In Silico Evaluation of IgG Antibody-antigen Complex Binding Affinity for Circulating COVID-19 Vaccines

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**Abstract**. The effectiveness of a vaccine is significantly influenced by the strength of the antibody–antigen interaction. In this study, the binding affinity between immunoglobulin G (IgG) and selected SARS-CoV-2 antigens—including spike glycoproteins, envelope proteins, membrane proteins, and nucleocapsid proteins—was investigated through in silico analysis. The results demonstrate a positive correlation between the number of inter-residue contacts (IC) and the Gibbs free energy (ΔG), indicating stronger binding interactions with increasing IC. The calculated ΔG values for the respective antigens are as follows: −8.8 kcal·mol⁻¹ (envelope protein), −10.3 kcal·mol⁻¹ (spike glycoprotein), −10.7 kcal·mol⁻¹ (BNT162b2 spike glycoprotein), −11.1 kcal·mol⁻¹ (nucleocapsid protein), −11.7 kcal·mol⁻¹ (mRNA-1273 spike glycoprotein), −11.7 kcal·mol⁻¹ (NVX-CoV2373 spike glycoprotein), −13.3 kcal·mol⁻¹ (Ad26.COV2.S), and −14.3 kcal·mol⁻¹ (membrane protein). Furthermore, the dissociation constant (Kd) values indicate high binding stability across all antigen–antibody complexes. The respective Kd values are: 3.3 × 10⁻⁷ M (envelope protein), 1.5 × 10⁻⁸ M (BNT162b2), 2.8 × 10⁻⁸ M (spike glycoprotein), 2.8 × 10⁻⁹ M (mRNA-1273 spike glycoprotein),

2.8 × 10⁻⁹ M (NVX-CoV2373 spike glycoprotein), 7.3 × 10⁻⁹ M (nucleocapsid protein), 1.7 × 10⁻¹⁰ M (Ad26.COV2.S), and 3.5 × 10⁻¹¹ M (membrane protein). These findings suggest that all evaluated antigens exhibit strong and stable binding to IgG, which may contribute to the overall effectiveness of COVID-19 vaccines.

# INTRODUCTION

Vaccination has emerged as the primary strategy to curb the spread of the SARS-CoV-2 virus, contributing significantly to the establishment of herd immunity and a consequent reduction in hospitalizations and mortality rates [1]. Data from various countries indicate that vaccine efficacy—defined as the ability to reduce infection rates—and effectiveness—defined as the ability to reduce hospitalization and mortality across diverse patient demographics (e.g., age, sex)—range between 50–98% and 30–50%, respectively [2,3]. Although comprehensive studies in Indonesia are lacking, a report from the Ministry of Health suggests that vaccine effectiveness among healthcare workers exposed to COVID-19 reached 84% [4].

Despite these promising outcomes, the humoral immune response, particularly antibody production, is transient. The emergence of new viral strains has led to antigenic drift, rendering memory B cells less capable of recognizing previously encountered antigens. In the case of COVID-19, the spike glycoprotein—the principal antigen targeted by vaccines—has undergone multiple mutations [5], resulting in conformational changes that compromise recognition by memory B cells [2]. Consequently, the duration of immunity is reduced [1], leading to vaccine escape events, wherein evolved viral variants evade the immune response elicited by vaccination and successfully infect the host [6]

To counteract waning immunity and antigenic variation, booster vaccinations have been introduced with the aim of reactivating immune memory and enhancing antibody production against newly circulating variants. In the United States, booster programs have been implemented over the past five years, with approximately 25% of the population receiving annual boosters [7]. However, recent findings from Austrian researchers indicate that the effectiveness of booster doses diminishes after the fourth administration. Specifically, the fourth dose showed no significant association with reduced mortality among individuals with prior COVID-19 infection, and while it temporarily lowered infection risk, this effect waned over time. Moreover, data on all-cause mortality suggest a potential bias due to healthier individuals being more likely to receive vaccination [8].

