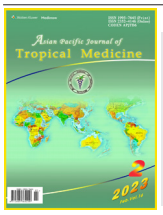

Letter to Editor

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Neutralizing possibilities of whole virion and mRNA vaccine triggered antibodies of Wuhan strain of SARS-CoV-2 with receptor binding domains of spike proteins of Delta and Omicron strains

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Mutations in the receptor binding domain (RBD) of SARS-CoV-2 spike protein have given birth to the new variants of concern *viz.* Delta and Omicron strain. As we are using vaccines which are either mRNA of spike protein of Wuhan strain or its whole virion vaccine, these vaccines will trigger antibodies to be able to bind with the epitopes of spike protein of Wuhan strain. There appears a need to study whether vaccine generated circulating neutralizing antibodies in vaccinated people are able to neutralize the receptor binding domain of spike protein of currently circulating Delta and Omicron strains as well. We need to address this contention in two phases: first to undertake docking studies of vaccine generated antibodies with Wuhan, Delta and Omicron strains and second to conduct the wet lab studies and observe antigen-antibody bindings employing Immunofluorescence and Cryo-Electron Microscopic studies. The present paper reports results of docking studies using bioinformatic softwares to provide the baseline information for wet lab studies.

The structures of two types of vaccine produced antibodies (Ab) were obtained from Research Collaboratory for Structural Bioinformatics Database Protein Data Bank (RCSB PDB). For whole virus inactivated vaccine (Vaccine 1), PDB ID 7WE9 and for mRNA vaccine (Vaccine 2), PDB ID 6XCA were used. Antibody of Vaccine 1 was in complex with spike protein of Omicron variant. The antibody structure was constructed using ABody Builder-ML tool. After downloading amino acid sequence of light chain and heavy chain in Fasta format and by using tool ABody Builder-ML, the antibody structure was built and further downloaded. The PDB Format of spike antigen of the 3 strains were also obtained *viz.* Wuhan strain (PDB ID 6VXX), Delta strain (PDBID 7W92) and Omicron strain (PDBID 7QO7). Docking was performed in Cluspro app in antibody mode in which antibody was used as receptor and antigen as ligand. After docking, the model structures were analyzed and the lowest energy score was selected. To analyze the antigen-antibody (Ag-Ab) interactions, Pymol software was used. In this, the Ag-Ab structure was drawn from the software and then values of site of binding of Ag-Ab were recorded and analyzed.

The antibody generated for Vaccine 1 when docked with Wuhan strain PDB ID 6VXX showed the lowest energy score of -309.7 (Figure 1A). The same when done for Delta strain PDB ID 7W92 and Omicron strain PDB ID 7QO7 showed the lowest energy score of -317.3 (Figure 1B) and -956.4 respectively (Figure1C). In the Ag-Ab interaction studies, it was observed that Wuhan strain showed good binidng with vaccine generated antibodies; however, both Delta and Omicron strains did not show any binidng (Figure 1A-1C).

The antibody generated by Vaccine 2 when docked with Wuhan strain PDB ID 6VXX showed the lowest energy score of -341.0 (Figure 1D). The same when done for Delta strain PDB ID 7W92 and Omicron strain PDB ID 7QO7 showed the lowest energy score of -374.2 (Figure 1E) and -375.0 respectively (Figure 1F). Vaccine generated antibodies also did not show binding with Delta and

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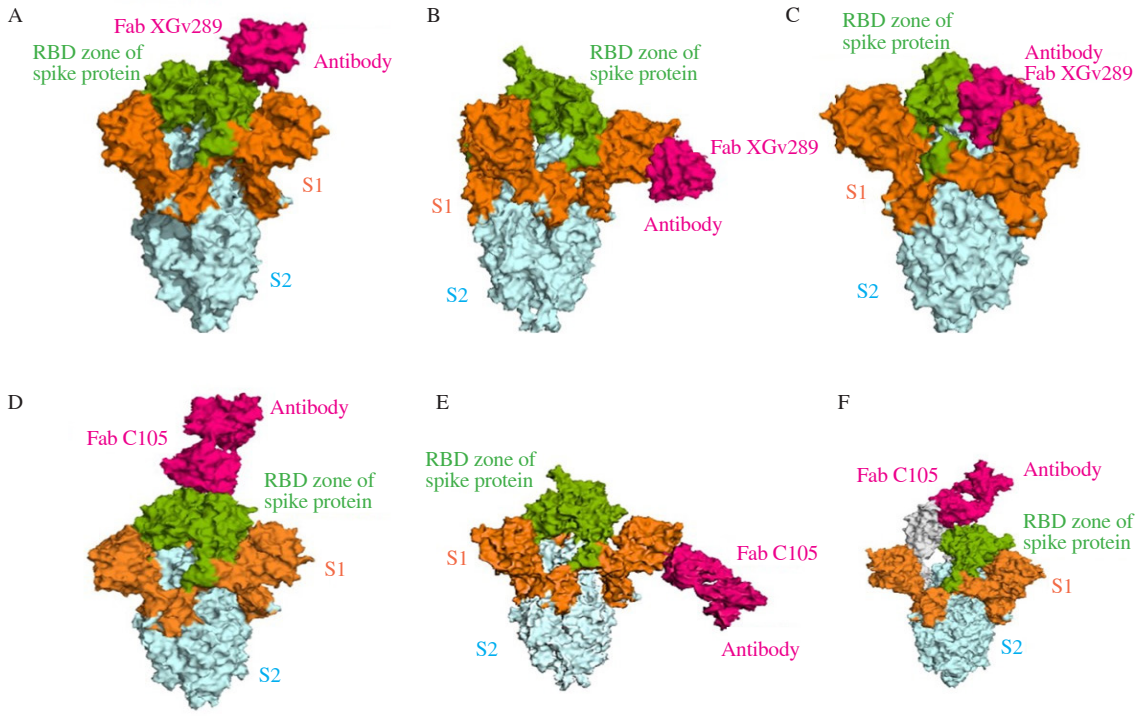

