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Long-term antibody response following SPUTNIK V primary vaccination in healthcare workers with and without history of SARS-CoV-2 infection: Prospective cohort study from a hospital in Argentina

A. Gentile [a], V.E. Castellano [a,*], A. Pacchiotti [a], N. Weinberger [b], S. Diana Menéndez [a], M. del Pino [a], G. Carciofi [b], P. Lamy [a], A.S. Mistchenko [c]

[a] Epidemiology, Ricardo Gutierrez Children's Hospital, Gallo 1330, Buenos Aires City, Argentina
[b] Department of Virology, Ricardo Gutierrez Children's Hospital, Gallo 1330, Buenos Aires City, Argentina
[c] Commission of Scientific Investigations of the Province of Buenos Aires, Calle 526, La Plata, Buenos Aires Province, Argentina

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ABSTRACT

Background: In December 2020, Sputnik V was incorporated to the National COVID-19 Immunization Plan in Argentina. Studies had shown 98% of antibody response rate. To date, data on immunogenicity and antibody persistence in Argentina are scarce.

The objective was to assess humoral immune response after two doses of Sputnik V in Health Care Workers (HCWs) at the Ricardo Gutierrez Children's Hospital (RGCH).

Methods: A prospective, cohort study in HCWs immunized with two doses of Sputnik V between February and March 2021. The following variables were assessed: age, gender, risk factors for severe COVID-19 or mortality, immunosuppressive therapy and history of SARS-CoV-2. Blood samples were drawn on the day of the first dose, 28 days and 180 days after the second. Anti-Spike IgG was measured using an ELISA assay. Differences in immune response were evaluated according to study variables. Comparison analyses between groups with or without history of infection were performed, with T-test and ANOVA or Mann-Whitney tests. For each subject, we compared baseline values with 28 days and 180 days after the second vaccine.

STATA version 14 and R Sofware were used for data analyses.

Results: We included 528 individuals, mean age 41.5 years, 82.9% female, 14.4% (76/528) reported previous SARS-CoV-2 infection.

All subjects developed antibodies post-vaccination. At day 28, concentrations were significantly higher in previously infected than naïve subjects ($p < 0.001$) with no differences according to age, gender and comorbidities.

At day 180, 17% (95% CI 13.17–21.53) of naïve subjects were negative. Antibody concentrations decreased significantly in all subjects except in those who reported SARS-CoV-2 infection after vaccination ($n = 31$). This last group had significantly higher antibody concentrations.

Conclusion: This study assessed immune response to a new COVID-19 vaccine in real life in a cohort of subjects. Antibody concentrations varied according to history of SARS-COV-2 infection and decreased over time.

Introduction

The rapid spread of the SARS-CoV-2 virus and the global impact of COVID-19 led to a prompt response from the scientific community to develop tools to control the pandemic. Vaccines authorized for emergency use are currently administered in many countries worldwide [1].

Gam-COVID-Vac (Sputnik V), developed by the Russian Gamaleya Research Institute, is a combined vector vaccine based on recombinant human adenovirus type 26 and recombinant human adenovirus type 5 [2]. Both vectors encode the gene for SARS-CoV-2 spike (S) glycoprotein. The vaccine doses are administered 21-days apart.

Most SARS-CoV-2 neutralizing antibodies elicited after vaccination are targeted against the receptor-binding-domain (RBD) included in the S protein, which is responsible for virus binding to a host cell receptor [3].

* Corresponding author.
E-mail address: hnrgvacunas@gmail.com (V.E. Castellano).

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According to the results of the phase 1/2 study, Sputnik V is safe and induces a strong humoral and cellular immune response [2]. An interim analysis showed that RBD SARS-CoV-2 specific antibodies were elicited in 98% of study subjects, 42 days after vaccination [4].

In December 2020, Sputnik V was the first vaccine to be used in Argentina under the frame of the Strategic Immunization Plan which initially prioritized vaccinating active health-care workers (HCWs) based on increased risk of exposure [5].

The objective of this study was to assess the immune response to two doses of Sputnik V and the long-term humoral immune response in naive and previously infected volunteers who received SPUTNIK V in HCWs at the Ricardo Gutierrez Children's Hospital (RGCH).

