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Research Letter

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Inactivated COVID-19 vaccine BBV152/COVAXIN effectively neutralizes recently emerged B.1.1.7 variant of SARS-CoV-2

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The rapid surge of SARS-CoV-2 cases due to the 'variant of concern (VOC) 202 012/01', also known as lineage B.1.1.7 or 20B/501Y.V1 in the UK,[1] in December 2020, raised concerns in several countries due to its high transmissibility. Many of these countries had direct flights to and from the UK. Since the identification of the new variants of Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in the UK and South Africa,[2] health experts have also expressed their concerns about their potential implications pertaining to vaccine efficacy. The root of such concerns was grounded in the structure of the SARS-CoV-2 variant, VOC-202012/01, which came to the centre stage of discussion due to its greater transmissibility in humans compared with the other known SARS-CoV-2 lineages. This variant carries 17 mutations in the genome, 8 of which have been found in spike receptor-binding domain (RBD), mediating the attachment of the virus to the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of human cells.[2] One of these mutations, N501Y, at position 501, has asparagine (N) replaced with tyrosine (Y) and has been identified to increase the binding affinity of SARS-CoV-2 to human and murine ACE2.[2] Therefore, it appeared that the majority of the vaccine candidates, being either recombinant or specifically targeting the single epitope of the original D614G ancestral spike sequence, might not be able to generate an efficient immune response against the new variants.

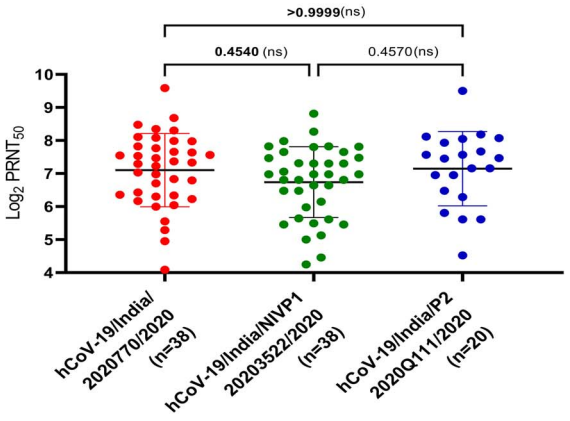
Here, we successfully isolated and characterized the hCoV-19/India/20203522 SARS-CoV-2 (VOC) 202 012/01 from UK returnees in India with all signature mutations of the UK variant.[3] The VOC 202012/01 hallmarks belonged to the GR clade of the viral isolates recovered from the UK returnees coming back to India.[3] The method used by us for virus isolation and culture from the clinical specimens of COVID-19 are described elsewhere.[4]

The SARS-CoV-2 strain (NIV-2020-770) used in developing the BBV152 vaccine was retrieved from tourists who arrived in New Delhi, India.[4,5] The virus isolation was performed in the 'Vero CCL-81' cells and the genome sequence was deposited in the GISAID (EPI_ISL_420545). The BBV152 vaccine candidate strain is located in the (G clade), containing the Asp614Gly mutation, which is characterized by aspartic acid to glycine shift at the amino acid (AA) position 614 of the spike protein. This was used for $PRNT_{50}$ assay in the present investigation.[4]

Earlier, we reported the development of an inactivated whole-virion SARS-CoV-2 vaccine BBV152, which elicited a remarkable neutralizing antibody response in Phase I clinical trial against hCoV-19/India/2020770 (homologous), and two heterologous strains from the unclassified cluster, namely, hCoV-19/India/2020Q111 and hCoV-19/India/2020Q100.[6] The hCoV-19/India/2020Q111 and hCoV-19/India/2020Q100 virus isolate strains contain the L3606F mutation, where leucine to phenylalanine shifted at AA position 3606 of the ORF1ab[5] have been observed.

In Phase II clinical trial, following two dose immunization schedule at Days 0 and 28 with 6 and 3 µg antigen with imidazoquinoline (TLR7/TLR8 agonist adsorbed on aluminium

A



B

SARS-CoV-2 strains used for PRNT	Clade	Mutations
hCoV-19/ India/2020770	G	Spike D614G, NSP3 S697F, NSP12 P323L
UK-variant *(VOC) 202012/01*	GR	Spike A570D, Spike D614G, Spike D1118H, Spike H69del, Spike N501Y, Spike P681H, Spike S982A, Spike T716I, Spike V70del, Spike Y144del, N D3L, N G204R, N R203K, N S235F, NS8 Q27stop, NS8 R52I, NS8 Y73C, NSP3 A890D, NSP3 G1447N, NSP3 I1412T, NSP3 S688L, NSP3 T183I, NSP3 T1446K, NSP6 F108del, NSP6 G107del, NSP6 S106del, NSP8 Q24R, NSP12 P323L, NSP13 K460R
hCoV-19/ India/2020Q111	O	NSP13:T351I, NSP1:M85del, NSP4:M33I, NSP2:R27C, NSP6:L37F, NS7b:L11F, NSP2:V198I

