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Evaluation of the Gam-COVID-Vac and vaccine-induced neutralizing response against SARS-CoV-2 lineage P.1 variant in an Argentinean cohort

Sebastián Blanco a,⁎, Brenda Salomé Königheim a,⁎, Adrian Diaz a,⁎, Lorena Spinsanti a, Juan Javier Aguilar a, María Elisa Rivarola a, Mauricio Beranek a,⁎, César Collino b, MinSalCba working group c,1, FCM-UNC working group d,2, Miguel Diaz b, María Gabriela Barbás e, Arnaldo Mangeaud f, Sandra Verónica Gallego a,⁎

a Instituto de Virología Dr. J. M. Vanella, Facultad de Ciencias Médicas, Universidad Nacional de Córdoba, Córdoba, Argentina
b Hospital Guillermo Rawson, Ministerio de Salud de la Provincia de Córdoba, Córdoba, Argentina
c Ministerio de Salud de la Provincia de Córdoba, Córdoba, Argentina
d Facultad de Ciencias Médicas, Universidad Nacional de Córdoba, Córdoba, Argentina
e Secretaría de Prevención y Promoción de la Salud, Ministerio de Salud de la Provincia de Córdoba, Argentina
f Facultad de Ciencias Exactas, Físicas y Naturales, Universidad Nacional de Córdoba, Córdoba, Argentina
g Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina

⁎ Corresponding author at: Facultad de Ciencias Médicas, Universidad Nacional de Córdoba, Instituto de Virología Dr. J.M. Vannella, Enfermera Gordillo Gómez S/N, Ciudad Universitaria, Córdoba, Córdoba 5000, Argentina.
E-mail address: sblanco@fcm.unc.edu.ar (S. Blanco).
1 Participants from MinSalCba working group: Hospital Rawson: Alejandra Álvarez, Lorena Ravera, Liliana Zappia, Aldo Barrera, Canela Brarda, Josefina Eynard Asua, Claudia Toledo, Carla Daniela Barrientos Alvarado, Julia Sabbatini, Laura Belén Coletti and Margarita Inés Cáceres;; Laboratorio Central: Gonzalo Manuel Castro.
2 Participants from FCM-UNC working group: Dean Rogelio Pizzi, Silvia Nates, Viviana Re and Belén Pisano.

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A B S T R A C T
We evaluated humoral immune-response elicited by Sputnik-V by measuring anti-Spike (S) IgG antibodies (Abs) and neutralizing antibodies (NAb) prior to, 14 and 42 days after-vaccination. The safety and disease rates among vaccinated individuals were also evaluated. Since SARS-CoV-2 lineage P.1 is rapidly spreading in Argentina, virus-neutralizing activity of Sputnik-V-elicited and infection-elicited NAb faced to P.1 were also assessed. A total of 285 participants were recruited; all reported good tolerance, without any severe adverse event. Nine COVID-19 cases were confirmed in fully vaccinated individuals and viable P.1 variant was successfully isolated from one of them. At day 42, 99.65% of the individuals had anti-S IgG; however, 23.15% had not detectable NAbs. Significantly higher neutralization potency against WT compared to P.1 (p < 0.001) was observed. Some samples failed to neutralize P.1, mainly among vaccinated-naïve subjects; however, no significant differences were observed among previously infected-vaccinated individuals. Our results corroborated that Sputnik-V is safe and induces an efficient humoral immune response, although not all immunized subjects develop Nabs. Herein, we show for the first time, evidence of infectious SARS-CoV-2 shedding from Sputnik-V fully vaccinated individuals, by the isolation of viable virus from the nasopharyngeal swab of one participant of our study, 139 days after receiving the second dose. Thereby, we provide evidence indicating that the vaccine might avoid severe forms of COVID-19 but does not prevent infection nor prevents transmission from a fully vaccinated individual.
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1. Introduction
On December 2020, the National Administration of Medicine, Food and Medical Technology of Argentina (ANMAT) registered and authorized the emergency use of Gam-COVID-Vac (Sputnik-V). Immediately and without delay, Argentina received the first doses of the vaccine and was the first country of Latin America to begin immunization with Sputnik V. This is a heterologous recombinant adenovirus (rAd)-based vaccine developed at Gamaleya National Research Centre for Epidemiology and Microbiology (Moscow, Russia). The rAd carries the gene for Severe Acute
Respiratory Coronavirus 2 (SARS-CoV-2) spike glycoprotein, which can induce protective immune response [1]. Phases 1 and 2 of the vaccine trials showed good safety profile and strong induction of humoral and cellular immune response in enrolled subjects. Moreover, Phase 3 clinical trial showed 91.6% efficacy against COVID-19 [1,2]. After publication of these results, several concerns regarding safety and efficacy were published in open letters [3–5]. Since Sputnik V became the vaccine administrated to the largest proportion of individuals immunized in Argentina and is being currently used in more than 60 countries, it is important to independently evaluate the primary outcome measures (antigen-specific humoral immunity and safety) and response of neutralizing antibodies, as demonstrated in Phase 1 and 2 research trials [1].