These observations underscore the limited understanding of vaccine-induced immune mechanisms and highlight the need for continuous evaluation and improvement of vaccine design. One promising approach involves rational vaccine design through computational methods, which enable the prediction of antigenic epitopes with conformations that optimally interact with antibodies secreted by B cells [9,10].

In this context, the present study aims to evaluate the molecular interactions between immunoglobulin G (IgG)— the predominant antibody produced by B cells—and various antigens derived from circulating COVID-19 vaccines by highlighting the systematic comparison of IgG binding across multiple vaccine antigens. The analysis was conducted in silico using widely adopted computational tools and platforms. The findings are expected to inform future vaccine development strategies by identifying antigenic targets with enhanced binding affinity and immunogenic potential.

# MATERIALS AND METHODS

## Materials

This research was carried out with hardware in the form of a laptop, ASUS operating system, Windows 10 64-bit processor, Intel Core i3, 7th Gen processor, NVIDIA GEFORCE 930MX graphics system, 4GB RAM. Meanwhile, the software used is ClusPro 2.0, PyMOL, and LigPlot+, PDB-Tools, PRODIGY Webserver, and I-TASSER, and NovoPro Bioscience Inc.

IgG (PDB ID: 7CM4) was obtained from RCSB - PDB (Research Collaboratory for Structural Bioinformatics - Protein Data Banak). Antigen sequences taken from various official WHO documents including SARS-CoV2’s inactivated structural protein (envelop (YP\_009724392.1); spike glycoprotein (YP\_009724390.1); nucleocapsids (YP\_009724397.2); membrane (YP\_009724393.1)); spike glycoprotein of BNT16b2b (WIW57999.1) vaccine, mRNA-1273 vaccine, and Ad26.COV2.S vaccine. NVX-CoV2373 glycoprotein spikes are modified based on Martínez-Flores [11].

## Methods

### Preparation of IgG

The antibody protein data is prepared through PDB-Tools by selecting the 'pdb\_delhetatm' tool, this process removes impurities such as ligands, water, and oligosaccharides from Fab (antigen-binding fragment). The next step was to discard unwanted chains, namely chains A and B by 'pdb\_delchain' tool, resulting only heavy chains (H) and the light chains (L) left. The output results in the form of PDB-formatted data are stored for the molecular docking stage.

The prepared PDB data is reprocessed in PDB-Tools to obtain the FASTA of each chain. This FASTA data is entered into Antibody CDR Annotation (https:/[/www.novoprolabs.com/tools/cdr)](http://www.novoprolabs.com/tools/cdr)) to identify the complementarity determining region (CDR) of each chain in Fab IgG. This method has been carried out according to [12].

### Preparation of antigens

Antigens with FASTA sequences are processed by I-TASSER for 2-5 days. The results are downloaded in PDB format and recorded as C-score (Confidence Score) and TM-Score (Template Modelling Score) [13]. Regarding

antigens with low C-score (e.g., the BNT162b2 spike glycoprotein), the predicted structures may have reduced reliability. These models should therefore be interpreted with caution.

Antigens without FASTA data are modified manually by substituting related amino acids, and processed by I- TASSER SERVER to obtain 3D protein model. The results are downloaded in PDB format and recorded their C-score and TM-score [13]. Modified amino acids will be shown through PyMOL.

### Molecular Docking

Each antigen protein from the COVID-19 vaccine is docked with IgG antibodies through the ClusPro 2.0 web server. This process is controlled by using antibody mode so that the algorithm used automatically covers the non- CDR region [14,15].

The results were selected based on the cluster that had the largest number of cluster sizes. The antibody-antigen complexes were then visualized using LigPlot+ [16] and traced for each binding affinities through PRODIGY Webserver [17].