Material and methods

A prospective, observational, analytical, cohort study in HCWs immunized with two doses of Sputnik V was undertaken. Subjects were enrolled between February and March 2021.

HCWs at the RGCH attending the COVID vaccination site were invited to participate and signed the informed consent form. We included individuals who received two vaccine doses with a minimum interval of 21 days, as recommended by the National Ministry of Health guidelines at the time [6]. Those subjects who presented with SARS-CoV-2 infection between the first dose and up to day 28 of the second dose and those who presented a second SARS-CoV-2 infection during follow-up were excluded.

Data collection

An epidemiological record was created in the REDCap database [7].

The following variables were included: age, gender, profession, risk factors for severe COVID-19 or mortality (Type 1 or 2 diabetes, grade 2 or grade 3 obesity, chronic cardiovascular disease, chronic kidney disease, chronic respiratory disease, cirrhosis, HIV, transplanted or waiting for transplantation, oncological and oncohematological disease, autoimmune diseases and/or immunosuppressive treatments) [8] and history of COVID-19 infection confirmed by PCR or the presence of anti-spike IgG antibodies before vaccination.

Epidemiological follow-up was undertaken using periodic online surveys at days 28, 60, 120 and 180, to assess COVID-19 incidence and clinical outcomes 14 days after the second dose up to 6 months in our study cohort.

Blood samples were drawn at baseline on the day of vaccination, 28 (21–40) days and 180 (180–210) after the second vaccine dose.

Quantitative SARS-CoV-2 anti-spike IgG antibodies were measured using the ELISA COVID-AR IgG® Kit immunoassay, manufactured by Lemos laboratory [9]. The assay was approved by ANMAT (the National Drug, Food and Medical Technology Administration) PM-1545–4, and distributed for epidemiologic and surveillance purposes. It consists of an indirect, non-competitive, enzyme-linked immunosorbent assay providing 96 polystyrene wells, coated with the spike protein and the RBD domain.

Presence or absence of IgG antibodies was determined according to a pre-established threshold, using the positivity index (PI) obtained by estimating the ratio between the optical density (OD) of the sample and the cut-off point (0.150 + mean OD of negative controls). Samples with a PI $\geq$ 1.1 were considered positive and PI < 1.1 negative.

The positive samples were quantitatively studied by performing a calibration curve, using the First WHO International Standard for human anti-SARS-CoV-2 immunoglobulin NIBSC Code 20/136 (version 2.0 of 12/17/2020). The extrapolation of the absorbances obtained from the samples in the corresponding curve, gives a concentration result in IU/ml. Measurements were carried out using the Stat Fax 2010 photometric reader, applying 450 nm and 620–630 nm filters following manufacturer guidelines.

Validation of COVID-AR IgG® Kit, carried out in our laboratory, showed 100% sensitivity (95 %CI: 91.59–100) and 100% specificity (95 %CI: 98.17–100). Validation method is described in the supplementary material.

Data analyses

STATA version 14 and R Sofware were used for data analyses. Differences in immune response were evaluated according to: age, gender, risk factors for COVID-19, immunosuppression and history of infection.

First, a descriptive analysis of each variable was carried out, the categorical ones as absolute and relative frequencies, the numerical ones with mean or median according to the normal distribution or not (Kolmogorov or Shapiro-Wilk test) and according to the sample size. The standard deviation and the 25th and 75th percentiles were used as measures of dispersion.

Table 1
Population characteristics and demographics.

