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RESEARCH ARTICLE

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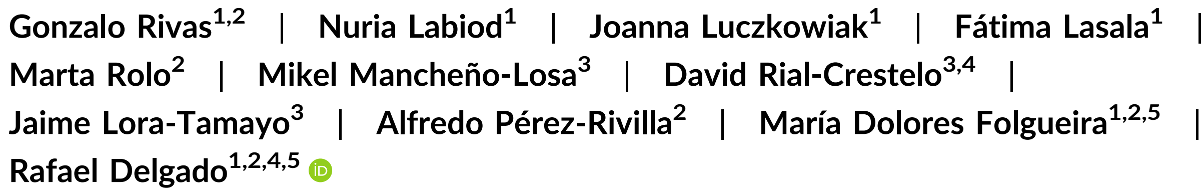
Superior neutralizing response after first versus second SARS-CoV-2 infection in fully vaccinated individuals



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Abstract

Currently, the majority of the population has been vaccinated against COVID-19 and/or has experienced SARS-CoV-2 infection either before or after vaccination. The immunological response to repeated episodes of infections is not completely clear. We measured SARS-CoV-2 specific neutralization titers by a pseudovirus assay after BA.1 infection and RBD-specific immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin M (IgM) in a cohort of COVID-19 uninfected and triple vaccinated individuals (breakthrough infection group, BTI) as compared with those previously infected by SARS-CoV-2 (reinfection group, REI) who underwent identical vaccination schedule. SARS-CoV-2 specific neutralizing response after BA.1 infection was significantly higher in the BTI group as compared with the REI. Furthermore, neutralization titers in REI were not significant different from convalescent non reinfected controls. RBD-specific IgG and IgA, but not IgM, were also significantly higher in BTI as compared with REI. Our results show that the first episode of SARS-CoV-2 infection induces a significant increase in neutralizing titers in triple vaccinated individuals and that previous SARS-CoV-2 infection compromise significantly the neutralization response induced by reinfection, even by divergent SARS-CoV-2 variants and at least up to 2 years postinfection, suggesting a fundamental limitation in inducing effective booster through the intranasal route in previously infected individuals.

KEYWORDS

coronavirus, humoral immunity, neutralization, reinfection, SARS coronavirus, vaccines/vaccine strains

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1 | INTRODUCTION

At this stage of the COVID-19 pandemics evolution, an important proportion of the population has been vaccinated in developed countries and has also experienced an episode of SARS-CoV-2 infection either before or after vaccination. This so-called hybrid immunity [1] is thought to confer the most complete level of protection to COVID-19. However, the sequence in which these different immunological stimuli occur might be relevant to understand the response to both vaccine and infection.

With the aim of developing a more effective mucosal response, the development of intranasal vaccines has been studied. In this context, it is especially interesting to know the differences in the immune response that develops through parenteral stimuli (such as traditional vaccines) and stimuli in the nasopharyngeal mucosa (such as natural infection and intranasal vaccination).[2]

In this report we show that SARS-CoV-2 infection in uninfected vaccinated individuals induces a higher neutralizing response against SARS-CoV-2 than in COVID-19 convalescent individuals subjected to the same vaccination schedule and afterwards experiencing a second SARS-CoV-2 infection episode.

2 | MATERIALS AND METHODS

2.1 | Cohort

We have studied individuals belonging to a cohort with extensive follow-up,[3,4] (Solidarity II cohort, IRB approval ref CEI 20/157). Seventeen triple vaccinated health care workers (HCW) from the Hospital Universitario 12 de Octubre and subsequent infected by SARS-CoV-2 Omicron subvariant BA.1 were studied. Infection was determined by polymerase-chain reaction (RT-PCR) in 10 cases, and by rapid antigen test in 7. In those samples in which the infection was determined by RT-PCR, it was confirmed that the infection was caused by the BA.1 Omicron subvariant using the Allplex SARS-CoV-2 Variant Assay (Seegene Technologies). All infections occurred between December 2021 and early March 2022, a period in which the most prevalent SARS-CoV-2 variant in Spain corresponded also to Omicron BA.1. Seven of these HCWs had a history of SARS-CoV-2 infection during the first pandemic wave in Spain (reinfection group, REI group), in March 2020, while the remaining 10 (breakthrough group, BTI group) had no history of previous infection. In the BTI group, prior infection was ruled out by the absence of clinical symptoms or positive PCRs test and by systematic testing for anti-Nucleoprotein antibodies (Elecsys Anti-SARS-CoV-2 test, Roche Diagnostics) as part of the follow up between their recruitment in March 2020 to September 2021.