# RESULTS AND DISCUSSION

## IgG Model

Ribbon model of IgG is shown in Figure-1. There are three *complementarity determining regions* (CDR) located at the heavy (H) and light chain (L) whose the function is to bind antigen residue.

|  |  |
| --- | --- |
|  |  |

**Figure 1**. Ribbon model of IgG Antibody Protein (PDB: 7CM4) The amino acids composition of each CDR is figured in Table-1.

**Table 1**. Amino acids residue of CDR region

|  |  |
| --- | --- |
| **CDR** | **IgG** |
| H1 | T31, S32, G33, V34, G35, V36, G37 |

H2 L52, I53, D54, W55, D56, D57, N58, K59, Y60, H61, T62, T63, S64, L65, K66, T67

I100, P101, G102, F103, L104, R105, Y106, R107,

H3 N108, R109, Y110, Y111, Y112, Y113, G114, M115, D116, V117

L1 S23, G24, S25, S26, S27, N28, I29, G30, N31, N32, Y33, V34, S35

L2 D51, N52, N53, K54, R55, P56, S57

L3 G90, T91, W92, D93, S94, S95, L96, S97, A98, G99, V100

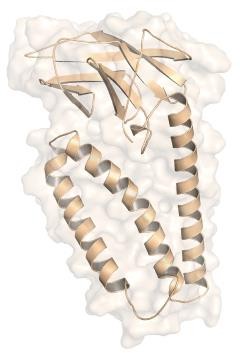
## Antigen Preparation

Only spike glycoprotein of BNT162b2 and all protein of inactivated virus are available on NCBI data bank. I- TASSER SERVER program pprovide 3D images as shown in Figure 2**.** The confidence levels (C-score) of the five models were very high (in the range of -5 to 2) (Table-2).

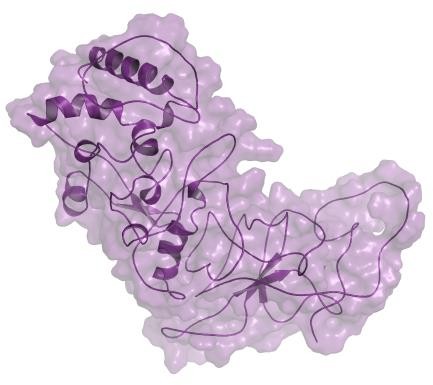
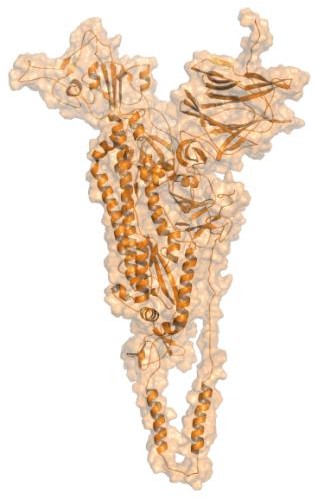
Of the five proteins, the envelope protein has the simplest structure (75 amino acids), while the spike protein has a complex structure (> 1200 amino acids). However, with TM-score > 0.5, the fifth has similar topological similarities (Table 2). The uncertainty associated with low C-score models introduces limitations to the interpretation of antigen structural features. Further validation using experimental structures or higher-confidence models would strengthen the findings

**Table 2** Scoring of Antigen Modelling of Inactivated Virus and BNT162b2 by I-TASSER

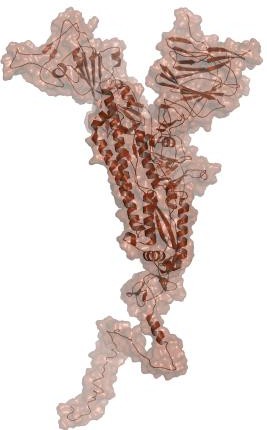
|  |  |  |  |
| --- | --- | --- | --- |
| **No.** | **Antigen** | **C-*score*** | **TM-*score*** |
| 1. | Envelope | -0.85 | 0.61 ± 0.14 |
| 2. | Membrane | 0.01 | 0.71 ± 0.11 |
| 3. | Nucleocapsid Phosphoprotein | 1.22 | 0.88 ± 0.07 |
| 4. | Spike Glycoprotein | -1.40 | 0.54 ± 0.15 |
| 5. | BNT162b2 spike glycoprotein | -2.05 | 0.47 ± 0.15 |

