

## Rapid communication

**Title:** Neutralization of Beta and Delta variant with sera of COVID-19 recovered cases and vaccinees of inactivated COVID-19 vaccine BBV152/Covaxin

**Running title:** Neutralization of Beta and Delta variants

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## Highlights

SARS-CoV-2 variant of concern mainly Delta and Beta is global public health concern due to its impact on existing vaccines. Here, we assessed the neutralization of sera from COVID-19 recovered cases and BBV152 vaccinees against Beta and Delta variants. BBV152 vaccine found to confer significant protection against both the variants.

## Text,

In the last several months, several SARS-CoV-2 variants have emerged from various countries worldwide.<sup>1</sup> Among them, variant of concern (VOC) i.e., Alpha (B.1.1.7), Beta (B.1.351), Gamma (B.1.1.28.1) and Delta (B.1.617.2) are serious public health threats because of their association with the higher transmissibility and the potential immune escape.<sup>1,2</sup> Various reports have been published on the neutralization efficacies with the sera of the currently available COVID-19 vaccines against these variants.<sup>1,2</sup> However, the immune escape of Beta variant has been serious concern for the COVID-19 vaccination program. It has shown reduced neutralization to several approved vaccines such as mRNA-1273, BNT162b2, ChAdOx1 nCoV-19, NVX-CoV2373.<sup>1</sup> Another reason of global concern is the recent emergence and detection of highly transmissible Delta variant from India and various other countries.<sup>2</sup> An inactivated SARS-CoV-2 vaccine, BBV152 was rolled out under the national COVID-19 vaccination program in India. The neutralization potential of the BBV152 has been already studied with the B.1, Alpha, Zeta, and Kappa found to be effective against these variants.<sup>3-5</sup>

Here, we assessed the neutralization of sera from COVID-19 recovered cases (n=20) post 5-20 weeks of infection and vaccinees 28 days after two doses of BBV152 (n=17)

against Beta, Delta variants and compared to prototype B.1 (D614G). The recovered cases were infected with B.1 (n=17) and B.1.617.1 lineage (n=3). SARS-CoV-2 isolates were propagated at ICMR-NIV, Pune from the clinical samples using Vero CCL-81 cells and were used for a 50% plaque reduction neutralization test (PRNT50).

Geometric mean titer (GMT) for vaccinees sera against B.1, Beta and Delta variants were found to be 187.5 (95%CI: 129.3-271.9), 61.57 (95%CI: 36.34-104.3) and 68.97(95%CI: 24.72-192.4) respectively. The GMT ratio of B.1 to Beta and Delta variants was 3.0 (95%CI: 2.6-3.6) and 2.7(95% CI: 1.4-5.2).

Similarly, GMT titers in sera of recovered cases against B.1, Beta and Delta variants were 97.8 (95%CI: 61.2-156.2), 29.6 (95%CI: 13.4-65.0) and 21.2(95% CI: 6.4-70.1) respectively. The GMT ratio of B.1 to Beta and Delta variants was 3.3 (95%CI: 2.4-4.5) and 4.6 (95% CI: 2.2-9.5). Sera of vaccinees and recovered cases had shown a significant reduction in neutralization titer for Beta and Delta variants in comparison to B.1 (p-value  $< 0.0001$ ) (Figure 1).

Several studies have reported the reduction in the neutralization efficacy with the sera of naturally infected cases and individuals vaccinated with BBIBP-CorV (1.6 $\times$ ), BNT162b2 (6.5 $\times$ ), mRNA-1273 (8.6 $\times$ ), ChAdOx1 nCoV-19 (86 $\times$ ) against B.1.351.<sup>1,6</sup> Reduced neutralization with the vaccinees sera of BNT162b2 mRNA (7 $\times$ ) and one dose of ChAdOx1 nCoV-19 was observed against Delta.<sup>2</sup>

Our study demonstrated that despite a reduction in neutralization titers with BBV152 vaccinees sera against Beta and Delta variants, its neutralization potential is well established. Lastly, the broad epitope coverage in an inactivated vaccine induces immune response against whole virion which decreases the magnitude of reduced neutralization

against emerging variants. Further mutation of Delta' variant known as 'Delta AY.1 and Delta AY.2' has been identified from India and other countries which has been a threat to existing vaccine and drugs. We still do not know how reduced neutralization activity results into reduced vaccine effectiveness; hence vaccine effectiveness studies are absolutely required to fully appreciate the effectiveness of COVAXIN against these two variants.<sup>7</sup>

### **Ethical approval**

The study was approved by the Institutional Biosafety Committee and Institutional Human Ethics Committee of ICMR-NIV, Pune, India under the project 'Comparative assessment of BBV152 vaccine (COVAXIN™) antibody and antigen-specific responses in immunized population without past COVID-19 infection, individuals vaccinated after recovery from COVID-19 and non-vaccinated individuals with past COVID-19 infection' (21-2-6N).

