Kinetics of antibody response to repeated vaccination with Sputnik V: a pilot study with a series of five cases

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A B S T R A C T

Objectives

Widespread vaccination is considered as one of the best methods in combating any pandemic including COVID-19. Gam-COVID-Vac also known as Sputnik V, is one of the first vaccines that was registered in 74 countries and received an emergency approval for immunization. Monitoring anti-SARS-CoV-2 antibodies over time is essential for evaluation of post-vaccination humoral immune response.

To date, there are only a limited number of clinical studies regarding the analysis of immune response after Sputnik V administration. It is of crucial importance to report independently on safety and efficiency of this vaccine with the aim to speed up the process of its final approval by the WHO.

Methods

Humoral immune response was monitored by seven immunoassays to analyze different classes of anti-SARS-CoV-2 Ig in five health workers after receiving the combined vector vaccination. This vaccine is based on two replication-deficient rAd26 and rAd5 viral vectors that carry the gene SARS-CoV-2 full-length glycoprotein S(rAd26-S and rAd5-S). Sputnik V was administered with a 21-day interval between the first and second dose. Venous blood was collected two hours before vaccination as a baseline, and then followed by 18 series up to 170-day post-vaccination.

Results

The participants in this study used a self-report form in which they noted their observations on safety at 72 h post-immunization. One participant reported mild side effects, such as muscle pain and fever, while the other four individuals had no noticeable complications. Seroconversion was detected in all individuals at 28 days of post-vaccination. Plateau of seropositivity has been achieved by 50th day of vaccination, while titer values decreased after 6 months.

Conclusion

This study provides some clinical data regarding the kinetics of antibody levels elicited after administration of heterologous rAd26-S and rAd5-S vaccine. Based on the preliminary data from this pilot study, it appears that Sputnik V vaccine generates a solid humoral immune response lasting at least 6 months after immunization.

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INTRODUCTION

The new coronavirus disease 2019 (COVID-19) disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection, which has resulted in a global pandemic.

The vast spread of this disease became a serious threat to global public health [1]. In essence, SARS-COV-2 is a single RNA virus and belongs to the beta-coronavirus of the family Coronaviridae, which most commonly induces respiratory symptoms, such as fever, unproductive cough, myalgia, and fatigue [2, 3]. Although several preventive actions, e.g., social distancing, hand hygiene, extensive use of face masks and contact monitoring have been implemented worldwide with the aim to limit the impact and spread of SARS-CoV-2 infection, the vast and enormous transmission of the SARS-CoV-2 coronavirus was unmanageable [4].

Currently, with the new variants emerging out of the Wuhan species, humanity is facing more than 6 million registered deaths as well as many unreported deaths with the possibility of the overall balance to account to the third leading cause of death, and the second largest cause of death due to viral infection within one century [5, 6, 7]. Furthermore, a new challenge in 2021 was to cope with the emergence of new, unknown and potentially more destructive variants of the virus [8].

According to the World Health Organization (WHO), vaccination is a safe and effective way of reducing the risk of developing serious disease and lowering the risk of generation of new, more powerful strains of the virus [9]. The reduction of severe COVID-19 disease after vaccination is associated with the synthesis of circulating neutralizing monoclonal antibodies, primarily IgG class, which specifically targets the SARS-CoV-2 spike protein, its S1 unit of receptor binding domain (RBD), to restrict or completely prevent the binding with host receptor (i.e., Angiotensin-Converting Enzyme 2, ACE2) [10].

Referring to WHO, as of September 17, 2020, 117 COVID-19 vaccine candidates were under clinical evaluation and 194 candidate vaccines were processed in the preclinical evaluation [11,12].

From those approved for clinical use, the vaccines based on mRNA technology were the first permitted and administered in many developed countries due to some technical advantages. Unfortunately, countries with smaller incomes lagged in procuring the vaccines and immunization began not only a few months later, but also with insufficient quantities for rapid vaccination of a large part of their populations. Additionally, the specific manner of proper storage of the new mRNA vaccines also made them less accessible. North Macedonia procured several different types of vaccines. One of the available vaccines was adeno-based vector vaccine Gam-COVID-Vac (Sputnik V), developed by Gamaleya National Research Centre, Russia. This vaccine still has not received the authorization for general use by the WHO yet, however it has been administered to millions around the globe, typically in low-income countries due to its low cost.

