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Research Letter

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Neutralization of Delta variant with sera of Covishield™ vaccinees and COVID-19-recovered vaccinated individuals

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The SARS-CoV-2 lineage B.1.617 was initially detected from India during October 2020 and since then further mutated as sublineages Kappa (B.1.617.1), Delta (B.1.617.2) and B.1.617.3 variants. Delta variant has now mutated as Delta AY.1 and Delta AY.2, which was detected in India and many other countries. Delta variant has been reported to be 60% more transmissible than the Alpha variant (B.1.1.7), and the WHO has designated Delta variant as a Variant of Concern (VOC). The second wave of the COVID-19 pandemic in India was dominated by Delta variant, affecting millions of people, causing a serious public health crisis. Similarly, it spread rampantly and dominated over the Alpha variant in the UK and gained foothold in over 92 countries.[1]

The worldwide endeavor of scientists to create a safe and effective COVID-19 vaccine has resulted in the availability of 18 vaccines, which have received Emergency Use Authorization.[2] Currently, available vaccines appear to induce robust humoral and cellular immune responses against the SARS-CoV-2 spike protein.[3,4] However, the newly emerged SARS-CoV-2 variants have led to breakthrough infections after completion of vaccination regimen.[5] Hence, it is crucial to evaluate the natural, vaccine-induced humoral immunity to SARS-CoV-2 and the phenomenon of breakthrough infection to understand the immune escape due to emerging VOCs.

Covishield™ is a replication-deficient viral vector-based-SARS-CoV-2 recombinant vaccine, which has been rolled out under the national COVID-19 vaccination program in India. Iacobucci *et al.* demonstrated significant immune responses following the first dose and complete seroconversion in the subjects after the second dose of Covishield™ in a study conducted in England and Wales.[6] As the Delta variant has important mutations in spike region; it could pose a real challenge to the vaccines specifically developed targeting spike gene.

Our earlier investigations demonstrated a reduction in the neutralizing antibody (NAb) titer in the sera of Covishield™ vaccinees against Kappa variant.[7] Here, we have assessed the NAb response of individuals immunized with Covishield™ (first dose and second dose), COVID-19-recovered individuals who were vaccinated (first dose and second dose) and breakthrough infections (due to Kappa and the Delta variants).

A comparative assessment of Covishield™ vaccinated individuals' ($n = 116$) sera in different categories was performed against prototype strain B.1 (D614G) and Delta variant. Sera under this study were grouped into five categories: (i) one dose ($n = 31$), (ii) two doses ($n = 31$), (iii) COVID-19-recovered plus one dose ($n = 15$), (iv) COVID-19-recovered plus two doses ($n = 19$) and (v) breakthrough COVID-19 cases ($n = 20$). All the sera were collected 4 weeks post-vaccination for Category I–IV participants. For Category V patients, sera were collected 2 weeks post-two-dose vaccination, which were SARS-CoV-2-positive, using rRT-PCR. COVID-19-recovered cases (Categories

