysis of Immunoglobulin G (IgG) antibodies using the Maglumi SARS-CoV-2-S-RBD IgG kit on a MAGLUMI 1000 analyzer (Snibe Diagnostic, Shenzhen New Industries Biomedical Engineering Co. Ltd., Shenzhen, China). This method is an in-vitro automated test, for which the manufacturer designates a sensitivity of 100% and specificity of 99.6%. Values above 1AU/ml were considered positive, aligned with the interpretation criteria provided with the product.

Statistical analysis

Descriptive statistic for the cohort was performed and is expressed using mean, median, standard deviation, standard error of the mean and ±95% confidence interval. Antibody data was $\log_{10}$-transformed before the analysis, to account for the skewedness of the values. The main objective of comparing antibody titers between the two regimens was performed using One-Way Repeated Measures analysis of variance (ANOVA). Additionally, a non-inferiority design was applied, with the main hypothesis being that the antibody titers elicited by the heterologous regimen were non-inferior to the ones inducted by the homologous regimen. To achieve this, we calculated the geometrical mean titers (GMT), which represent the mean value of the $\log_{10}$-transformed antibody titers, of the two regimens at each of the six testing checkpoints. The geometric mean ratio (GMR) was subsequently calculated as the antilogarithm of the difference between the GMTs in the heterologous group and in the homologous group (as the reference). GMR with values greater than 0.67 were considered evidence of non-inferiority; this cut-off was chosen on a pragmatic basis to approach the WHO criterion of 0,67 for licensing new vaccines when using GMR as the primary endpoint, while still allowing rapid study delivery.[14] Finally, comparison between the antibody titers elicited by the two regimens at each singular testing time point was achieved by means of Mann-Whitney-U test, to take into account the presence of possible outliers, which could influence the ANOVA test's results.

The difference in antibody titers relative to the age strata (<40, 40-60 and >60 years) was estimated as a secondary objective, utilizing One-Way Repeated Measure ANOVA with age group as an additional between-subjects factor and Kruskal-Wallis's test for multigroup comparison.

We analysed the reactogenicity of the vaccine schedules as an exploratory objective, by listing the absolute numbers and percentages of the symptoms that the participants self-reported in the COVID-19 questionnaire. Comparison of the perceived side-effect by one participant after the primary versus after the booster vaccination was analysed using a paired t-test, while the differences between the homologous and heterologous vaccine regimens' reactogenicity as a whole were established using the independent samples t-test on the cARS from each participant. The second exploratory objective that estimates the difference in COVID-19 disease incidence between the two schedules was analysed using Fisher's exact test of independence, comparing cases of a SARS-CoV-2 infection (confirmed by PCR or a rapid antigen test) occurring after the administration of the second dose of the primary vaccination.

Missing values were not imputed. $P<0.05$ was considered statistically significant.

Data availability

The datasets used and/or analysed during the current study are available on request from the corresponding author, [A.P. and S.N.]. The data is not publicly available due to containing information that could compromise the privacy of the participants in this research.

RESULTS

Study population

The baseline characteristics of the cohort are shown on Table 2. Based on that data, the heterologous and homologous group are age-matched, confirmed by p=0.5168, output from the independent samples t-test ran on the mean age for each group. Gender on the other hand, showed greater variance between the two groups.

Table 2. Baseline characteristics of the cohort

Demographic parameter	Vaccine regimen	
	Heterologous	Homologous
Age		
Mean±SD	46.25±14.85	48.42±9.39
SEM	4.29	1.69
Median	51	49
95% CI	36.82 - 55.68	44.97 - 51.86
n	21	32
Gender		
Male; n (%)	3 (14.29%)	10 (31.25%)
Female; n (%)	18 (85.71%)	22 (68.75%)

Legend: both groups are age-matched (P=0.5168, independent samples *t*-test); SD - standard deviation; SEM - standard error of the mean; CI - Confidence Interval; n – absolute number.