SARS-CoV-2 was identified for the first time in Wuhan, China, during 2019. The emergence of variants that may escape from the immune response has arisen concern regarding the efficacy of available vaccines and the threat of increased number of re-infections. In Latin America, a rapid resurgence in SARS-CoV-2 transmission and mortality during late 2020 and early 2021 was associated with the emergence and rapid spread of a new SARS-CoV-2 variant of concern in Manaus, Brazil named lineage P.1 [6]. This variant acquired 17 mutations, including a virtually identical triplet in the spike protein (K417N/T, E484K and N501Y) compared to B.1.351 variant, neutralization has been communicated against monoclonal antibodies (mAbs), authorized for emergency use, as well as for the panel of convalescent plasma and sera from vaccinated individuals who received Moderna SARS-CoV-2 mRNA-1273 and Pfizer BNT162b2 Covid-19 vaccines [8]. Nevertheless, a recent study shows that sera from subject vaccinated with Sputnik V retain neutralizing activity against P.1 [9]. Consequently, our aim was to independently evaluate the safety and disease rate among Sputnik-vaccinated individuals, antigen-specific humoral immunity and response of neutralizing antibodies generated by the vaccine. The efficacy of humoral response in the population immunized with Sputnik V faced with P.1 is a matter of great concern, with priority of elucidating if this new variant could be a threat for countries vaccinated mostly with Sputnik-V. Also, virus-neutralizing activity of Sputnik-V-elicted and infection-elicited NAb faced to P.1 was also assessed.

