Rheumatology International (2023) 43:449–457
https://doi.org/10.1007/s00296-022-05265-3

Rheumatology
INTERNATIONAL

OBSERVATIONAL RESEARCH

Effects of the second dose of COVID-19 vaccines in patients with autoimmune rheumatic diseases with hybrid immunity

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Received: 4 October 2022 / Accepted: 19 December 2022 / Published online: 30 December 2022

Abstract

Patients with autoimmune rheumatic diseases with a previous infection by the SARS-CoV-2 virus have exaggerated responses to a single dose of COVID-19 vaccination as compared to fully vaccinated infection naive patients. The second dose is currently recommended at an extended gap after the infection, but the information available regarding response to the second dose in this subgroup is limited. Patients with AIRDs previously infected with COVID-19, who have received at least one dose of AZD1222/ChAdOx1 ($n=200$) were included and stratified based on vaccine doses (V), and infection (I) into I + V, I + V + V, V + I, V + V + I. Anti-RBD (receptor binding domain) antibodies were compared across the four groups. In 49 patients of the I + V + V group (AZD12222), paired sera were compared for antibody levels and neutralization after each vaccine dose. Thirty patients with hybrid immunity after BBV152 and 25 with complete vaccination without infection were included as controls. The highest anti-RBD antibody levels were observed in the V + V + I group (18,219 ± 7702 IU/ml) with statistically similar titers in the I + V + V (10,392 ± 8514 IU/ml) and the I + V (8801 ± 8122 IU/ml). This was confirmed in the 49 paired samples that paradoxically showed a lowering of antibody titers after the second dose [9626 (IQR: 4575–18,785)–5781 (2484–11,906); $p<0.001$]. Neutralization of the Delta variant was unaffected but Omicron neutralization was significantly reduced after the second dose [45.7 (5.3–86.53)–35% (7.3–70.9); $p=0.028$]. Ancillary analyses showed that only the hybrid immune sera could neutralize the Omicron variant and AZD1222 hybrids performed better than BBV152 hybrids. The second dose of AZD1222 did not boost antibody titers in patients with RD who had COVID-19 previously. In the analysis of paired sera, the second dose led to a statistically significant reduction in antibody titers and also reduced neutralization of the Omicron variant.

Keywords SARS-CoV-2 · BBV152 COVID-19 vaccine · COVID-19 Vaccines · ChAdOx1 nCoV-19 · COVID-19 · Vaccination

Introduction

Individuals with the previous COVID-19 (coronavirus-2019 disease), who have received at least one dose of a SARS-CoV-2 (Severe Acute Respiratory Syndrome-Coronavirus-2) vaccine, are referred to have developed hybrid immunity against SARS-CoV-2 [1]. Various studies in previously infected healthy individuals have shown that even a single dose of mRNA vaccine produces 10–45 times higher circulating and neutralizing anti-Spike (S) antibodies than in uninfected, fully vaccinated individuals [2–5].

In India, the two widely used vaccines against SARS-CoV-2 are the adenoviral vector-borne vaccine AZD1222 or ChAdOx1 ("Covishield") and the heat-inactivated BBV152 ("Covaxin"). A couple of studies from India on healthcare workers demonstrated a better antibody response in formerly infected individuals vaccinated with a single dose of AZD1222 or BBV152 than among the uninfected fully vaccinated group [5, 6].

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We have previously shown the safety of the first dose of COVID-19 vaccines in patients with AIRD. Similarly, the safety of the second dose has been proven in patients with AIRD. The phenomenon of hybrid immunity is present even in patients with autoimmune rheumatic diseases (AIRD) and they develop a more robust antibody response as compared to vaccination-induced immunity [6–8]. We have also shown that antibody response is a surrogate for protection against breakthrough infection in patients with AIRD [9]. Other studies have also validated that hybrid immunity leads to better protection from breakthrough infections in healthy individuals [10].