#### (a) (b)

#### (c) (d)



(e)

**Figure 2.** Protein 3 D structure: **(a** Envelope protein **(b)** Membrane protein **(c)** Nucleocapsid Phosphoprotein **(d)**

Spike Glycoprotein **(e)** Spike Glycoprotein Mutant BNT162b2

## Protein Modification (mRNA-1273, Ad26.COV2.S, NVX-CoV2373 Vaccine Antigens) and 3D Protein Modelling

The manually mutated vaccine model is given in Figure 3**.** The green sphere structure indicates the presence of K986P and V987P modifications in each vaccine antigen protein, the blue sphere structure indicates R682S and R685G modifications in the Ad26.COV2.S vaccine antigen modelling, and the purple sphere structure indicates R682Q, R683Q, and R685Q modifications in the NVX-CoV2373 vaccine antigen modelling.

|  |  |
| --- | --- |
|  |  |
| (a) | (b) |
|  |  |
| © |  |

**Figure 3.** Results of Vaccine Antigen Modelling of (a) mRNA-1273 spike glikoprotein **(b)** Ad26.COV2.S spike glikoprotein and **(c)** NVX-CoV2373 spike glikopreotein

The fact that C-score values are in the range of -5.2 indicates a high level of model confidence, while a TM-score of > 0.5 indicates topological similarity (Table-3).

**Table 3.** Scoring Antigen Modelling of mRNA-1273, Ad26.COV2.S, and NVX-CoV2373 Vaccines by I-TASSER

|  |  |  |  |
| --- | --- | --- | --- |
| **No.** | **Antigen** | **C-score** | **TM-score** |
| 1. | mRNA-1273 spike glycoprotein | -1.87 | 0.51 ± 0.15 |
| 2. | Ad26.COV2.S spike glycoprotein | -1.58 | 0.52 ± 0.15 |
| 3. | NVX-CoV2373 spike glycoprotein | -1.73 | 0.50 ± 0.15 |

## IgG-Antigen Molecular Docking

Table 4 shows the recapitulation of the IgG-antigens docking results. The interactions of IgG antibodies with antigen epitopes residues are described by the amount of hydrogen bonds, hydrophobic interactions, and electrostatic interactions. Envelope proteins, for example, have 6 hydrogen bonds, 13 mutually negating hydrophobic interactions,

and one electrostatic interaction. This total number of interactions does not yet reflect the strength of the antibody- antigen interaction.