Characteristics		N = 528	% (IC 95 %)
Age			41.54 (SD 11.23)
Gender	Female	438	82.95 (79.47–86.06)
	Male	90	17.05 (13.94–20.53)
Profession	Physician	279	52.84 (48.48–57.17)
	Nurse	58	10.98 (8.45–13.97)
	Technician	41	7.77 (5.63–10.39)
	Administrative	27	5.11 (3.4–7.35)
	Other	123	23.3 (19.75–27.14)
Risk factors	No	485	91.86 (89.19–94.04)
	Yes	43	8.14 (5.96–10.81)
Type of risk factors*	Obesity	18	3.41 (2.03–5.33)
	Chronic respiratory disease	12	2.27 (1.18–3.94)
	Diabetes	10	1.89 (0.91–3.45)
	Immunosuppressive therapy **	5	0.95 (0.31–2.19)
	Cancer ***	2	0.38 (0.04–1.36)
	Cardiovascular disease	1	0.19 (0.0–1.1)

* Multiple options.
** Ankylosing spondylitis (n: 2), rheumatoid arthritis (n: 1), multiple sclerosis (n: 1), multiple myeloma (n: 1).
*** Breast cancer (n: 1), multiple myeloma (n: 1).

Two groups of participants were defined for the analysis at baseline:

Group 1: those subjects with evidence of SARS-CoV-2 infection prior to vaccination.

Group 2: those subjects without infection prior to vaccination. At day 180 those who presented SARS-CoV-2 infection between days 28 and 180 post second dose were subclassified as subgroup 2A, and those who did not report infection during follow-up as subgroup 2B.

Comparison analyses between groups with or without history of infection were performed, fulfilling the assumptions, with parametric (T-test and ANOVA) and non-parametric (Mann-Whitney) tests. A significance level of 0.05 was considered.

For each subject, we compared baseline values with values 21–40 days and 180–210 days after the second dose.

Additionally, incidence of SARS-CoV-2 infection in each group was estimated and then relative risk (RR) was calculated.