However, there is emerging evidence that the second dose of vaccine may not be beneficial to those already possessing hybrid immunity. The second dose of AZD1222 possibly works better when the gap between the doses is increased to 12 weeks [11]. Continuing waves of the pandemic along with the commencement of booster vaccinations call for better evidence in support of these boosters; especially in the background of constrained vaccine availability. Patients with AIRD have been more affected by the pandemic and are identified as a priority group worldwide for boosters [12]. Again, there is very limited evidence to suggest the efficacy of repeated dosages in previously infected individuals with AIRD [13]. Data regarding non-mRNA vaccines such as AZD1222 and BBV152 are even more scarce.

Thus, we evaluated the effectiveness of the second dose of a COVID-19 vaccine by comparing antibody levels and the neutralization potentials of sera after a single versus double dose of the vaccines in individuals with AIRDs who were previously infected with SARS-CoV2.

Methods

Design

Prospective cohort study.

The cohort

The COVID-19 vaccination cohort from CARE (CVCC) in Kochi, India was used for this study. It is a prospective cohort of patients with RD who had received at least one dose of either SARS-CoV2 vaccines (AZD1222 or BBV152) and includes 630 patients [9]. All events like primary symptomatic COVID-19 or detection of asymptomatic COVID-19 or breakthrough infection were prospectively recorded and sera were collected from patients at 4–6 weeks after each "event" (infection or vaccination).

The cohort was initiated in March 2020 when the first COVID-19 cases were reported in India. The follow-up is continuing at present. The serum collection had been completed in late December 2021 and hence the hybrid immunity groups do not include anyone exposed to Omicron. The analysis of stored serum has been carried out in March 2022 just after the peak of the Omicron wave in India.

Inclusion criteria

Patients with hybrid immunity are defined as those with COVID-19 infection in the past and receipt of one or both doses of primary vaccination against SARS-CoV-2.

Exclusion criteria

Patients who had received booster doses of SARS-CoV-2 vaccines were excluded from this study.

Matching and selection of the groups

The patients with hybrid immunity in the CVCC cohort were stratified based on the infection (I) and the number of vaccine (V) doses received and their order of occurrence into four groups: I + V, I + V + V, V + I, V + V + I. Two patients of the sequence V + I + V were excluded from the analysis since the number was too small. Since the majority of the cohort had received the AZD1222 vaccine, we have primarily analyzed the effect of AZD1222. Demographic details, type of RD, immunosuppressive drugs, comorbidities, details of vaccination, and COVID-19 infection were analyzed.

Out of the entire cohort of 440 patients with hybrid immunity, 410 had received AZD1222 and 30 BBV152. To minimize confounders, the first 50 patients in each of these four groups (I + V, I + V + V, V + I, and V + V + I) were matched for age, sex, and underlying RD by the Greedy nearest neighbor method.

Controls

The 30 hybrid patients who had past infections and had received at least 1 dose of BBV152 were included as controls. In addition, for the neutralization assays, 25 who had 2 doses of COVID-19 vaccines (14 AZD1222 and 11 BBV152) but no previous COVID-19, were taken as controls (Fig. 1). These 25 had no known history of COVID-19 or contact with COVID-19 (as per the World Health Organization definition of contact). Moreover, antibody testing before vaccination was used to confirm the absence of previous infections. The number of controls was determined as per availability.

