Antibody- and T cell-dependent responses elicited by a SARS-CoV-2 adenoviral-based vaccine in a socially vulnerable cohort of elderly individuals

Martin Moya (martinmoya@unc.edu.ar)
Universidad Nacional de Córdoba: Universidad Nacional de Cordoba https://orcid.org/0000-0002-4870-8169

Ariel Aleksandroff
Secretaria de Salud Cordoba, Argentina

Marcela Marrama
Secretaria de Salud, Cordoba, Argentina

Florencia Veigas
IBYME: Instituto de Biologia y Medicina Experimental

Montana N. Manselle Cocco
IBYME: Instituto de Biologia y Medicina Experimental

Tomás Dalotto Moreno
IBYME: Instituto de Biologia y Medicina Experimental

Gabriel A Rabinovich
IBYME: Instituto de Biologia y Medicina Experimental

Research Article

Keywords: COVID-19, Immune Function, Health Disparities, Nursing Home Issues

Posted Date: April 14th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1538891/v1

Antibody- and T cell-dependent responses elicited by a SARS-CoV-2 adenoviral-based vaccine in a socially vulnerable cohort of elderly individuals

Martin P. Moya[1-3]; Ariel Aleksandroff[1]; Marcela Marrama[1]; Carina D´Orazio[1]; Florencia Veigas[2]; Montana N. Manselle Cocco[2]; Tomás Dalotto Moreno[2]; Gabriel A Rabinovich[2].

Affiliation

[1] City Council of Cordoba, 5000 Córdoba, Argentina.

[2] Laboratorio de Glicomedicina, Instituto de Biología y Medicina Experimental (IBYME), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), C1428 Ciudad de Buenos Aires, Argentina.

3Facultad de Ciencias Médicas, Universidad Nacional de Córdoba, 5000 Córdoba, Argentina.

Correspondence

Dr. Martin P. Moya can be contacted at martinmoya@unc.edu.ar

Word count: 3,858

Abstract word count: 292

Figures: 4

Abstract

Background: In spite of compelling evidence demonstrating safety and immunogenicity of adenoviral-based SARS-CoV-2 vaccines in the general population, its effects in socially vulnerable elderly individuals is poorly understood Here we aimed to investigate the efficacy of two doses of combined vector vaccine, the Gam-COVID-Vac (Sputnik V), at 14, 42 and 180 days after immunization, in a nursing home for low-income and homeless individuals.

Methods: A phase 3, open-label clinical trial involving administration of two adenoviral vectors (Ad26 - Ad5) vaccine, in elderly individuals over the ages of 60 years was performed. SARS-CoV-2 Spike RBD-specific IgG antibodies at days 21-, 42- and 180 post-vaccination was analyzed in sera of individuals receiving two doses of the Sputnik V vaccine with an interval of 21 days. SARS-CoV-2-specific CD8 T cell responses, measured by intracellular tumor necrosis factor (TNF) was determined by flow cytometry following antigen-specific cultures.

Results: A total of 72 elderly adults with a mean age of 72.6 ±9.5 years-old was selected after applying the inclusion criteria, all corresponding to a very low-income population. Two-doses vaccination with Sputnik V vaccine elicited an antibody-mediated immune response (revealed by quantitative detection of SARS-CoV-2-specific IgG antibodies, CMIA) 70% at day 21, 90% at day 42s and 66.1% at day 180. Fully vaccinated individuals had robust SARS-CoV-2-specific T cell responses, evidence by TNF production in CD4+ and CD8+ T cells in all time periods analyzed.

Conclusion:

Six months after receipt of the second dose of the Gam-COVID-Vac vaccine, SARS-CoV-2-specific IgG levels declined substantially among the tested population, whereas CD4+ and CD8+ T-cell-mediated immunity remained at high levels. These data suggest

that two doses of combined adenoviral-based vaccine elicits a considerable level of SARS-CoV-2 immune responses in elderly individuals, highlighting its safety and immunogenicity in this highly vulnerable population.

Keywords: COVID-19, Immune Function, Health Disparities, Nursing Home Issues

INTRODUCTION

Since the first cases of coronavirus disease 2019 (COVID-19) in Wuhan, China, in December 2019, this disease has spread to millions of individuals worldwide. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in January, 2020. This virus is highly transmissible between humans and has spread rapidly, causing the COVID-19 pandemic[1-2]. Patients infected with SARS-CoV-2, especially older patients and those with pre-existing respiratory or cardiovascular conditions are at greater risk to develop complications, including severe pneumonia, acute respiratory distress syndrome, multiple organ failure, and in some cases death[3-4]. By March 3, 2022 SARS-CoV-2 had infected more than 440 million people and killed more than 5.9 million worldwide[5].

SARS-CoV-2 elicit detectable antibody and T cell-mediated immune responses[6]. Although previous studies suggested detectable humoral responses at least 4 months after infection[7;] the durability of anti-SARS-CoV-2 IgG antibodies after vaccination without repeated exposure is variable. In contrast, robust and durable T cell mediated memory responses have been documented following natural SARS-CoV-2 infection and immunization with different vaccine platforms, including mRNA-1273, BNT162b2, Ad26.COV2.S, and NVX-CoV2373) that cross-recognize viral variants from Alpha to Omicron[8-9]. Although most of studies focused on safety and immunogenicity of vaccines in the general healthy population, the long-term effects of combined adenoviral-based vaccines in a socially-vulnerable elderly population has not been explored.

