Research Article

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Effectiveness after immunization with BNT162b2 and Gam-COVID-Vac for SARS-CoV-2 and neutralizing antibody titers in health care workers

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Abstract

Objectives: The aim of this study was to describe the effectiveness of the vaccines (Tozinameran and Sputnik V), administered on a convenience sample of healthcare workers, and also to describe the relationship between the levels of neutralizing antibodies (NAbs) and the type of vaccine used, as well as their association with incident cases during follow-up.

Methods: The study included 262 participants, who underwent vaccination during the period from September 2021 until August 2022. For determining the levels of NAbs we used the CLIA based method, and all the samples were processed with the SNIBE Maglumi 800 analyzer. The patients were observed for one year for occurrence of incident infection.

Results: The participants with prior SARS-CoV-2 positivity showed substantially higher titer of NAbs (8.86 vs. 0.94, p<0.001). The participants in the Gam-COVID-Vac group had median levels of NAbs of 1.57 (IQR 0.42–5.73), while they in the Tozinameran group showed substantially higher levels of 2.37 (IQR 0.9–6.27). The incident cases after immunization had substantially lower median values of NAbs when compared to the rest (0.48 vs. 3.97, p<0.001), and the interval between the second dose and the serological measurements were similar.

Conclusions: The current study showed that the tested vaccines demonstrated vaccine effectiveness of over 50 % during the first year after the vaccination in a sample of health care workers. Although health care workers remain separate population group, when compared to the rest, the results could be extrapolated to populations with similar age and immune experience.

Keywords: Maglumi 800; neutralizing antibodies; Tozinameran; Gam-Cov-Vac; SARS-CoV-2; health care workers

Introduction

The effectiveness of vaccines under new circumstances can be limited by multiple factors that go beyond its availability, including distribution and storage requirements, established health practices, changes that can occur in the population of interest [1]. Currently, three and a half year after the emergence of the SARS-CoV-2 pandemic, there are over 20 vaccines under WHO emergency listing [2], that are currently administered worldwide. Although the efficacy of some has been demonstrated beyond reasonable doubt, different opinions exist about their long-term outlook due to changes in the virus itself, due to uncertainties about vaccine scheduling, and due to range of results from risk-benefit analysis, when taking into consideration different age-groups or patient populations. During early phases, the availability was limited not only by pace of innovation, but also by manufacturing and distribution limitations [3], and

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by the requirements for storage and preparation before use [4]. Since vaccines are species-specific, new variants of the same virus can potentially create breakthrough infections. All these factors can hamper the estimated efficacy of a vaccine to a point at which it won't produce its intended effects. Beyond efficacy, the effectiveness of an intervention (vaccine) describes the effect of the intervention, taking into consideration the limitations that occur under real circumstances. Vaccine effectiveness (VE) has been shown to vary due to many factors and it is typically estimated at geographical/administrative level over some specific period [5].There are multitude of measurements of specific humoral elements or parts of immunity (proxies), that are used to assess for previous infection or vaccine exposure and to predict vaccine success and protection [6, 7]. In the case of SARS-CoV-2, the neutralizing IgG antibodies to SARS-CoV-2 are antibodies that target part of the pathogen and can block the spread of the infection, out of which most specific are antibodies targeted towards the S1 subunit of the receptor-binding-domain (RBD). Hence, their measurement is used as proxy for determining immunity towards the SARS-CoV-2, or to predict duration of protective effect.