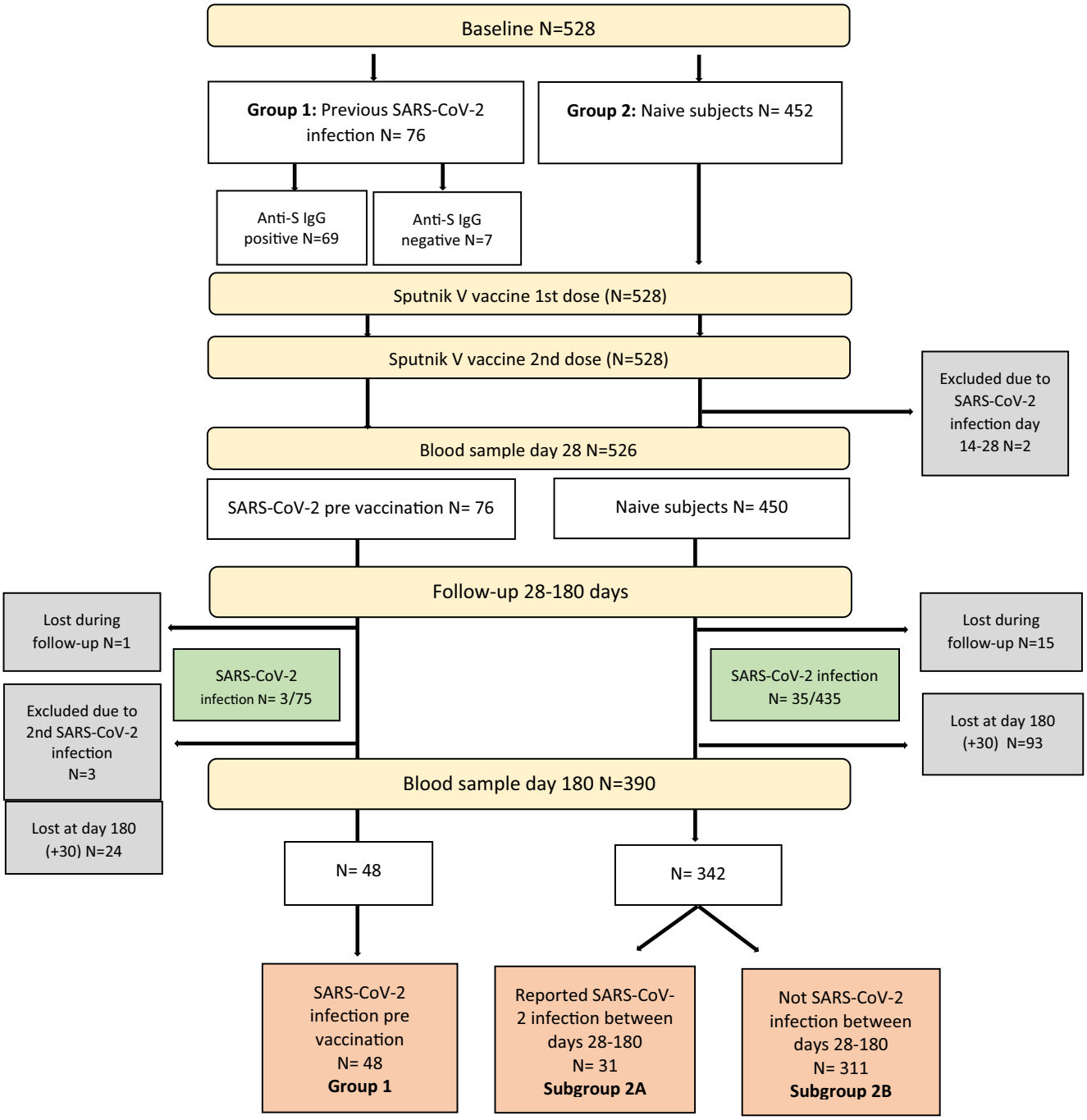

Fig. 1. Study flow chart. HCW who received two vaccine doses were included. Blood samples were drawn at day of first dose to determine previous seroprevalence. Two groups were defined at the beginning of the study according to the history of SARS-CoV-2 before vaccination: **Group 1:** those subjects with evidence of SARS-CoV-2 infection prior to vaccination, **Group 2:** naïve subjects. Epidemiological follow up during 180 days was performed to asses SARS-CoV-2 infection and two blood samples were drawn at days 28 and 180 after second dose. Those subjects who presented SARS-CoV-2 infection between the first dose and up to day 28 of the second dose and those who presented a second SARS-CoV-2 infection during follow-up were excluded. Losses during follow up were documented. At day 180 participants in group 2 were subclassified: **subgroup 2A**: those subjects without infection prior to vaccination who presented SARS-CoV-2 infection between days 28 and 180 post second dose, and **subgroup 2B**: those seronegative subjects in the baseline sample, who did not report infection during follow-up.

Ethics

The study was approved by the Research and Ethics Review Committee at the RGCH (register number 4033). Subjects voluntarily agreed to participate in the research and signed an inform consent form, no monetary compensation was provided and confidentiality was ensured.

Results

A total of 528 participants were included (Table 1). Seventy six individuals (14.4%) had had prior SARS-CoV-2 infection, seven of whom (9.2%) were seronegative at baseline; seroprevalence rate was 13.1% (69/528).

In Fig. 1 the flowchart including reported infections, excluded subjects and losses during the follow-up is described. Those who reported SARS-CoV-2 infection after vaccination had mild symptoms without complications.

Mean interval between first and second vaccination doses was 24.2 days (median 22 days, interquartile range (IQR) 21–52 days).

Antibody response in HCW after vaccination with Sputnik V is shown in Fig. 2.

All subjects had positive antibody titres 28 days after the vaccination series. The mean (SD) antibody concentration was 993 IU/ml (7805.1) in naive subjects (Group 2) and 32725 IU/ml (110009.9) in those with previous infection (Group 1). Significantly greater increase in concentration was observed in individuals with prior infection ($p < 0.001$). No significant differences were found in antibody response for different age, gender and risk factors.

At day 180, mean antibody concentrations (SD) were 4575.2 IU/ml (27788.9) in group 1, 685.5 IU/ml (854.6) in subgroup 2A and 87.5 IU/ml (147.1) in subgroup 2B. In this last group 17 % (95% CI 13.17–21.53) of subjects were negative; in groups 1 and 2A all subjects were positive.

Antibody concentrations decreased significantly in group 1 and subgroup 2B. For subgroup 2A, a significant increase in antibody concentration was observed between days 28 and 180.

When concentrations at 180 days were compared between groups, those who had SARS-CoV-2 infection during follow-up (subgroup 2A) had significantly higher antibody concentrations compared to those who were not infected (subgroup 2B). No differences were observed between group 1 vs 2A and 1 vs 2B.