All participants were vaccinated in January–February 2021 with 2 doses of the Pfizer-BNT162b2 vaccine, 21 days apart, and in December 2021 with the Moderna mRNA-1273 vaccine.

In the BTI group, a blood sample was obtained 66.8 days (range: 41–100) after the third dose and 32.1 days (range: 21–62) after BTI, while in the REI group it was obtained 78.3 days (range: 58–100) after third dose and 26.3 days (range: 21–53) after REI.

Additionally, we selected 15 convalescent and 12 uninfected triple vaccinated HCW from the same cohort without BA.1 infection after their third dose. Blood samples were obtained 50.0 days (range: 41–57) after the third dose for the convalescent control group and 47.3 days (range: 42–55) for the uninfected control group. None of the participants from the uninfected control group had detectable anti-nucleoprotein antibodies at any point of the 2-year follow up of the main cohort. Schematic summary of the vaccine, infection and sample time points in Figure 1.

Minimal variations in the sample extraction times in the different groups arose due to a deliberate waiting period of at least 21 days between infection and sample extraction. This precaution ensures that sufficient time has elapsed for the humoral response to the infection to develop.

No statistically significant differences in age or sex were found between groups. Demographics shown in Table S1.

2.2 | Neutralization assays

Neutralizing antibody response was measured by using a SARS-CoV-2-Spike pseudotyped vesicular stomatitis virus (rVSV-ΔG-luc) assay.[3] Pseudovirus incorporating SARS-CoV-2 Wuhan-hu-1614G and Omicron BA.1 and BA.5 spikes were used at a multiplicity of infection (MOI) of 0.5–1. Serum samples were tested at 1:80, 1:160, 1:320, 1:640, 1:1280, 1:2560, 1:5120, 1:10 240, and 1:20 480 dilutions. Pseudovirus were incubated with sera for 1 h at 37°C in 96-well plates. After incubation, 20 000 VeroE6 cells were seeded into the virus-plasma mixture and incubated at 37°C for 24 h. Then, cells were lysed using Glo Lysis Buffer (Promega), and luciferase activity was tested using Luciferase Assay Reagent (Promega) in the GloMax Navigator (Promega), following manufacturer's instructions.

Neutralizing titer 50% (NT50) was calculated using a nonlinear regression model fit with settings for log inhibitor versus normalized response curves, in NT50 was calibrated and then transformed into International Units per mL (IU/mL) using the World Health Organization (WH)O International Standard 20/136.[5]

2.3 | Production of rVSV-ΔG-luc-SARS-CoV-2-S pseudovirus

The SARS-CoV-2 Spike mutant Wuhan-hu-1 D614G was generated by site-directed mutagenesis using a vector encoding SARS-CoV-2 Spike_614D protein (kindly provided by J. Garcia-Arriaza, CNB-CSIC). SARS-CoV-2 variant Omicron BA.1 (B.1.1.529, GISAID: EPI_ISL_6640917) and SARS-CoV-2 variant Omicron BA.5 (B.1.1.529, GISAID: EPI_ISL_12278971) were synthesized and cloned into pcDNA3.1 (Geneart). VSV-G pseudotyped rVSV-ΔG-luc recombinant viruses were produced as described in previously published protocols.[6] In short, pseudovirus were produced following a two-step protocol. First, plasmids containing the mutant SARS-CoV-2-Spikes were transfected into BHK-21 cells using Lipofectamine 3000 (Thermo-Fisher), following manufacturer's instructions. Twenty-four-hour later, cells were infected with