**Table 4** Recapitulation of IgG – Antigens Interaction

|  |  |  |  |
| --- | --- | --- | --- |
| **Antigen** | **Interaction** | | |
| **Hydrogen Bond** | **Hydrophobic** | **Electrostatic** |
| Envelope | Tyr106-Glu8 Arg109-Thr11 Arg109-Glu8 Arg109-Ser3 Tyr33-  Val5 | Glu7, Tyr2, Met1, Leu104, Tyr110,  Tyr111, Ser3, Phe4, Asn31, Asn32, Lys54, Lys67 | Arg109-Glu8 |
| Membrane | Ser32-Tyr204 Arg99-Ala104 Pro101-Arg107 Arg109-His210 Arg109-Ser212 Tyr110-Ser212 Tyr33-Ser214 Tyr33-Asn216 Lys54-Asp215  Pro56-Gln222 Ile59- Gln22 | Arg101, Phe100, Arg174, Arg105, Leu206, Asn203,  Gln1, Gly26, Ser30, Thr31, Trp55, Asp56, Ser211, Asp209, Ser213, Asp215, Leu104, Tyr106, Tyr111, Tyr113, Ile217,  Asp51, Arg55 | - |
| Nucleocapsid phosphoprotein | Arg107-Ile130 Arg109-Glu136 Arg109-Asp22 Arg109-Ser21 Tyr50-Ser32 Lys54- Ser26 Lys54-Gly25 Ser57-Glu31 Ser57-  Arg32 | Gln9, Pro20, Arg14, Trp132, Ser23, Gly19, Gly18, Phe17, Ser32, Leu104, Tyr106, Tyr111, Tyr113,  Thr24, Ser23,  Asn27, Tyr33 | - |
| Spike Glycoprotein | Arg107-Asp1199 Asn108-Asp1199 Tyr106-Asp1199 Arg109-Ile1198 Arg109-Glu1195 Tyr113-Asn1187  Lys54-Leu1186 Lys54-Asn1187 Tyr50-Asn1187 Ser57-Gln1180 | Lys1191, Asn1194, Leu1200, Leu104, Tyr110, Tyr111, Leu1200, Ala1190, Ile1183, Asn1194,  Asn31, Asp51, Tyr33 | - |
| BNT162b2  (spike glycoprotein) | Asp116-Tyr1150  Arg99-Tyr1150 Arg107-Asn1114 Arg107-Thr1111 Arg107-Gln1108 Arg107-Asp1113 Tyr106-Asp1113 Arg109-Glu1139 Arg109-Pro1135 Pro101-Lys1149  Gln1-Asp1158 Ser57-Asp1158 | Phe1143, Ser1142, Glu1146, Tyr111, Leu104, Gly102, Tyr113, Asn1153, His1154, Tyr1150, Phe1143, Pro56,  Ile59, Tyr50, Tyr33 | Arg107-Asp1113  Arg55-Asp1160 |

|  |  |  |
| --- | --- | --- |
|  | Arg55-Asp1160 |  |
| Gly58-Asp1160 |
| Tyr106-Glu1144 |
| Arg107-Tyr1138 | Lys1157, Asp1146, |
| Arg109-Ser1147 | Pro1143, Lys1149, |
| Arg109-Glu1150 | Asp1153, Lys1154, |
| mRNA-1273 | Arg109-Glu1151 | Gly102, Leu104, |
| (spike | Gly58-Pro1162 | Tyr111 - |
| glycoprotein) | Ser57-Ser1161 | Lys1154, Val1164, |
|  | Ser57-Asp1163 | Lys1157, Tyr33, |
|  | Tyr50-Ser1161 | Arg55, Pro56 |
|  | Tyr50-Thr1160 |  |
|  | Lys54-Asn1158 |  |

Ad26.COV2.S

(spike glycoprotein)

NVX-CoV2373

(spike glycoprotein)

Arg99-Gln677 Ser32-Thr1231 Ser30-Lys1266 Thr31-Glu1262 Arg109-Ser659 Arg109-Ser698 Arg109-Glu661 Arg109-Gly700 Asn52-Asn657 Tyr33-Asn657 Tyr33-Asn658 Lys54-Glu654 Ser57-Gly685 Ser57-Val687

Tyr106-Gly381 Arg109-Tyr380 Arg109-Asp428 Asp56-Ala520 Lys54-Gln414 Lys54-Ala419 Arg55-Asn460 Tyr33-Asp427

Leu1244, Asn658, Tyr660, Trp1217, Glu702, Asn703, Phe1220, Gly1223, Ile1227, Ala1226, Val1230, Tyr111, Arg107, Asn108,

Tyr60, Asn58, Asp56, Tyr106, Val656, His655,

Ser686, Asp51, Pro56, Tyr50, Arg55.