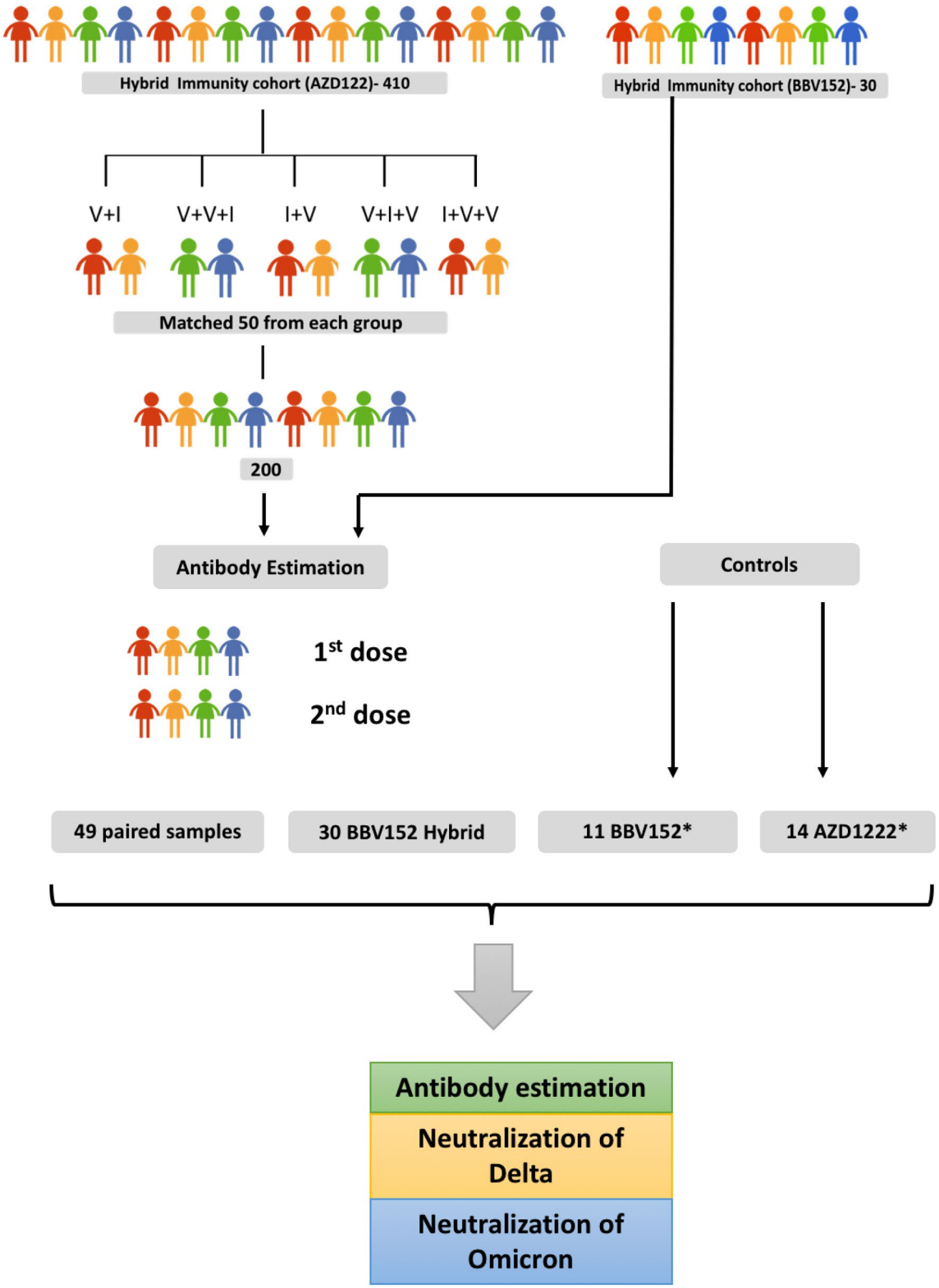

Fig. 1 A flowchart of the methodology

Antibody titers

For these 4 groups of matched 50 patients each, the antibody against the RBD (Receptor Binding Domain) of the Spike protein of SARS-CoV-2 was estimated by ELISA using Elecsys kit (Roche, Switzerland) as per the manufacturer's instructions. The kit can estimate up to a maximum of 250 IU. Whenever this threshold was reached, the sera were diluted 10 × and titers re-estimated. In such cases, the titer after dilution was taken as final. As per the manufacturers' instructions, any titer below the cutoff of 0.8 IU was taken as negative.

Subsequently, to analyze how antibody titres behave in paired sera, we searched our cohort for those with hybrid immunity for whom paired sera were available after the first and the second doses of vaccination. We could identify 49 patients with hybrid immunity who had taken the AZD1222 vaccine and had documented COVID-19 before the first vaccine dose and serum samples were available 4–6 weeks after both doses. Since the number of hybrids after BVV152 with available paired samples was too small, we could not analyze those.

Neutralization assays

For the neutralization assays, the same paired samples from 49 patients of the AZD1222 hybrid were selected and all 30 of the BBV152 hybrids were taken as controls. As mentioned above, 14 and 11 patients without past COVID-19 who had completed two doses of AZD1222 and BBV152, respectively, were also included as non-hybrid controls.