Immunogenicity

Figure 1 displays the mean values and the 95% confidence interval of the antibody titers elicited by the different regimens. After the administration of the booster dose, the robustness of the humoral immunity evoked by the heterologous schedule greatly increases. It must be noted, the data representing the antibody titers was $\log_{10}$-transformed before the analysis, to account for the skewedness of the values. For our main objective of comparing antibody titers regarding the different vaccine regimens, we utilized three approaches. Firstly, One-Way Repeated Measures ANOVA, as a general linear model, was used to detect variances in antibody titers between the two groups (Figure 2). The graph that this analysis outputs, shows the trend lines for the two regimens, with several key takeaways: while the homologous schedule elicited higher means of antibody titers at each of the first five testing time points, the

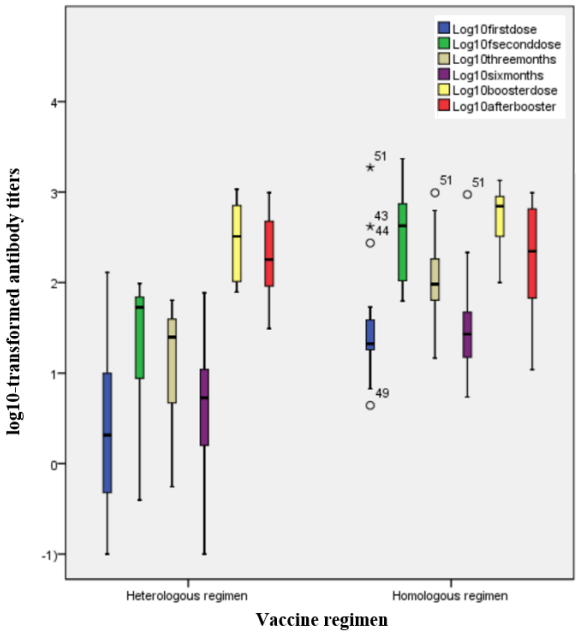

Figure 1. Chart displaying the log10-transformed antibody titers elicited by the two vaccine regimens at each of the six testing checkpoints. Bars show geometric mean titers (GMT) and whiskers show 95% confidence interval.

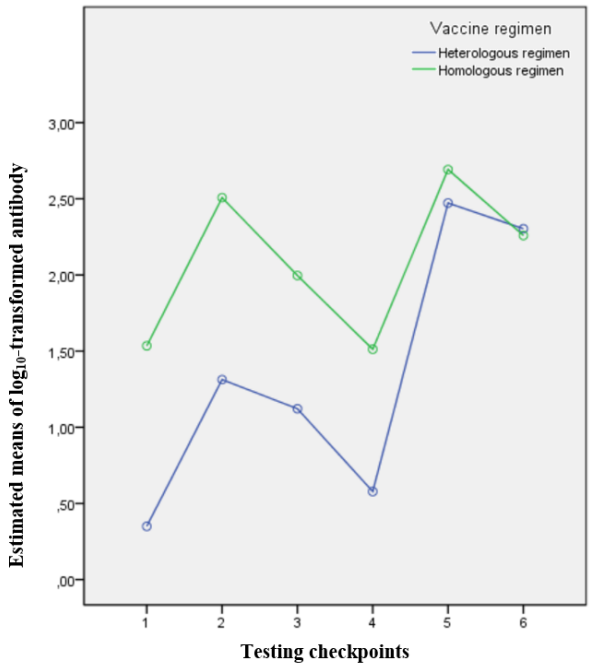

Figure 2. One-Way Repeated Measures ANOVA and the graph that this analysis outputs. The six testing checkpoints are shown on the x-axis, while the y-axis displays log10-transformed antibody titers. The green curve represents the antibody titers' means elicited by the homologous regimen, while the blue curve represents the heterologous regimen-evoked antibody titers.