We conducted a population-based longitudinal sero-epidemiological study in Cordoba, Argentina, starting in April 2021, and three successive follow-ups in May and September 2021. Vaccine immunogenicity was assessed by analyzing SARS-CoV-2-specific

immunoglobulin (Ig) G and SARS-CoV-2-specific T cell-mediated immunity evaluated by intracellular cytokines by flow cytometry

METHODS

Trial Design and Participants

We initially conducted a Phase 3, open-label clinical trial of two adenovirus vectors (Ad26 - Ad5) vaccine, involving participants over the ages of 60 years, for the determination of IgG antibodies for Spike RBD. at 21- and 42-days post-vaccination We subsequently expanded the trial to include testing at 180 days after the first dose of Sputnik V vaccine.

The trial was conducted at the Padre La Monaca home for senior citizens, an institution dependent of the Secretary of Health of the City Hall of Córdoba, Argentina. Enrolled individuals were healthy and provided written informed consent before undergoing any study procedures. We did not screen for evidence of past or current SARS-CoV-2 infection by testing blood or nasal specimens before enrollment. However, in order to overcome this limitation, we determined whether individuals had asymptomatic infection from the detection of the rapid test for SARS-CoV-2 nucleoprotein (Abbott Panbio, COVID-19 IgG/IgM).

Sputnik V Vaccine

This vaccine is based on two adenovirus vectors (Ad26 - Ad5) expressing the Spike protein.

Study Oversight

The Secretary of Health of the City Hall of Córdoba served as the trial sponsor and made all the decisions regarding study design and implementation.

The manuscript was written entirely by the authors, with the first two authors serving as overall lead authors. All the authors guarantee for the completeness and accuracy of the

data and for the adherence of the study to the protocol. No one who is not an author contributed to the writing of the manuscript.

Trial Procedures

The two adenoviral vectors (Ad26 - Ad5) vaccine was administered as a 0.5-ml intramuscular injection into the deltoid on days 1 and 21 of the study; the same dose of the vaccine was administered on both days. Follow up for antibody detection was scheduled 21, 42 and 180 days after the administration of the first dose of vaccine. At 180 days, a sample of EDTA-anticoagulated blood of 24 individuals was taken to study T-cell mediated responses of vaccinated individuals, using the 'COVID-T Platform[8]', an optimized strategy to study SARS-CoV-2-specific T cell responses. Purification of peripheral blood mononuclear cells (PBMC) was performed as described[10]. A standard toxicity scale was used to grade adverse events. Local and systemic adverse events were analyzed 7 days after each vaccination dose. Data regarding unsolicited adverse events were collected through day 60. Collection of specimens, as well as monitoring for medically attended adverse events, development of new chronic medical conditions, and serious adverse events, was scheduled to continue through 1 year after the last dose.

Assessment of Antibody Responses

Qualitative (rapid test), semi-quantitative (ELISA) and quantitative (CMIA - chemiluminescence) analysis was used to determine SARS-CoV-2-specific IgG responses recognizing S-2P containing an Asp (D) residue at position 614 and to the receptor-binding domain on days 21, 42 and 180.

Asymptomatic infections were assessed using the rapid SARS-CoV-2 nucleoprotein (Abbott Panbio, COVID-19 IgG/IgM). test Pooled data were obtained in unidentified

format from the nursing home resident health record system and institutional review board approval was obtained.

Assessment of T-cell responses by flow cytometry

For evaluation of the SARS-CoV-2-specific T cell responses, cryopreserved PBMCs were thawed in complete RPMI 1640 (Serendipia) in the presence of 0.1 mg/ml of DNasa I (Roche) and cultured in the presence of 1 ug/ml SARS-CoV-2-specific peptides pools (Miltenyi) for 6 h. Cultures in the absence of peptides, were used as negative controls and stimulation with phorbol-12-myristate-13-acetate (PMA) plus ionomycin was included as positive control. Brefeldin A and Monensin (Biolegend) were added to cultures for the last 4 h. Cells were then washed, and surface stained for 25 min at room temperature, fixed with 1% paraformaldehyde (Sigma) for 25 min and intracellularly stained following incubation with permeabilization buffer (BD) for 25 min. All samples were acquired on BD LSR Fortessa^{TM} X-20 and analyzed with FlowJo software. Determination of interferon-γ (IFN-γ), interleukin-2 (IL-2), tumor necrosis factor (TNF) as well as assessment of the frequency of CD154+ cells was performed Antibodies used in the assay are listed in **Table S1**.

Statistical Analysis

Safety analyses included all the participants who had received at least one dose of two adenovirus vectors (Ad26 – Ad5) vaccine. The data were extracted from the "Padre la Mónaca" Home for the Elderly and were collected in a Microsoft® Excel spreadsheet. A database was then generated in SPSS, IBM® for statistical analysis.