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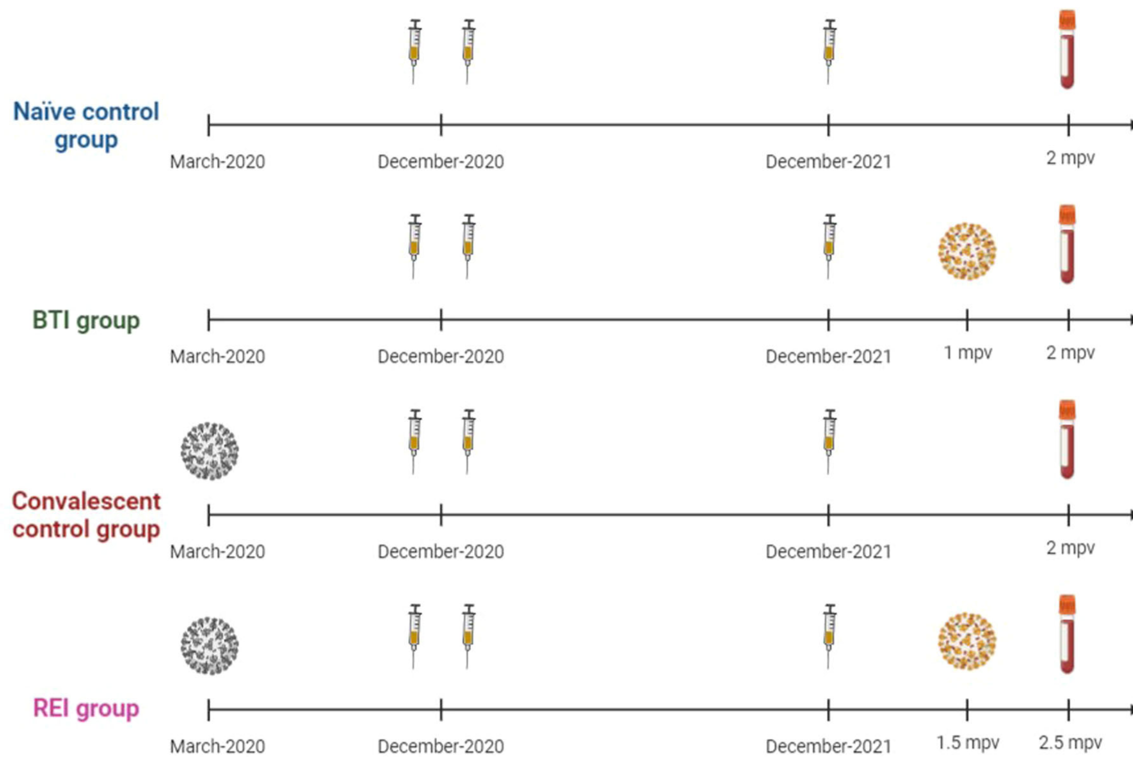

FIGURE 1 Schematic summary of the groups studied. mRNA vaccination shown as syringes, infection during the first pandemic wave as a grey virus, BA.1 infection as a yellow virus, and blood sample extraction as a tube icon. mRNA, messenger RNA.

VSV-G pseudotyped rVSV-ΔG-luc viruses at a MOI = 3 and incubated at 37°C for 1 h. Cells were then washed up to five times with phosphate buffered saline (PBS) to fully remove remaining traces of VSV-G pseudotyped rVSV-luc, and incubated in Opti-MEM medium (Gibco/Thermo-Fisher) at 37°C for 20 more hours. Supernatants were harvested, centrifuged, and stored at −80°C.

2.4 | Anti-RBD total antibody

Anti-RBD total antibody concentrations were determined using the Elecsys Anti-SARS-CoV-2-S assay (Roche Diagnostics). Results were converted from Arbitrary Units per milliliter (AU/mL) into WHO international standard binding antibody units and expressed as "Binding Antibody Units" per milliliter (BAU/mL) following manufacturer's instructions.

2.5 | Anti-RBD immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA)

An ELISA protocol was performed.[6] Briefly, 96-well plates were coated for 24 h with 50 µL of a 1 mcg/µL solution of wild type RBD (kindly provided by Florian Krammer). Plates were then washed three times with PBS-0.1% Tween (PBST), and a blocking solution of PBST-3% nonfat Milk was added for at least 2 h. After incubation, plates were washed three times with PBST. Following the incubation, plates were washed as described in the previous step. Serial dilutions ranging from 1:20 to 1:40 980 (IgA and IgM) and from 1:500 to 1:1 024 000 (IgG) of the participants' sera were then inoculated in duplicate and incubated for 2 h at room temperature. As a negative control, 12 aliquotes of a 1:100 diluted serum, extracted from a healthy donor in 2018, were used. Another washing cycle was performed and 50 µL per well of a 1:1.500 diluted goat anti-human IgG, IgA or IgM–horseradish peroxidase (HRP) conjugated secondary antibody dilution (Thermo Fisher Scientific) was added to each well. After 1 h, the plates were again washed three times. Next, 100 µL SIGMAFAST OPD solution was added to each well. Following 10 min of incubation time, the reaction was stopped by adding 50 µL per well of 3 M hydrochloric acid. Optical density (OD) at 490 nm (OD490) was measured using the Thermo Scientific Multiskan FC plate reader (Thermo Fisher Scientific). A positivity cut-off was calculated as two times the standard deviation plus the mean of the OD obtained from the negative control wells. Titers were calculated as the highest dilution with a higher OD value than the cut-off.[7]