C

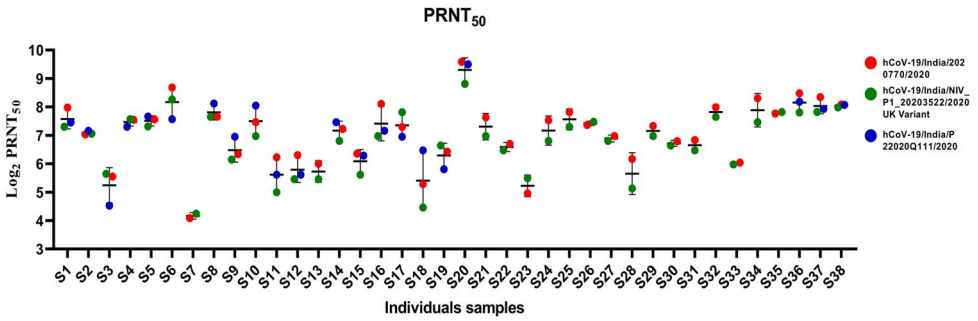


Figure 1. (A) Neutralizing antibody response of BBV152/COVAXIN vaccinated sera against SARS CoV-2 strains: neutralizing antibody titres ($PRNT_{50}$ value) of vaccinees'sera against hCoV-19/India/2020770 (homologous Asp614Gly mutation G clade), hCoV-19/India/20203522 (heterologous UK variant '(VOC) 202 012/01' hallmarks belonged to GR clade) and hCoV-19/India/2020Q111 (heterologous unclassified cluster with L3606F mutation). The bar represents the geometric mean and standard deviation (SD) of the respective group titres. Non-parametric Kruskal–Wallis test was used for the comparison of the $PRNT_{50}$ values from different groups. The *P* values above 0.05 were considered non-significant and are marked on the figure (ns, non-significant). (B) Details of SARS-CoV-2 strains used for plaque reduction neutralization test with respective mutations. (C) Comparison of $PRNT_{50}$ value of each vaccine recipient's sera with three strains of SARS CoV-2: neutralizing antibody titres ($PRNT_{50}$ value) of each vaccinee's sera against hCoV-19/India/2020770 (homologous Asp614Gly mutation G clade), hCoV-19/India/20203522 (heterologous UK variant '(VOC) 202 012/01' hallmarks belonged to GR clade) and hCoV-19/India/2020Q111 (heterologous unclassified cluster with L3606F mutation). The bar represents the mean and SD of the respective sera.

hydroxide gel), the vaccine candidate showed noteworthy results in plaque reduction neutralization test ($PRNT_{50}$)-based assay, with the seroconversion rates of neutralizing antibodies being 98.6%.[7]

Here, we present the NAb titres ($PRNT_{50}$) of sera collected (4 weeks after the second dose) from 38 vaccine recipients, who received the BBV152 vaccine candidate in Phase II trial[7] to underline the immunogenicity of the BBV152 vaccine candidate against SARS-CoV-2 UK variant with (VOC) 202 012/01 hallmarks belonging to GR clade and strain hCoV-19/India/2020770 belonging to G clade.

A representative set of 20 serum samples of vaccine recipients were also tested against the heterologous strains hCoV-19/India/2020Q111 (unclassified cluster) using $PRNT_{50}$ test assay described earlier.[8] Briefly, all the sera were heat-inactivated and serially diluted 4-fold. Further, these samples were mixed with an equal amount of virus suspension containing 50–60 plaque-forming units (PFUs) in 0.1 ml. After incubating the mixtures at 37°C for 1 h, each virus-diluted serum sample (0.1 ml) was inoculated onto a 24-well tissue culture plate containing a confluent monolayer of 'Vero CCL-81 cells'. After incubating the plate at 37°C for 60 min, an overlay medium consisting of 2% carboxymethyl cellulose (CMC) with 2% fetal calf serum (FCS) in 2× MEM was added to the cell monolayer, and the plate was further incubated at 37°C in 5% CO_2 for 5 days. Plates were stained with 1% amido black for an hour. Antibody titres were determined as the highest serum dilution that resulted in >50% ($PRNT_{50}$) reduction in the number of plaques.