Numerical variables were presented as means and standard deviations and nominal variables as percentages. Comparisons of numerical variables were performed with the

158 Student's t test for numerical variables and if the distribution was abnormal, the Wilcoxon
159 test was used; nominal variables were analyzed with the Chi-square or Fisher test as
160 appropriate. Correlations between variables and simple and multiple linear regressions
161 were performed; models were tested with the test for comparison of means of related
162 variables. Formulas for predictive models were created.
163
164

RESULTS

Trial Population

A total of 72 elderly adults with a mean age of 72.6 ±9.5 were eligible after applying the inclusion criteria, all of them corresponding to a very low-income group. They received the first and second doses of the vaccine with 21 days interval. The demographic characteristics of the participants are shown in Table 1. The studied population had the following general features: 30.1% were women, the mean age of the population was 72.6 ± 9.4 years and the mean body mass index (BMI) was 25.1 ± 7.7, stratified as follows: underweight 23.9%, normal 28.2%, overweight 21.1% and obese 27.8%. Of the total number of patients, 68.5% were self-supporting or independent and 31.5% were semi-dependent, dependent or were receiving palliative cares

In the cohort analyzed, Sputnik vaccine induced a robust immune response (quantitative detection of IgG antibodies against Spike RBD CMIA) at 21 days in 70%, at 42 days in 90% and at 180 days in 66.1% of the participants (Figure 1).

Those individuals who were previously infected (whose sera had antibodies against the nucleoprotein), produced higher levels of Spike RBD-specific IgG upon receiving the vaccine than individuals who had never been in contact with the virus, in spite of receiving full immunization protocol. The frequency of RBD-specific antibodies at 42 days post-vaccination in the previously infected group (individuals who had no symptoms, but asymptomatic infection was detected by the presence of antibodies) was significantly higher (22945.5 AU/mL vs. 1495 AU/mL $p = 0.014$) as compared with patients not previously infected (Figure 2). Likewise, exposure to other viruses, such as hepatitis B (HBV; core positive), was also reflected by an increase in the production of antibodies to SARS CoV-2 (9487.6 vs. 1832.2; $p = 0.013$), when compared to vaccinated individuals without previous infection.

Patients receiving the Sputnik vaccine were stratified according to age. Of those aged 61 – 70 years, 63.6% developed reactive antibodies at 21 days and 87.9% did so at 42 days; while among those over 70 years, reactivity was 66.7% and 83.3% respectively. Stratification of patients into age ranges of 60 – 69 years, 70 – 79 years, 80 – 89 years and 90 – 99 years showed that the 60 – 69 years group presented higher antibody concentration values, 3078.4 ± 1585.5 AU/mL and 4947 ± 2268.1 AU/mL for measurements taken on days 21 and 42, respectively (Figure 3).

T cell immunity plays a central role in the control of SARS-CoV-2 infection and is a key component of immunization strategies. Particularly, both CD4 and CD8 T cells have been reported control multiple viral infections and provide protection against subsequent re-infections by generating immunological memory[11]. Previous studies have shown that both convalescent COVID-19 patients and individuals vaccinated with any of the different COVID-19 vaccine platforms develop long-term immunity mediated by $CD4^+$ and $CD8^+$ specific T cells[11].We analyzed SARS-CoV-2 specific T cell responses at 180 days post-vaccination in our cohort as measured by cytokine production after stimulation with peptide pools that cover the immunodominant sites of SARS-CoV-2 Spike protein. We found that fully vaccinated individuals had robust specific T cell responses as shown by the increased percentage (2-fold) of cells positive for TNF compared to the unstimulated controls (Figure 4). Moreover, we also found higher percentage of IFN-γ+ when comparing stimulated vs. unstimulated samples ($p = 0.013$) being this effect statistically significant. A similar outcome was observed when IL-2 was evaluated (data not shown).

Vaccine Safety

No serious adverse events were reported, and no pre-specified trial-halting rules were met in any of the individuals analyzed. The most common solicited adverse events were headache, fatigue, and injection-site pain. Local events were more common after the administration of the second dose of the vaccine. These symptoms typically occurred on the day of vaccination or 1 day afterward and resolved soon. Those patients who had nonspecific symptoms were treated with ibuprofen or acetaminophen.

DISCUSSION

On February 2, 2021, the County Government of the city of Cordoba (Argentina) ordered that the elderly residents of the long-term care facility (Padre Lamónaca) will receive the Sputnik-V vaccine. In this study we determined the levels of IgG antibodies at days 21, 42 and 180 after the first dose in individuals who had not been exposed to SARS-CoV-2 and who received the 2 doses 3 weeks apart.

