Review 2: "Neutralization against B.1.351 and B.1.617.2 with sera of COVID-19 recovered cases and vaccinees of BBV152"

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RR:C19 Evidence Scale rating by reviewer:

Strong. The main study claims are very well-justified by the data and analytic methods used. There is little room for doubt that the study produced has very similar results and conclusions as compared with the hypothetical ideal study. The study's main claims should be considered conclusive and actionable without reservation.

Review:

In the manuscript, Yadav et al. investigate the effects of hyper-immune batches generated from SARS-CoV-2 convalescent plasma on several parameters concerning SARS-CoV-2 infection. Initially, the authors explored the antibody epitope repertoire using the Genome Fragment Phage Display library approach (GFPDL) against wild-type spike and spike from VOCs: Alpha, Beta, and Gamma. The analysis identified a diverse epitope repertoire of spike epitopes, spanning the entire spike,, including RBD, NTD, and fusion peptide. The key peptides identified during the analysis were chemically synthesized,, and tested for their binding to antibodies within each of the six hCoV-2IG. The investigators compared hCoV-2IG antibodies to antibodies in naïve and convalescent plasma samples. As expected from the GFPDL analysis, antibodies within the immunoglobulin hCoV-2IG exhibited the highest antibody binding titers to spike peptides consisting of the fusion peptide sequence of the spike. This sequence is conserved between variants. The research also visualized recognition of the hCoV-2IG samples towards NTD and RBD.

Additionally, the researchers performed pseudovirus-neutralization analysis. The authors compared six hCoV-2IG batches and nine convalescent plasma lots against wild-type SARS-CoV-2 and several variants of concern. The control sample, pre-pandemic, exhibited low neutralization titers. The convalescent plasma lots were more efficient in neutralization potential and exhibited higher titers. Moreover, all hCoV-2IG batches presented high neutralizing potential against the wild-type pseudovirus. As already reported, the ability of tested samples to neutralize Alpha and Beta VOCs was compromised because there was a loss of titers. Analysis of PRNT assay on target Vero cells confirmed pseudovirus analysis.

Finally, the researcher explored the possible contributions of key spike mutations with direct binding to hCoV-2IG, using wild-type or mutated purified RBD proteins. The

results confirm previous data on the impact of K417N; N501Y,, and E484K spike mutations on neutralization and neutralizing Ab binding.

The work is well structured and the data is presented clearly. Obviously, the use of hyperimmune preps for efficient combat with the COVID-19 pandemic is relevant. Convalescent plasma has been around for more than 100 years. Convalescent plasma has been used to both prevent and treat infectious diseases in the past, such as polio and 1918 flu, and recent years, like MERS SARS and Ebola.

I suggest the authors to elaborate more on their findings regarding of previous literature and emphasis on the specifics of the system that provide higher chances of success.

Moreover, please discuss the advantages and pitfalls of this approach in the discussion section. With this addition, the reader can have an idea about the authors' opinion on this approach and how to overcome the drawbacks. These pitfalls mainly include standardization between samples, titer determination, and side effects of transfusion-related injury hemolytic reactions and immunomodulation. Transmission of autoantibodies against immune response elements, like IFN, is also a risk. Significantly, ADE is another adverse reaction that needs to be taken into account. Accordingly, characteristics of the convalescent and hyperimmune IgG need to be defined. H-IgG also removes IgM,, which may be required against viruses like SARS-CoV-2.