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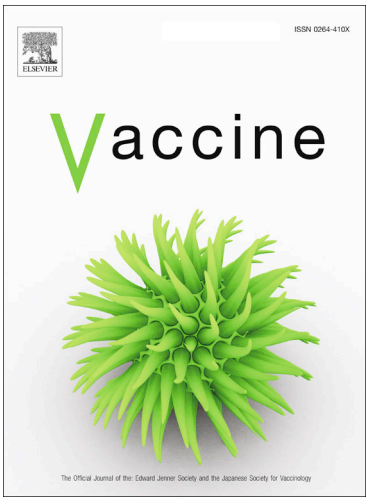

Short communication

Neutralizing response elicited by homologous and heterologous prime booster vaccination against ancestral SARS-CoV-2 B.1, P.1, C.37 and B.1.617.2 variants

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Title: Neutralizing response elicited by homologous and heterologous prime booster vaccination against ancestral SARS-CoV-2 B.1, P.1, C.37 and B.1.617.2 variants.

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Title: Neutralizing response elicited by homologous and heterologous prime booster vaccination against ancestral SARS-CoV-2 B.1, P.1, C.37 and B.1.617.2 variants.

Abstract

Heterologous Covid-19 vaccination strategies arose due to interruption of vaccination programs plus delay and shortage of vaccine supplies. We analysed neutralizing response against ancestral SARS-CoV-2 B.1 and P.1, C.37 and B.1.67.2 variants elicited by 16 homologous and heterologous protocols combining Gam-COVID-Vac, ChAdOx1-S, Ad5-nCorV, BBIBP-CorV and mRNA-1273 vaccines. Homologous mRNA-1273 and heterologous schemes of a non-replicative viral vector/inactivated virus-based vaccine combined with mRNA-1273 induced significantly broader and greater neutralizing antibody-response. Moreover, serum from participants vaccinated with combinations of ChAdOx1-S/Ad5-nCorV and BBIBP-CorV/non-replicative viral vector-based vaccines showed higher or equivalent neutralizing response compared to homologous protocols, pointing them as good alternative platforms. BBIBP-CorV used as second dose exhibited significantly lower neutralizing response compared to other protocols, demonstrating that it should not be recommended as second dose. The information provided herein is valuable to redesign vaccination strategies, especially for low-income countries that still struggle with low percentages of immunized populations and vaccine supply shortage.

Keywords: COVID-19; Heterologous vaccination; Vaccine; Shortage; Neutralizing Antibodies; variants of concern

Title: Neutralizing response elicited by homologous and heterologous prime booster vaccination against ancestral SARS-CoV-2 B.1, P.1, C.37 and B.1.617.2 variants.

Introduction

The interruption of vaccination programs due to unwanted events, such as the occurrence of thrombosis associated with ChAdOx1-S vaccine [1], the rare side effects reported for mRNA-based vaccines [2] and mainly the delay and shortage of vaccine supplies has hampered government strategies to immunize the global population against SARS-CoV-2. This has led to urgent actions to ensure continuity of vaccination programs. Thereby, several countries have recommended heterologous booster strategies combining available approved or authorized vaccines. Given the emergence of SARS-CoV-2 genetic variants, the use of heterologous vaccination schedules has also been discussed as a way to expand the breadth of immunity against SARS-CoV-2 to overcome the genetic mutations within SARS-CoV-2 variants [3,4]. During year 2021, low to middle-income countries began to receive vaccines through the COVAX mechanism. The first and most widely vaccine supplied by COVAX in Africa was ChAdOx1-S, being one of the most accessible licensed Covid-19 vaccines. Nevertheless, a two-dose regimen of ChAdOx1vaccine did not show protection against mild-to-moderate Covid-19 due to B.1.351 variant [5]. Due to the reduced protection against variants of concern plus safety and supply issues of ChAdOx1-S vaccine, heterologous prime booster-dose with alternative vaccines for individuals with a prime dose of ChAdOx1-S was recommended [6].

An early challenge in Covid-19 vaccination progress was a halt in prime boost immunization due to vaccine stock out. The most frequent causes were production issues and global shortage. In Argentina, Gam-COVID-Vac was the vaccine administrated to the largest proportion of individuals immunized until mid-2021 [7]. The delay on delivery of the second component of this vaccine challenged the

possibility of completing the vaccination schedule since there were not enough second doses available within the recommended three-month period after the prime dose. Thus, to mitigate Gam-COVID-Vac supply shortage and interruptions, alternative vaccine platforms were proposed and applied [8].