On the basis of published results from vaccine trials and other data sources, it is estimated that people immunized against SARS-CoV-2 would experience a decline in approximately half of their protective antibodies every 108 days or so. As a result, vaccines that initially offered, 90% protection against mild cases of disease might only be 70% effective after 6 or 7 months[12]. In fact, immunological studies have documented a steady decline of antibody levels among vaccinated individuals[13]. Long-term follow-up of vaccine trial participants has revealed a growing risk of breakthrough infection[14]. Health-care records from countries such as Israel, the United Kingdom and other countries all show that COVID-19 vaccines lose their potency through time. In our study we observed a similar behavior in the case of humoral immunity, where antibodies titers increased progressively until 42 days post-vaccination, and then decreased to values below those reached at 21 days post-vaccination. A possible explanation for the observed decrease in the production of antibodies stimulated by the Sputnik V vaccine, in comparison to the work published previously[15], include the study of a population of older adults (mean 72.6 ± 9.5; minimum 61 - maximum 97), history of malnutrition in the population studied (23.9% of older adults were underweight and 48.9% were overweight) and the fact that all these individuals belong to a vulnerable population with a very low socioeconomic level, being many of them homeless In this sense, a multiple regression was performed with all the numerical variables collected and the only variable that

248 remained in the model was calf muscle circumference, a measure that is generally used
249 to detect nutritional alterations in older adults. These data suggest that malnutrition could
250 potentially be linked to a decrease in the capacity to generate immunity in older adult
251 patients.
252 The antibody concentration values obtained 14 days after the second dose of the vaccine
253 is promising. However, it also highlights the importance of monitoring antibody
254 responses post-vaccine administration, especially among the elderly socially-vulnerable
255 population which could be immunocompromised.
256
257 In addition to humoral responses, understanding the nature and magnitude of SARS-CoV-
258 2-specific T cell responses is essential to monitor vaccine effectiveness. In other
259 coronaviruses of the family (i.e. SARS-CoV-1), antibody levels fall below the detection
260 limit between 1 and 3 years[16], while memory T lymphocytes remain active up to 11 years
261 later[17].At the same time, recent studies in patients recovered from COVID-19, revealed
262 the fundamental value of T-lymphocytes (both CD4 and CD8)[11].in conferring protection
263 against SARS-CoV-2. In order to monitor the immunological memory elicited by
264 vaccination ,we measured the antigenic specific T cell responses. Individuals involved in
265 this study exhibited a robust T cell response against SARS-CoV-2 peptides. Circulating
266 memory T cells elicited by Sputnik V vaccine in elderly individuals produced high
267 amounts of TNF and IL-2 following stimulation with SARS-CoV-2 Spike-derived
268 peptides. Particularly, statistically significant differences were observed for TNF and IL-
269 2-producing CD4 and CD8 T cells with respect to unstimulated cells ($p = 0.013$ and $p =$
270 0.01 respectively).
271
272

Neutralizing antibodies that can intercept viruses before they infect cells might not be protective during the whole infection cycle. Although antibody levels typically rise after vaccination, they rapidly decline months later. In contrast, cellular responses are longer lasting. Memory B cells, which can rapidly deploy more antibodies in the event of re-exposure to the virus, tend to stay on-site, and so do memory CD8 T cells, which can exert cytotoxic activity toward infected target cells. Both memory cell populations provide a critical protection in case SARS-CoV-2 infection. In fact, vaccination stimulated long-lasting responses when both arms of adaptive immunity were considered simultaneously[18]. Memory B cells continued to grow in number for at least six months, and enhanced their ability to fight the virus over time. On the other hand, T-cell counts remained relatively stable, decreasing only slightly during the study period[18].

In this regard, analysis of lymph nodes from vaccinated individuals revealed the appearance of germinal centers that produced increasingly potent activated follicular B cells over time[19]. The B cells in these structures randomly mutated their genes (somatic hypermutation) to create an entirely new set of antibodies. Cells that produced the best antibody repertoires eventually prevailed through an evolutionary process that enhanced the immune system's ability to fight other SARS-CoV-2 variants[8-9]. These germinal centers persisted for 15 weeks after immunization with an RNA platform-based vaccine, a response which was much longer than those previously seen with older technology vaccines for other diseases. Our work shows that vaccinated individuals, with only two doses of a combined adenoviral vaccine, display robust T cell -mediated responses and do not acquire moderate nor severe COVID-19 infections, highlighting the safety and immunogenicity of this vaccination strategy in socially vulnerable elderly individuals.

Lowering infection rates should help break the cycle of viral transmission, ultimately resulting in fewer cases of severe COVID-19 infection and reduced death rates, thus keeping the emergence of vaccine-resistant variants at bay resistant viruses are more likely to emerge when transmission is not controlled[20]. Getting more people vaccinated and protecting the most vulnerable population is the most effective intervention to keep transmission rates low.

Conclusion

This work reaffirms the efficacy of the Sputnik-V vaccine, showing high levels of immunization, even in an elderly, underprivileged population with very low resources. We also found that immunity decreases as the age of the vaccinated individuals increases. Finally, we found that cellular immunity persists even after humoral immunity declines, giving us the indication that immunized older adults, and we can extend this to the general population, continue to be protected even if antibodies decline. We understand that this is a great advance in the knowledge of the protection provided by vaccines and this is one of the first studies that evidences this cellular protection against COVID-19 in an elderly population.