The use of viral vector-based vaccines allows the signaling pathways to produce both humoral immunities through antibody expansion and cellular immunity by stimulating a robust cytotoxic T lymphocyte (CTL) response to eliminate virus-infected cells [13]. Phase III trials have shown that these vaccines are effective in alleviating the severity of COVID-19 as a result of the development of effective humoral and cellular immunity, in particular the development of neutralizing antibodies against SARS-COV-2 [14, 15]. However, to the best of our knowledge, there is still a lack of published data describing the early and comprehensive humoral immune response after Sputnik V in subjects not included in clinical trials.

Since the immunological response varies between different types of COVID-19 specific vaccines, here our aim was to evaluate the humoral immune response after heterologous recombinant adenovirus (rAd26-S + rAd5-S) vaccine from the Gamaleya Research Institute-Sputnik V in samples of healthcare workers who were seronegative before vaccination via the assessment of antibodies of IgG and IgM classes targeting the entire SARS-CoV-2 Spike protein trimer (anti-spike trimeric IgG), the RBD (anti-spike RBD IgG) or the S1 subunit. We have used different assays for the analysis of antibodies for reliably reflecting the immunological response developed after vaccination with Sputnik V.

MATERIALS AND METHODS

Study design and participants

This five-case series was based on four female participants (at the age of 45, 50, 52 and 58 years) and one male participant who was 39 years old. All participants in this study were healthcare workers at the University Clinic for Gynecology and Obstetrics, Skopje, Macedonia who underwent vaccination with two doses of vector-based vaccine Sputnik V. The vector vaccine consists of adenovirus DNA, in which the SARS-CoV-2 coronavirus gene was integrated. Adenovirus is used as a "flask" to deliver the coronavirus gene to the cells for synthesizing the envelope proteins of SARS-CoV-2 virus.

The first received dose of replication-deficient human adenovirus-26 expressing full-length S protein (1011 viral particles) was administered between 7-10 April 2021. The second dose of human adenovirus- 5 expressing full-length S protein (1011 viral particles) was administered after 21 days following the protocol given by the manufacturer [15]. The participants in this study were healthy volunteers and none of them were taking immunomodulatory drugs. In addition, these volunteers did not have any infectious diseases at the time of vaccination or 14 days before vaccination and did not receive any other vaccination within the whole period of study. On the day of the administration of the first dose, all participants had a negative SARS-COV-2 specific RT-PCR test as well as negative result for the titers of anti-SARS-CoV-2 IgG and IgM antibodies.

Baseline venous blood sample was collected two hours before the vaccination by venipuncture using 6 ml serum tubes containing gel and clot activator (Becton Dickinson, Plymouth, UK), and then on the 4, 8, 12, 14, 18, 21, 23, 29, 32, 35, 38, 42, 50, 55, 63, 73, 80, 170 days. Blood samples were centrifuged at 1500 x g for 15 min, aliquoted and frozen at -70 °C.

Immunoassays

After the time of collection all samples were thawed, centrifuged and sera were tested with seven different anti-SARS-CoV-2 Ig immunoassays for detection of SARS-CoV2 antibodies to measure total IgG or IgM and IgA SARS-CoV-2 antibody according to the manufacturer protocol instructions (Table 1).

During this study, each participant was asked to report on any self-perceived post-vaccination adverse reactions that included local reactions (e.g., injection site pain, redness, and swelling) and/or systemic reactions (such as fatigue, headache, myalgia, arthralgia, chills and fever). All volunteers signed two written consents: one according to the national standard for receiving vaccination, and another one for the participation in the serological monitoring study.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 17.0 for Windows, SPSS Inc., Chicago, IL, USA). Results are expressed as the mean ± standard deviation (S.D). Cumulative results of antibodies testing were presented as mean ± standard deviation (SD), as ratio with baseline antibodies level (i.e., [time point value]/[baseline value and/or limit of detection]). Spearman test was used to test the correlation of levels of different antibodies over time. The clinical and laboratory characteristics in the groups were compared by analysis of variance (ANOVA test).

