

Comparable neutralization of SARS-CoV-2 Delta AY.1 and Delta with individuals sera vaccinated with BBV152

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Highlights

Sera of COVID-19 naive vaccinees, COVID-19 recovered cases with vaccination and breakthrough cases demonstrated 1.3, 2.5 and 1.9-fold reduction in neutralization titers

against Delta and 1.5, 3.5, 2.8-fold against Delta AY.1 compared to B.1 respectively. However, high neutralization titers would still effectively protect against Delta, Delta AY.1 and B.1.617.3 variants.

Text

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) Delta variant (B.1.617.2), a variant of concern (VOC), was associated with the second wave of pandemic in India during March-May 2021. Delta variant has outpaced the other two sub-lineages Kappa (B.1.617.1) and B.1.617.3 and was responsible for 90% of the cases reported in India.¹ It has spread across 112 countries and found to be more infectious than the Alpha, Beta and Gamma variants. Reduced neutralization has been reported with the sera of individuals vaccinated with BNT162b2, BBV152/Covaxin and chAdOx1-s against Delta variant in recent reports.^{2,3} Delta variant has also been identified as the leading cause of breakthrough infections globally among vaccinated individuals.⁴

Delta variant with its characteristic spike protein mutations (L452R, T478K, D614G and P681R) has mutated further into four sub-lineages with additional mutations which are associated with higher transmission and probable immune escape.¹ Recently, Delta variant has mutated to Delta AY.1, AY.2 and AY.3. Of these, apparently highly infectious Delta AY.1 variant was first detected in India in April 2021 and subsequently from twenty seven other countries as well.¹ Cases of Delta AY.1 have also been reported from Europe, Asia and America with the highest prevalence observed in United States of America, Portugal, Japan, United Kingdom and Switzerland.⁵ The variant has characteristic mutations in the genome at ORF1a (A1306S, P2046L, P2287S, V2930L, T3255I, T3646A), ORF1b (P314L, G662S, P1000L, A1918V), S (T19R, L452R, T478K, D614G, P681R), ORF3a

(S26L), M (I82T), ORF7a (V82A, T120I), ORF7b (T40I), ORF8 (del119/120) and N (D63G, R203M, G215C, D377Y) which probably enhances the ability to escape immune response and becomes a major concern for the ongoing vaccination programs.⁵ Moreover, this variant contains an additional K417N mutation in the spike protein and emerging evidence suggests that this mutation could lead to resistance against monoclonal antibodies i.e., Casirivimab and Imdevimab.⁶ However, it is uncertain whether Delta AY.1 is capable of causing higher transmissibility, severe disease and evasion of immune response compared to Delta variant. The prevalence of Delta AY.1 is found to be low in India and the rest of the world. As of now no information is available on the efficacy of currently available vaccines against Delta AY.1 variant.

The clinical efficacy against COVID-19 infection of BBV152, a whole-virion inactivated SARS-CoV-2 vaccine was assessed in a double-blind, randomized, multicentre, phase 3 clinical trial on 25,798 participants to evaluate the efficacy, safety, and immunological lot consistency of BBV152. Overall efficacy against symptomatic COVID-19 disease was 77.8% and 65.2% protection against Delta variant has been reported with BBV152.⁷

The second wave of the SARS-CoV-2 pandemic was devastating for public health system of India and breakthrough cases were reported during this period. Besides this, the association of Delta variant in the breakthrough cases created serious concerns among the public health experts regarding the effectiveness of the available COVID-19 vaccines.

Considering this, we conducted this study to determine the neutralization potential in sera of the BBV152 vaccinated individuals against Delta and Delta AY.1 variant.

