Overstated conclusions of a non-inferiority trial testing immunogenicity and safety of homologous and heterologous booster – authors' reply

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We thank the author for the comments[1] on our recently published article "Immunogenicity and safety of homologous and heterologous booster vaccination of ChAdOx1 nCoV-19 (COVISHIELD™) and BBV152 (COVAXIN®): a non-inferiority phase 4, participant and observer-blinded, randomized study". The responses to the comments are as follows:

1. Our analysis was based on IgG antibodies against SARS-CoV-2 spike (S), spike receptor-binding domain (RBD), spike N terminal domain (NTD), nucleocapsid antigen and SARS-CoV-1 spike. We also presented the ACE2 binding inhibition assay results which is a surrogate neutralization assay with high throughput, requires lesser stringent infection control measures, and has been shown to correlate with conventional neutralization techniques.[2,3] In data that we did not include in the paper, we also performed plaque reduction neutralization tests (PRNT-50) to the wild type virus as shown below and the results are consistent with the ACE2 binding inhibition assay results.
2. The correspondence also points out that the some of the recruitment for the COVAXIN® primed individuals took place during the Omicron wave. When we stratified the results based on the onset of the Omicron wave, the results were similar in those participants recruited before and during the Omicron wave. These data are presented in Supplementary Fig 3 and have been presented in the main manuscript in the section titled 'Antibody response to VOC'.
3. With regards to the COVAXIN® primed participants having more co-morbidities compared to COVISHIELD™ primed participants, since the comparison of homologous and heterologous

Wild Type PRNT-50 immune responses by booster dose vaccine allocation at baseline and 28 days post booster dose among COVISHIELD™ primed and COVAXIN® primed population

COVISHIELD GROUP	Covaxin Arm (n=98)	Covishield Arm (n=99)	p value
Day 1 GMC (95%CI)	98.42 (67.22-144.11)	123.09 (82.7-183.2)	0.4216
Day 28 GMC (95%CI)	328.66 (258.12-418.48)	990.92 (777.82-1262.42)	0.0000
Geometric Mean Fold Rise	3.34 (2.59-4.3)	8.05 (5.51-11.76)	0.0002
#Adjusted Day 28 GMR $_{B/A}$	2.77 (2.08-3.69)		

COVAXIN GROUP	Covaxin Arm (n=99)	Covishield Arm (n=100)	p value
Day 1 GMC (95%CI)	142.18 (94.97-212.86)	108.11 (72.18-161.92)	0.3423
Day 28 GMC (95%CI)	613.34 (438.92-857.07)	4221.05 (3189.21-5586.73)	0.0000
Geometric Mean Fold Rise	4.31 (3.01-6.19)	39.04 (26.58-57.34)	0.0000
#Adjusted Day 28 GMR $_{B/A}$	7.60 (5.17-11.15)		

Adjusted for age and baseline PRNT (ANCOVA)

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boosting is made within the COVAXIN® group, the within group randomization would account for any effect of co-morbidities.

4. Finally, the author has misunderstood the supplementary Table 4. In those seronegative in the COVISHIELD™ primed group, there was 96.3% seropositivity after COVAXIN® boost and 95% seropositivity after COVISHIELD™ boost. Similarly in those that were seronegative in the COVAXIN® primed group, seropositivity was 92.1% and 100% after COVAXIN® and COVISHIELD™ boost respectively. In supplementary Table 4, we did not show fold rise for those who were seronegative at baseline.

Contributors
WR drafted the response; GK reviewed and both approved the final response.

Declaration of interests
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References

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