The incidence of SARS-CoV-2 infection was 4% (3/75) in group 1 and occurred at days 48, 68 and 109 post vaccination. In group 2 incidence was 8% (35/435) and took place at a mean of 74.17 days (SD 40.9). The RR was 0.50 (CI 95% 0.16–1.58) without significant differences.

Discussion

The study population comprised mainly middle-aged, female medical staff with no risk factors for severe COVID-19 since, from

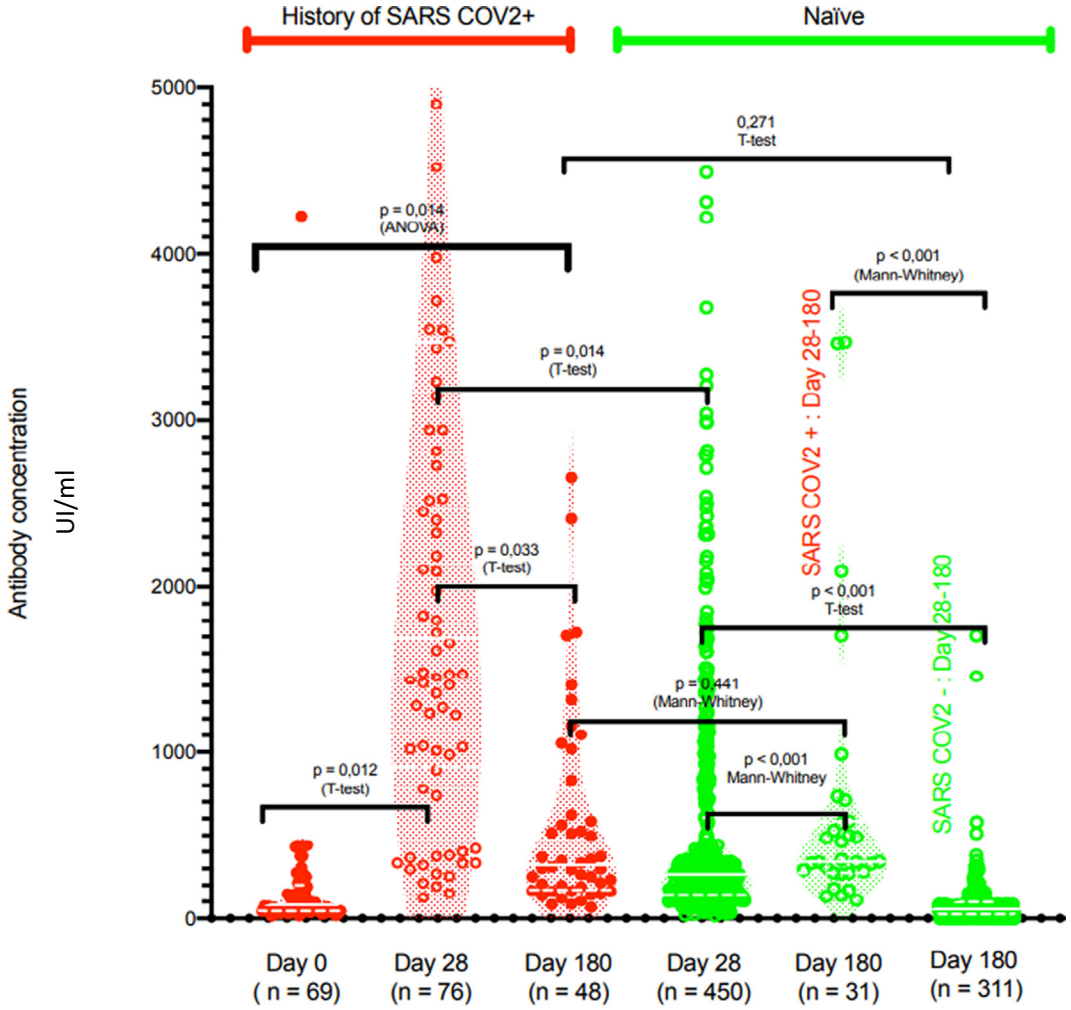

Fig. 2. Antibody response after vaccination with Sputnik V. Red colour describes antibody response in group 1 at days 0, 28 and 180. Green colour shows antibody response at day 28 in subjects without previous SARS-COV-2 infection (group 2), and at day 180 in subgroups 2A and 2B.

the outset, active healthcare workers were an important target of the vaccination programme.