Figure 1. Docking results of whole inactivated virion vaccine (Vaccine 1) generated antibodies with spike protein of different variants of SARS-CoV-2 (1A-Wuhan, 1B-Delta and 1C-Omicron) and of mRNA vaccine (Vaccine 2) generated antibodies with spike protein of different variants of SARS-CoV-2 (1D-Wuhan, 1E-Delta and 1F-Omicron).

Omicron strains (Figure 1D-1F).

The study of interactions of amino acids of spike proteins of Wuhan strain with Vaccine 1 generated antibodies showed that 3 amino acids of heavy chain (H) and 1 amino acid of light chain (L) of vaccine generated antibodies formed 4 bonds with corresponding of antigen amino acids (spike protein). In case of Delta strain, 4 amino acids of H chain of vaccine generated antibodies interacted with 10 amino acids of Chain C of spike protein which is not the targeted site of interaction. In case of Omicron strain, 3 amino acids of Chain C of spike protein interacted with 2 amino acids of H chain and 1 amino acid of the L chain of antibody (Supplementary Table 1).

Study of Vaccine 2 showed binding of 7 amino acids of Chain A of spike protein of Wuhan strain with 3 amino acids of H chain and 6 amino acids of L chain of antibodies. In case of Delta strain, 6 amino acids of C chains of spike protein which is not in the RBD zone showed binding with one amino acid on the H chain and 5 amino acids on the L chain of antibodies. Similarly, 11 amino acids of spike protein of Omicron strain (10 of Chain C which is within the RBD zone and 1 with Chain A which is also within the RBD zone) interacted with 5 amino acids of H chain and 7 amino acids of the L chain of antibodies (Supplementary Table 1).

The SARS-CoV-2 has emerged as one of the deadliest forms of coronaviruses causing severe lower respiratory tract complications, pneumonia and associated mortalities[1]. Although we had quick availability of the whole virion as well as mRNA vaccines to prevent the virus entry into human cells, yet the limitations of the available vaccines are that these were developed against Wuhan strain whereas other mutated variants had emerged as the cause of the second and third waves of COVID-19[2–5]. Our results clearly showed that vaccine generated antibodies by the whole virion as well as mRNA vaccines showed binding with the spike protein of Wuhan strain but they did not bind with the RBD of spike protein of Delta and Omicron strains. There have been number of studies which report the presence of IgG antibodies in vaccinated people[6]. However, presence of IgG may not ensure the neutralizing abilities of antibodies against mutated strains. The present paper also reports that in case of Delta strain, the sites of antigen-antibody interactions were outside the RBD of spike protein and hence there could hardly be any protection offered by vaccine against Delta strain. This could perhaps be the reason why huge number of mortalities were reported in India during the 2nd wave of COVID-19 which was caused by Delta strain[7]. Although other researchers have reported phenotypic variations in the antibody responses produced against different strains of SARS-CoV-2[8]. yet further implications of these variations for the vaccine efficacy have not been studied.

Our observations also highlight the issue whether we should choose a large peptide like spike protein as vaccine molecule or should select still finer sequence which can be less liable to change through serial mutations. Relatively large peptide like S protein will offer multiple epitopes to naive B cells and will sensitize phenotypically

different antibodies which may bind with many epitopes of the large peptide, surrounding the peptide but may not bind with small epitope of its RBD which enters the cell through ACE-2 receptor. Perhaps this could be the reason why many researchers have already started working on the possibility of making vaccines for nucleocapsid proteins of SARS-COV-2 which does not undergo many mutations[9]. However, in the present paper, we focused on how best we can modify the currently available spike proteins-based vaccines to be protective enough against mutated strains. In fact, we need to re-think whether higher molecular weight protein is a pre-requisite for epitope selection by B cells or we need heavy peptides to produce cytokines by Th cells to sensitize the B cells. For a vaccine to be protective, we just need antibodies against RBD of spike proteins and not against the whole spike protein. RBD of spike protein contains 223 amino acids, out of which, approximately 16 amino acids have undergone the changes (mutations). The remaining 207 amino acids of RBD zone are still conserved and we can select an epitope from these 207 amino acids, for the vaccine to be effective against all the strains. Added to this, to sensitize B cells, instead of depending upon Th cells for cytokines, we can conjugate proposed small epitope vaccine with IL-1 and IL-6 to have the protection against mutated strains.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Authors' contributions

VJ, BA, AA and RJ conceptualized the research; BMS, SB, PK, ASK, RJ, NP, KY, KT, BS, NS and SPS were involved in methodology; SB and BMS did the formal analysis; SB, BMS, PK and ASK collected the resources; BA, AA and RJ did the data curation; VJ, BA, AA, RJ and BMS did the original draft preparation; BS, NS, KT, KY and RJ did the review and editing; VJ, AA, BA, BMS and RJ did the visualization; VJ, BA, and AA were involved in funding acquisition.

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