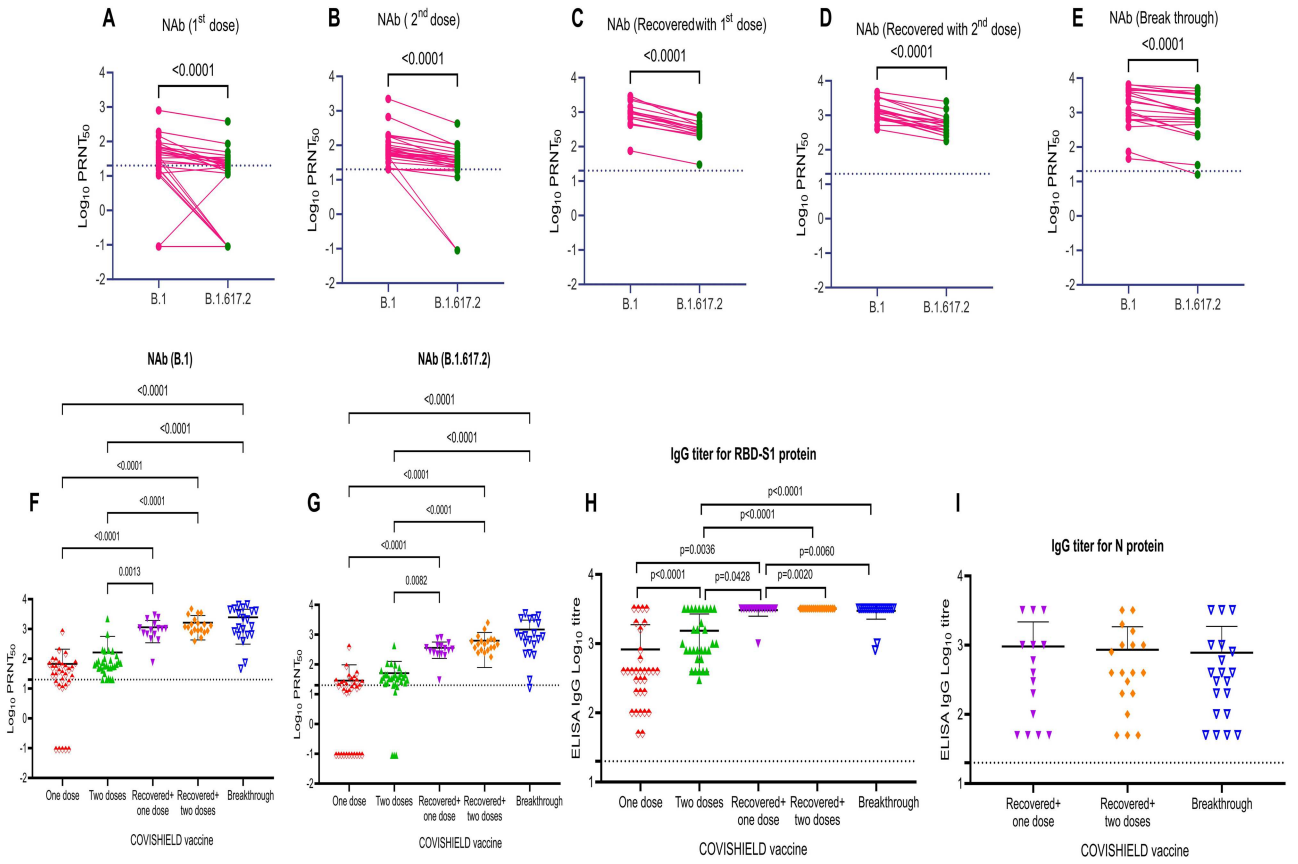

Figure 1. Neutralization antibody titer of individual sera from different categories against SARS-CoV-2 B.1 (D614G) and Delta (B.1.617.2) strains and RBD-S1 and N protein titer: NAb titer against the B.1 (pink) and Delta (green) was compared between participants administered with one dose Covishield™ vaccine (A), two doses of vaccine (B), COVID-19-recovered individuals administered with one dose Covishield™ vaccine (C), COVID-19-recovered individuals administered with two doses (D) and breakthrough participant (E); a two-tailed pair-wise comparison was performed using the Wilcoxon matched-pairs signed-rank test to analyze the statistical significance; comparison of NAb titer between participants administered with one dose Covishield™ vaccine (red color), two doses of Covishield™ vaccine (green color), Covishield™ vaccine to COVID-19-recovered individuals administered with one dose (purple color) and two doses (orange color) and breakthrough (blue color) participants against B.1 strain (F) and Delta strain (G); IgG titers of participant's sera from different categories for SARS-CoV-2 RBD protein (H) and N protein ELISA (I); the statistical significance was assessed using two-tailed Kruskal Wallis test with Dunn's test of multiple comparisons to analyze the statistical significance, and a *P* value less than 0.05 was considered to be statistically significant; the dotted line on the figures indicates the limit of detection of the assay; data are presented as mean values +/− standard deviation (SD).

III and IV) were of B.1 lineage, whereas breakthrough cases (Category V) belonged to lineages Kappa and Delta variants as confirmed by next-generation sequencing. The samples were also screened for S1-RBD and N protein ELISA. Except for Categories I and II samples, which were not screened for N protein ELISA.