2. Material and methods

Since health-care workers (HCW) were considered the priority group to receive the vaccine against COVID-19 in Argentina, we recruited 285 HCW from a single Hospital from Córdoba City, who were immunized with Sputnik V on December 2020 and early January 2021, upon vaccine arrival. Participants with and without prior SARS-CoV-2 infection (76 and 209, respectively) were randomly recruited. The vaccine (0.5 ml/dose) was administered intramuscularly in a prime-boost regimen: a 21-day interval between the first dose (rAd26) and the second dose (rAd5). Safety of the two components of the vaccine was assessed among vaccinated individuals by monitoring self-reported adverse events. All participants were instructed to contact the team to report any sign or symptom that could be considered an adverse effect. The disease rate was assessed through a 6-month evaluation of HCW who received both doses of the vaccine. Thus, when COVID-19 symptoms were reported by a participant, PCR test was performed and if positive, the participant was considered a COVID-19 case. Following recommendations from the National Ministry of Health [10], samples from vaccinated subjects with Ct less than or equal to 30 in real-time PCR for the N, S or E gene were further evaluated by the Taqman SARS-CoV-2 mutation panel (Life technologies corporation, California, USA) for investigation of new variants. Also, attempts for viral isolation in cell cultures were carried out in these samples, as already described [11]. All participants completed the follow up period. To evaluate the immunity elicited by Sputnik V, we measured anti-Spike (S) IgG antibodies (Abs) and neutralizing antibodies (NAb) in samples collected from the HCW cohort at three different times: at baseline, prior to vaccination (when possible), after the first dose of the vaccine (at day 14) and after the second dose (21 days after the 1st dose, at day 42). We also analysed the cohort by the condition of having history of confirmed SARS-CoV-2 infection prior to vaccination. The cohort was divided by individuals: I- with history of previous infection, basal time (N = 67); II- without previous SARS-CoV-2 infection, 14 days post vaccination (N = 201); III- with history of previous infection, 14 days post vaccination (N = 68); IV- without previous infection, 42 days post vaccination (N = 209), V- with history of previous infection, 42 days post vaccination (N = 76). The detection of anti-S IgG Abs was assayed by COVIDAR IgG (Laboratorio Lemos, Buenos Aires, Argentina) and by SARS-CoV-2 IgG II Quant (Abbott, Sligo, Ireland). Samples with discordant or negative results were further tested by an “in house” indirect immunofluorescence assay carried out as already described [12]. The neutralizing ability of the Abs from samples of vaccinated HCW was evaluated by a Plaque Reduction Neutralization technique (PRNT) against SARS-CoV-2 live wild type strain (WT) B.1 lineage (hCoV-19/Argentina/PAIS-G0001/2020, GISAID ID: EPI_ISL_499083) using Vero C176 cells (ATCC CRL-587). The NAb titre was established as the maximum dilution of plasma with the ability to neutralize at least 80% of the inoculated Plaque Forming Units (PFU), as previously described [11]. In order to determine the effectiveness of vaccine-induced NAbS and those elicited by natural infection by SARS-CoV-2 WT to neutralize live SARS-CoV-2 lineage P.1, 157 plasma samples corresponding to the following categories were evaluated: Group A: Individuals recovered from natural infection by SARS-CoV-2 WT (N = 44), Group B: Individuals recovered from natural infection by SARS-CoV-2 WT who received one or two doses of Sputnik V (N = 67), and Group C: Individuals without previous infection by SARS-CoV-2 who received one or two doses of Sputnik V (N = 46). The individuals recovered from natural infection by SARS-CoV-2 WT were defined as those who had a laboratory-confirmed COVID-19 diagnosis prior to the introduction of the SARS-CoV-2 variants in Argentina. The determination of the neutralizing ability of the NAbS against the P.1 variant was performed using a PRNT with wild virus SARS-CoV-2 lineage P.1 (hCoV19/Argentina/PAIS-G0234/2021, GISAID ID: EPI_ISL_2037442), as formerly reported [11]. In parallel, the neutralizing properties of NAbS in the named samples were assayed against the WT as previously described.

The results are described in tables and figures with absolute frequencies and percentages. Chi-square test of independence (with Monte Carlo correction) was performed to analyse the associations. The detection of IgG antibodies against SARS-CoV-2.

### Table 1

| Antibodies | Baseline Sample N | % | Day 14 N | % | Day 42 N | % |
|------------|-------------------|---|----------|---|----------|---|
| Negative   | 183               | 74.69 | 39       | 14.5 | 1        | 0.35 |
| Positive   | 62                | 25.31 | 230      | 83.5 | 284      | 99.65 |
| ND         | 40                |        | 16       |       | 0        |       |
| TOTAL      | 245               |        | 269      |       | 285      |    |

ND = Not performed. TOTAL = assayed samples.
Fig. 1. Neutralizing antibodies in a cohort of individuals vaccinated with Sputnik V in Córdoba City, Argentina. Results in a Cohort of 285 subjects vaccinated with Sputnik V. 1a. Distribution of NAb titres in basal samples, at days 14 and 42 after vaccination, respectively. 1b. Distribution of NAb titres in I: Individuals with history of previous infection, basal time; II: Individuals without previous SARS-CoV-2 infection (naïve), 14 days post vaccination; III: Individuals with history of previous infection, 14 days post vaccination; IV: Individuals without previous infection (naïve), 42 days post vaccination, V: Individuals with history of previous infection, 42 days post vaccination. 1c. Geometric Mean Titres of neutralizing antibodies (GMT) in I, II, III, IV, and V groups. Means with a common letter are not significantly different (Kruskal Wallis test).
calculated. Furthermore, antilogarithms of GMTs were calculated. Titres lower than 1/10 were considered as 1 and titres more than 1/640 were considered 1280. Comparisons of GMTs between groups and inside each group (NAbS against WT and P.1 variant) were conducted using mixed linear models and Tukey’s post-hoc test. Soft R-Medic [13] and InfoStat [14] were applied, and in all cases, the significance level was 5%.