Declarations

- ***Ethical Approval and Consent to participate*** The work performed was accepted by the Internal Review Board. Although this work is framed within the nursing home standard of treatment, all participants had to consent to participate.
- ***Consent for publication*** All authors have consented to the publishing of this article.

- ***Availability of data and materials*** The data and materials are open to all health agents who wish to view and analyze them.
- ***Competing interests*** There were no conflicting interests in carrying out the proposed work.
- ***Funding*** The work was carried out with the resources of the Health Secretariat of the Municipality of Córdoba; we did not receive any grant to carry out the work. However, for the evaluation of cellular immunity, the Institute of Biology and Experimental Medicine (IBYME) did receive funds as stated in another section.
- ***Authors' contributions***

Martin P. Moya: literature search, figures, study design, data analysis, data interpretation, writing, funding acquisition,

Ariel Aleksandroff: study design, data analysis, data interpretation, funding acquisition,

Marcela Marrama: study design, data collection,

Carina D´Orazio: study design, data collection,

Florencia Veigas: literature search, data analysis,

Montana N. Manselle Cocco: literature search, data analysis,

Tomás Dalotto Moreno: literature search, data analysis,

Gabriel A Rabinovich: literature search, data analysis, data interpretation, writing, funding acquisition,

- ***Acknowledgements*** We thank the many dedicated persons at Hogar Padre la Monaca home for senior citizens, the Secretariat of Health at city Hall of Cordoba, Argentina and the epidemiology department of the same secretariat for the diligent efforts and contributions that made this study possible. We especially want to thank Dr. Arturo J. Lucchetta for his dedication and for opening the doors of the nursing home to us. T cell assays were supported by grants from the Minister of Science and Technology

(FOCEM, Mercosur), Bunge and Born Foundation, Williams Foundation and Sales Foundation to G.A.R.

- ***Authors' information***

Martin P. Moya: martinmoya@unc.edu.ar

Ariel Aleksandroff: aaleksandroff@hotmail.com

Marcela Marrama: marcela_marrama@hotmail.com

Carina D´Orazio: caridorazio@hotmail.com

Florencia Veigas: flveigas@gmail.com

Montana N. Manselle Cocco: montanamanselle@gmail.com

Tomás Dalotto Moreno: tomasdalotto@gmail.com

Gabriel A Rabinovich: gabyrabi@gmail.com

REFERENCES

1. Zhu N, Zhang D, Wang W. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727–733.
2. Li Q, Guan X, Wu P. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382:1199–1207.
3. Grein J, Ohmagari N, Shin D. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med. 2020 doi: 10.1056/NEJMoa2007016NEJMoa2007016. published online April 10.
4. Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. Lancet. 2020;395:1014–1015.
5. WHO Coronavirus disease (COVID-2019) situation reports. 2022. **¡Error! No se encuentra el origen de la referencia.**
6. Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, Dela Cruz CS, Wang Y, Wu C, Xiao Y, Zhang L, Han L, Dang S, Xu Y, Yang QW, Xu SY, Zhu HD, Xu YC, Jin Q, Sharma L, Wang L, Wang J. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). Clin Infect Dis. 2020 Jul 28;71(15):778-785.
7. Wajnberg A, Amanat F, Firpo A, Altman DR, Bailey MJ, Mansour M, McMahon M, Meade P, Mendu DR, Muellers K, Stadlbauer D, Stone K, Strohmeier S, Simon V, Aberg J, Reich DL, Krammer F, Cordon-Cardo C. Robust neutralizing antibodies to SARS-CoV-2 infection persist for months. Science. 2020 Dec 4;370(6521):1227-1230.
8. Pozzetto B, Legros V, Djebali S, Barateau V, Guibert N, Villard M, Peyrot L, Allatif O, Fassier JB, Massardier-Pilonchéry A, Brengel-Pesce K, Yaugel-Novoa M, Denolly S, Boson B, Bourlet T, Bal A, Valette M, Andrieu T, Lina B; Covid-Ser study group, Cosset FL, Paul S, Defrance T, Marvel J, Walzer T, Trouillet-Assant S.

385 Immunogenicity and efficacy of heterologous ChAdOx1-BNT162b2 vaccination.
386 Nature. 2021 Dec;600(7890):701-706.
387 9. Tarke A, Coelho CH, Zhang Z, Dan JM, Yu ED, Methot N, Bloom NI, Goodwin B,
388 Phillips E, Mallal S, Sidney J, Filaci G, Weiskopf D, da Silva Antunes R, Crotty S,
389 Grifoni A, Sette A. SARS-CoV-2 vaccination induces immunological T cell memory
390 able to cross-recognize variants from Alpha to Omicron. Cell. 2022 Mar
391 3;185(5):847-859.e11.
392 10. ManselleCocco MN, Veigas F, Bach CA, Blidner AG, Cagnoni AJ, D'Alotto-Moreno
393 T, Hockl PF, Mahmoud Y, Scheidegger MA, Sirino AB, Torres NI, Wiersba V,
394 Rabinovich GA. COVID-T: A functionalplatformto monitor SARS-CoV-2-specific T
395 cell responses in vaccinatedindividuals and COVID-19 recoveredpatients]. Medicina
396 (B Aires). 2021;81(5):683-687.
397 11. Moss P. The T cell immune response against SARS-CoV-2. Nat Immunol. 2022
398 Feb;23(2):186-193. doi: 10.1038/s41590-021-01122-w.
399 12. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, Subbarao K,
400 Kent SJ, Triccas JA, Davenport MP. Neutralizing antibody levels are highly
401 predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med.
402 2021 Jul;27(7):1205-1211.
403 13. Naaber P, Tserel L, Kangro K, Sepp E, Jürjenson V, Adamson A, Haljasmägi L,
404 Rumm AP, Maruste R, Kärner J, Gerhold JM, Planken A, Ustav M, Kisand K,
405 Peterson P. Dynamics of antibody response to BNT162b2 vaccine after six months: a
406 longitudinal prospective study. Lancet Reg Health Eur. 2021 Sep 6:100208.
407 14. Thomas SJ, Moreira ED Jr, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL,
408 Pérez Marc G, Polack FP, Zerbini C, Bailey R, Swanson KA, Xu X, Roychoudhury
409 S, Koury K, Bouguermouh S, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL,