For neutralization against the Delta variant, the SARS-CoV-2 delta surrogate virion neutralization test (sVNT) kit was used. Similarly, for the Omicron variant, the corresponding sVNT kit (GenScript) was used.

Effect of the second dose of vaccine

This was analyzed separately at the end from the results of the antibody and neutralization tests of the 49 paired samples.

Statistical analysis

Data are expressed as Mean and Standard Deviation. Statistical analysis was carried out using the R (version 3.6) with a p-value of < 0.05 as statistically significant. All intra-group comparisons of antibody titers and neutralization assays were done by independent samples t-test after log transformation of antibody levels. For paired analysis comparing the effects of the first versus the second dose of vaccine in the 49 paired samples, Wilcoxon signed-rank test was used for antibody titers and neutralization assays as the data were not distributed normally.

Ethics approval and consent

It was a prospective observational cohort study carried out at the Centre for Arthritis and Rheumatism (CARE), Kochi, Kerala after obtaining ethics approval from Sree Sudheendra Medical mission and informed consent from all participants.

Results

Two hundred and thirty patients were included from the hybrid cohort with a mean age of 50.73 ± 10.61 and a male-to-female ratio of 1:12. Rheumatoid Arthritis (RA) (125, 54.3%) was the most common AIRD followed by Spondyloarthritis (SpA) (22, 9.5%) (Table 1).

Antibody levels across various subgroups of hybrid immunity

In the AZD1222 hybrid immunity cohort (Supplementary Table S1), the highest antibody titers were in the group that developed a breakthrough infection after completing two

Table 1 Baseline details of the hybrid immunity cohort

	AZD1222, $n = 200$	BBV152, $n = 30$
Age (mean, SD)	51.37 (10.8)	46.53 (8.3)
Gender, female (%)	161 (80.5)	24 (80)
Diagnosis (%)		
Rheumatoid arthritis	109	16
Spondyloarthritis	24	4
Systemic lupus erythematosus	6	1
Connective tissue disease	10	1
Vasculitis	10	0
Others	41	8
Drugs (%)		
Methotrexate	90	13
Sulfasalazine	23	4
Leflunomide	14	4
Azathioprine	2	0
Mycophenolate mofetil	6	0
Hydroxychloroquine	124	15
Glucocorticoids	13	0
Tofacitinib	11	0
TNF inhibitors	2	2
Rituximab	6	1