heterologous regimen resulted in a bigger increase in antibody titers after the booster dose was administered, 4.2-fold (95%CI, 2.21-46.66) versus the 1.78-fold (95%CI, 1.49-2.19) increase observed in the homologous regimen; six-to-eight months after the

booster BNT162b2 dose, the mean antibody titers induced by the heterologous regimen was higher than the one induced by the homologous schedule (2.30AU/ml versus 2.26AU/ml, log_{10}-transformed); the two aforementioned statements regarding the fifth and sixth testing time points, show a steadier decline in antibody titers in the heterologous vaccine group. Additionally, non-inferiority testing was applied to test the null hypothesis stating that the heterologous regimen is non-inferior to the homologous at each of the six testing checkpoints. Values for GMR above 0.67 were considered evidence for non-inferiority. The null hypothesis was rejected for the first five testing points (GMR values of 0.13; 0.05; 0.12; 0.10 and 0.55, respectively), but the heterologous vaccine group showed non-inferiority to the homologous at the last testing point (GMR=0.98), result that is aligned with the aforementioned ANOVA output. Finally, the Mann-Whitney-U test was utilized to determine possible statistically significant differences between the antibody titers elicited by the two regimens at each of the testing time points separately. The first four checkpoints confirmed a significant difference in antibody titers (P=0.001; P=0.000; P=0.000; P=0.000, respectively). On the other hand, at the "after the booster dose" and "longer after the booster dose" checkpoints, the schedules showed no statistically significant differences in antibody titers (P=0.059 and P=0.89, respectively).

The variance in antibody titers relative to the age strata as a secondary objective is shown on Figure 3, that displays One-Way Repeated Measure ANOVA, with the age group as an additional between-subjects factor. Furthermore, by means of Kruskal-Wallis's test for multigroup comparison, no differences were found in elicited antibody titers between the three age groups. Therefore, no post-hoc tests were necessary.