For all analysis, a P-value less than 0.05 were considered statistically significant.

RESULTS

None of the participants experienced any clinical sign or symptom related to SARS-CoV-2 infection, and molecular nasopharyngeal PCR testing remained negative during the whole period of the study in all five tested subjects. One of the participants recorded moderate systemic side effect after the first and second dose, i.e., body temperature of more than 38,9 °C, headache, fatigue, chills, shivers and arthralgia. Three subjects suffered from mild pain at the injection site lasting no more than 48 hours after receiving the first and the second dose.

A total number of 100 samples were collected at the end of the study during a period of 20 weeks. The kinetics of antibodies against SARS-CoV-2 was determined all together at 19 time points for the five study volunteers. The cumulative data and kinetics of antibody development after the combined adenovirus-based Gam-COVID-Vac vaccine are shown in Figure 1.

Serological testing of the participants in the study revealed that all participants were seronegative for the virus specific immunoglobulins of IgM, IgA and IgG classes and initially began to produce anti-SARS-2 antibodies between days 12 and 14 of the first dose of the vaccine, with slight differences in kinetics of seroconversion (Table 2).

Anti-S1-RBD total IgG seroconversion began to elevate and increased gradually between 182.7 (IQR, 137.3 – 228.2) to 899.8 (IQR, 587.5 – 1212.1) folds from day 21 after the first dose, when the first pick was reached. Seroconversion for SARS-COV-2 IgG antibodies on the 21st day after the first dose increased from 335.7 (IQR, 276.3-434.7) to 1,624.7 (IQR, 1,154.2-4,424.8) folds. The first vaccine dose initiated a median increase of 38.8 (IQR, 20.8- 56.7) folds for IgG anti-S1-RBD, and 769.2 (IQR, 305.8-834.4) folds

for S1-RBD, and 30.4 (IQR, 16.26- 44.58) for total IgG anti-N and S. Further slow increase was noted after the second dose, and on the 38th day the second peak was reached. The second vaccine dose prompted a median increase from baseline of 898.0 (IQR, 578.5-1.212.0) folds for RBD total Ig and 1625.1 (IQR, 1.154-2.096) folds for SARS-COV-2 IgG, 177.0 (IQR,112.0-242.1)

for SARS-COV-2 IgG anti-S1-RBD, 5361.1 (IQR, 2132.0-8591.0) for anti-S1-RBD and 159.0 (IQR, 83.64-234.3) for total IgG anti-N and S. After this exact time period and up to the 50th day, a plateau was achieved and the level of antibodies then started to slowly decline, however, 16 weeks after the first dose, the values were still higher than the first peak (Figure 2).

Table 1	Technical and analytical characteristics of anti-SARS-CoV-2 immunoassays used in this study						
Test	**Company**	**Analyzer**	**Principle**	**Detection**	**Ig class**	**Target**	**Cut-off**
Elecsys Anti-SARS-CoV-2	Roche	COBAS ELECSYS	Sandwich	ECLIA	SARS-COV-2 total Ig	N	1.0 U/ml
Elecsys Anti-SARS-CoV-2 S	Roche	COBAS ELECSYS	DAGS	ECLIA	SARS-COV-2 total Ig	S RBD	0.8 U/ml (1.03 BAU/ml)
Vidas Sars-CoV-2 IgG II	bioMerieux	VIDAS	Sandwich	ELFA	SARS-COV-2 IgG	S1-RBD	1.00 index (20.33 BAU/ml)
SARS-CoV-2 IgG II Quant	Abbott	ARCHITECT	Indirect	CMIA	SARS-COV-2 IgG	S1-RBD	50.0 AU/ml (7.1 BAU/ml)
SARS-CoV-2 IgG (SCOVG)	Siemens	CENTAUR XPT	DAGS-2 steps	DCLIA	SARS-COV-2 IgG	S1-RBD	1.00 index (21.8 BAU/ml)
COVID-19 VIRCLIA IgG MONOTEST	Vircell	VIRCLIA	indirect	CLIA	SARS-COV-2 IgG	N, S	0.7 (index)
COVID-19 VIRCLIA IgM+IgA MONOTEST	Vircell	VIRCLIA	indirect	CLIA	SARS-COV-2 IgM+IgA	N, S	0.6 (index)