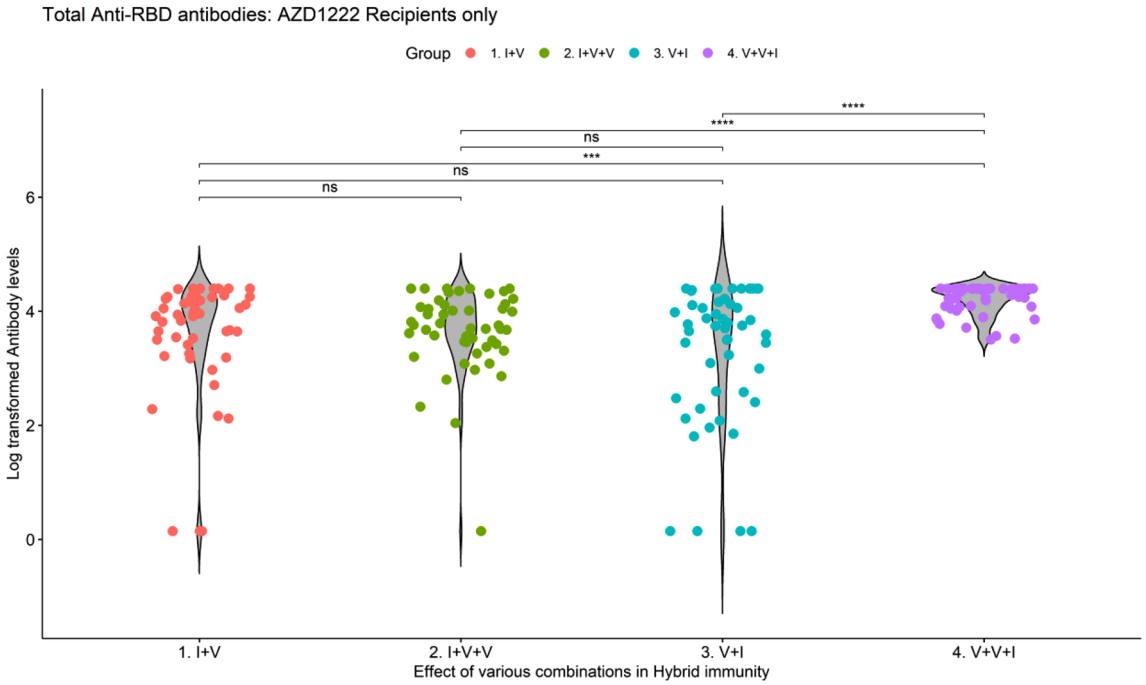

Fig. 2 Anti-RBD antibodies across the hybrid immunity subgroups (AZD1222 vaccine only)

doses of vaccinations (V + V + I group) (Fig. 2). Figure 2 also shows that in patients who had COVID before vaccination, there was little difference between those who received two doses of vaccine (I + V + V) and those who had received only one dose of (I + V). Analysis for BBV152 hybrid immunity was not done due to small numbers.

Neutralization assays

Neutralization of the Omicron variant was assessed in the sera of patients with full (double dose) vaccination with either vaccine and was compared with the sera of patients with hybrid immunity. Not even a single fully vaccinated individual (without prior infection) had significant neutralization (> 30%). However, individuals with hybrid immunity had good neutralization and AZD1222 hybrids did better as compared to BBV152 hybrids (Fig. 3).

Effect of the second dose of vaccine in previously infected individuals

Of the 49 patients for whom paired samples were analyzed (AZD1222 vaccine recipients), the mean age was 48.46 ± 9.4 with the majority being females (42, 85.7%). The most common RD was RA (34, 69.38%) followed by SpA (6, 12.2%) (Supplementary Table S2).

The analysis of the paired sera (Fig. 4) showed that after the second vaccine dose, antibody titers decreased significantly [9626 (IQR: 4575–18,785)–5781 (2484–11,906); Wilcoxon signed rank: $p < 0.001$]. Delta neutralization was unaffected by the second dose [96.8 (74.8–99.5)–92.3 (82.2–99); Wilcoxon signed rank: $p = 0.32$]. However, the Omicron neutralization was significantly reduced after the second dose [45.7 (5.3–86.53)–35 (7.3–70.9)%; Wilcoxon signed rank: $p = 0.028$].

Discussion

In this study, we first analyzed anti-RBD antibodies across different subgroups of hybrid immunity and found that the best antibody response occurred in patients who had COVID-19 infection after two doses of vaccination. We then demonstrated that neutralization of Omicron occurred with the sera of patients with hybrid immunity much better than with that of those who had completed two doses of either vaccine. Neutralization of the Omicron variant was better with hybrid immunity with the viral vector AZD1222 vaccine than with the inactivated BBV152 vaccine. Lastly, in patients with prior SARS-CoV-2 infections, the second dose of the vaccine led to a reduction in antibody levels as well as the percentage of Omicron neutralization.

Former studies have shown that hybrid immunity offers a better antibody response and protection against breakthrough infections than vaccination alone across different