This study evaluated alternative schedule booster strategies as second-dose vaccines, to mitigate delay in manufacturing/distribution and supply shortage of Covid-19 vaccines.

Materials and methods

Participants

Participants were enrolled in a National collaborative study for evaluation of heterologous vaccination schemes against Covid-19 in Argentina. Individuals with none or well-controlled mild/moderate comorbidities (obesity, chronic cardiovascular disease, chronic kidney disease, chronic respiratory disease, cirrhosis, HIV infection) aged 18 to 82 years, who had received a first dose of Gam-COVID-Vac rAd26, ChAdOx1-S, mRNA-1273 or BBIBP-CorV 28-56 days prior to enrolment, were recruited. Exclusion criteria included previous laboratory-confirmed SARS-CoV-2 infection, immunocompromised patients, pregnant and breastfeeding women, and individuals with history of severe allergic reactions to any vaccine. Other exclusion criteria include bleeding disorders, thrombocytopenia, neurological disorders, and current alcohol or drug dependence.

The vaccines Gam-COVID-Vac rAd26/rAd5, ChAdOx1-S, mRNA-1273, BBIBP-CorV or Ad5-nCoV were administered in previously-immunized participants in doses and routes previously authorized by the local regulatory entity, based on information provided by manufacturer laboratories. The minimum interval between doses was 4 weeks when the first dose corresponded to an inactivated virus vaccine and 8 weeks in cases in which the scheme had started with platforms based on viral vectors or mRNA. Blood samples were obtained by venipuncture 28 days after the second dose.

SARS-CoV-2 Isolation

Vero Cl76 cell-line (ATCC CRL-1587) was used for SARS-CoV-2 Wild type (WT) B.1 (GISAID Accession ID: EPI_ISL_499083), P.1 (EPI_ISL_2037442), C.37 (EPI_ISL_3183946) and B.1.617.2 (EPI_ISL_6032417) variants isolation assays, as previously described [9].

Detection of live SARS-CoV-2 Neutralizing Antibodies

Plasma samples were tested for their neutralization ability against SARS-CoV-2 WT B.1, P.1, C.37 and B.1.617.2 variants by plaque-reduction neutralization test (PRNT). Virus neutralization tests were performed in 24-well plates. Vero Cl76 cells (ATCC CRL-1587) were sowed 48 h before infection. Plasma samples were heat-inactivated by incubation at 56°C for 20 minutes and centrifuged at 10,000 rpm 30 minutes before use. Treated-samples were two-fold diluted and then, an equal volume of virus stock containing 100 plaque forming units (PFU) was added to each corresponding well until reaching final dilutions. Sample dilutions-virus were incubated at 37°C for 60 min and then added to each well of the cell culture plate. After incubation for 1 hour at 37°C in a 5% CO2 incubator, cells were incubated with 0.5% agarose with DMEM supplemented with 2% FBS during 4 days at 37°C in a 5% CO_2 incubator. After 4 days, the 24 well plates were fixed and inactivated using a 10% formaldehyde/PBS solution and stained with crystal violet 1%. NAbs titres corresponded to the maximum dilution of plasma that neutralized 80% of the PFU, compared with PFU from the viral controls included in the test.

Statistical Analysis

To compare the titres of AcNT against each viral variant, general linear models were developed with Student Newman Keuls as a multiple comparison test, as indicated in the figure legends. The different vaccination schedules were used as factors. The reciprocals of neutralization titres were transformed into base 2 logarithms and Geometric Mean Titres (GMTs) were calculated. Furthermore,

antilogarithms of GMTs were calculated. Titres lower than 1/10 were considered as 1 and titres higher than 1/640 were considered 1280. Comparisons of GMTs between groups were conducted using mixed linear models and Tukey post-hoc test. Soft R-Medic®[10] and InfoStat®[11] were applied and in all cases, significance level was 5%. Ggplot2 [12] was used to generate Figure 1 in R language.

