Journal Pre-proof

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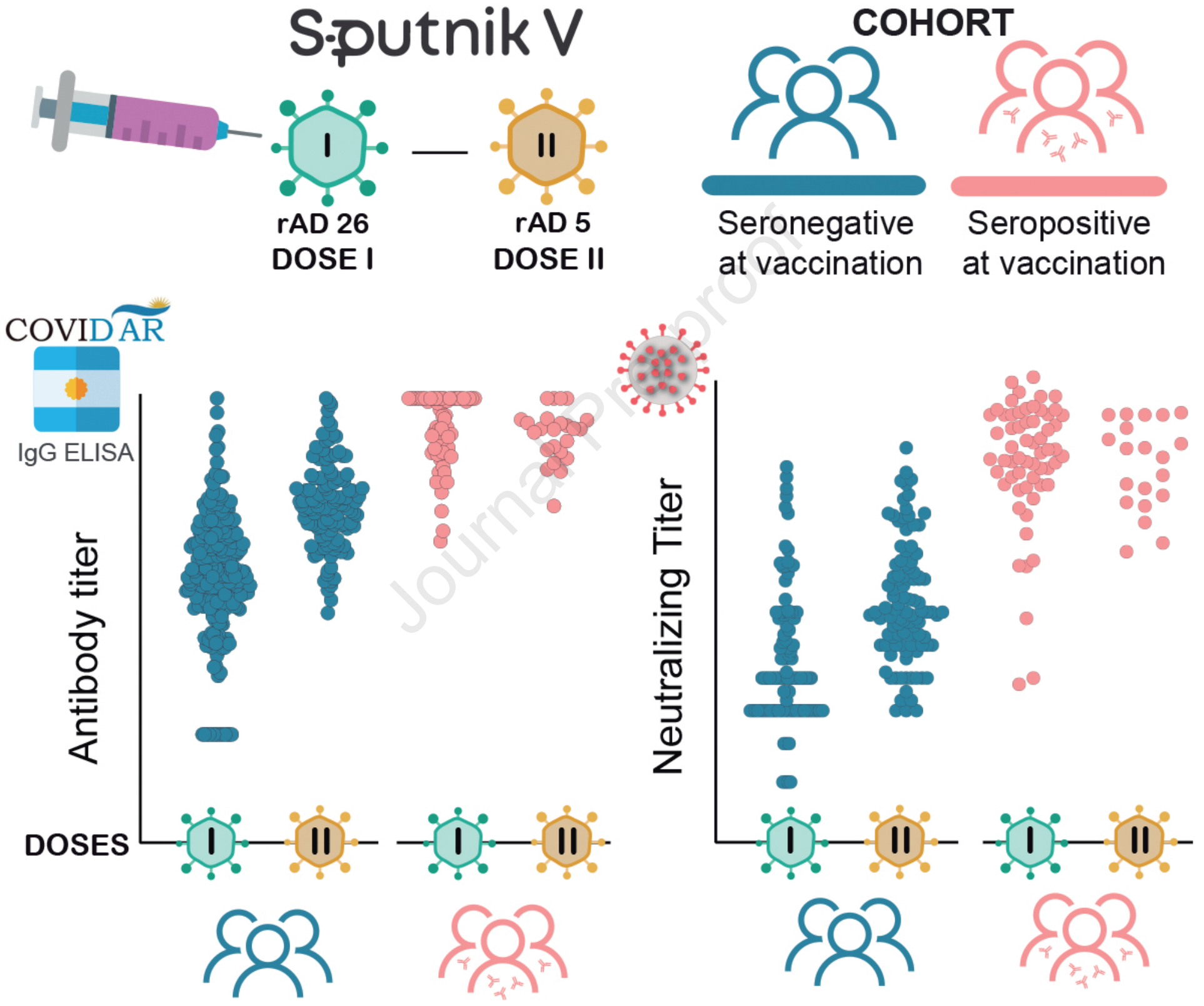
SARS-CoV-2 vaccination



Sputnik V Vaccine Elicits Seroconversion and Neutralizing Capacity to SARS CoV-2 after a Single Dose

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Summary

Massive vaccination offers great promise for halting the global COVID-19 pandemic. However, limited supply and uneven vaccine distribution create an urgent need to optimize vaccination strategies. We evaluate SARS-CoV-2-specific antibody responses after Sputnik V vaccination of healthcare workers in Argentina, measuring IgG anti-spike titers and neutralizing capacity after one and two doses in a cohort of naïve or previously infected volunteers. By 21 days after receiving the first dose of vaccine, 94% of naïve participants develop spike-specific IgG antibodies. A single Sputnik V dose elicits higher antibody levels and virus neutralizing capacity in previously infected individuals than in naïve ones receiving the full two-dose schedule. The high seroconversion rate after a single dose in naïve participants suggests a benefit of delaying second dose administration to increase the number of people vaccinated. The data presented provide information for guiding public health decisions in light of the current global health emergency.