Abbreviations: DAGS, double-antigen sandwich assay; ECLIA, Electro-chemiluminescent Immunoassay; ELFA, Enzyme Linked Fluorescent Assay; CMIA, Chemiluminescent Microparticle Immunoassay; DCLIA, Direct Chemiluminescent Immunoassay CLIA, Chemiluminescent Immunoassay; Ig, Immunoglobulin; N, nucleocapsid; RBD, Receptor Binding Domain; BAU, binding antibody unit.

Table 2	Kinetics of anti-SARS-CoV-2 antibodies development after Sputnik V vaccination				
Antibodies	**Baseline**	**21 days**	**38 days**	**77 days**	**170 days**
COBAS ELECSYS ASARS-COV-2, anti-S-RBD total Ig					
Serum values (WHO BAU/mL)	0.412	75.3 (56.6-94.04)	370.72 (242.05-499.39)	175.1 (129.39-221.71)	142.35 (53.35-231.17)
VIDAS SARS-COV-2 anti-S1-RBD IgG					
Serum values (WHO BAU/mL)	0.19	67.621 (52.57-82.67)	308.77 (219.3-398.24)	164.87 (67.28-262.47)	59.98 (54.12-65.86)
ARCHITECT SARS-COV-2 anti-S1-RBD IgG					
Serum values (WHO BAU/mL)	1.47	57.08 (30.58-83.44)	260.3 (164.7-355.9)	66.9 (41.04-92.76)	37.56 (19.35-55.77)
SIEMENS CENTAUR XPT SCOVG anti-S1-RBD IgG					
Serum values (WHO BAU/mL)	0.1	76.92 (55.67-98.19)	536.11 (213.2-859.1)	173.37 (37.47-309.29)	45.86 (34.79-56.93)
VIRCLIA SARS-COV-2 anti-N and S IgG					
Serum values (index)	0.05	1.52 (0.81-2.22)	7.95 (4.18-11.71)	5.9 (2.05-9.74)	2.3 (1.37-3.25)
COBAS ELECSYS SARS-COV-2 anti-N total IgG					
Serum values (index)	0.08	0.08	0.082 (0.077-0.086)	0.082 (0.077-0.086)	0.082 (0.077-0.086)
VIRCLIA SARS-COV-2 S, anti-N and S IgM + IgA					
Serum values (index)	0.01	0.04 (0.001-0.08)	0.091 (0.04-0.14)	0.18 (0.04-0.33)	0.048 (0.096-0.087)

Abbreviations: BAU, binding antibody units; Ig, Immunoglobulin; RBD, Receptor Binding Domain; S1, Spike protein S1 subunit.

Anti S1-RBD IgA+IgM antibody levels did not display any kinetic during the full period of study and stayed on the primary low levels as before vaccination. In a similar manner, the kinetics of total IgG anti-N antibodies response with the immunoassay used in this study, did not provide any response after vaccination. The levels of total IgG anti-N antibodies in all patients, and in all tested points have remained on the basal, undetectable levels and therefore are not presented in this study.

The Spearman's correlations between the levels of different antibodies over time were performed and these results are shown in Table 3.

Significant correlation was found between VidasSARS-CoV-2 IgG S1-RBD and Architect SARS-CoV-2 IgG-S1-RBD (r=0.98; p<0.001), Vidas SARS-COV-2 IgG S1-RBD and Virclia IgG anti N/S (r=0.966; p<0.001), whereas a smaller but statistically significant correlation was found among the other anti-SARS-CoV-2 antibody classes.

As a reference for comparison among laboratories, IgG levels were expressed in international units (IUs) after normalization with the WHO International Standard for anti-SARS-CoV-2 antibody (Table 1).