Türeci Ö, Nell H, Schaefer A, Ünal S, Yang Q, Liberator P, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Gruber WC, Jansen KU; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. N Engl J Med. 2021 Sep 15.

15. Logunov DY, Dolzhikova IV, Shcheblyakov DV, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet. 2021 Feb 20;397(10275):671-681.
16. Cao WC, Liu W, Zhang PH, Zhang F, Richardus JH. Disappearance of antibodies to SARS-associated coronavirus after recovery. *N Engl J Med* 2007; 357: 1162-3.
17. Ng OW, Chia A, Tan AT, et al. Memory T cell responses targeting the SARS coronavirus persist up to 11 years post-infection. *Vaccine* 2016; 34: 2008-14.
18. Goel RR, Painter MM, Apostolidis SA, Mathew D, Meng W, Rosenfeld AM, Lundgreen KA, Reynaldi A, Khoury DS, Pattekar A, Gouma S, Kuri-Cervantes L, Hicks P, Dysinger S, Hicks A, Sharma H, Herring S, Korte S, Baxter AE, Oldridge DA, Giles JR, Weirick ME, McAllister CM, Awofolaju M, Tanenbaum N, Drapeau EM, Dougherty J, Long S, D'Andrea K, Hamilton JT, McLaughlin M, Williams JC, Adamski S, Kuthuru O; UPenn COVID Processing Unit, Frank I, Betts MR, Vella LA, Grifoni A, Weiskopf D, Sette A, Hensley SE, Davenport MP, Bates P, LuningPrak ET, Greenplate AR, Wherry EJ. mRNA Vaccination Induces Durable Immune Memory to SARS-CoV-2 with Continued Evolution to Variants of Concern. bioRxiv [Preprint]. 2021 Aug 23:2021.08.23.457229. Update in: Science. 2021 Oct 14.
19. Turner JS, Kim W, Kalaidina E, Goss CW, Rauseo AM, Schmitz AJ, Hansen L, Haile A, Klebert MK, Pusic I, O'Halloran JA, Presti RM, Ellebedy AH. SARS-CoV-2

infection induces long-lived bone marrow plasma cells in humans. Nature. 2021 Jul;595(7867):421-425.

20. Rella SA, Kulikova YA, Dermitzakis ET, Kondrashov FA. Rates of SARS-CoV-2 transmission and vaccination impact the fate of vaccine-resistant strains. Sci Rep. 2021 Jul 30;11(1):15729.

444 **Table 1.**

Table1. Characteristics of the participants at baseline	
Characteristic	**All Participants (N = 72)**
Sex – no. (%)	
Male	51 (69.9)
Female	22 (30.1)
Age – yr*	72.6 ± 9.4
Body-mass index (BMI)*ˆ	25.1 ± 7.7
BMI Category – no. (%)	
Underweight	17 (23.9)
Normal range	20 (28.2)
Overweight	15 (21.1)
Obese (Class I)	4 (5.6)
Obese (Class II)	4 (5.6)
Obese (Class III)	
Type of patient	
Ambulatory	50 (68.5)
Bedridden	23 (31.5)
* Plus–minus values are means ±SD. ˆThe body-mass index is the weight in kilograms divided by the square of the height in meters.	