3. Results

From a cohort of 285 vaccinated HCW in Córdoba City, 800 samples were collected and analysed. The average age of the individuals was 39.24 years (±9.76) with a minimum of 20 years and a maximum of 65 years; 26.67% (N = 76) had previous exposure to SARS-CoV-2 virus and confirmed infection.

The vaccine demonstrated to be safe and well tolerated and no severe adverse events were informed by the participants. The most common mild adverse effects spontaneously reported were hyperthermia (47%), myalgia (42%), asthenia (39%), headache (33%), pain at injection site (28%) and shivers (6%), all of them were mild reactions.

Within the group of vaccinated subjects without history of previous infection (N = 209), nine COVID-19 cases were confirmed after the second dose of the vaccine, at days 87, 113, 116, 119, 128, 129, 139, 152, and 158 respectively. Thus, disease rate during the observation period among HCW who received both doses of the vaccine was 4.3% (9/209). Only the sample corresponding to the subject with confirmed infection at day 139 after the second dose had Ct less than 30 by PCR (Ct values: 17 and 19 for N and ORF 1ab genes, respectively), so it was further analysed. The virus was successfully isolated from a nasopharyngeal sample collected one day after onset of symptoms, showing cytopathic effect within 48 h after inoculation in cell culture. SARS-CoV-2 was confirmed by PCR and lineage P.1 was identified. The most frequent symptoms in COVID-19 cases were nasal congestion (3/9), odynophagia (3/9), cough (2/9), rhinitis (2/9), fever (2/9), rhinorrhea (2/9), dysgeusia (1/9), anosmia (1/9) y headache (1/9). Noteworthy, while five of these infected subjects had no detectable NAbS 42 days post vaccination (dpv), three of them did (two of them had titres of 1/20 and one 1/40, respectively). Among these three samples with NAbS, only the COVID-19 case from which we isolated infectious SARS-CoV-2 lineage P.1. (Nab titre of 1/20, 42 dpv against WT) was negative when faced to P.1, evidencing that, in this case, pre-existing vaccination antibodies failed to neutralize the P.1 variant.

Results of the detection of anti-S IgG Abs against SARS-CoV-2 in baseline samples prior to vaccination, in addition to samples from days 14 and 42 post vaccination are shown in Table 1. We observed that Sputnik V induced efficient humoral response in immunized individuals, since 99.65% of them had detectable antibodies after the second dose of the vaccine (day 42 after the first dose). However, not all the immunized HCWs developed NAbS. The presence and titres of NAbS in baseline samples, days 14 and 42 pv respectively, are shown in Fig. 1a. At day 42, 23.15% were negative for NAb detection (titres < 1/10). We also analysed the cohort by the condition of having history of confirmed SARS-CoV-2 infection prior to vaccination. Sixty-eight out of the 76 individuals with prior infection were screened for anti-SARS-CoV-2 antibody detection; 91.2% (62/68) of them yielded positive results. Fifty-seven of these samples were studied by PRNT and NAbS were detected in 93% of them (53/57) (Median 1/20 (Q1: 1/10; Q3: 1/40; Mode 1/20). Significant differences were observed comparing anti-S IgG Abs between vaccinated HCW with previous infection and those without previous infection at day 14 pv (98.57% vs 80.9%, respectively; p < 0.001), while there were not significant differences between both groups at day 42 pv (100% vs 99.5%; p = 0.546). The analysis of frequencies of NAb titres in participants with SARS-CoV-2 infection prior to vaccination compared to those who did not showed significant differences, both at days 14 and 42 pv (p < 0.001 and p < 0.001, respectively). Thus, most of the uninfected (88.61%) subjects did not have NAbS 14 days after the first dose of the vaccine, while only 8.70% of those with previous SARS-CoV-2 infection were negative after the first dose. Furthermore, at day 42 pv, subjects without NAbS in both groups were reduced to 30.62% and 2.63%, respectively.