Vaccine deployment in R. N. Macedonia began in early 2021 and it was consisted of deliveries of Tozinameran (or BNT162b2; mRNA-based) [8], Sputnik V (or Gam-COVID-Vac; rAd26 and rAd5 vector-based heterologous) [9] and (later) BBIBP-CorV (inactivated) [10]. The first applications were conducted in February 2021, on health care workers (HCWs), prioritizing those that were deemed as having high risk for contact with the virus. Chains for distribution utilized specific facilities for storage, such as the Institute for Transfusion Medicine of Republic of Macedonia, to meet the specific requirements. Facilities for serological testing for SARS-CoV-2 were available before hand, where the Institute for Medical and Experimental Biochemistry Skopje became the first accredited laboratory for such practice at national level. The process of vaccine deployment was done under coordination with public institutions, including the Ministry of Health, which were included extensively in the delivery and logistics for the arrival of the first batches of vaccines. The process of vaccination was initiated in February 2021, when the vaccines were prioritized to health care workers, on voluntary basis, leaving to them to choose one of the designated sites for vaccination (and type of vaccine).

Previous studies have estimated the prevalence of seropositivity in the Skopje area at different time points [11], prevalence of seropositivity among health care workers [12], but also effectiveness of different schedules and combinations of vaccines [13, 14]. Yet, the effectiveness of the administered vaccines according to standard scheduling remains unconfirmed at national level, despite the need to estimate its duration of effect. The primary aim of the current study is to describe the effectiveness of the vaccines available at time of initiation of the study (Tozinameran and Sputnik V), administered on a convenience sample of health care workers, over period of 12 months. The secondary aim is to describe the relationship between the levels of neutralizing antibodies and the type of vaccine used, as well as their association with incident cases during follow-up. The present study is conducted using one of the first deliveries of vaccines that were deployed to our country, in a sample of health care workers, during time when the δ-variant of the virus was prevalent [15].

Materials and methods

The study is an open label trial on convenience sample of healthcare workers. All health care workers from Skopje area that accepted the call for vaccination and received two doses of the vaccine were considered for the study. All the participants were informed about the study procedures and were asked for consent to participate. The participants underwent vaccination with with either Sputnik V or Tozinameran (2 doses, with recommended interval of 21 days). The participants were asked for their demographics and were checked for previous infections or positive tests for SARS-CoV 2 before vaccination. There were no recommendations on how to deal with subsequent changes in recommendations for vaccination, such as eventual recommendation for booster doses etc. Additionally, participants were asked to visit the laboratory to obtain peripheral blood for determining the levels of neutralizing antibodies. This involves the use of the chemiluminescent immunoassay (CLIA) based method, and all the samples were processed with the SNIBE Maglumi 800 analyzer. Antibodies detected by this test directly target the CoV spike (S1 and S2) antigens, according the manufacturer. As described previously, the threshold serum level of NAbs was 0.3 μg/mL (Snibe Diagnostic, Shenzen New Industries Biomedical Engineering Co. Ltd., Shenzen, China) for conferring immunity. The patients were checked one year after the date of their second dose of vaccine for incident infections and testing. Of note is that all participants are active health care workers that require to report symptoms of febrile illness and are readily tested for SARS-CoV-2 using PCR-based methods, while the results are electronically verifiable through the national electronic health system MojTermin. The reported analysis and results were processed using Microsoft Office Excel and R Studio. The patient data was summarized in

terms of patient inclusion, missingness of data, baseline measurements, NAbs levels, subsequent immunization(s) or positivity during follow up, while day differences were calculated between significant dates of the participant timeline.

Outcomes of interest (proportion of patients with incident SARS-CoV-2 infection, subsequent immunizations, measured levels of NAbs) were summarized by groups divided along (1) positivity before vaccination, (2) type of vaccine received, (3) use of booster dose during follow up, to check for distributional assumptions and differences in baseline measurements. To approximate VE, two sets for analysis were used, the first set (DS1) with all patient data, and second set with exclusion of patients that received booster dose during analysis (DS2). The proportion of patients with subsequent positive test was directly compared between groups, by using the chi^2 test for differences, and to check whether the overall effectiveness is above 50 %. To examine the factors that influence the generation of NAbs, while considering the day differences of measurements, binomial logistic regression modeling was used. Additionally, we also sought to examine which of the collected variables (besides the level of NAbs) are associated with cases of incident infections (dependent variable) by using the same method. The accepted α level for rejecting the null hypothesis was declared to be 0.05.