All sera had equivalent NAb titres to hCoV-19/India/2020770 homologous strain and two heterologous strains, including the characteristic N501Y substitution of the UK variant, hCoV-19/India/20203522 (UK strain) as well as hCoV-19/India/2020Q111 (Figure 1A and B). The median ratio of 50% neutralization of sera was 0.8 when compared with hCoV-19/India/2020770 against the mutant hCoV-19/India/20203522 (UK variant) and was 0.9 when compared with hCoV-19/India/2020Q111. Non-parametric Kruskal–Wallis test for the comparison of the $PRNT_{50}$ values from different groups revealed non-significant difference ($P > 0.05$).

Andreano *et al*. reported an escape of the UK variant with E484K substitution, which was followed by a 11-AA insertion in the NTD N5 loop ($_{248a}$KTRNKSTSRRE$_{248k}$) from high NAb

in convalescent plasma, which was a serious concern.[9] Our study evidently highlighted comparable neutralization activity of vaccinated sera against the new UK variant as well as heterologous SARS-CoV-2 strains. Interestingly, the results showed that the vaccinees' sera could neutralize the new UK variant strain and heterologous strains with equal efficiency, discounting the uncertainty of possible neutralization escape. The statistically non-significant difference observed (Figure 1) for the UK variant, and other tested strains demonstrated reassuringly similar viral neutralization profile. Similarly, Wu *et al*. assessed the neutralizing capacity of the sera from humans and non-human primates immunized with mRNA-1273 vaccine and demonstrated effective neutralizing response against B.1.1.7 variant.[10]

Mutations are expected to occur during viral proliferation in SARS-CoV-2 as witnessed worldwide. Importantly, our study showed that the sera from the vaccine recipients could neutralize the UK variant strains, discounting the uncertainty around potential escape. It was reassuring from the $PRNT_{50}$ data generated in our laboratory that the indigenous BBV152/COVAXIN, following its roll out in the vaccination programme, could be expected to work against the new UK variant. It is unlikely that the mutation 501Y would dampen the potential benefits of the current vaccination programme.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

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

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Conflict of Interest

None declared.

References

1. Rambaut A, Loman N, Oliver Pybus O *et al. Preliminary Genomic Characterisation of an Emergent SARS-CoV-2 Lineage in the UK Defined by a Novel Set of Spike Mutations*. https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563. (1 February 2021, date last accessed).
2. Starr TN, Greaney AJ, Hilton SK *et al*. Deep mutational scanning of SARS-CoV-2 receptor binding domain reveals constraints on folding and ACE2 binding. *Cell* 2020; **182**:1295–310.
3. Yadav PD, Nyayanit DA, Sahay RR *et al*. Isolation and characterization of VUI97 202012/01, a SARS-CoV-2 variant in travellers from the United Kingdom to India. *J Travel Med*. 2020; **28**:taab009. doi: 10.1093/jtm/taab009.
4. Sarkale P, Patil S, Yadav PD *et al*. First isolation of SARS-CoV-2 from clinical samples in India. *Indian J Med Res* 2020; **151**:244.
5. Potdar V, Cherian SS, Deshpande GR *et al*. Genomic analysis of SARS-CoV-2 strains among Indians returning from Italy, Iran & China, & Italian tourists in India. *Indian J Med Res* 2020; **151**:255–60.
6. Ella R, Vadrevu KM, Jogdand H *et al*. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial. *Lancet Infect Dis* 2021 Jan 21; S1473–3099(20)30942-7. doi: 10.1016/S1473-3099(20)30942-7 Epub ahead of print. PMID: 33485468.
7. Ella R, Reddy S, Jogdand H *et al*. Safety and immunogenicity clinical trial of an inactivated SARS-CoV-2 vaccine, BBV152 (a phase 2, double-blind, randomised controlled trial) and the persistence of immune responses from a phase 1 follow-up report. *medRxiv* 2020.12.21.20248643. doi: 10.1101/2020.12.21.20248643 December 22, 2020, preprint: not peer reviewed.
8. Deshpande GR, Sapkal GN, Tilekar BN *et al*. Neutralizing antibody responses to SARS-CoV-2 in COVID-19 patients. *Indian J Med Res* 2020; **152**:82–7.
9. Andreano E, Piccini G, Licastro D *et al*. SARS-CoV-2 escape in vitro from highly neutralizing COVID-19 convalescent plasma. *bioRxiv* 2020. doi: 10.1101/2020.12.28.424451 December 28, 2020, preprint: not peer reviewed.
10. Wu k, Werner AP, Moliva JI *et al*. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. *BioRxiv* 2021. doi: 10.1101/2021.01.25.427948 January 25, 2021, preprint: not peer reviewed.