Here, we present the data from a cross-sectional study, where the sera of the fully vaccinated study participants with two doses of BBV152 vaccine were evaluated for neutralizing antibodies. The participants were divided in three separate groups viz. COVID-19 naïve vaccinees (CNV), COVID-19 recovered cases (real time RT-PCR positive) and vaccinated (CRV) and breakthrough infections post vaccination (BTI). The data of the variants responsible for SARS-CoV-2 infection in CRV and BTI groups was not available. However, the participants of CRV group were infected before the emergence of Delta variant in India when the predominant circulating SARS-CoV-2 strain was B.1. The BTI occurred mainly during the second wave of pandemic in India when the commonly circulating variant in the country was Delta in March-May 2021.⁸⁻⁹

The sera of individuals of CNV group [n=42; Female (n=24; median age: 43.5yrs); Male (n=18; median age: 46 yrs)] was collected between 2.5 to 22 weeks [median: 16 weeks] after second dose, CRV group [n=14; female (n=8; median age: 44.5yrs); male (n=6; median age: 42 yrs)] 14-70 weeks [median: 38 weeks] after second dose and BTI group [n=30; female (n=17; median age: 45 yrs); male (n=13; median age: 39 yrs)] collected between 2-18 weeks (median: 9 weeks). The neutralizing potential of the individuals was determined against Delta, Delta AY.1, B.1.617.3 compared to B.1 variant. Neutralizing antibody titers of the serum samples against all the variants were determined using 50% plaque reduction neutralization test. IgG response was also assessed using whole inactivated SARS-CoV-2 antigen, nucleocapsid and S1-RBD protein IgG ELISA.

The sera of individuals of CNV group showed a geometric mean titer (GMT) of NAb to be 310.6 (95% confidence interval (CI): 222-434.6); 241.6 (95% CI: 167.8-347.7); 209.1 (95% CI: 146.5-298.3); 165.3 (95% CI: 115.6-236.5) against B.1, Delta, Delta AY.1 and

B.1.617.3 respectively. The sera of the individuals of CRV showed uniformly increased NAb titer with GMT of 820.1 (95% CI: 469-1434), 328.6 (95% CI: 186.9-577.9), 234.5 (95% CI: 138.7-396.4) and 217.8 (95% CI: 136.7-347.1) against B.1, Delta, Delta AY.1 and B.1.617.3 respectively. Sera of individuals of BTI group had higher NAb titer compared to the CNV and CRV groups. The GMT titers were 896.6 (95% CI: 550.3-1461), 465.6 (95% CI: 213.2-1016), 317.2 (95% CI: 125.5-801.4), 259.7 (95% CI: 157.1-429.4) against B.1, Delta, Delta AY.1 and B.1.617.3 respectively (Figure 1a-d).

The sera of individuals of CNV group showed moderate fold-reduction in the NAb titer against Delta, Delta AY.1 and B.1.617.3 [1.29 (p-value: < 0.0001); 1.49 (p-value: <0.0001); 1.88 (p-value: <0.0001)] compared to B.1 (Figure 1e). However, the sera of individuals of CRV and BTI groups had higher fold-reductions in the NAb titer [2.5 (p-value: 0.0011); 3.5 (p-value: 0.0007); 3.77 (p-value: 0.0007)] and [1.93 (p-value: <0.0001); 2.83 (p-value: <0.0001); 3.45 (p-value: <0.0001)] against Delta, Delta AY.1 and B.1.617.3 variants respectively compared to the B.1 strain (Figure 1f-g). However, NAb titer of sera of CRV and BTI groups were significantly higher compared to CNV group.

Sera of individuals of CNV and BTI groups had 3.04 fold (p-value: 0.0019), 3.56 fold (p-value: <0.0001) and 4.42 fold (p-value: <0.0001) higher antibodies than sera of CRV group for inactivated SARS-CoV-2, S1-RBD protein and N protein based anti-SARS-CoV-2 ELISA respectively (Figure 1h-j).