Introduction

Sputnik V (Gam-COVID-Vac) is a combined vector vaccine based on recombinant adenovirus (rAd) type 26 and rAd5 [1]. A two-dose protocol displays 91.6% efficacy against COVID-19 [2]. In the context of the current pandemic, an important question is whether administration of a single Sputnik V dose would achieve a greater public health benefit than a two-dose protocol, allowing protection of a larger population more quickly. The vaccine developed by AstraZeneca, also a two-dose, single rAd-vectored vaccine, showed 76.0% (59.3–85.9%) efficacy after a single standard dose [3], supporting a longer interval between the two doses. In the case of the mRNA vaccines, mRNA-1273 (Moderna) and BNT162b2 (Pfizer), individuals with prior infection might acquire sufficient immunity after a single dose, with no apparent benefit of a two-dose protocol [4,5].

Results

We evaluated antibody responses and viral neutralizing capacity in participants receiving one and two doses of Sputnik V, with or without prior SARS CoV-2 infection (N=227 and N=62, respectively). Plasma samples were taken on three occasions: before vaccination (baseline), 21 days after the first dose and 21 days after the second dose. SARS CoV-2 spike IgG was measured using a previously described enzyme-linked immunosorbent assay by titration [6] and quantification with the WHO International standard for comparing data from different

laboratories[7]. Virus neutralizing antibodies were evaluated using a wild-type (WT) SARS CoV-2 and a pseudotyped VSV spike expressing GFP [8].

After the first dose of Sputnik V, 94% of seronegative participants at baseline showed a positive SARS CoV-2 IgG response with a geometric mean titer (GMT) of 244 (CI95%, 180–328) (Figure 1A). Segregation of participants by age showed seroconversion in 96% and 89% of individuals under or over 60 years old, respectively (Figure 1B). After the second dose, 100% of participants showed seroconversion with a GMT of 2148 (CI95% 1742–2649).

Participants with SARS CoV-2 antibodies at baseline developed high antibody titers within 21 days of receiving the first vaccine dose. The GMTs were 531 (CI95%, 380–742) before and 9850 (CI95%, 8460–11480) after the first dose, showing a 19-fold increase in specific antibody levels. By contrast, IgG anti-spike titers after one or two doses were not significantly different: GMTs of 9850 (CI95%, 8460–11480) and 9590 (CI95%, 7410–12408) after one and two doses, respectively.

As reference for comparison among laboratories, IgG levels were expressed as International Units (IU) after normalization with the WHO International Standard for anti-SARS-CoV-2 Antibody (Figure 1C). The geometric mean (GM) of IgG concentrations in IU/ml was 104.2 (CI95%, 92.3–157.5) after the first dose and 787.8 (CI95%, 626.0–936.2) after the second dose in naïve individuals, and 181.1 (CI95%, 105.2–243.7), 6,356 (CI95%, 5,409–14,763) and 5,609 (CI95% 3,621–8,496) for baseline, one and two doses, respectively, in previously infected individuals.

Notably, antibody titers after one dose in participants with preexisting immunity were significantly higher than those in naïve vaccinees receiving one or even two doses ($P < 0.0001$, two-tailed Mann Whitney test). GMTs for previously infected participants after one dose were 40- and 4.6-fold higher than those for naïve individuals receiving one or two doses, respectively (Figure 1A). This highlights the robust response to vaccination of previously infected individuals, suggesting that naturally acquired immunity might be enhanced sufficiently by a single dose, in agreement with recent studies using mRNA vaccines [4,5].