DISCUSSION

In less than a year, the entire world population has experienced a change in psychological, economic, medical as well as sociological and mental status as a result of the high rates of infection and mortality rate due to the novel SARS-CoV-2 virus infection. Universal and

| Figure 1 | Kinetics of anti-SARS-2 antibodies following Gam-COVID-Vac-Adeno-based recombinant vaccine. Values are shown as mean ± SD |

Abbreviations: Ig,Immunoglobulin; N,nucleocapsid; RBD,receptor binding domain; S, spike protein.

| Figure 2 | Median increase-peak values of different classes of anti-SARS-CoV-2 antibodies elicited by two doses of adeno-vector based "Sputnik V" -Gamaleya vaccine. The day of the peak is reported in the text. |
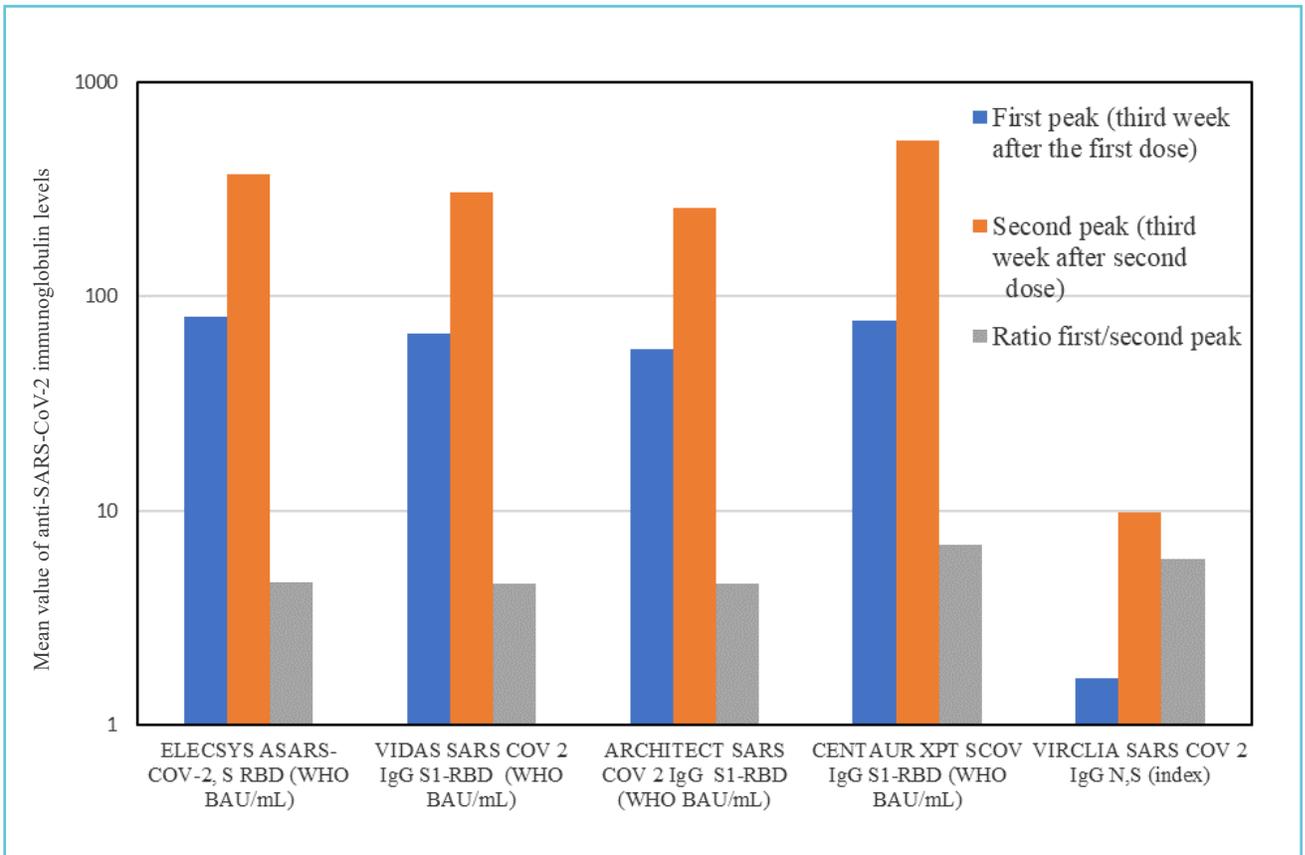
Abbreviations: Ig, immunoglobulin; N, nucleocapsid; RBD, receptor binding domain; S, spike protein.