A significant increase in the NAb titer against B.1, Delta, Delta AY.1 and B.1.617.3 variants in CRV and BTI groups was observed compared to the CNV group individuals. This demonstrates the possible role of memory cells in immune boosting with post-infection or infection after immunization. The NAb titre in sera of the individuals from CRV and BTI

groups were higher due to boosting effect of vaccination and natural infection or vice versa than individuals from CNV group. In a recent studies by Gupta et al., has shown that two dose vaccinated individuals though got infected with COVID-19 with Delta variant; but severity, admission to ICU and mortality was negligible during second wave of Pandemic in India.⁹ The comparative analysis of three different cohorts revealed that B.1.617.3 variant showed reduced neutralization followed by Delta AY.1 and Delta variants when compared to B.1 (Figure 1a-g). A recent study demonstrated a reduction in neutralization by 4 fold and 11 fold against Delta variant with the sera of healthy individuals vaccinated with two doses of ChAdOx1 and BNT162b2 vaccine respectively.² Our earlier studies with BBV152/Covaxin™ and Covishield™ have shown 2.7- and 3.2-fold reduction in NAb titer against Delta variant compared to B.1.^{3,10} The present study revealed 1.5, 3.5, 2.8-fold reduction in NAb titer for Delta AY.1, 1.3, 2.5 and 1.9-fold reduction against Delta variant compared to B.1 variant in sera of CNV, CRV and BTI respectively.

The primary objective of this study was to determine the neutralization efficacy of BBV152 vaccine against Delta variants in real time scenario as oppose to the controlled clinical trial scenario. The time interval for collection of the serum samples is a limitation of this study. However, the results demonstrated reduction in the neutralization titer in the individual cohorts against the Delta, Delta AY.1 and B.1.617.3 variants compared to B.1 strain. In conclusion, reduction in the NAb titer was observed in the sera of COVID-19 naïve vaccinated individuals, COVID-19 recovered followed by vaccination and breakthrough cases post two doses of BBV152. The sera of individuals belonging to three different cohorts had high NAb titer. This suggests that BBV152 would still be able to protect vaccinated individuals with severe disease from Delta, Delta AY.1 and B.1.617.3 variants.

Ethical approval

The study was approved by the Institutional Human Ethics Committee of ICMR-NIV, Pune, India under the project 'Assessment of immunological responses in breakthrough cases of SARS-CoV-2 in post-COVID-19 vaccinated group'.

Author Contributions

PDY contributed to study design, data analysis, interpretation and writing. RRS, GS, GRD, DAN, AMS, DYP and SK contributed to data collection, data analysis, interpretation and writing. PA, NG, SP, and BB contributed to the critical review and finalization of the paper.

Conflicts of Interest

Authors do not have a conflict of interest among themselves.

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Legend of Figures:

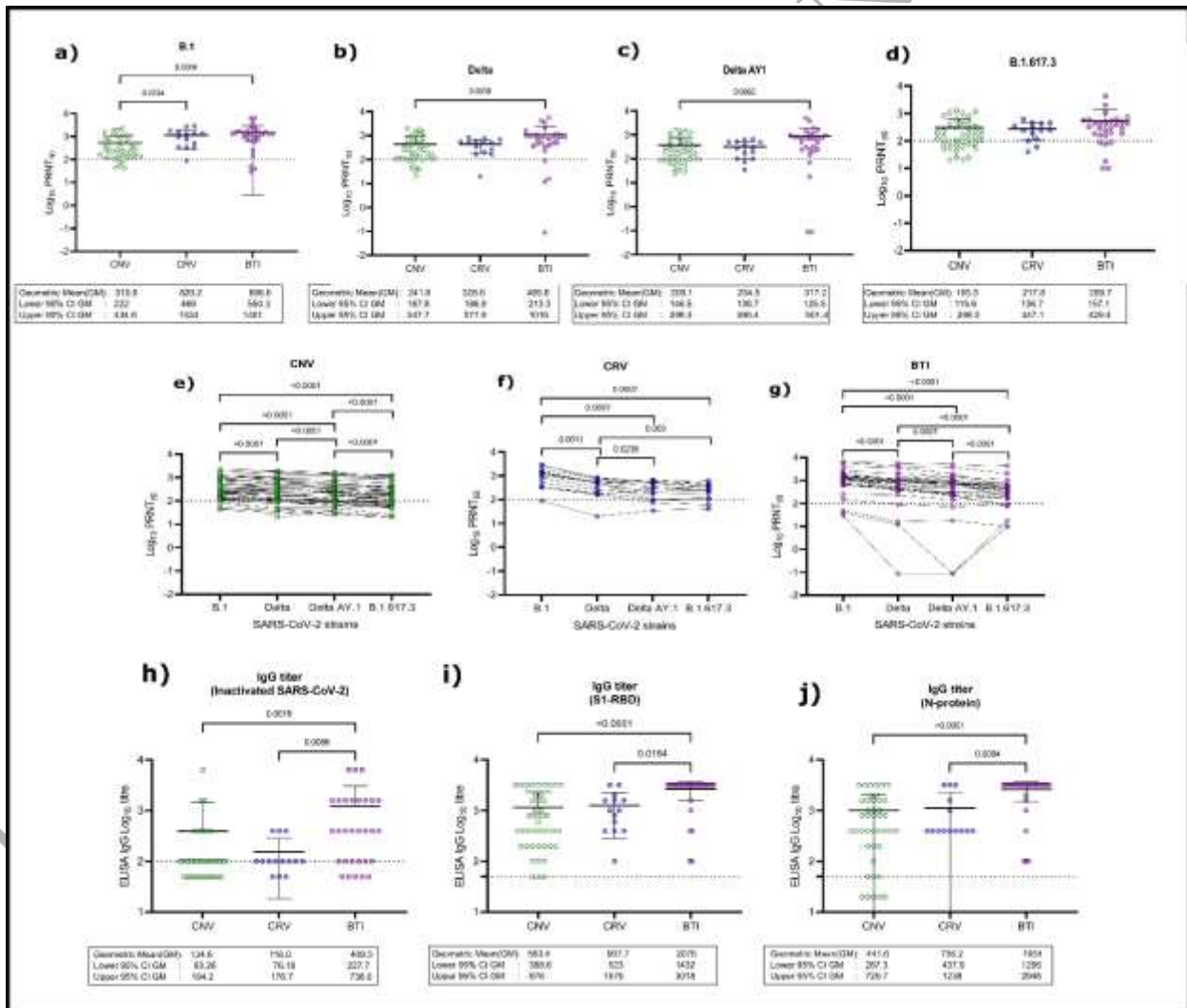


Figure 1: Neutralization of individual sera vaccinated with BBV152 vaccines from different scenarios against B.1, Delta, Delta AY.1 and B.1.617.3 strains and ELISA titer of individual sera vaccinated from different scenarios:

Neutralization titer comparison of individual cases sera immunized with two dose vaccine BBV152, recovered case sera immunized with two dose vaccine BBV152 and breakthrough cases; B.1 (GISAID identifier: EPL_ISL_825088). Dotted lines represents the cut-off value of the assay (20) (a), Delta (GISAID accession number: EPI_ISL_2400521) (b), Delta AY1 (GISAID accession number EPI_ISL_2671901) (c), and B.1.617.3 (GISAID accession number: EPL_ISL_2497905) (d). The statistical significance was assessed using a two-tailed Kruskal Wallis test with Dunn's test of multiple comparisons was performed to analyze the statistical significance. NAb titer of individual sera vaccinated with two doses of BBV152 (e), recovered cases administered with two doses of BBV152 (f) and breakthrough cases (g). A matched pair two-tailed pairwise comparison was performed using the Wilcoxon signed-rank test to analyze the statistical significance. Anti-SARS-CoV-2 IgG titers of vaccinated individual's sera for inactivated SARS-CoV-2, dotted lines represents the cut-off value of the assay (100) (h), S1-RBD protein, dotted lines represents the cut-off value of the assay (50) (i) and N protein, dotted lines represents the cut-off value of the assay (50) (j). 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 tests applied. The dotted line on the figures indicates the limit of detection of the assay. Data are presented as mean values +/- standard deviation (SD).