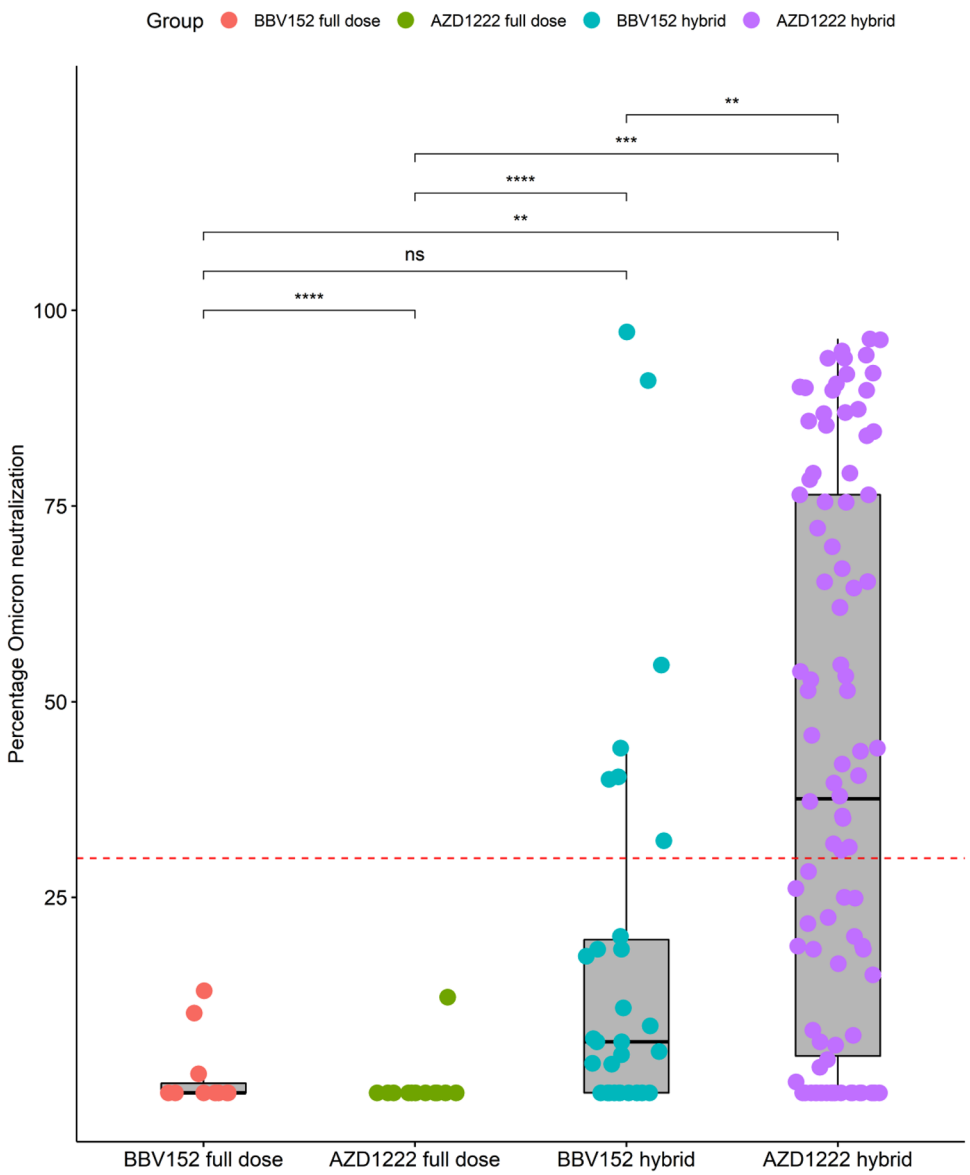

Fig. 3 Omicron neutralization by fully vaccinated versus hybrid immunity sera

SARS-CoV2 vaccines in various groups—healthy individuals, elderly, and patients with RDs [6, 14–18]. A 60–80% reduction in reinfection rate was observed in previously infected individuals who had received one dose of the mRNA vaccine across studies from the United Kingdom, Italy, Israel, and the United States of America [10, 17–19]. In the current study, we observed that the most robust humoral response occurred in the group that had breakthrough infection after completing two doses of vaccines (V + V + I group). This means that a breakthrough infection provided a better immune boost than (one or) two vaccine doses in previously infected individuals.

A breakthrough infection post two doses of vaccination might provide a greater boost due to different routes of antigen exposure, a broader repertoire of antigens, and a higher antigenic load [20].

Another significant finding was that antibody titers were not different in previously infected persons who had received either one or two vaccine doses. This has public health importance that in patients with hybrid immunity, and the second dose may be delayed prioritizing other individuals first.