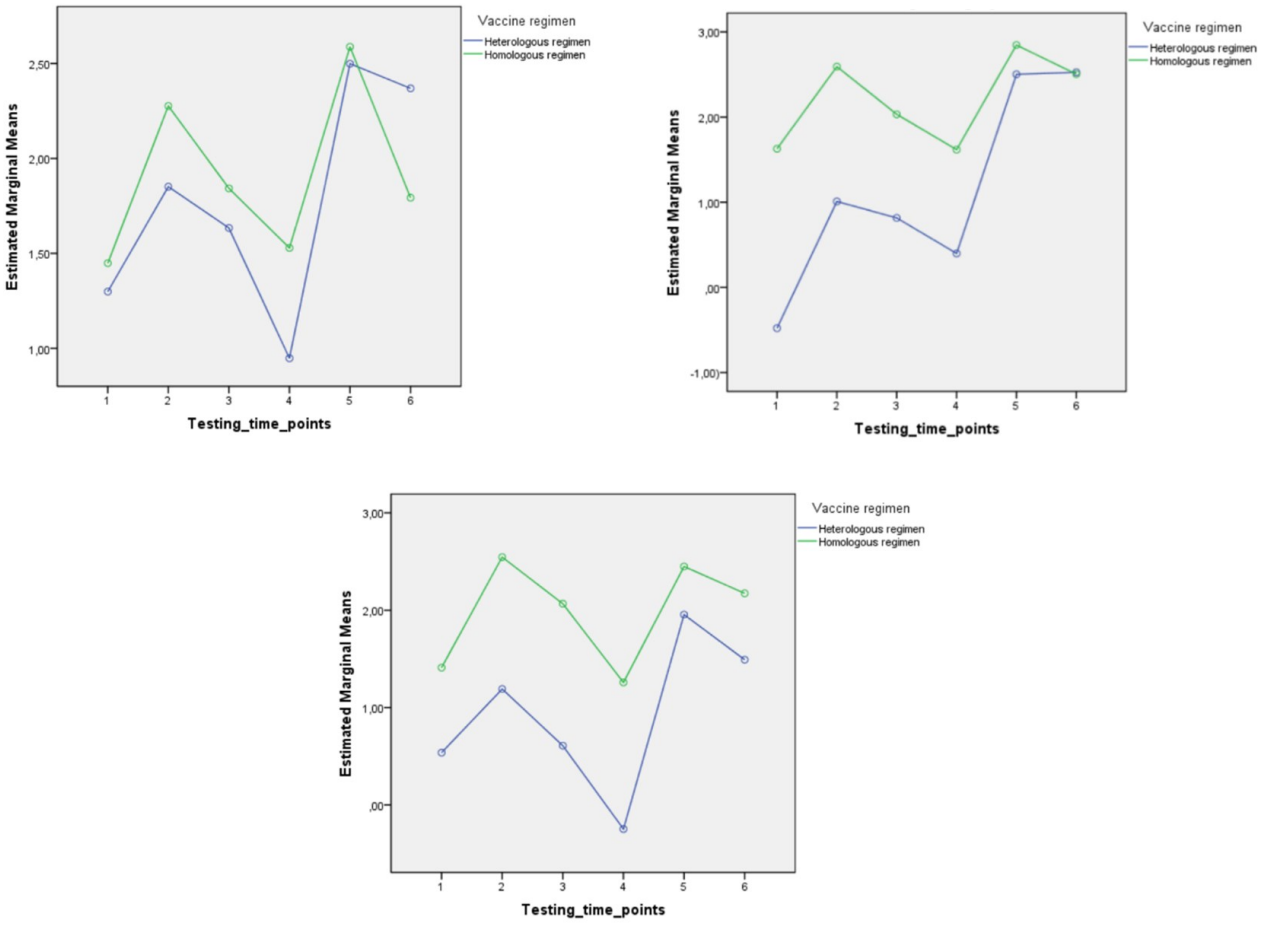

Figure 3. Difference in antibody titers relative to the age strata as a secondary objective. One-Way Repeated Measure ANOVA with the age group as an additional between-subjects factor is displayed on the three graphs. No statistically significant difference in RBD-specific antibody titers was found between the three age groups (<40, 40-60 and >60 years), as indicated by the trend lines from the upper graphs

Reactogenicity

Analysis of reactogenicity was our first exploratory objective. Table 3 shows the absolute number and the percentages of the solicited adverse reactions, as perceived by the vaccines. Since not all participants gave information regarding the possible vaccine side effects, the percentages are calculated relative only to those who have given the said information. The cumulative adverse reactions score (cARS) was utilized for comparisons of the reactogenicity within and between the vaccine regimens. Paired t-test was used to determine whether the same vaccine from a given regimen experienced change in severity or duration of the adverse reactions after the second dose versus after the booster dose. No such difference is found, both in the heterologous (P=0.852) and in the homologous (P=0.148) regimen. Contrast in perceived adverse reactions after the third, booster dose between the two schedules was analysed using the independent samples t-test on the cARS from each group, again reaching statistically non-significant difference (P=0.498).

SARS-CoV-2 infection incidence

Comparison of the SARS-CoV-2 infection incidence was our second exploratory objective. A case of SARS-CoV-2 infection was considered relevant if it occurred after the vaccination with the second dose in each regimen and if it was confirmed by a PCR or rapid antigen test. By means of Fisher's exact test of independence, no statistically significant difference was established (P=0.546) in the incidence of COVID-19 disease between the two vaccine schedules (Figure 4).

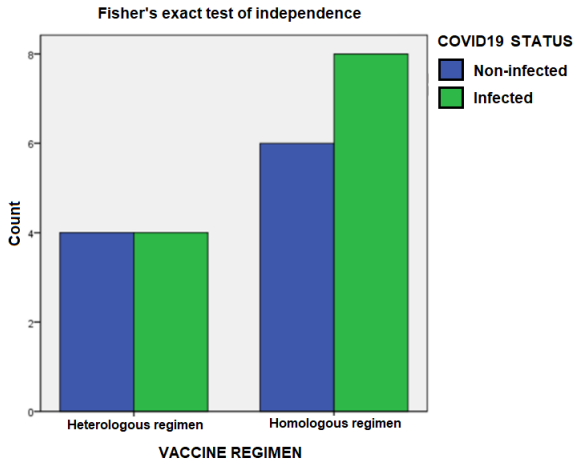

Figure 4. Comparison of the SARS-CoV-2 infection incidence as the second exploratory objective, by means of Fisher's exact test of independence