### **Conflicts of Interest**

RE and KMV are employees of Bharat Biotech International limited, Hyderabad, with no stock options or incentives. PY, GS, RRS, DAN, DYP, GD AS, PA, NG, SP, and BB are the employees of the Indian Council of Medical Research, New Delhi and they doesn't have any a financial or non-financial interest in the subject matter or materials discussed in this manuscript.

### **Author Contributions**

PDY, RE and PA contributed to study design, data collection, data analysis, interpretation and writing and critical review. GS, RRS, DAN, DYP, GD and AS contributed to data collection, interpretation, writing and critical review. NG, SP, VKM and BB contributed to critical review and finalization of the paper.

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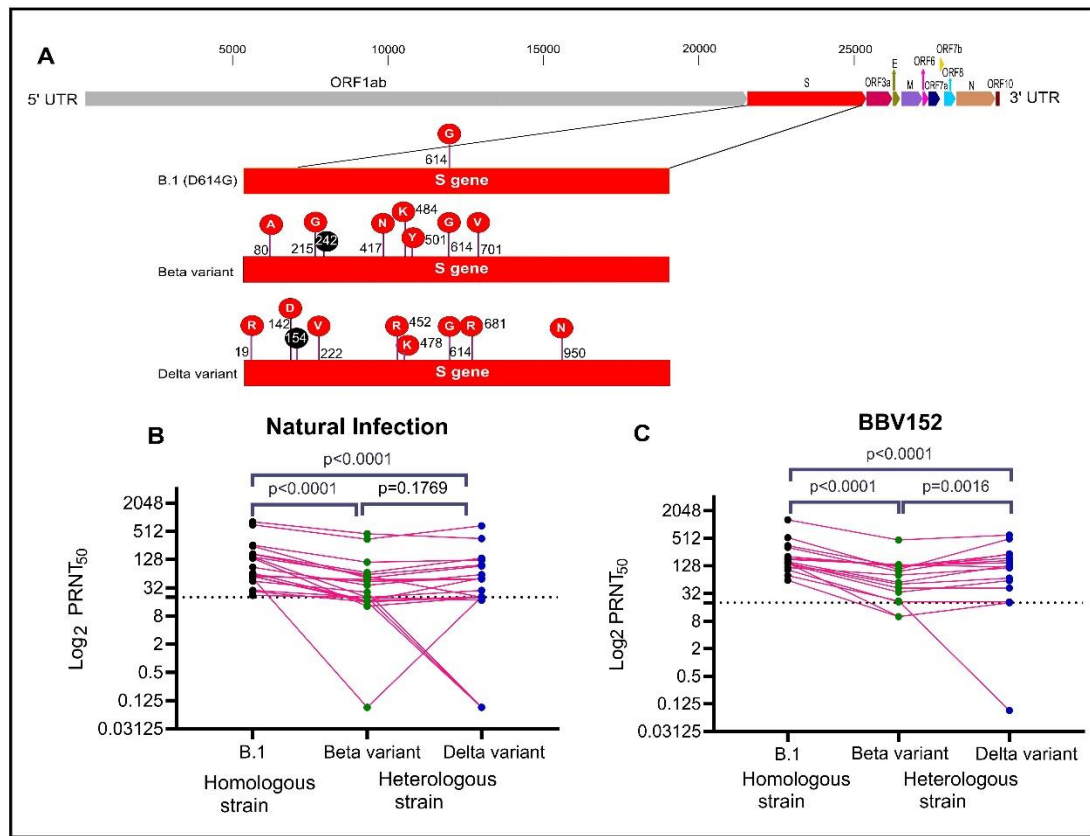
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#### **Legend to figure**

UNCORRECTED MANUSCRIPT



**Figure 1: Mutation in Spike protein and neutralization of SARS CoV-2 for B.1.351, B.1.617.2 and B.1:** A) The complete genome of SARS-CoV-2 indicating the different genes encoded by it. The inset highlights the amino acid changes in the spike region of the B.1 (D614G) (NIV2020-770, GISAID accession number: EPI\_ISL\_420545), Beta (NIV2021-893, GISAID accession number: EPI\_ISL\_2036294) and Delta (NIV2021-1916, GISAID accession number: EPI\_ISL\_2400521) are indicated in comparison to Wuhan isolate HU-1(NC\_045512.2). Black color depicts deletion of amino acids. The amino acid changes marked in spike protein for B.1 are D614G; Beta are D80A, D215G, L242del, K417N, E484K, N501Y, D614G, and A701V; and Delta are T19R, G142D, E154del, A222V, L452R, T478K, D614G, P681R and D950N. Black color depicts deletion of amino acids. Neutralization titer of naturally infected cases sera (B) and Vaccinees sera (C) against B.1 (Black color), Beta



(pink color) and Delta (Blue color) are shown as matched-pair plot. A paired two-tailed comparison was performed using a two-tailed Wilcoxon matched-pairs signed-rank test with a p-value of 0.05. \*\*\*\* represent p-value  $<0.0001$  and \*\*p value=0.0038, ns= non-significant p-value. The dotted line indicates the detection limit of the test.

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