The second part of the study dealt with the neutralization of the Omicron variant. Only the hybrid immune sera were able to neutralize the Omicron variant. This might account for the reduced severity of the Omicron wave in India as compared to the nations that had mRNA vaccines but reduced virus exposure in the previous waves. The seroprevalence of COVID-19 antibodies after the second wave in India was around 75% and about 1 billion individuals had received at least 1 dose of a COVID-19 vaccine before the onset of the Omicron wave [21, 22]. Thus, even though

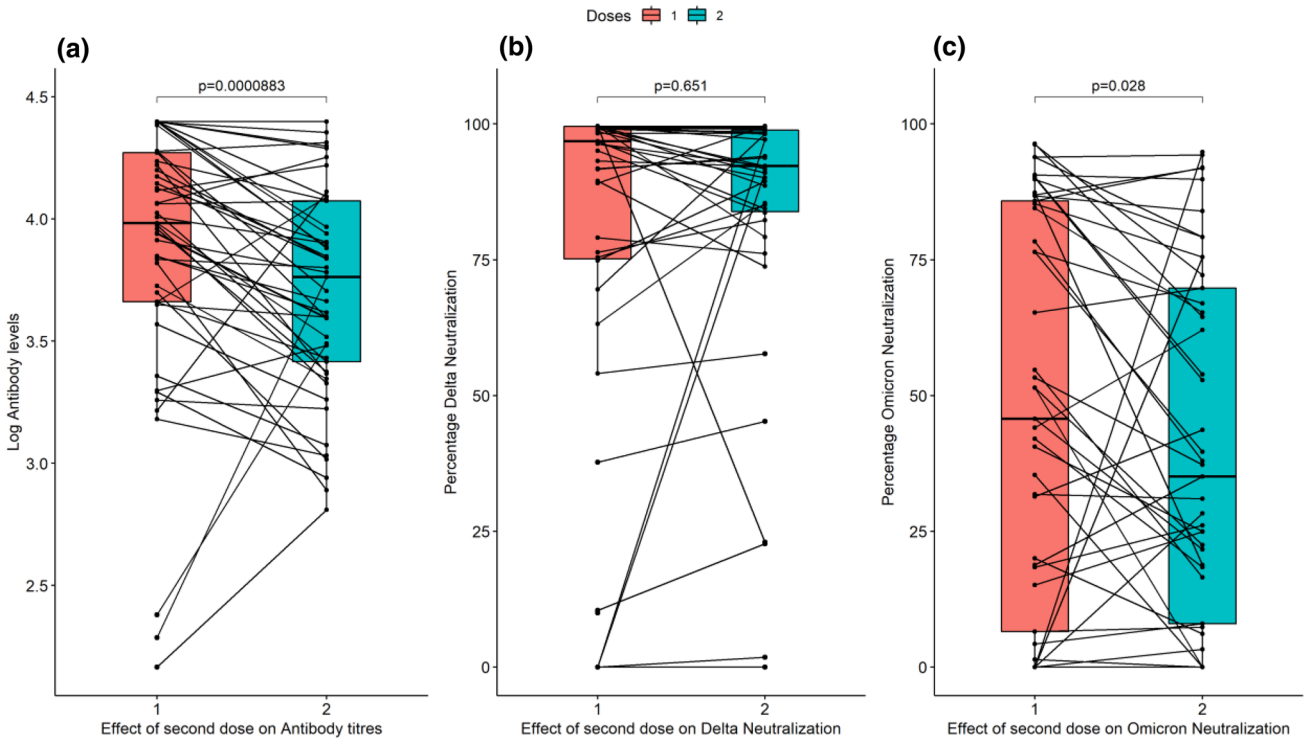

Fig. 4 Effect of second dose in those previous COVID-19 infection

the majority had received one dose of vaccine, the population-adjusted death rate in India was less when compared to countries that had a higher proportion of the population fully vaccinated than India [18]. The difference between the neutralization potential for the delta variant in previously infected individuals was not different after the first and second doses of vaccination. This is reflected in studies from other parts of the world in which vaccine effectiveness in terms of protection from breakthrough infections did not increase after the second dose of vaccination [10, 13, 18, 19] (Supplementary Table S3).

Studies in healthy individuals have previously shown that those with hybrid immunity had better neutralization of the Omicron variant as compared to those who were fully vaccinated (but previously uninfected) [23, 24]. It has been shown that hybrid immunity leads to better protection across other variants too [25]. The neutralization of the Omicron surrogate virion was higher with the AZD1222 hybrid than with the BBV152. This may be due to different mechanisms of action and different immunogenicity of different vaccines [26, 27]. It has been shown that even full immunization with the mRNA vaccine, BNT162b2, was not sufficient for Omicron neutralization [28]. The ADZ1222 in combination with BNT162b2 or with infection (hybrid immunity) provided the best protection against Omicron [29]. Whether this is unique for Omicron or true also for future SARS-CoV-2 variants remains to be seen. Interestingly, hybrid immunity appears to provide at least as many neutralizing antibodies as persons who had a booster (third) shot [30, 31]

In the third part of our study, we explored the effects of a second vaccine dose in previously infected individuals. We found that when anti-RBD antibodies were serially assessed, they showed a significant rise after the first vaccine dose which then significantly declined after the second vaccine dose. Similar findings were seen in the neutralization assays for Omicron but not for the delta variant. The neutralization of the Omicron variant was reduced after the second dose of the vaccine in previously infected individuals. Some other studies have also demonstrated similar results.

The reduction of antibody titers and of neutralizing antibodies may be due to two reasons. First, the vaccine S-protein antigen, being in small amounts, may be cleared by the high levels of circulating neutralizing antibodies that are present in patients with hybrid immunity. Second, they could be part of the natural trajectory of the waning of antibodies which could not be boosted by additional vaccination [2]. Repeated immune stimulus or antigen exposure is well known to induce tolerance. But, in the context of COVID-19, we still do not know what doses and frequencies of vaccines will have the optimal response without inducing tolerance. These findings raise important questions on the dosing of vaccines, especially the timing of boosters, in people with hybrid immunity.

The distinct strengths of our study are that it is one of the primary studies evaluating the effect of the order of infection and vaccination on anti-RBD antibodies and neutralizing antibodies in patients with AIRDs. A distinct strength is that we have studied consecutive serum samples to understand the effects of the second dose of a COVID-19 vaccine in a subset of patients with hybrid immunity. Though the number of BBV152 hybrids was less, we also showed the superiority of AZD1222 over BBV152.

This study enables us to put forward an explanation of how India had a less severe Omicronwave [32, 33]. It also has important implications for vaccination policies since it has shown some evidence that repeating vaccine doses in patients with hybrid immunity may attenuate the humoral response. This is especially relevant when the world is rolling out boosters for patients at higher risk such as those with AIRD.

We acknowledge limitations like the inclusion of multiple RDs under a single cohort, a small sample size for the BBV152 cohort, and the lack of paired samples for the entire cohort. We have not studied the cell-mediated response to SARS-CoV2 and have used surrogates like anti-RBD and neutralization potential over actual reinfection rates to study the efficacy of vaccines in previously infected individuals. However, we have previously shown that anti-RBD titers are independent markers for the risk of breakthrough infections [9]. Again, these studies were carried out in patients with AIRD on various immunosuppressant drugs. But, the same immune phenomenon can be expected in healthy individuals but in a higher proportion since they do not have any immune alterations.

In conclusion, previously infected individuals with COVID-19 appear to have a better response with a single dose of a COVID-19 vaccine. The normally scheduled second dose appears to attenuate the antibody response. Thus, there is a need for better evidence to inform about the optimum number of vaccine doses and, more importantly, the optimum gaping between doses for people with hybrid immunity.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00296-022-05265-3.

Author contributions Conceptualization: SP. Acquisition CS, PA, MRA, SP, AS, KK, BL, and MS. Methodology: SP and AS. Writing, original draft: AS and SP. Writing, review and editing: SP, MP, AS, and MRA. All the authors have approved the final manuscript and take full responsibility for the integrity of the data and the contents of the manuscript.

Data availability Data are available on reasonable request. Data will be available from the corresponding author on reasonable request.

Declarations

Conflict of interest Sakir Ahmed has received honorarium as speaker from Pfzer (unrelated to the current study) and has no other potential conflict of interest. The other authors have no potential conflict of interest to disclose.

Consent for publication Patient consents for publication. Consent obtained directly from the patient(s).

Ethical approval The study was approved by the Ethics Committee of Sree Sudheendra Medical mission (IEC/2021/35) and written informed consent of all the participants was taken.

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