Table 3. Solicited adverse reactions following the second dose of the primary immunization and the booster dose, as part of the heterologous or the homologous vaccine regimen

Solicited adverse reactions	Vaccine regimen			
	Heterologous (N=14)		Homologous (N=25)	
	Second dose n (%)	Booster dose n (%)	Second dose n (%)	Booster dose n (%)
Injection-site pain	7 (50%)	6 (42.86%)	17 (68%)	12 (48%)
Fatigue	7 (50%)	4 (28.57%)	12 (48%)	4 (16%)
Headache	3 (21.43%)	2 (14.29%)	2 (8%)	3 (12%)
Fever	3 (21.43%)	2 (14.29%)	4 (16%)	1 (4%)
Chills	3 (21.43%)	3 (21.43%)	2 (8%)	2 (8%)
Arthralgia	1 (7.14%)	3 (21.43%)	5 (20%)	2 (8%)
Injection-site erythema and edema	0 (0%)	1 (7.14%)	1 (4%)	1 (4%)
Chest pain	1 (7.14%)	0 (0%)	0 (0%)	0 (0%)
Back pain	1 (7.14%)	1 (7.14%)	0 (0%)	0 (0%)
Eyes pain	0 (0%)	0 (0%)	1 (4%)	0 (0%)
Sleepiness	0 (0%)	1 (7.14%)	0 (0%)	1 (4%)
Axillary lymph nodes edema	0 (0%)	1 (7.14%)	0 (0%)	1 (4%)
Tachycardia	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Hotness perception	1 (7.14%)	0 (0%)	0 (0%)	0 (0%)

Legend: % - percentages are given relative only to the number of participants who gave information regarding side effects after vaccination, not the group as a whole; n - the number of who gave information regarding side effects after vaccination.

DISCUSSION

As per our findings, the heterologous Gam-COVID-Vac/BNT162b2 schedule induced a strong humoral immune response and slowly-waning antibody titers after the booster dose. For starters, Figure 1 provides us with a key takeaway: while at the first four testing points, the adenovirus/mRNA vaccine combination is less immunogenic than the homologous mRNA schedule, even containing several non-responders, after the administration of the booster dose its robustness greatly increases. Hence, the yellow and red bars are not only comparable between the schedules, but the 'mix-and-match'-induced antibody titers at the sixth testing checkpoint show pronounced homogeneity. The raw data confirms the findings of non-responders between the vaccines that have received the adenoviral vector vaccine. More precisely, seroconversion after the first dose was achieved in all 32 vaccinees (100%) that were immunized with the BNT162b2 mRNA vaccine and that percentage remained unchanged after the second dose from the primary vaccination. On the other hand, five non-responders (31.25%) were observed after the first Gam-COVID-Vac dose. That number reduced to one non-responder (5.88%) after the second Gam-COVID-Vac dose, still below the seroconversion rate previously reported for this vaccine.[15, 16] After the booster mRNA dose however, all participants from both regimens have seroconverted, even the non-responders previously mentioned. As a next step, we conducted a general linear model analysis, to display the variation in antibody titers elicited by each regimen at the six testing checkpoints. It is apparent that the increase in antibody titers after the booster BNT162b2 vaccine as a heterologous dose is bigger than the one after the same vaccine as a homologous dose. The sera analysis conducted 6-8 months after the boosting, showed an even higher mean of $\log_{10}$-transformed antibody titers in the heterologous adenoviral vector/mRNA vaccine schedule relative to the homologous mRNA regimen, so by connecting the fifth and sixth testing checkpoints, we obtain a steadier declining line in this regimen, evidence for the stability and longevity of the humoral immune response elicited by the Gam-COVID-Vac/BNT162b2 combination. For further confirmation of our findings, we conducted non-inferiority testing at each time point. While the homologous regimen proved superior in the first five testing points, no inferiority was observed at the 'longer after booster dose' time mark; results aligned with the previously discussed. There are several potential mechanisms explaining the robust immune response following a heterologous vaccine schedule. mRNA vaccines, such as the BNT162b2, elicit high titers of binding and neutralizing antibodies, combined with a relatively low CD8+ T-cell response.[17] The adenovirus vector vaccines on the other hand, induce a multifunctioning antibody response, with lower titers of binding and neutralizing antibody titers. Nevertheless, this polyclonal antibody production may evoke protective immunity by other fragment-of-crystallization (Fc) effector mechanisms: antibody-dependent phagocytosis, complement activation and antibody-dependent cell-mediated cytotoxicity.[18] Palgen J-L et al. hints at other possible ways of action, including the potential role of trained innate cells[19] and the circumvention of vector immunity. The aforementioned mechanisms enable the 'mix-and-match' principle to combine the benefits from the different vaccine platforms it includes. Furthermore, boosting adenoviral vector with mRNA vaccines increases titers of neutralizing antibodies, by avoiding interference of anti-adenovirus antibodies, elicited by previous adenoviral immunization.[20] Since no studies regarding the Gam-COVID-Vac/BNT162b2 schedule were available, our immunogenicity results can be described as similar to the ones obtained by researching various vaccine schedules that combine different vaccine platforms.[21-26, 27, 28]