Results

A total of 429 plasma samples were collected. Distribution of age and sex is shown in Table 1 (extended data). There were no significant differences in sex ratio values among the evaluated schedule booster strategies ($p=0.787$). Although significant differences were found in the mean age among the schedules ($p<0.001$), when both age and sex were incorporated as covariates or factors in analyzes, no significant differences were observed ($p>0.05$). Significant differences were found in the time elapsed between the first and second vaccine doses (Table 2, extended data) ($p<0.001$); however, when time was incorporated in the analyses as a covariate, it did not show significant effects in any case ($p>0.05$).

Of all samples, 105 (24.48%) corresponded to participants immunized with homologous schedules while 324 (75.52%) corresponded to participants that received heterologous vaccination schedules. Distribution of enrolled participants among the different vaccine scheme is shown in Table 1 (extended data). In each of the 16 protocols, a minimum of 14 and a maximum of 38 samples were evaluated. There were no significant differences between n included in each protocol (chi square: 22.99, $p=0.0843$). Only one of the participants, who had received homologous vaccination with mRNA-1273, became infected within 60 days of starting the study.

Results are shown in Figure 1 and Tables 3-6 (tables are available as extended data). Significant differences were found in neutralizing responses between different vaccination protocols considering each of the SARS-CoV-2 variants. The results highlight that SARS-CoV-2-targeting neutralizing

antibody titres were highest when the boost dose consisted of mRNA-1273, independent of the vaccine used for priming, and this was so against ancestral WT B.1, P.1, C.37 and B.1.617.2 variants. In addition, in the protocols in which Ad5-nCoV, Gam-COVID-Vac (rAd26 or rAd5) or ChAdOx1-S vaccines were applied as second dose, NAbs titres were intermediate (Figure 1). ChAdOx1-S/Ad5-nCoV scheme was an exception since Nabs titres were comparable to protocols that involved mRNA vaccines. The lowest average level of NAbs was observed when BBIBP-nCorV vaccine was used as second dose, regardless of which vaccine was applied as first dose.

Discussion

This study evaluated the neutralizing activity of antibodies elicited by homologous and heterologous prime-booster vaccination against SARS-CoV-2 WT B.1 and against P.1, C.37 and B.1.617.2 variants.

Heterologous immunization with non-replicative viral vector platforms and mRNA-1273 vaccines induced significantly broader and higher NAb titres than homologous protocols. In case of Gam-COVID-Vac, the combination of Gam-COVID-Vac rAd26/mRNA-1273 showed better neutralizing response than the Gam-COVID-Vac rAd26/rAd5 schedule. These results agree with previous studies assessing the use of alternative schemes to complete Gam-COVID-Vac rAd26 vaccine [8]. Our findings extended the data, showing that heterologous boost also enhances titres and expand the breadth of NAbs against P.1, C.37 and B.1.617.2 variants. On the other hand, our results regarding combination of Gam-COVID-Vac rAd26/ChAdOx1-S do not agree with published data [8], since no significant differences were observed in our study when compared them with Gam-COVID-Vac rAd26/rAd5 (GMT: 4.83 vs 5.46, respectively; Table 3, extended data). Moreover, we showed that Gam-COVID-Vac rAd26/Ad5-nCoV combination induced similar NAb titres than Gam-COVID-Vac rAd26/rAd5 scheme, without significant differences, demonstrating that this heterologous

combination could be recommended in a context of vaccine shortage. However, extensive studies including cellular immunity would be necessary to get a more complete picture.

After rare but serious adverse events, heterologous vaccination combining ChAdOx1-S and mRNA-based vaccine was evaluated, showing improved immunity against SARS-CoV-2 ancestral strain compared to a homologous ChAdOx1-S platform [4,13]. Our results confirmed that individuals vaccinated with heterologous schemes presented significantly broader and more potent neutralizing response, regardless of the SARS-CoV-2 variant, since they enhanced the breadth of variant recognition compared to ChAdOx1-S homologous regimen. Otherwise, it is noteworthy that, when a first dose of ChAdOx1-S was combined with a second dose of Ad5-nCoV, NAbs titres were comparable to protocols involving mRNA vaccines. These data demonstrate that heterologous ChAdOx1-S followed by Ad5-nCoV can be considered a better alternative scheme to the homologous ChAdOx1-S scheme.