Neutralizing capacity was evaluated by measuring antibody neutralizing titers for seronegative and seropositive individuals at baseline, using the wild type SARS-CoV-2 or CoV2pp GFP pseudovirus infection. For the wild type SARS-CoV-2, neutralization titers were defined as the highest serum dilution without any cytopathic effect on the monolayer, and for the pseudotyped virus antibody concentration for 80% inhibition of infection (IC80) was determined (see Figure 2,

and for 50% inhibition of infection IC50 see supplemental Figure S1). At 21 days after administration of the first dose, neutralizing antibodies were detected in 90% of naïve participants (seronegative at baselines), with GM neutralizing titers of 12 (CI95%, 10–14) with WT SARS-CoV-2 (Figure 2, left panel). Neutralizing GM titers after the complete two-dose vaccine protocol in naïve individuals was 42 (IC95%, 33–53) (Figure 2, left panel), which was higher than that observed for convalescent individuals (seropositive at baseline) prior to vaccination that was 28 (CI95%, 23–40) (Figure 2, right panel). Notably, a robust increase in neutralizing antibody activity was observed after a single vaccine dose in participants with prior infection. In this regard neutralizing GM titers were 500 (CI95% 341-732) and 782 (IC95% 557-1099) following infections with the WT and pseudotype virus, respectively (Figure 2, right panel), indicating that a single dose of the vaccine triggers a large production of neutralizing antibodies in convalescent individuals, which did not increase after a second dose.

Conclusion

This study provides new data about antibody responses to Sputnik V vaccine in SARS CoV-2 naïve and previously infected volunteers. We observed a high seroconversion rate following a single vaccine dose in naïve individuals. A global 94% of vaccinees elicited specific anti-spike antibody responses, with 90% displaying WT virus neutralizing capacity. Importantly, a single dose of Sputnik V vaccine caused a fast and robust immune response in seropositive participants, with neutralizing titers that exceeded those found in seronegative participants who received two doses. Although a protective role of anti-spike antibodies against COVID-19 has been reported, the level of protection required for a beneficial outcome during infection is uncertain, and further efficacy studies combined with quantitative information on levels of anti-spike antibodies are needed to define the minimum threshold required for protection. Presentation of our data in IU allows comparison of measurements obtained using different technologies, helping to define antibody levels associated with protection after vaccination. Evidence based on quantitative information will guide vaccine deployment strategies in the face of worldwide vaccine supply restriction.

Limitations of study

This study shows high humoral responses after Sputnik V administration using a cohort of 288 volunteers from over 200,000 vaccinated healthcare workers. However, an efficacy study has not been carried out yet and will be necessary to assess vaccine protection in the population

and to define correlates with antibody titers. In addition, follow up studies are necessary to evaluate duration of the immune response.

Figure legends

Figure 1. Immune response to SARS-CoV-2 Sputnik V Vaccine. Panel **A** shows quantitative SARS-CoV-2 spike antibody titers for 288 participants, with or without prior infection (indicated as seropositive or seronegative at baseline, respectively). Measurements were performed before vaccination (baseline), 21 days after the first dose and 21 days after the second dose. Geometric means with 95% confidence intervals are shown. The Mann-Whitney *U* test was used to compare at various time points antibody titers. Statistical significance is shown with the following notations: ****:p < 0.0001; ns: not significant. Panel **B** shows seroconvertion after one dose in participants > or < that 60 years old. Panel **C** shows quantification of antibody levels by International WHO Standard.

Figure 2 Neutralizing capacity with and without prior SARS-CoV-2 infection after one and two doses of Sputnik V vaccine. Neutralizing titers were measured by 80% inhibition for the pseudotyped virus (CoV-2pp-GFP) in 232 participants. For WT SARS-CoV-2, neutralization titer was defined as the highest serum dilution without any cytopathic effect on the monolayer. Titers at baseline, and 21 days after 1 or 2 doses are shown. Left and right panels display data from individuals that were seronegative or seropositive at baseline, as indicated on the top respectively. Geometric means with 95% confidence intervals are shown in dash lines. The Mann-Whitney *U* test was used to compare at various time points antibody titers. Statistical significance is shown with the following notations: ****:p < 0.0001; ns: not significant.

STAR★Methods

Resource availability

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Andrea V. Gamarnik (agamarnik@leloir.org.ar).

Materials availability

This study did not generate new unique reagents.