In previously uninfected individuals, NAb titres significantly increased from day 14 to day 42 pv (p < 0.001); while the Median was < 1/10 at day 14 and 1/10 at day 42 pv, respectively (GMTs: 0.44 and 3.19, respectively). However, in participants with history of infection prior to vaccination the higher NAb titre was observed at day 14 pv. In this group, Median was 1/20 at baseline time, 1/320 at day 14 pv and 1/160 at 42 pv (GMTs: 8.5 and 7.6 at days 14 and 42 pv, respectively), being all these differences significant (p < 0.001) (Fig. 1b and c).

3.1. Neutralizing humoral response against the P.1 variant

Plasma samples from 157 individuals were assayed and categorized as previously described. When considering the samples overall, a higher significant neutralizing potency was observed against the wild type B.1 (WT) compared to P.1 (p < 0.001). Although both Medians of the NAbS titres were the same (1/80), quartile 1 was 1/40 and 1/20 for the WT and P.1 variants, respectively (Table 2). Furthermore, despite SARS-CoV-2 Lineage P.1 variant could be neutralized by plasma samples from all the categories (see Material and Methods), some of the samples with NAbS against the WT strain were negative against the P.1 variant (Fig. 2b).

Analysing NAbS titres among the categories (Groups A, B, and C), a significantly higher neutralizing capacity against WT strain was observed for groups A and C with no differences in the group of vaccinated individuals previously infected (Tables 3, 4, and Fig. 2). The analysis between categorized groups A, B, and C also demonstrated significant differences in the ability of the corresponding NAbS to neutralize the P.1 variant (Table 4).
Fig. 2. Neutralization of WT and P.1 by vaccine-elicited and COVID-19 convalescent plasma in Córdoba City, Argentina. Comparison of neutralizing antibody properties against wild type (WT) B.1 (hCoV-19/Argentina/PAIS-G0001/2020, GISAID ID: EPI_ISL_499083) (WT) and SARS-CoV-2 Lineage P.1 (hCoV19/Argentina/PAIS-G0234/2021, GSAID ID: EPI_ISL_2037442)(P.1). 1- Group A: Individuals recovered from SARS-CoV-2 WT natural infection, 2- Group B: Individuals recovered from SARS-CoV-2 WT natural infection that received one or two doses of Sputnik-V vaccine, and 3- Group C: Individuals without previous infection, vaccinated with one or two doses of Sputnik-V vaccine. 2a. Results of the analysis of neutralizing antibodies GMTs against WT and P.1 in each group performed with mixed linear models and Tukey's post-hoc test. Means with a common letter are not significantly different. 2b. Distribution of NAb titres against WT and P.1 lineages in each group. 2c. Neutralizing GMTs are shown as pair wise connected against the WT and P.1 lineages in the categorized Groups A, B, and C. P values obtained by the Wilcoxon paired test.
Comparison of virus-neutralizing activity against WT and P.1 in the categorized samples showed that the neutralization ability of the samples assayed against P.1 was significantly lower than against WT strain in groups A and C; however, only a small fraction of the samples lost neutralizing activity against P.1. By contrast, no differences in neutralization properties were found in group B (Fig. 2a and c).

4. Discussion

This study corroborated the safety of the Sputnik vaccine since no severe adverse events were reported among the participants. Even more, most of the reported systemic and local reactions were mild, and all the participants showed good tolerance to the vaccine and remained in good clinical conditions. Although we followed up all the participants only six months, the disease rate among HCW who received both doses of the vaccine was 4.3%, owing to nine COVID-19 cases. Due to the lack of a control group, the vaccine efficacy could not be accurately calculated. This is a limitation of our study.