comprehensive vaccination against COVID-19 is most likely the key to all strategies for stopping or reducing the circulation and reducing the contagiousness of SARS-COV-2. Several published studies have provided evidence that there is a direct correlation between the distribution of vaccines and the reduction of the number of SARS-COV-2 positive cases, hospitalization and mortality due to COVID-19 [18]. Although the efficacy of most currently licensed vaccines appears to be considerably high, especially in reducing the risk of clinical exacerbation among patients in different clinical risk groups [19], little is known about the immunogenicity of adenoviral vector-based vaccine Sputnik V. Although this vaccine has not been licensed by the WHO yet,

it has been accepted to use by many countries in the relentless race for vaccines which have failed to provide doses of those vaccines approved by the WHO. Here we present our preliminary data on the safety, tolerability and immunogenicity of Sputnik V. In this study, only candidates who had no previous contact with the SARS-CoV-2 virus and have developed antibodies to the SARS-CoV-2 before the first dose of vaccine were eligible to participate. In terms of vaccine safety, we found that Sputnik V vaccine was well tolerated among participants and the most common reported systemic side effect were influenza-like symptoms. Only one participant had moderate side effects. All observed minor side effects during the study were transient, lasting no more than

48 hours and no serious adverse reactions have been reported. Tukhvatulin et al. have reported about the safety and immunogenicity of single-dose vaccine "Sputnik Light" vaccine, where only 5.2% of participants without immunity to SARS-CoV-2 complained of muscle and joint pain after vaccination, and only 5.5% participants had moderate grade adverse effects who persisted no more than 24 hours. A group of seropositive participants after vaccination demonstrated less and milder adverse effects when compared with seronegative participants [20].

The high seroconversion rates found in the participants of this study are in an agreement with what has been previously published for Sputnik V and other COVID-19 vaccines [14,20, 21]. Rossi et al. monitored antibody response in 62 seronegative

participants and 227 participants with prior SARS-COV-2 infection receiving two doses of Sputnik V vaccine [22]. They reported that 94% of seronegative participants showed positive SARS-CoV-2 IgG response with geometric mean titer (GMT) of 244 [95% CI 180-328], and after second dose 100% of seroconversion with GMT of 2.148 [95% CI 1.742-2.649]. Antibody response was stronger in seropositive people receiving Sputnik V adeno-based vaccine compared with those negative at baseline, interestingly with no significant differences after one or two doses. In our study, 4 of 5 participants had a seroconversion before receiving the second dose, and after the second dose, all participants have developed specific antibodies against SARS-CoV-2. Salvagno et al. have demonstrated that two doses of Pfizer

Table 3	Spearman correlations and CI (95%) between overall serum increase of anti-S-RBD total Ig, anti-S1-RBD IgG, IgG anti-N and S elicited after administration of two doses of Sputnik V			
	VIDAS (SARS-COV-2 anti-S1-RBD IgG)	**ARCHITECT (SARS-COV-2 anti-S1-RBD IgG)**	**CENTAUR XPT (SCOVG anti-S1-RBD IgG)**	**VIRCLIA (SARS-COV-2 anti-N and S IgG)**
ELECSYS (SARS-COV-2S-RBD total Ig)	0.903 (CI 95% 0.761-0.962) P<0.001	0.883 (CI 95% 0.716-0.954) P<0.001	0.890 (CI 95% 0.731-0.957) P<0.001	0.937 (CI 95% 0.841-0.976) P<0.001
VIDAS (SARS-COV-2 anti-S1-RBD IgG)		0.982 (CI 95% 0.953-0.993) P<0.001	0.942 (CI 95% 0.853-0.978) P<0.001	0.966 (CI 95% 0.912-0.987) P<0.001
ARCHITECT (SARS-COV-2 anti-S1-RBD IgG)			0.957 (CI 95% 0.889-0.984) P<0.001	0.933 (CI 95% 0.831-0.974) P<0.001
CENTAUR XPT (SCOVG anti-S1-RBD IgG)				0.940 (CI 95% 0.848-0.977) P<0.001