The NAb titers against B.1 and Delta variants were compared for sera of each category. NAb against B.1 were not observed in 11/31 (35.5%) participants in Category I. Similarly, NAb against the Delta were not observed in 18/31 (58.1%) and 5/31 (16.1%) participants of Categories I and II, respectively. The GMT ratio of the Delta vs B.1 for Categories I–V were 0.22 [95% confidence interval (CI): 0.19–0.25; *P* value < 0.0001]; 0.31 (95% CI: 0.22–0.43; *P* value < 0.0001); 0.34 (95% CI: 0.32–0.37; *P* value < 0.0001); 0.38 (95% CI: 0.38–0.39; *P* value < 0.0001) and 0.53 (95% CI: 0.49–0.56; *P* value < 0.0001), respectively (Figure 1A–E). NAb titers for Delta relative to B.1 were reduced in the sera of the participants belonging to Categories I (78%), II (69%), III (66%), IV (38%) and V (47%). This finding suggests increased susceptibility of two-dose vaccinees to Delta variant.

The GMT for B.1 strain in Categories I–V was 16.12 (95% CI: 6.507–39.94; *P* value < 0.0001), 73.47 (95% CI: 50.7–106.5; *P* value < 0.0001), 868.9 (95% CI: 533.3–1416; *P* value > 0.999), 1312 (95% CI: 949.3–1813; *P* value > 0.999) and 1344 (95% CI: 700.2–2580), respectively. This indicates that sera of COVID-19-recovered participants who were vaccinated with either one (Category III) or two doses (Category IV) and breakthrough had higher NAb titers relative to COVID-19-negative participants of Categories I and II (Figure 1F). Higher NAb titers in sera of COVID-19-recovered cases (Categories III and IV) as compared to COVID-19-negative cases (Categories I and II) highlights that even one dose of vaccine is enough to protect against reinfection of SARS-CoV-2. Our results corroborated with study conducted with mRNA vaccine by Goel *et al.*[8] It also supports the role of cross-reactive SARS-CoV-2-specific T-cell-mediated immune response as described by Geers *et al.*[9]

Similarly, GMT for Delta variant in Categories I–V was 3.553 (95% CI: 1.252–10.08), 22.43 (95% CI: 10.96–45.9), 298.8

(95% CI: 196–455.5), 501.3 (95% CI: 368.6–681.7) and 706.2 (95% CI: 342.8–1455), respectively (Figure 1G). Participants in Category I (4.5-fold) and II (3.2-fold) showed reductions in NAb titers against Delta variants as compared to B.1 lineage. Reduction in GMT was evident in Categories III–V, however, NAb titers remained significantly higher to provide enough protection. An increase in NAb titers was observed for both B.1 and Delta variants in the sera of the participants who had completed two vaccine doses relative to one dose. NAb titers against B.1 and Delta variants were highest among breakthrough participants, which may be due to spike-specific T-cell responses.[10]

IgG specific to RBD protein showed higher antibody response (1:3200) in Categories III–V group (Figure 1H). N protein-based ELISA indicated a similar pattern of IgG titer in participants in Categories III–V (Figure 1I).

We observed significantly lower NAb titers (3.2–4.5-fold) for the Delta relative to B.1 variant. However, NAbs in breakthrough participants and the COVID-19-recovered individuals with one or two-dose vaccination had relatively higher protection against Delta in comparison to the vaccinees with one or two-dose vaccination.

Long-term follow-up of participants could help to understand the impact of natural infection and vaccination on long-term protection from SARS-CoV-2 offered by Covishield™. It is important to track the breakthrough infections for immune-escape mutants.

Authors' contributions

G.N.S., P.D.Y. and P.A. contributed to the study design, data analysis, interpretation and writing and critical review. R.R.S., G.D., D.A.N., D.Y.P., A.M.S. and S.K. contributed to the data collection, data analysis, interpretation, writing and critical review. N.G., S.P. and B.B. contributed to the critical review and finalization of the paper.

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Conflict of interest

None declared.

Ethical approval

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

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