As for the reactogenicity data, both the Gam-COVID-Vac and the BNT162b2 vaccines showed adverse effects similar in severity and in frequency relative to available reports.[15, 29] Pain at injection site, fatigue and headache were the most common perceived side effects in both groups. However, no significant increase in reactogenicity was observed in the heterologous regimen, contrary to the findings[30] by Robert H. Shaw et al. One possible reason is that the latter study obtained the data only from 50 years and older participants, while our vaccinees were of younger mean age. Other articles on the other hand, confirm our finding of similar and tolerable reactogenicity between vaccine regimens.[28, 31]

Having both the robust immunogenicity and tolerable reactogenicity in mind, the heterologous adenovirus/mRNA vaccine combination might prove to have several indications for usage in the effort to contain the COVID-19 pandemic. First of all, it can mitigate fluctuating vaccine supplies in non-developed and developing countries, aiding them in achieving heard immunity in time. Another potential benefit would be the recommendation to improve humoral immune response in non-responders following the primary immunization with the Gam-COVID-Vac vaccine. Additionally, vaccines with severe adverse reactions following administration of one vaccine should be advised to boost with a different vaccine type. Finally, Schmidt et al. reported that heterologous adenoviral/mRNA regimens help immunocompromised patients to mount stronger immunity compared to homologous schedules.[32]

Our study has its limitations, which can be attributed to the usual factors that affect studies similar to this, in the region, as well as globally. Firstly, the cohort consists of a relatively small number of participants, due to the fact that Republic of North Macedonia is a small country to begin with, and has limited financial and human resources. Secondly, the time elapsed since the second Gam-COVID-Vac or BNT162b2 dose administration and the BNT162b2 booster dose administration was not standardized. Additionally, we only analysed the humoral immune response following vaccination, while

the cellular immunity was not researched. Furthermore, while providing comparison of the SARS-CoV-2 infection incidence between the homologous and heterologous regimen, our small cohort can only give an estimate for the real-world data about the efficacy and subsequently, efficiency of the given regimen. Finally, since no genetic sequencing was used for the SARS-CoV-2 variants that infected the participants, we cannot speak of a vaccine-induced immunity relative to the viral strain.

In conclusion, our study for the first time provides important evidence concerning the heterologous Gam-COVID-Vac/BNT162b2 vaccine regimen. The results indicate a strong and robust immunogenic response after the administration of the booster dose and subsequently, an even longer-lasting humoral immune response compared to the homologous BNT162b2 schedule. The slower waning of the 'mix-and-match'-induced protection, coupled with the similar reactogenicity relative to the homologous regimen, imply that the Gam-COVID-Vac/BNT162b2 schedule might be a feasible approach in the effort to contain and end the COVID-19 pandemic, especially in countries facing fluctuating supplies of individual vaccine types.

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