Leu517, Thr430, Phe562, Lys424, Asp427, Pro463, Lys462, Asn394, Leu104, Tyr111, Tyr113, Asp116,

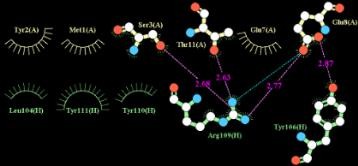
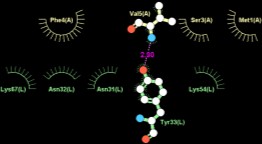
Ser32, Leu461, Lys462, Ser459,

Gly413, Tyr50, Pro56, Ser57, Gly58

-

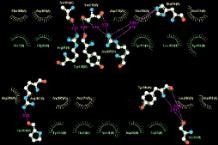
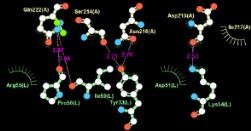
#### Arg109-Asp428 Lys54-Asp420 Asp51-Lys424

The interactions are visualized in Figure 4. Upper part is antigen, and the lower one is IgG. Hydrogen interactions are shown by colored lines and indicate the length of the bounds.

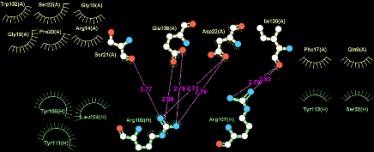
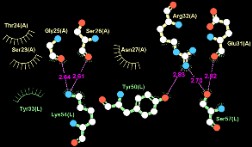
Inactivated virus (Envelope protein) – Heavy chain Inactivated virus (Envelope protein) – Light

chain

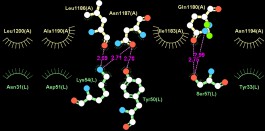
Inactivated virus (Membrane protein) – Heavy chain

Inactivated virus (Membrane protein) – Light chain

Inactivated virus (Nucleocapsid protein) – Heavy chain Inactivated virus (Nucleocapsid protein) –

Light chain

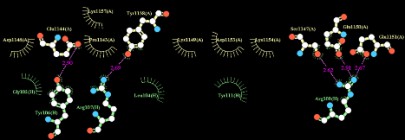
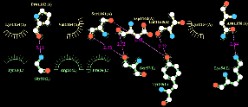
 

Inactivated virus (Spike glycoprotein) – Heavy chain Inactivated virus (Spike Glycoprotein) – Light

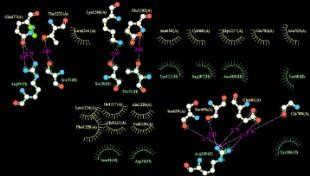
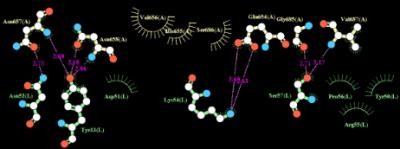
Chain

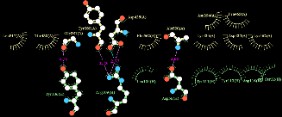
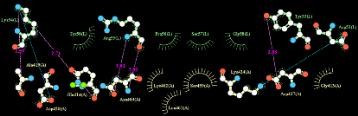
BNT162b2 – Heavy chain BNT162b2 – Light chain

mRNA-1273 – Heavy Chain mRNA-1273 – Light Chain

Ad26.COV2.S – Heavy Chain Ad26.COV2.S – Light Chain

NVX-CoV2373 – Heavy Chain NVX-CoV2373 – Light Chain



**Figure 4**. Interaction between Heavy and Light region of IgG with antigens

A recapitulation of the profile of interaction in each CDR region is given in **Table 5.** The number of CDR amino acid residues involved reflect the bound strength of IgG-antigen complex. It is a surprising fact that the membrane protein (M) obtained from the inactivated vaccine, has the highest number of interactions.