Results

The study included 262 participants that were enrolled by September 2021. There were no participants that had positive test or febrile illness due to SARS-CoV-2 between the period from vaccination to serological measurement. Laboratory measurements were completed at the initial visit for every participant. All participants finalized the observation period, which ended in August 2022 and there were no cases of loss during follow-up. The sample was consisted of 111 (42 %) males and 151 female health care workers, with a median age of 36 years, and 70 participants (27 %) had records for infection before vaccination (before February 2021). Half of the sample have received Gam-COVID-Vac and 131 patients have received Tozinameran. All the participants finished the study period. Overall, the median day difference between the administration of the second dose of the vaccine and the serological testing was 128 days (IQR 116.0–162.5 days), and the median NAbs level was 2.03 (IQR 0.58–5.88), while 74 (28 %) participants contracted the virus during follow-up. During follow up, 75 (29 %) participants received a booster dose (all of them with Tozinameran).

Sample

Participants with prior SARS-CoV-2 positivity and according to vaccine type

From the whole sample, 70 participants (26.7 %) had an episode of SARS-CoV-2 before immunization, with median difference of 130 days (range 123–163 days). Compared to the participants that did not have prior SARS-CoV-2 infection, this group of participants were slightly older (38.5 vs. 36.0 years, associated p-value=0.027, see Figure 1), while the two groups did not differ in terms of gender, type of vaccine received or other described variables. The participants with prior SARS-CoV-2 positivity showed substantially higher titer of NAbs (8.86 vs. 0.94, p<0.001). The results are presented in Table 1.

Regarding to the vaccine type received, participants showed similar age distribution, previous SARS-CoV-2 positivity and the interdose interval (in days); however, the serological measurements were done earlier in patients that received Gam-COVID-Vac, when compared to the Tozinameran group (127 vs. 165 days, p<0.001). The participants in the Gam-COVID-Vac group had median levels of NAbs of 1.57 (IQR 0.42–5.73), while the participants in the Tozinameran group showed substantially higher levels of 2.37 (IQR 0.9–6.27). This was not compared due to the differences in time from vaccination to measurement, but it is obvious that such comparison would yield statistically significant

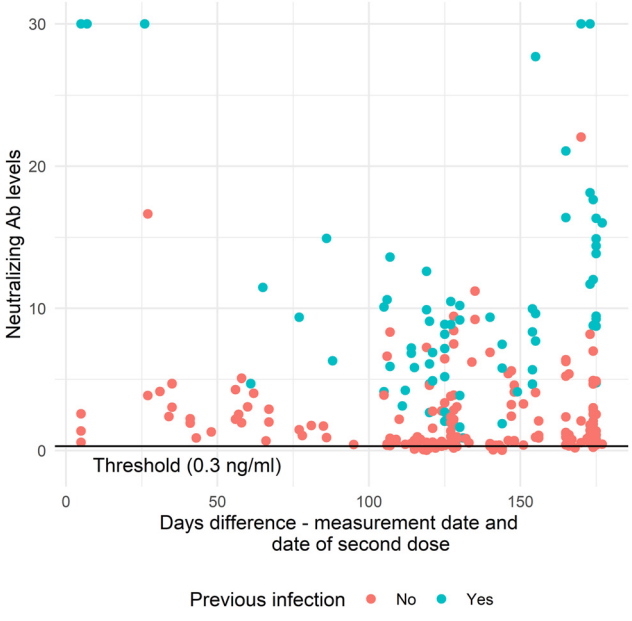

Figure 1: Scatterplot of neutralizing antibody levels and day difference of measurement date and date of second dose, colored by previous infection. The black line shows the threshold value.

Table 1: Summary of the sample by previous SARS-CoV-2 infection.