Abbreviations: IgG - Immunoglobulin G, RBD - Receptor binding domain, S1 - spike protein S1 subunit, N - Nucleocapsid.

and Moderna mRNA vaccines have elicited secretion of different classes of anti-SARS-CoV-2 where the first vaccine dose triggered an increase from baseline to the median of 103.3 folds for anti-spike trimeric IgG, 210.9 folds for anti-spike RBD IgG, and 13.3 folds for anti-spike S1 IgA, but the second boost triggered additional modes median increase of antibodies of 6.3 folds for anti-spike trimeric IgG, 7.2 folds for anti-spike RBD IgG, and 1.5 folds for anti-spike S1 IgA, respectively [23].

Even though our report is limited to 5 cases, it has many strengths in assessing post-vaccination immune response. Namely, we have presented an extensive sequence of blood sampling, which has given us an opportunity to present an early identification of SARS-CoV-2 antibodies as well as monitoring their progression over period of 6 months. In this study, we have also presented measurement of different antibodies responses (total IgG anti-S-RBD, IgG anti-S1-RBD, IgM+IgA anti-S and N) after vaccination with "Sputnik V" vaccine giving the opportunity for monitoring the elicited humoral response. In view of all above, it is possible for us to show that in total IgG anti-S-RBD and IgG anti-S1-RBD a constant linear increase was observed after the first vaccine, showing additional growth induced by the second vaccine dose.

As known for many viral infections, humoral immune kinetics show that antibody levels peak after natural contact with the viruses or after vaccination begin to drop after a certain number of weeks [24]. Similar as with other viruses, antibodies following the infection with SARS-CoV-2 decline after 8 months [25]. Few studies have evaluated the half-life of the antibodies elicited by mRNA-vaccines, suggesting that they may last for 6-8 months [26, 27]. We have demonstrated that after the adeno-based vaccine Sputnik V, the plateau of seropositivity was achieved at the 50th day and remained in the same range until it started to decline slowly after the 80th

postvaccination day, thus 16 weeks after the first dose values were still higher than the first pick and dropped after 180 days, providing sustainable immunity in the same manner as other available vaccines against SARS-CoV-2.

Although the year of 2021 was supposed to be a year of equality and solidarity, in which the approved vaccines for SARS-CoV-2 would be equally distributed, in the race for timely vaccination, small and poor countries managed to procure and vaccinate their population with adeno-based vector "Sputnik V" vaccine. One of the currently available vaccines is Sputnik V, developed and manufactured by the Gamaleya, National Research Center for Epidemiology and Microbiology in Moscow, Russia. Although more than 80 countries, mainly in Eastern Europe such as Serbia, North Macedonia, but also in many countries in South America and Africa etc., have approved the vaccine, not many studies have been published on the effects and efficacy of this vaccine [28]. The few studies that have been officially published have confirmed the safety and efficacy of Sputnik V, as originally reported in phase 1/2/3 [29]. In contrast to this lack of peer-reviewed and published studies there is a growing number of published studies and abundance of data and information on the mRNA-1273 (Moderna/NIAID), BNT162b2 (Pfizer/BioNTech) and AZD1222 (AstraZeneca/University) vaccines [26,27,30].

The results of our study provide further knowledge about "Sputnik V", since in this study we aim to provide evaluation of the synthesis and viability of antibodies up to 6 months after immunization with this vaccine. Our data provide evidence that seronegative individuals with a negative titer prior to vaccination achieve an adequate and long-lasting humoral immune response that is maintained for more than 180 days after immunization with this vaccine. The disadvantage of our study is the limited number of individuals and that we were not able to examine

cellular immunity, as is the case for most Sputnik V research reports. We believe that Sputnik V should be approved for immediate use by the WHO and the European Medicines Agency, the first of which is crucial for the vaccine to be deployed in low-income countries through the COVID Global Access 19 (COVAX) initiative [28].

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