**Table 5** Profile of CDR – antigens interaction. E=envelope; M=membrane; N=nucleocapsid; S=spike glycoprotein

**CDR**

**Amino acids**

**Antigens**

**Inactivated virus BNT162b2 (S) mRNA-1273**

**Ad26.COV2.S**

**NVX-COV2373**

**residue**

CDRH1 Thr31

Ser32

Trp55

E M N S

**(S)**

**(S)**

**(S)**

CDRH2

CDRH3

CDRL1

CDRL2

Non- CDR

Asp56 Asn58 Tyr60 Tyr106 Arg109 Tyr111 Leu104 Arg107 Tyr113 Tyr110 Pro101 Gly102 Asn108 Asp116 Asn31 Asn32 Tyr33 Asp51 Asn52 Lys54 Arg55 Pro56 Ser57 Gln1 Gly26 Ser30 Thr31 Tyr50 Gly58 Ile59 Lys67 Arg99

: positive interaction

: no interaction

This finding is supported by the binding affinity (ΔG or Kd) values (Table-6). According to Vangone and Bonvin [17], the PRODIGY Webserver predicts binding affinities by using a model trained and reliable dataset of 81 protein- protein complexes, resulting an unprecedented accuracy (R = −0.73, ρ < 0.0001; RMSE = 1.89 kcal mol-1). In this study, membrane proteins provide the highest Gibbs-free energy (-14.3 kcal/mol) and the lowest complex dissociation rating (Kd =3.5 x 10-11 M). This shows that the IgG-protein membrane complex is most strongly bound and is directly proportional to the number of ICs (inter-residue contacts). By chemical perspective, this membrane protein is the first antigen to be bounded and then destroyed by IgG. Other antigens will be destroyed later according to their ΔG or Kd values. Nevertheless, our discoveries are hypothesis-generating and require experimental validation to be proven. However, referring to the classification of Kastritis (2011) [18], the affinity binding of all antigens, is relatively high. This means that other antigens are always potential to be used as a target for vaccine design. Nonetheless, this study didn’t perform Molecular Dynamics (MD) simulations as the limitation.

**Table 6** *Binding Affinity* of IgG-antigens complex

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Antigen** | | **IC (*Inter-Residue Con tact)*** | | |  | **ΔG**  **(kcal/mol)** | **Kd at 25 oC (M)** |
| **Charged- Charged** | **Charged-**  **Apolar** | **Polar- Polar** | **Polar- Apolar** |
|  | Envelope | 3 | 6 | 0 | 9 | -8,8 | 3,3x10-7 |
| Inactivated virus | Membrane | 6 | 22 | 3 | 29 | -14,3 | 3,5x10-11 |
| Nucleocapsid Phosphoprotein | 4 | 20 | 2 | 15 | -11,1 | 7,3x10-9 |
|  | Spike Glycoprotein | 5 | 23 | 3 | 10 | -10,3 | 2,8x10-8 |
| BNT162b2 (S) | | 9 | 33 | 2 | 5 | -10,7 | 1,5x10-8 |
| mRNA-1273 (S) | | 9 | 29 | 2 | 11 | -11,7 | 2,8x10-9 |
| Ad26.COV2.S (S) | | 7 | 25 | 5 | 23 | -13,3 | 1,7x10-10 |
| NVX-CoV2373 (S) | | 14 | 29 | 5 | 11 | -11,7 | 2,8x10-9 |

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This evidence can be used as a basis to explain the ineffectiveness of most Spike glycoprotein-based vaccines generally used, the membrane proteins located on the outside of the virus will also be recognized by antibodies, and will most likely be stored in the memory of B-cells. This is in accordance with the results of previous research, that the humoral response in patients affected by SARS-COV-2 infection is caused by spike glycoproteins, membrane proteins [19] and nucleocapsids [20].

# RECOMMENDATION

This is a preliminary study to see the effectiveness of the vaccine in terms of antibody-antigen complex interactions. The high binding affinity of membrane proteins provides an alternative reference to develop more effective vaccines. However, SARS-CoV-2 mutation need to be considered also and investigation on the binding- affinity values of each protein of circulating virus should be determined. Moreover, the future studies should incorporate MD to validate binding stability under physiological conditions.

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