This real life study assessed SARS-CoV-2 IgG antibody response in a group of HCWs at a Children's Hospital after receiving two doses of Sputnik V. All HCWs developed antibodies 21 to 40 days after the second vaccine dose, similar to results of immunogenicity reported by Logunov et al. in an interim analysis of a phase three trial [4]. Studies with other vaccine platforms also described high rates of immune response [10–12].

We compared the immune response between subjects with and without a history of COVID-19, those that had previous infection (around 14%) elicited higher antibody concentrations. In Argentina, Rossi et al. [13] assessed antibody response in 289 HCWs, 21% of whom had had prior infection. They found significantly higher anti-spike IgG titres in the latter group compared to naïve subjects after the first vaccine dose, although no significant differences were observed after the second dose. Similar results were observed by Claro et al. in Venezuela [14]. Baseline seroprevalence rates, however, were different to those in our study because study populations included HCWs in general hospitals who have greater occupational risk of exposure to SARS-CoV-2. Chahla et al. also found higher antibody levels in individuals with a history of COVID-19 [15]. Besides, Cordova et al. [16] found that history of COVID-19, mainly symptomatic, systemic reactogenicity and interval between doses $\geq$ 4 weeks were associated with elevated antibodies response after two doses of Sputnik V vaccine. Studies evaluating other vaccine platforms also found differences in response rates between previously infected and naïve participants [17–20].

We did not find significant differences in the immune response according to age, presence of co-morbidities or immunosuppression, however these results should be interpreted with caution since our population sample was small. In the phase three study interim analysis, 18 to 30 year-olds reached higher titres than older age groups [4]. Chahla [15] and Claro [14] did not find significant differences between age groups.

This study assessed the persistence and concentration of antibodies at 180 days post vaccination. It was observed that only 83% of those who had not reported infection had positive antibodies. Similar studies with other platforms have also reported a drop in antibody levels [10,11,21] as well as in effectiveness over time and new variants. [22] These findings support national dynamic recommendations of periodic vaccine boosters throughout the pandemic [23,24].

In addition, naïve group presented significant differences in long-term concentrations when compared to those previously infected. This finding was observed in other publications [25,26], as well as for other platforms [21] and has been taken into account in the national immunization program, which recommends those infected to postpone the booster for 3 months [23].

One of the limitations of this study is the fact that neutralizing antibodies were not measured, albeit evidence suggests that levels of anti-spike IgG measured by the COVID-AR test correlate with neutralization activity [3,27,28].

A second limitation is that we included few individuals receiving immunosuppressive therapy. Despite a positive immune response in all subjects, this limitation reduces external validity.

Finally, the incidence of SARS-CoV-2 infection during follow-up was calculated by self-report of the subjects. This condition could represent a bias in the concentrations of the naive group (subgroup 2B) at day 180, possibly including asymptomatic cases.

Additional research regarding immune response to boosters and effectiveness given new variants is needed.

The strength of this study is that it is an evaluation of the immune response to a new COVID-19 vaccine in real life in a cohort of subjects. This may provide valuable evidence for public health decisions.

Conclusions

All HCWs immunized with two doses of Sputnik V developed anti-spike antibodies at 28 days. Prior SARS-CoV-2 infection was associated with a greater immune response.

At day 180, 17 % of subjects without history of infection were negative. Antibody concentrations decreased significantly in all subjects except in those who reported SARS-CoV-2 infection after vaccination.

Data sharing

Anonymous participant data will be available upon request to the corresponding author. Proposals will be reviewed and approved by the researchers, and staff on the basis of scientific merit and absence of competing interests. Once the proposal has been approved, data can be transferred through a secure online platform after the signing of a data access agreement and a confidentiality agreement.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2022.100187.

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