Prime-dose immunization with inactivated virus vaccine followed by mRNA vaccines as second dose induced an increased neutralizing response compared to homologous inactivated virus vaccination. In addition, when combining inactivated virus vaccine as first-dose with non-replicative viral vector platforms, the achieved neutralizing response was equivalent or higher than homologous non-replicative viral vector schemes, indicating that this vaccine combination is a suitable alternative. On the contrary, a booster by inactivated virus vaccines elicited lower NAb titres than any of the homologous vaccine protocols evaluated. These findings indicate that inactivated virus vaccines (BBIBP-CorV) should not be recommended as booster of a primary vaccination. Response induced by a third dose of BBIBP-CorV should be carefully assessed before recommending it. On the other hand, combination of BBIBP-CorV with a non-replicative viral vector-based vaccine elicited higher response and extended the breadth of neutralizing response against SARS-CoV-2 variants compared to BBIBP-CorV homologous protocol. This finding demonstrates that the mentioned heterologous vaccination is certainly a better alternative.

Covid-19 vaccine booster (third dose) to complete primary vaccination series of approved or authorized platforms are recommended to address potential waning immunity over time and reduced effectiveness against SARS-CoV-2 variants [14,15]. However, unequal access to vaccines has led to the lowest Covid-19 vaccination rates in low-income countries. As Singh Bajaj et al express, "Widening gaps in global vaccine equity have led to a two-track pandemic with booster Covid-19 vaccination proliferating in high-income countries and first doses not yet reaching all populations in low-income countries" [16]. Without effective vaccination and equitable vaccination allocation strategies, advances in epidemic control cannot be fully performed and the risk of prolonging the pandemic is perpetuated [16]. Herein, we show the results of two-dose alternative regimens by different vaccine combinations that elicited efficient neutralizing activity against SARS-CoV-2. Our results could help to design interventions to speed up effective development of vaccination programs, especially for regions with high rates of still-not vaccinated populations. Thus, people who received at one Covid-19 vaccine dose hampered by limited supplies would be mainly benefited.

In conclusion, the evidence obtained in this study confirms that combination of non-replicative viral vector or inactivated virus vaccines and mRNA vaccines produce the highest titres of NAbs against ancestral B.1 WT, P.1, C.37 and B.1.617.2 variants compared to homologous vaccination. We also demonstrated that combination of heterologous inactivated virus with non-replicative viral vector-based vaccines can be a good alternative scheme and that inactivated virus-based vaccines should not be recommended as second doses.

As new variants are emerging and spreading, countries with low percentages of immunized populations need effective interventions to strengthen development of vaccine strategies. Heterologous prime-boost vaccines are being recommended due to higher immunogenicity and enhanced protection, even for unvaccinated or partially vaccinated individuals [6]. The information provided herein demonstrates the efficacy of the combination of different available vaccines to induce neutralizing response against SARS-CoV-2 ancestral B.1, P.1, C.37 and B.1.617.2 variants. Many

countries, especially low-income countries, are still struggling with scarcity of Covid-19 supplies, finding it difficult, if not impossible to get enough vaccines [17]. Recommendations of alternative vaccination schedules are required to guarantee stable and adequate access to vaccine supply and overcome shortages/stockout. Our findings could have important implications for vaccination strategies and logistics, to improve protection already achieved with some vaccination platforms, and to allow greater flexibility in the occurrence of vaccine shortages or availability issues.

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.

Data Availability

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

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Statement of Ethics

Participants were enrolled in the framework of a collaborative study within the School of Medical Science of the National University of Cordoba and the Ministry of Health of Cordoba province, for the evaluation of heterologous vaccination schemes against Covid-19 in Argentina. The study was approved by the Institutional Committee of Ethics on Health Research (CIEIS) HCN - FCM under

the Local Registry of Health Research (RePis) number 4371, August 2021. All participants provided a written informed consent.

This research was 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.

Authorship contributions

SB, BSK, AD, LS, JJA, MER, MB, and SVG conceived and designed the study.

SB, BSK, AD, LS, JJA, MER, MB, and SVG performed SARS-CoV-2 isolations, Plaque Reduction Neutralization technique, analyzed and interpreted the data and drafted the manuscript.

AM and EF performed statistical analysis, analyzed and interpreted the data and revised the final version of manuscript.