We successfully isolated SARS-CoV-2 lineage P.1 from one of the cases. Since genomic sequencing is not widely performed in Argentina, and given that only cases that meet National Recommendations [10] are eligible for genomic surveillance, molecular identification and characterization of SARS-CoV-2 were not attempted in 8 of the 9 COVID-19 cases, which is another limitation of this study. However, this finding did not surprise us since several cases of local SARS-CoV-2 lineage P.1 transmission among fully vaccinated individuals have been reported in Argentina since April 2021. In this sense, infections with P.1 variant were confirmed in 25 HCW who had received both doses of Sputnik V vaccine in a regional Hospital outbreak [15].

Herein, we show for the first time, evidence of infectious SARS-CoV-2 shedding from Sputnik-V fully vaccinated individuals by the isolation of viable virus from nasopharyngeal swab of one participant in our study. Nevertheless, none of our 9 cases neither the 25 from the mentioned outbreak developed severe forms of the disease. All these evidences demonstrate that Sputnik-V vaccine might avoid severe forms of the disease; however, it does not prevent infection or shedding of infectious viruses from fully vaccinated individuals. The limited 6-month follow up, together with the fact that within this period the participants without signs or symptoms associated to COVID-19 were not evaluated for SARS-CoV-2 asymptomatic infections are the reasons why we consider that further studies would be necessary to assess vaccine efficacy and protection. Nevertheless, there were no cases of moderate or severe COVID-19 in the vaccinated group, at least during the observation period.

Results showed that Sputnik V induced efficient humoral response in immunized individuals. Although 91.2% of the individuals with previous infection had antibodies anti-SARS-CoV-2 in the baseline sample (62/285), 14 days after the first dose 85.5% of the cohort had anti-S IgG Abs against the virus and 21 days after the second dose (day 42 pv) 99.65% had detectable anti-S IgG Abs, with only one participant remaining seronegative at day 42. These results are consistent with data of humoral immune response communicated in earlier Phase 1/2 and 3 trials [1,2] and with a recent publication of an Argentinean cohort [16]. However, data presented herein regarding production of NAb in our cohort are not consistent with previous reports [1,2,16]. The participants of this study received the complete scheme of immunization (first dose rAd26, second dose rAd5). Remarkably, the analysis of NAb to SARS-CoV-2 showed seroconversion level of 76.85% in fully immunized individuals. The analysis of NAb production in uninfected
individuals (209/285) showed that at day 14 pv, most of the individuals without SARS-CoV-2 infection prior to vaccination (88.61%) had no Nabs, and after receiving the second dose (42 dpv), seroconversion rate was 69.39%. These data demonstrated the importance of administering the second dose to those without previous exposure to SARS-CoV-2. In our cohort, not only the proportion of individuals with anti-S IgG Abs was higher, but also the Nabs titres increased significantly. In this sense, differences with statistical significance were found in the levels of Nabs between samples of days 14 and 42, yielding neutralizing antibodies GMTs of 0.44 and 3.19, respectively. On the other hand, in the group with confirmed infection prior to vaccination, we observed that the highest NAb titres were obtained after the first dose of the vaccine (day 14) and subsequently the titres declined despite receiving the second dose. The neutralizing antibody GMTs values of the plasma panel of this group at days 14 and 42 pv were 8.05 and 7.60, respectively, with no substantial differences. These data agree with several findings that have independently reported high Abs titres and neutralization activity after the first dose of mRNA vaccines in individuals with history of SARS-CoV-2 infection [17] and also with a recent publication that evaluates Sputnik-V antigen specific humoral immunity [16].