Characteristic	No previous infection n=192	With previous infection n=70	Associated p-value
Age, years, median (q1, q3)	36 (31, 42)	38.5 (34, 42)	0.027
Gender, male, n (%)	79 (41 %)	32 (46 %)	0.51
Days between two doses, median (q1, q3)	21 (21, 22)	21 (21, 24.7)	0.31
Neutralizing Ab's titer, median (q1, q3)	0.94 (0.44, 2.81)	8.86 (5.3, 12.5)	<0.001
Type of vaccine			0.40
Gam-COVID-Vac (group 1)	93 (48 %)	38/70 (54 %)	
BNT162b2 (group 2)	99 (52 %)	32/70 (46 %)	

differences. Additionally, there were statistically significant differences in terms of gender (p=0.018) in terms of choice of the vaccine, where substantially higher proportion of females were vaccinated with Tozinameran.

During follow-up, 42 (32 %) participants in group 1 and 33 (25 %) participants in group 2 received a booster dose (ns, p-value=0.22). The proportion of patients with infection during follow-up was 28 % in both groups, and after excluding cases with subsequent booster doses, the proportions rose to 42 % of the participant in group 1 and 38 % of the participants in group 2 (ns, p=0.59).

Incident cases after immunization

The incident cases, when compared to the rest, were with similar and gender composition. None of the incident cases received booster dose during follow up, and one only one participant that had SARS-CoV-2 prior immunization got infected during follow up. The incident cases had substantially lower median values of NAbs when compared to the rest (0.48 vs. 3.97, p<0.001), and the interval between the second dose and the serological measurements were similar (134 vs. 128 days difference). None of the incident cases developed need for hospitalization. The median time (from second vaccine) to positivity (for incident cases) in our sample was 268 days (IQR 239–307 days), where the earliest incident case was after 147 days, and it coincided with distinguishable peak of cases on national level during the end of 2022. The calculated raw odds ratio is 1, given the fact that equal number of incident infections were noticed in both groups.

Factors for subsequent infection

A binomial logistic regression model with incident infection as a dependent variable and levels of NAbs, prior infection, type of vaccine and day difference between application and measurement as independent variables was specified, excluding cases that did received additional booster dose (Table 2). The AIC value of the model was 40.82 and revealed that only the NAbs value remained statistically significant predictor for subsequent positivity (Table 3). According to the model, any subsequent rise in the NAbs levels by 0.1 ng/mL was associated with reduction in the log odds for subsequent infection by −2.76.

Table 3: Results from binary logistic regression with subsequent infections as dependent variables.

Variables	Beta	St. error	Confidence interval (95 %)	Associated p-value
Intercept	4.86	2.05	[1.50–9.88]	0.012
NAbs levels	−2.76	0.65	[−4.41 to −1.76]	<0.001
Day difference between second application and measurement	0.01	0.01	[−0.00 to 0.03]	0.1407
Infection with SARS-CoV-2 before vaccination	0.57	1.64	[−2.98 to 3.93]	0.724
Vaccine used: BNT162b2	−0.51	1.21	[−3.08 to 1.88]	0.674

Table 2: Summary of the sample by at baseline and follow up, overall and by vaccine received.

Characteristic	Gam-COVID-Vac, n=131	BNT162b2, n=131	Associated p-value
Age, years, median (q1, q3)	36 (32, 42)	36 (32, 42)	0.86
Gender, male, n (%)	65 (50 %)	46 (35 %)	0.018
Previous SARS-CoV-2 infection, n (%)	38 (29 %)	32 (24 %)	0.40
Days between two doses, median (q1, q3)	21 (21, 24)	21 (21, 24)	0.24
Days between 2nd dose and measurement, median (q1, q3)	127 (119, 131)	165 (86–174)	<0.001
Neutralizing Ab's titer, median (q1, q3)	1.57 (0.42, 5.73)	2.37 (0.90, 6.27)	0.003
NAb titre above threshold value (0.3), n (%)	111 (85 %)	128 (98 %)	<0.001
Positive test during follow-up, n (%)	37 (28 %)	37 (28 %)	>0.99
Received additional booster in the following 6 months, n (%)	42 (32 %)	33 (25 %)	0.22