Data and code availability

Datasets generated in this study have been uploaded to https://data.mendeley.com at https://doi: 10.17632/5bjwph8xkr.1

Experimental model and subject details

Human subjects and samples

This study monitors the humoral immune response over time in health care workers immunized with Sputnik V vaccine. Study enrollment started in January 2021 and is ongoing. Ethical approval was obtained from the central committee of the Ministry of Health of Buenos Aires and all participants provided written informed consent prior to collection of data and specimen (Cod#2021-00983502). Blood was collected by venipuncture into SST tubes (BD Sciences) for serum and stored at −20°C. All specimens were de-identified prior to processing and antibody testing for all serum specimens.

Cell lines

Vero E6 cells (ATCC) and 293T ACE2/TMPRSS2 cells, kindly provided by Dr. Benhur Lee, were cultured at 37°C in 5% CO2 in Dulbecco's Modified Eagle's high glucose medium (Thermo Fisher Scientific) supplemented with 10% fetal bovine serum (FBS) (Gibco).

Recombinant VSV

Viral stocks (VSV-eGFP-SARS-CoV-2), generated in Sean Whelan laboratory[8], were amplified in our laboratory using 293T ACE2/TMPRSS2 cells at an MOI of 0.01 in Dulbecco's Modified Eagle's medium containing 2% FBS at 37ºC. Viral supernatants were harvested upon extensive cytopathic effect and GFP positive cells. The media was clarified by centrifugation at 1,000 x g for 5 min. Viral stocks were titrated by fluorescence forming units per milliliter (UFF/ml) in Vero cell line. Aliquots were maintained at -80ºC.

SARS-CoV-2

SARS-CoV-2 strain 2019 hCoV-19/Argentina/PAIS-G0001/2020 was obtained from Dr. Sandra Gallegos (InViV working group). Virus was passaged in Vero E6 cells. Work with SARS-CoV-2 was approved by the INBIRS Institutional Biosafety Committee at Biosafety level 3 with negative pressure.

Method details

SARS-CoV-2 antibody ELISA

Antibodies to SARS-CoV-2 spike protein were detected using an established two step ELISA previously described[6]. This assay has plates coated with a mixture of spike and the receptor binding domain (RBD). For end point titrations, samples were serially diluted in IgG SARS-CoV-2 negative serum or fetal bovine serum (FBS) from 1/50 to 1/12800. The SARS-CoV-2 antibody concentration of each sample expressed in International Units/mL (UI/mL)[7] was calculated by

extrapolation of the OD 450 nm value on a calibration curve. For construction of the calibration curve, we determined OD 450 nm of serial dilutions of the WHO International Standard for anti-SARS-CoV-2 immunoglobulin. The linear range used was 0.2-1.5 OD 450nm. Therefore, we performed serial dilutions of the samples in order to find conditions where the OD 450nm of each sample fit adequately in the linear range.

SARS-CoV 2 neutralization assay

Serum samples were heat-inactivated at 56°C for 30min and serial dilutions from 1/2 to 1/8192 were incubated for 1hs at 37ºC in the presence of WT SARS-CoV-2 (hCoV-19/Argentina/PAIS-G0001/2020, GISAID Accession ID: EPI_ISL_499083) in DMEM 2% FBS. Fifty µl of the mixtures were then deposited over Vero cells monolayers for an hour at 37°C (MOI=0.01). Infectious media was removed and replaced for DMEM 2% FBS. After 72 hs, cells were fixed with PFA 4% (4°C 20min) and stained with crystal violet solution in methanol. The cytopathic effect (CPE) of the virus on the cell monolayer was assessed visually, if even a minor damage to the monolayer (1-2 «plaques») was observed in the well, this well was considered as a well with a manifestation of CPE. Neutralization titer was defined as the highest serum dilution without any CPE in two of three replicable wells.

Pseudovirus neutralization assay

Neutralization assays were carried out with SARS-CoV-2 pseudotyped particles (CoV2pp-GFP), generated in Sean Whelan laboratory[8]. CoV2pp-GFP carries vesicular stomatitis virus as viral backbone, bearing the E gene in place of its G glycoprotein (VSV-eGFP-SARS-CoV-2), and expresses full length wild type spike from Wuhan on its envelope. Vero cells were used for these assays. Cells were maintained with DMEM high glucose with 10% FBS and were seeded in a 96-well plate the day before infection. Patient sera were heat inactivated at 56°C for 30 minutes and serially diluted in DMEM high glucose medium. Serum neutralizations were performed by first diluting the inactivated sample 2-folds and continuing with a 2-fold serial dilution. A pre-titrated amount of pseudotyped particles was incubated with a 2-fold serial dilution of patient sera for 1 h at 37ºC prior to infection. Subsequently, cells were fixed in 4% formaldehyde containing 2 µg/mL DAPI nuclear stain (Invitrogen) for 1 hour at room temperature, and fixative was replaced with PBS. Images were acquired with the InCell 2000 Analyzer (GE Healthcare) automated microscope in both the DAPI and FITC channels to visualize nuclei and infected cells (i.e., eGFP-positive cells), respectively (4X objective, 4 fields per well, covering the entire well). Images were analyzed using the Multi Target Analysis Module