445

Figures

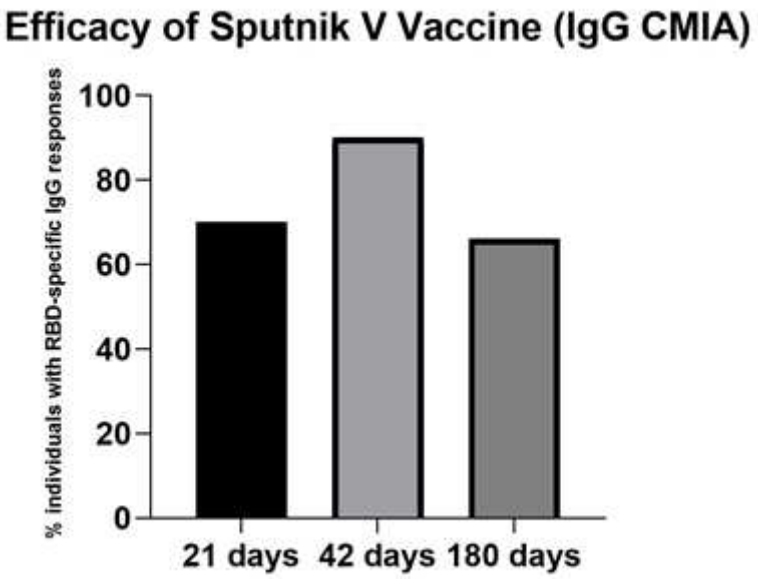

Figure 1

Efficacy of the Sputnik vaccine as measured by the percentage of individuals displaying RBD-specific IgG responses at days 21, 42 and 180 post-immunization.

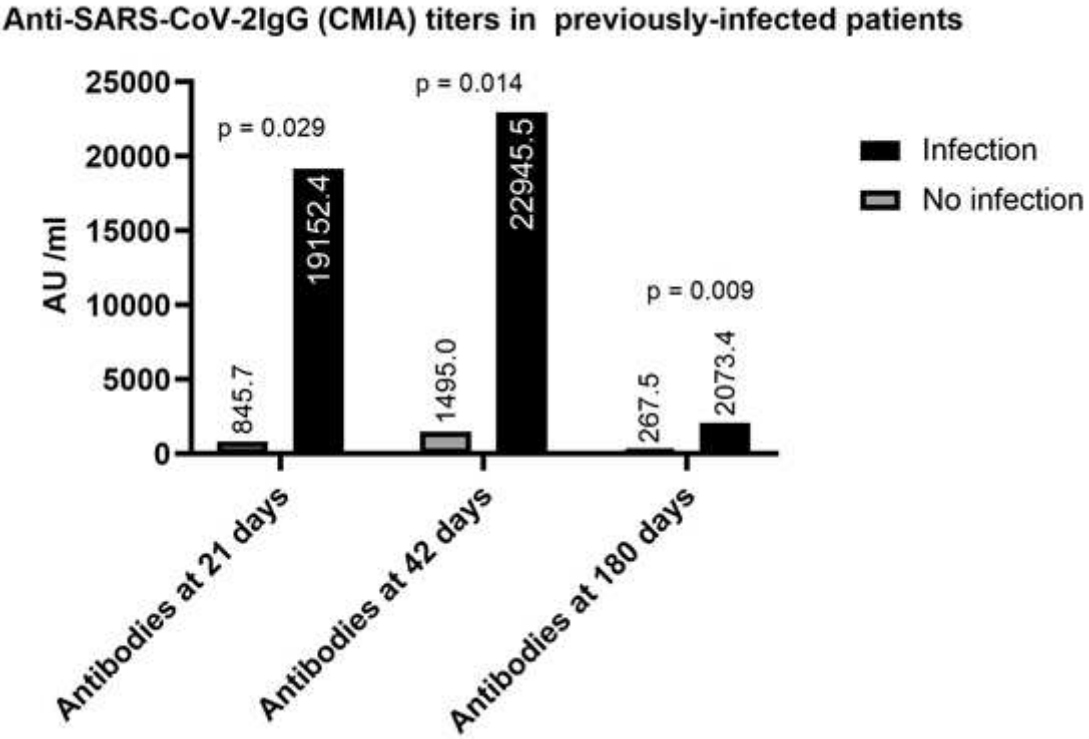

Figure 2

Difference in RBD-specific IgG antibodies in previously infected individuals immunized with Sputnik vaccine versus those who have not been infected or were asymptomatic