Discussion

The present study is the first study from our country that describes the effectiveness of two different vaccine formulations used for prevention of SARS-CoV-2 infection, using standard scheduling, over period of 12 months at national level. The effectiveness was described in terms of positivity, in a cohort of medical health workers that were involved in the pandemic. Due to the narrow age range and the specifics of the sample, the results of the present study can be extrapolated only cases that have similar age, socioeconomic status, and for a strain of SARS-CoV-2 that has similar epidemiological characteristics to the δ-variant. Most limiting factor of the present study is that the study did not restrict the participants to use additional vaccines in the follow up period, leading to loss of power of the study and possible introduction of bias. Although vaccine effectiveness is estimated using different endpoints, such as subsequent hospitalization due to viral illness, our sample consisted of population that was not likely to develop such consequences, owing to their age range and previous exposure to the virus. Additional consideration in mind is the changing nature of the virus: namely, the last months of the observation period were periods when the omicron-variant became prevalent [16, 17]. Regarding the secondary objectives of the study, the study did show that higher levels of NAbs (above 0.3) show lower incidence of subsequent infection. Although the time difference between vaccine application and measurement of NAbs differed substantially, it is obvious that patients that were vaccinated with Tozinameran did show higher levels of NAbs, which were measured later than the patients that did receive the other vaccine – Sputnik V. The vaccine effectiveness of both vaccines showed the same result, after removing the patients that did receive additional booster dose during observation. The results point out that even if we do include the patients that did receive additional booster dose during observation, the vaccine effectiveness remained the same between these two groups. The vaccines were not regarded in terms of their safety, as that was beyond the scope and the power of the study.

The present study found that 68 % of the patients vaccinated with Sputnik V and 72 % of the patients vaccinated with Tozinameran, that did not receive any additional booster dose, were negative during the observation period of 12 months. None of the infected patients developed a need for hospitalization and substantial respiratory illness. According to previous study conducted on health care workers [18] using the Tozinameran and the ChAdOx1 nCoV-19 vaccine in UK, the results showed high degree of protection in the first 6 months, while patients that contracted the virus before the vaccination did show longer immunity.

Regarding the antibody response, the patients that belonged to the Tozinameran group showed higher titers, although their levels were determined later than the first group, that did receive Sputnik V. Such results were found in a large study on health care workers in the Netherlands [19]. The study compared Tozinameran with mRNA-1273, AZD1222 or Ad26.COV2.S, with consistent superiority of antibody response after Tozinameran, when compared to the other vaccines, over 12 months period. Despite that, the study did not report subsequent infections in the sampled participants.

Conclusions

The study expectingly confirmed that participants that were with previous registered exposure to the virus had substantially higher antibody titers after vaccination, when compared to those without previous documented infection. The vaccines that were used in our study produced similar efficacy outcomes, maintaining that the available vaccine options at that time were indeed a successful effort in putting control over the spread of the pandemic. The results of the study are generalizable only to similar populations, e.g. health care workers under the specific circumstance of working with infected patients, due to their exposure to the virus and ill patients, their educational level and information asymmetry (when compared to the general population). The study is limited only to efficacy measures, without undertaking the task of determining the safety, which was beyond the scope of the study and beyond the required time to observe such data.

Research ethics: Our study was approved by the Ethics Committee for human research of University “Ss. Cyril and Methodius”, Faculty of Medicine in Skopje, with approval number 03-2389/3, dated Jul 9, 2020.
Informed consent: Informed consent was obtained from all individuals included in this study.
Author contributions: ME, DC and VA contributed substantially to the concept and design of the study. ME wrote the manuscript. DC performed statistical analysis. CK contributed to the collection of data. HA and IK performed laboratory analysis. KTT, DCP and VA revised and edited the manuscript and interpreted the results. The authors have read and approved the manuscript for publication.
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