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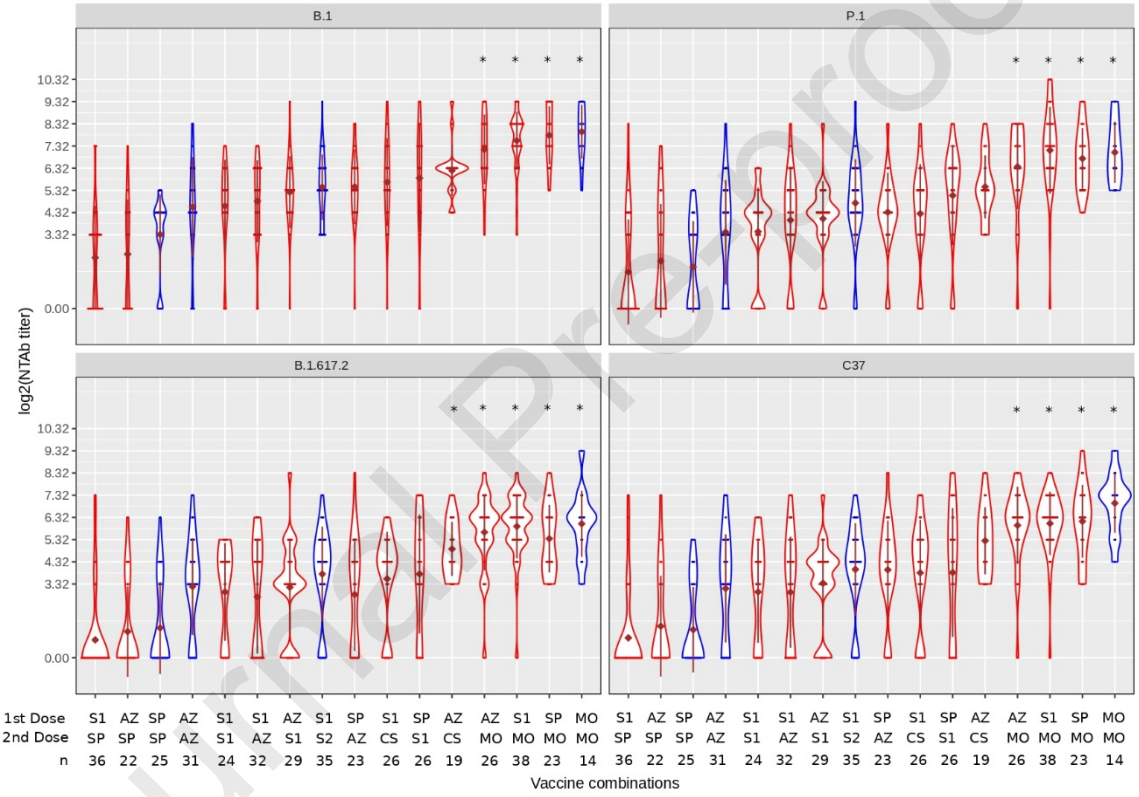
Title: Neutralizing response elicited by homologous and heterologous prime booster vaccination against ancestral SARS-CoV-2 B.1, P.1, C.37 and B.1.617.2 variants

Figure 1: Comparison of the neutralizing capacity of antibodies elicited by homologous and heterologous booster vaccination against SARS-CoV-2 ancestral Wild type (WT) B.1 and P.1, C.37, and B.1.617.2 variants.



Legend: The graphics show the values of geometric means titres (GMT) (Test of Student Newman Keuls). The asterisks indicate the protocols for which the highest geometric means of neutralizing antibody titres were obtained, being the response significantly higher when comparing homologous and heterologous protocols. References: S1: (**S**putnik Component **1**) Gam-COVID-Vac recombinant adenovirus 26 (Gamaleya Institute); S2: (**S**putnik Component **2**) Gam-COVID-Vac recombinant adenovirus 5 (Gamaleya Institute); AZ: ChAdOx1-S (**A**straZeneca/**O**xford University); SP: BBIBP-

CorV (**S**ino**p**harm); CS: Ad5-nCoV (**C**an**S**ino); MO: mRNA-1273 (**Mo**derna/NIAID); n= number of enrolled participants classified according the different vaccine schemes.

Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: