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Letter to the Editor

SARS-CoV-2 Delta and delta derivatives impact on neutralization of Covishield recipient sera

Dear editor

Recently Faustini et al., demonstrated cross reactive high immune response against highly infectious SARS-CoV-2 Variants of concerns (VOCs) Delta and Omicron in cohort immunized with booster dose with homologous or heterologous vaccines i.e., ChAdOx1 nCoV-19 and BNT162b2.[1] The emergence of SARS-CoV-2 VOCs with distinctive mutations has made the pandemic situation gruesome. A devastating second wave emerged globally fueled by the highly transmissible and increased pathogenic Delta variant. This VOC was first identified in India and subsequently reported from other countries worldwide.[2] In a short span of time Delta variant has rapidly mutated into several sub-lineages known as 'Delta derivates' (Delta AY.1 to AY.133).[2] Of these, AY.4.2 is currently increasingly being reported in United Kingdom and also detected in Europe, including Denmark and Germany.[3] This was preceded in the past with, another Delta sub-lineage Delta AY.1 and was said to be more threatening than the Delta variant. Delta AY.1 was initially identified in India and traced to many cases across the globe[4] and has raised a concern about the vaccine efficacy. AY.1 variant have ≥20% high prevalent mutation than the Delta variant which has T19R, E156G, W258L, K417N, L452R, T478K, D614G, P681R and D950N amino acid mutations in the spike gene. Although the worldwide cumulative prevalence of Delta AY.1 (<0.5%) is lower than Delta variant (17%), it is still not clear whether Delta AY.1 variant is deadlier than Delta.[2,3] Delta variant is the major reason for the breakthrough infections world over.[4] Several studies have reported the neutralization potential of the approved COVID-19 vaccines against Delta variant.[4] Studies have also observed 4 to 9-fold reduction in the neutralization antibody (NAb) titer with sera of ChAdOx1 vaccinees against Delta variant.[4] Liu et al., have reported the susceptibility of Delta AY.1 variants to neutralization with the sera of BNT162b2 vaccinee.[5] We have previously demonstrated minor reduction in the NAb titer of the sera of COVID-19 recovered individuals with BBV152 vaccination and breakthrough cases against Delta AY.1 compared to Delta variant.[6] However, the data on the neutralization potential of the approved COVID-19 vaccines against Delta AY.1 still remains limited. Considering this, we have assessed the susceptibility of Delta, Delta AY.1 and B.1.617.3 variants to Covishield vaccine (ChAdOx1 nCoV-19) which is widely administered in India.

We determined the NAb titre of sera obtained from 25 COVID-19 naïve vaccinees (CNV) immunized with two doses of vaccine (8 weeks post vaccination), 16 COVID-19 recovered cases immunized with two doses of vaccine (CRV) (8 weeks post vaccination) and 26 breakthrough infections (BTI) post immunization with two doses of vaccine against Delta, Delta AY.1 and B.1.617.3 using 50% plaque reduction neutralization test (PRNT50). Prototype B.1 variant was used for comparative analysis. An IgG immune response was also assessed using anti-S1-RBD ELISA as described earlier.[7] The statistical significance was assessed using a two-tailed Kruskal-Wallis test with Dunn's test of multiple comparisons. P-value less than 0.05 were considered to be statistically significant for the test applied.

The geometric mean titer (GMT) of NAb against B.1, Delta, Delta AY.1 and B.1.617.3 were determined with the sera of the subjects from CNV group (30.8, 1.1, 9.8, 1.6), CRV group (1248, 489.8, 403.8, 314) and BTI group (876.7, 499.8, 415.8, 235.8) respectively (Fig. 1). The magnitude of anti-S1-RBD antibody immune response among CNV group (range 100–3200, mean 1312), CRV group (range 1000–3200, mean 2717) and BTI group (range 400–3200, mean 1933) correlated with Neutralization. NAb titer in CNV group was found to be very low against all the variants compared to CRV and BTI groups. This suggests the need for the booster vaccination to cope up with waning immune response among vaccinees. Delta variant has shown highest reduction of 27.3-fold in NAb titer among CNV group compared to other groups and variants. This finding implies highest probability of the breakthrough infection with Delta variant. Of the 26 cases from BTI group, SARS-CoV-2 genome sequences of 14 breakthrough cases could be retrieved using Next generation sequencing. These cases were found to be affected with Delta ($n = 8$) and Kappa ($n = 6$) variants. A total of 21 cases were found to be asymptomatic; while 5 cases had mild disease. Reduction in the NAb titer was also observed in CNV (19.17-fold), CRV (3.97-fold), BTI (3.72-fold) groups with B.1.617.3 variant. This necessitates the exploration of vaccine efficacy of currently available COVID-19 vaccines against B.1.617.3 and other variants under monitoring.

Several studies have reported the increase in immune response in COVID-19 recovered cases and breakthrough infections post vaccination.[4]Such a rise in immune response effectively neutralizes the immune escape due to mutants among breakthrough cases compared to naïve COVID-19 cases. The main reason for waning immunity post vaccination in SARS-CoV-2 infected individuals or COVID-19 naïve vaccinees is short time survival of plasma blast cells.[8] Once the individual get re-infection after vaccination or vaccination post recovery, memory B cells are triggered that generate higher level of immune response.[8–10] In conclusion, our findings suggest that Covishield vaccine was able to neutralize Delta derivatives and prevent serious disease and fatality among breakthrough cases. A booster dose vaccination of COVID-19 naïve vaccinees would achieve protective immune response to fight against emerging SARS-CoV-2 variants.

Ethical approval

The study was approved by the Institutional Human Ethics Committee of ICMR-NIV, Pune, India under the project 'Assessment

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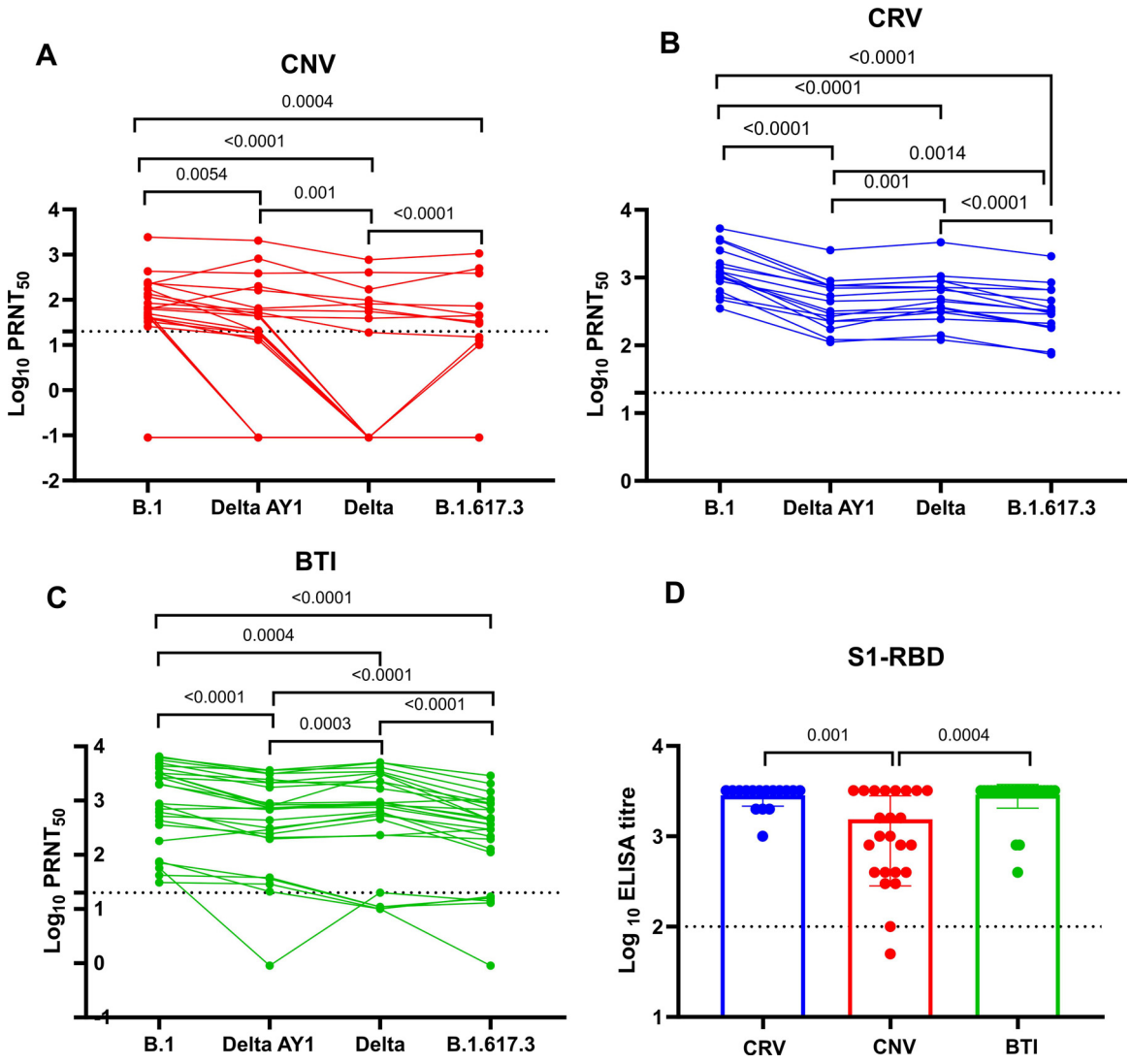

Fig. 1. Neutralization of Covishield vaccinees sera from different scenarios against B.1, Delta AY.1, Delta and B.1.617.3 strains and ELISA titer of vaccinees sera from different scenarios: Comparisons of neutralization titer of naive individuals sera immunized with two dose vaccine Covishield (CNV), recovered cases sera immunized with two dose vaccine Covishield (CRV) and breakthrough cases post two doses of Covishield vaccine (BTI). The B.1 (EPI_accession: EPL_ISL_825,088) (a), delta AY.1 (EPI_accession:EPI_ISL_2,671,901) (b), delta (EPI_accession: EPI_ISL_2,400,521) (c), and B.1.617.3 (EPI_accession: EPL_ISL_2,497,905) (d). The statistical significance for the neutralizing titer was assessed using a matched pair Wilcoxon signed-rank. Anti-SARS-CoV-2 IgG titers of CRV, CNV and BTI 's sera for inactivated SARS-CoV-2 (h), S1-RBD protein (i). The dotted line on the figures indicates the limit of detection of the assay. Data for both the neutralizing titer and IgG titers are presented as mean values +/− standard deviation (SD).

of immunological responses in breakthrough cases of SARS-CoV-2 in post-COVID-19 vaccinated group'.

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Declaration of Competing Interest

Authors do not have a conflict of interest.

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