2.6 | IgG avidity assay

A modification of a previous protocol was performed to determine the avidity. In short, instead of inoculating serial dilutions of the sera from participants, samples were inoculated in duplicate wells at a concentration which would give an optical density reading close to 1, as described elsewhere,[8] and incubated for 2 h at room temperature. One of the duplicates was then incubated for 15 min with PBS while the other duplicate was incubated with a 5 M solution of urea. As secondary

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antibody, an IgG–HRP conjugated antibody (Thermo Fisher Scientific) was used. Avidity index (AI) was calculated for each sample by dividing the OD obtained in the urea and the PBS wells.

2.7 | Statistical analysis

Differences between groups were calculated by Mann–Whitney test in GraphPad Prism v8.

3 | RESULTS

Neutralizing titers were significantly higher after BTI than after REI against 614 G (6597 IU/mL vs. 3073 IU/mL, 2.1 fold, $p = 0.02$), BA.1 (2941 IU/mL vs. 1182 IU/mL, 2.5 fold, $p = 0.02$) and BA.5 variants (2285 IU/mL vs. 880 IU/mL, 2.6 fold, $p = 0.03$) (Figure 2).

Higher neutralization titers were found after BTI when compared with the uninfected control group, without infection, at the same time. This difference was statistically significant against all variants: 614G (6597 IU/mL vs. 2821 IU/mL, 2.3 fold, $p = 0.01$), BA.1 (2941 IU/mL vs. 955 IU/mL, 3.1 fold, $p = 0.002$) and BA.5 (2285 IU/mL vs. 390 IU/mL, 5.9 fold, $p = 0.0002$). However, no statistically significant difference was found between the REI group and the not-reinfected convalescent control group in the same period (Figure 2).

Significantly higher total antibody concentrations were found in the BTI group than in the REI one (52320 BAU/mL vs. 24300 BAU/mL, 2.2 fold, $p = 0.009$). This was also observed when comparing IgG anti-RBD titers, with a median titer of 1:32 000 for the BTI group and of 1:8000 for the REI group ($p = 0.0017$) (Figure 3 and Figure S3). Anti-RBD IgA titers were also significantly higher in the BTI group than in the REI group (1280 vs. 80, $p = 0.012$) (Figure 3). Additionally, no differences between groups were found in IgM anti-RBD titers (Figure S2), nor in the AI (Figure S1).

4 | DISCUSSION

The neutralizing antibody response after COVID-19 vaccination in individuals who were previously infected with SARS-CoV-2 has clearly been shown to be higher than the response induced by vaccination alone[9] We and others have shown than this difference is considerably reduced after the administration of a third dose of vaccine that induces high levels of neutralizing antibodies in uninfected individuals through the process of affinity maturation, this results in antibodies with higher avidity and a wider coverage against VoCs.[3,4] Fewer studies have compared the neutralizing response induced by primary infection versus reinfection in fully vaccinated individuals.[10,11]

Here we show that SARS-CoV-2 BTI in triple vaccinated individuals induced higher neutralization titers than those generated by REI. In fact, the first episode of SARS-CoV-2 infection induced a significant booster effect in neutralizing titers in triple vaccinated individuals (BTI group) as compared with noninfected controls, however this was not the case in previously infected individuals in the REI group. This difference is remarkable since the COVID-19 convalescent groups had exhibited the highest levels of neutralization along the first two doses of vaccine and only after the third dose neutralizing levels and VoC coverage were comparable to those produced only through vaccination[3,12] suggesting that the first, and not subsequent events of SARS-CoV-2 infection,