Regarding SARS-CoV-2 Lineage P.1, a significant 0.94- and 1.68-fold decrease of the neutralization GMT against P.1 compared with WT, in Groups A and C were observed, respectively. Moreover, 9% (4/44) and 28% (13/44) of the tested samples from groups A and C respectively, lost neutralizing activity against P.1 (Fig. 2a, b, and c). Noteworthy, five out of nine COVID-19 cases did not present detectable NAbs 21 days after the second dose of the vaccine, while the remaining three had detectable NAbs against WT and one of them failed to neutralize P.1. In spite of lacking Nabs, all of the cases developed mild disease.

Taking the latter into account, together with the fact that the vast majority of the samples from Group C neutralized P.1 evidencing P.1-epitopes effective recognition, it would be interesting to assess the impact of the P.1 variant in T-cell recognition. Thus, although some Nabs from individuals recovered from natural infection by SARS-CoV-2 WT and some vaccinated individuals without previous infection failed to neutralize P.1, no differences in neutralization potency against WT and P.1 were found in Group B (recovered and vaccinated individuals). These data are in agreement with previous publications assessing NAb evasion of lineage P.1 [7,8,18]. Data presented herein show the neutralization response elicited by Sputnik V against this lineage of concern, in agreement with a recent publication assessing neutralizing activity of sera from Sputnik-V-vaccinated individuals against variants of concern [9]. In the mentioned study, sera from Sputnik V-vaccinated against SARS-CoV-2 lineage P.1 showed 2.8-fold decrease in virus neutralization titres. Our study showed a statistically significant 1.68-fold decrease of virus neutralizing titres against P.1 in vaccinated-naive individuals. The differences in viral neutralization potency observed in individuals vaccinated with Sputnik V may be due to differences regarding population, even though statistically significant decrease in virus neutralizing activity against P.1 was observed in both studies. Thus, we agree with Gushchin et al on the fact that the decreasing neutralization effects are of concern and require further surveillance and epidemiological studies [9].

A previous publication assessing serum samples from recipients of the Sputnik vaccine showed efficient neutralization against B.1.1.7 but a moderately reduced activity against E484K substitution alone and failure to neutralize B.1.351 variant [19]. The authors concluded that there is a concerning potential of B.1.351 and to a lesser extent, any variant carrying the E484K substitution to escape from the neutralizing Ab responses that Sputnik elicits [19]. Considering our results alongside with results by Gushchin et al, and taking into consideration that lineage P.1-harbor E484K substitution, we cannot agree with this statement. Differences may be due to sample size, different population background, categories evaluated, and also probably to different techniques/methodologies used to characterize the neutralization activity of vaccine-elicted sera.

Finally, our results are consistent with those showing that a single dose of immunization in previously infected subjects boosted NAb titres against different SARS-CoV-2 variants [16,17,20]. Further studies evaluating long-lasting humoral immune response in both previously infected and uninfected persons should be performed. These data might have implications for vaccination strategies and policies, allowing the available vaccine supply to be optimized.

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6. Statement of ethics

This report has been performed in accordance with specific local regulations (provision number 32/2016, dated September 8, 2016, by the Council for the Ethical Evaluation of Health Research, Ministry of Health of Córdoba province, Argentina). The study observed the ethical standards established in the Declaration of Helsinki in 1964 and its subsequent modifications.

7. Authorship contributions

SB, BSK, AD, LS, JJA, MER, MB, CC, MD, MGB and SVG conceived and designed the study.
SB, BSK, LAD, LS, JJA, MER, MB and SVG performed Plaque Reduction Neutralization technique, analysed and interpreted the data and drafted the manuscript.
AM performed statistical analysis, analysed and interpreted the data and revised the final version of manuscript.
MinSalChA working group and CC collected samples, performed anti-Spike IgG antibodies detection and performed the PCR test.
CC, MD, MinSal working group, FCM-UNC working group and MGB recruited and followed-up the participants, collected their personal and clinical information and revised the final version of manuscript.

8. Data sharing

All data collected for the study will be made available with publication, upon requests directed to the corresponding author. The request will be reviewed and approved by the investigators and collaborators on the basis of scientific merit. After approval the request, data can be shared through institutional mails after signing the data access and confidentiality agreement. All data will be made available for a minimum of 3 years from the publication of the manuscript.

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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