of the InCell Analyzer 2000 Workstation Software (GE Healthcare). GFP-positive cells were identified in the FITC channel using the top-hat segmentation method and subsequently counted within the InCell Workstation software. Absolute inhibitory concentrations (absIC) values were calculated for all patient sera samples by modeling a 4-parameter logistic (4PL) regression with GraphPad Prism 8. The 4PL model describes the sigmoid-shaped response pattern. For clarity, it is assumed that the response can be expressed so that the slope increases as the concentration increase. Absolute inhibitory concentration (absIC) was calculated as the corresponding point between the 0% and 100% assay controls. Eighty % inhibition were defined by the controls for all the samples on the same plate. For example, the absIC80 would be the point at which the curve matches inhibition equal to exactly 80% of the 100% assay control relative to the assay minimum. Furthermore, 50% inhibition was also calculated by modeling a 4-parameter logistic (4PL) regression with GraphPad Prism 8.

Quantification and statistical analysis

All statistical tests and plots were performed using GraphPad Prism 8.0 software. Comparisons of the antibody titers at various time points were made using the Mann Whitney *U* test in Figure 1A, Figure 2 and Figure 1S. Statistical significance is shown in the figure legends with the following notations: ****:p < 0.0001; ns: not significant. Geometric means with 95% confidence intervals were calculated in all time points. In all figures “N” represents the number of human serum sample tested.

Acknowledgments

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Desimone, Alejandra Musto**. HIGA "Dr. Pedro Fiorito":** Aime Balanzino, Katherina Prost, Miriam Pereiro, Eliana Correa, Noelia Portillo, Cynthia Leguizamon, Alicia Quetglas**. HIGA "San Roque":** Mariana Artazcoz, Agustina Venturi Grossi, Rosana Toro, Anabella Masci, Sofía Padín**. HAC "El Cruce- Néstor Kirchner":** Mabel Skrypnik, Blanca Guevara, Virginia Aniasi, Alan Estigarribia.

Author contribution

Conceptualization: A.H.R., J.G., G.D., M.P., N.K. and A.V.G. General coordination: M.P., A.H.R., A.A.J. and A.V.G. Collection of serum samples and clinical data: D.P., A. R., C.E., R.E., P.G., S.M., M.Z., Y.L. and N.L. Production of SARS-CoV-2 antibody ELISA (IgG) Kit (COVIDAR): D.S.O., L.S., M.M.G.L.L., H.P., G.C.N., D.A., J.J.C. and J.C. IgG anti-Spike titer determination: D.S.O., L.S., N.R., C.I.G., S.D.W., L.Y.R., M.G.B., M.J.L., E.H., S.S., L.B., A. Ríos, M.S.T.C., Y.L. and N.L. Determination of neutralizing titers using WT SARS-CoV-2 virus: A.V., I.M and J.G. Determination of neutralizing titers using CoV2pp-GFP pseudotyped virus: D.S.O., L.S., M.M.G.L.L., D.A. and S.O.R. Data curation and analysis: D.S.O., L.S., S.O.R., J.J.C, M.J.Y, and A.V.G. Writing original draft: M.M.G.L.L., D.S.O., L.S., S.O.R., M.Y., and A.V.G. Funding Acquisition. A.V.G.

Declaration of interests

The authors declare no competing interests

Inclusion and diversity

One or more of the authors of this paper self-identifies as a member of the LBGTQ+ community. One or more of the authors of this paper self-identifies as underrepresented ethnic minority in science. We worked to ensure sex balance in the selection of human subjects. While citing references scientifically relevant for this work, we also actively worked to promote gender balance in our reference list.