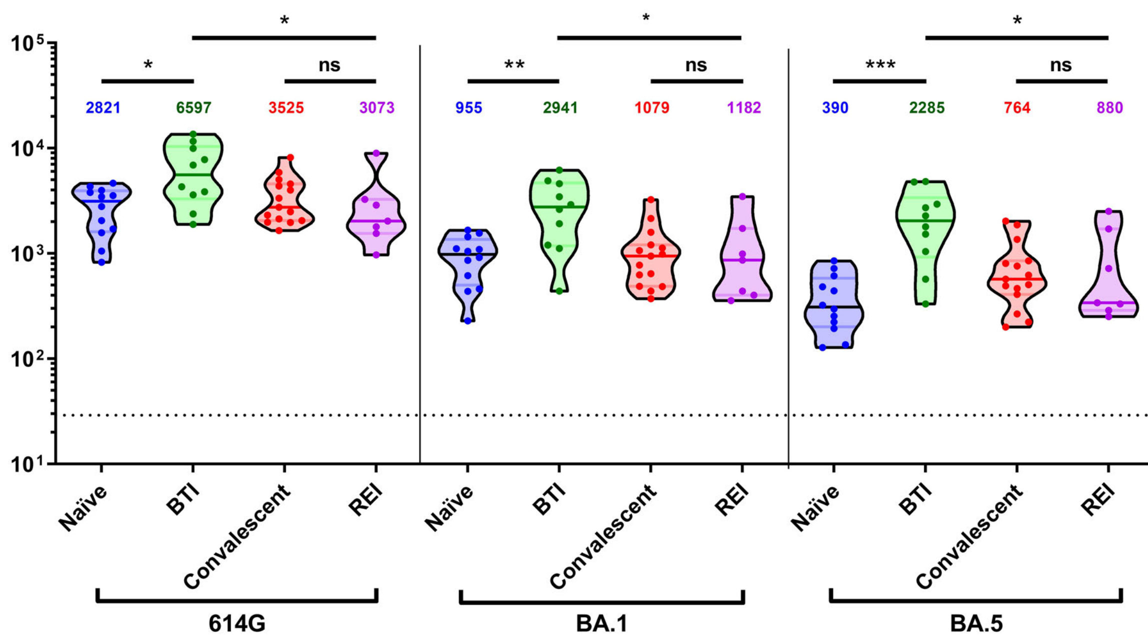

FIGURE 2 Neutralization titers against SARS-COV-2 variants. Mean neutralizing titers and violin plots from SARS-COV-2 convalescent individuals are shown in red, from uninfected individuals in blue, from the BTI group in green and from the REI group in purple. Dashed line marks the cut-off titer for neutralization assay (29 IU/mL). Neutralization titers are normalized using the WHO International Standard 20/136 and are expressed as International Units per milliliter (IU/mL). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. BTI, breakthrough infection group; ns, not significant; REI, reinfection group; WHO, World Health Organization.

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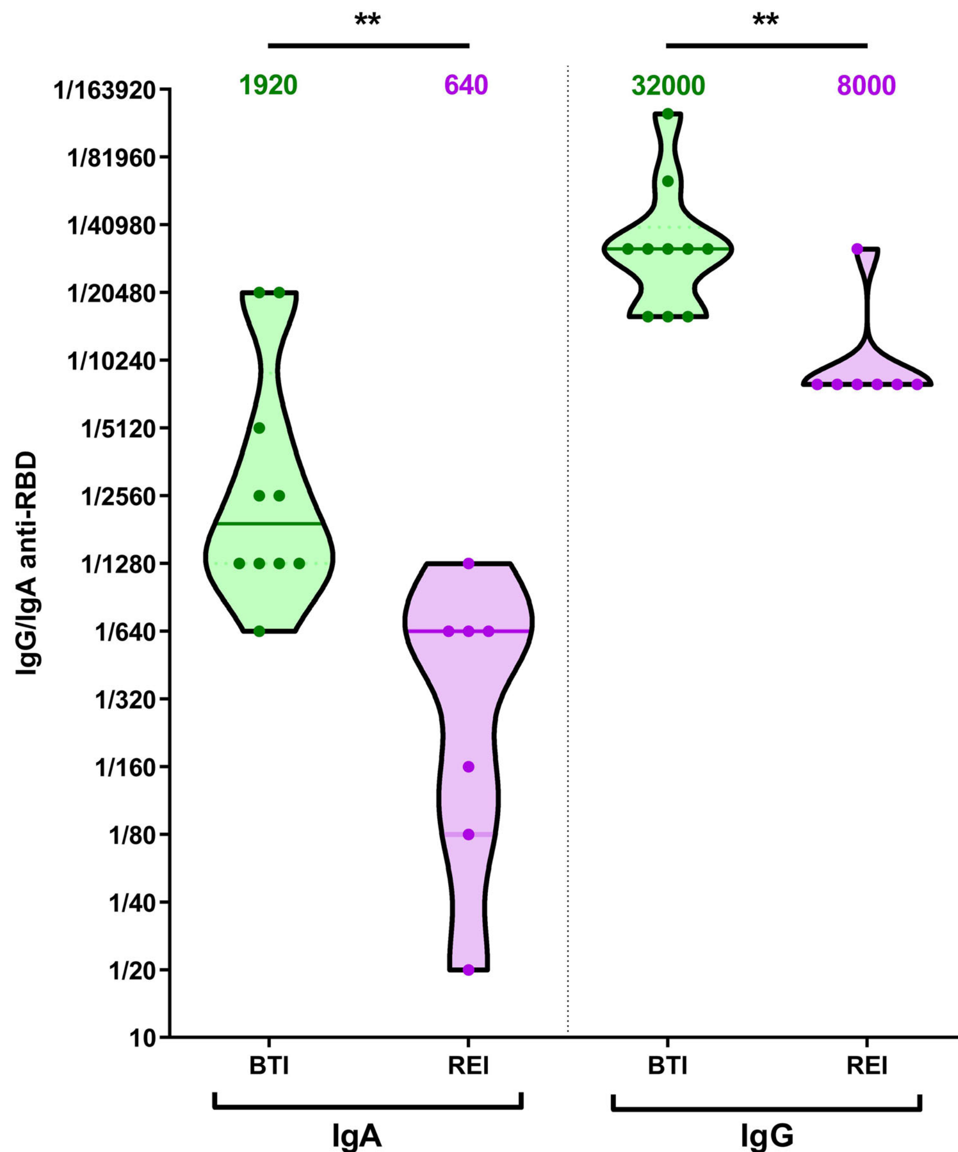