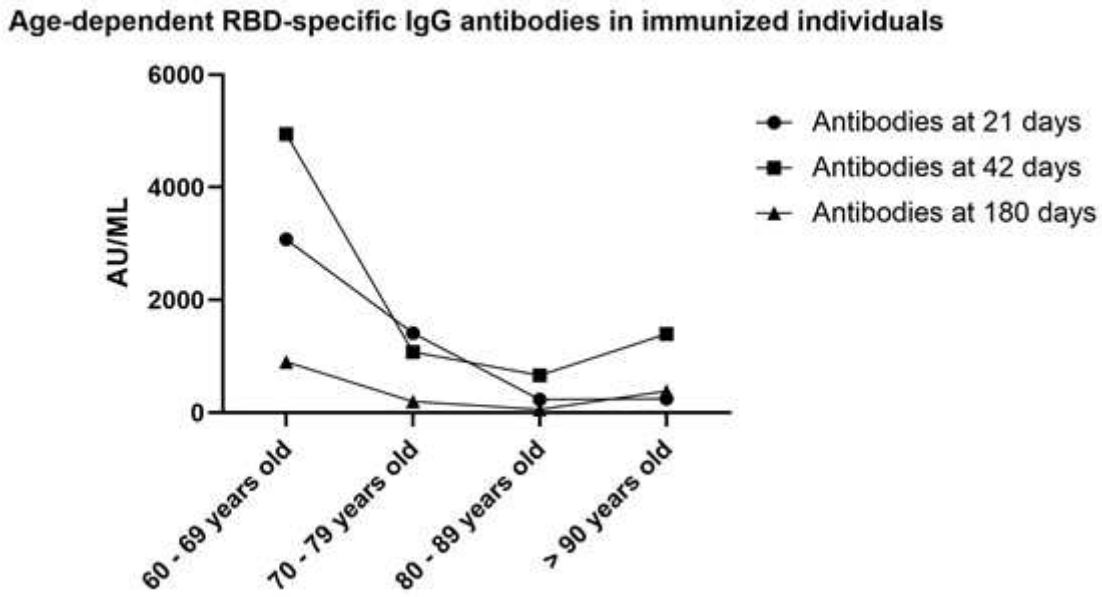

Figure 3

Antibody levels obtained at 21-, 42- and 180-days post-vaccination, following stratification into 4 different groups according to their age (60 to 69 years; 70 to 79 years, 80 to 89 years and over 90 years).

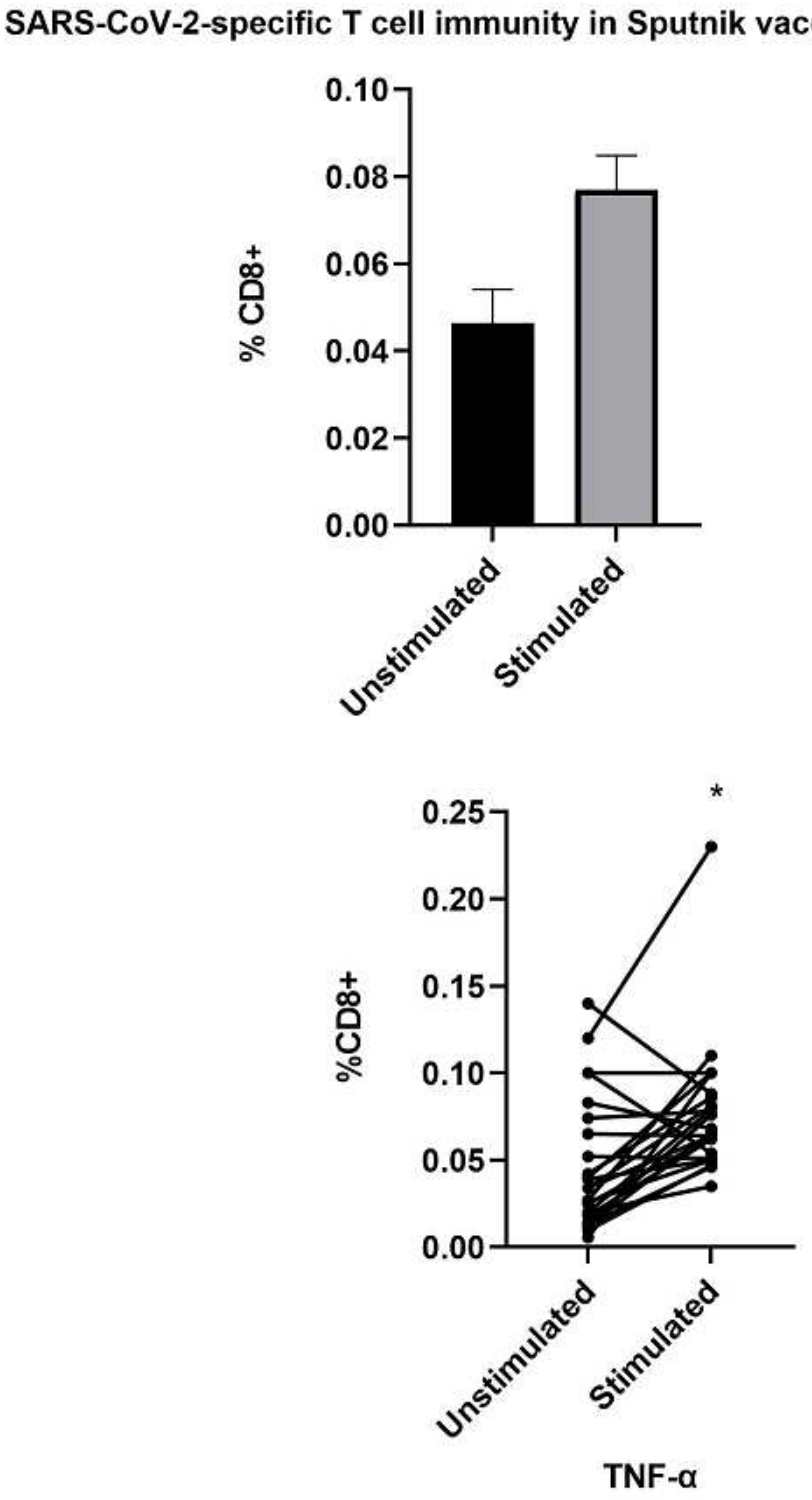

Figure 4

Determination of SARS-CoV-2-specific CD8 T cell immunity in Sputnik vaccinated individuals as measured by TNF synthesis