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Highlights

- First dose of Sputnik V results in 94% seroconversion rate in naïve individuals
- A second dose greatly increases antibody titers and neutralizing capacity
- One dose in seropositive individuals elicits higher titers than two doses in naïve
- There is no evident benefit of using a second dose in previously infected individuals

eTOC Summary

Rossi et al. provide data on antibody responses to Sputnik V vaccine in naïve and previously infected volunteers. This study shows a high seroconversion rate following the first dose in naïve individuals. In seropositive participants a single dose of Sputnik V elicits a fast and robust antibody response without apparent benefit from a second dose.

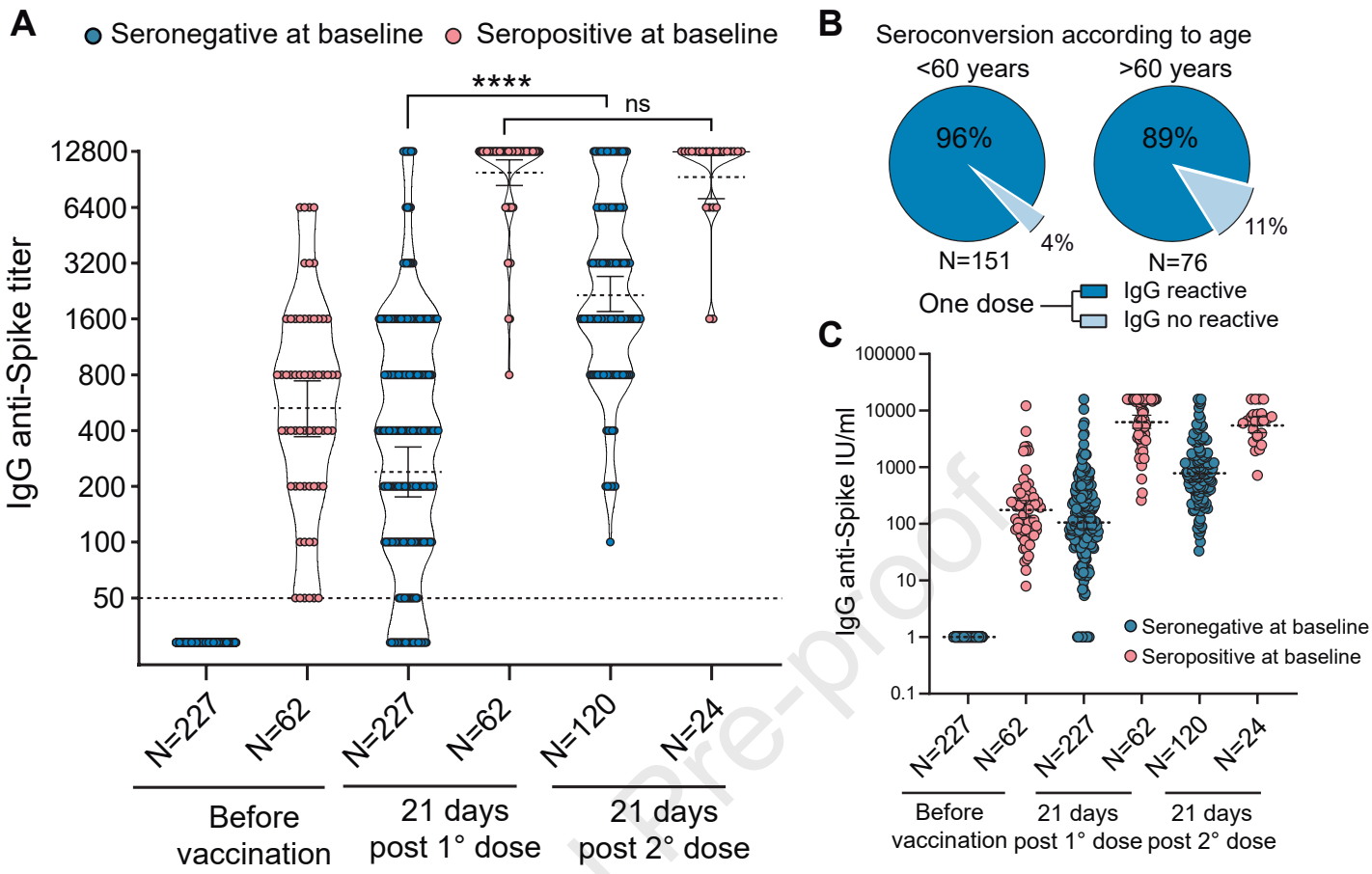

FIGURE 2