FIGURE 3 IgA and IgG anti-RBD titers. Titers are calculated as the highest dilution with higher OD than the cut-off (which is calculated as the mean of the negative controls plus two times the standard deviation). Ancestral variant RBD was used as antigen. Median titers and violin plots from the BTI group are shown in green and from the REI group in purple. **$p < 0.01$. BTI, breakthrough infection group; IgA, immunoglobulin A; IgG, immunoglobulin G; OD, optical density; REI, reinfection group.

induces a significant immune response through mucosal and systemic effector mechanisms. Interestingly, REI after the third vaccine dose did not induce higher neutralizing titers against any VoC compared to the control group of convalescent HCW without reinfection in the same period, indicating a poor immunological stimulus through a previously exposed respiratory mucosa despite active viral replication. These differences in neutralization were also observed with the techniques associated with high correlation with the neutralizing activity, such as the quantification of IgG, IgA and total antibodies against RBD (Figure 3 and Figure S3).[13]

We hypothesized that REI has a limited capacity to induce a strong neutralizing response at the nasopharyngeal track while BTI acts as a complete, mucosal and systemic, stimulus.[14] This is supported by the fact that BTI induced higher IgA titers than REI,[14] while anti-RBD IgM titers or avidity did not vary between groups,[15] indicating a superior mucosal effector participation in the response. The similar levels of neutralization in the REI groups as compared with noninfected convalescent controls is an indication of a certain anergic state at the mucosal level after primary infection despite active viral replication of a divergent SARS-CoV-2 VoC, such as Omicron BA.1, and occurring close to 2 years after primary infection by the ancestral Wuhan-hu-1 sequence. This could be an indication of the limitation of the booster effect mediated by subsequent infections and might question intranasal strategies of immunization in individuals already exposed to SARS-CoV-2, this would require conducting specific studies on intranasal immune response.

Our study has several limitations. First, we had a small sample size. Secondly, the vaccination booster campaign in our center coincided in time with the BA.1 Omicron pandemic wave. Thus, we were unable to obtain samples from participants after they received their booster dose but before they got infected. However, we were able to recruit noninfected control participants for both the BTI and REI groups at the same time points after the third dose.

Although no live virus assays were performed, measure of neutralizing activity in sera in COVID-19 infection and/or vaccination with pseudovirus assays is an accepted technical approach that has been validated in a number of studies.[16] Our findings show that SARS-CoV-2 infection compromise the neutralization response to repeated infection and suggests a fundamental limitation in the booster effect of natural infection and that the response to potential intranasal vaccine strategies can be also limited in previously infected individuals.[15]

AUTHOR CONTRIBUTIONS

Gonzalo Rivas, Joanna Luczkowiak, Nuria Labiod, and Fátima Lasala: performed experimental work. **Gonzalo Rivas, Marta Rolo, Jaime Lora-Tamayo, Mikel Mancheno-Losa, David Rial-Crestelo, Alfredo Pérez-Rivilla, and María Dolores Folgueira**: were responsible of clinical cohort, sampling and database management. **Rafael Delgado**: designed the study and wrote the first version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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