Annex: Statement on the antigen composition of COVID-19 vaccines

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Annex 1: Evidence to support considerations of an update to COVID-19 vaccine antigen composition

The TAG-CO-VAC convenes a subgroup comprised of Members and Advisors with virological and immunological expertise. The TAG-CO-VAC and its subgroup has reviewed published and unpublished data on the antigenicity and cross-protection following infection and/or vaccination with currently approved or candidate vaccines in the context of currently circulating XBB.1 descendent lineages. The data highlighted below, while not exhaustive, were specifically reviewed and considered by the subgroup, as well as by the TAG-CO-VAC to inform the recommendations for COVID-19 vaccine composition update:

1. SARS-CoV-2 evolution, including genetic and antigenic characteristics of earlier and current SARS-CoV-2 variants, including XBB.1 descendent lineages, and its impact on cross-neutralization and cross-protection following vaccination and/or infection;

2. Vaccine effectiveness (VE) of currently approved vaccines during periods of XBB.1 descendent lineage circulation;

3. Antigenic cartography analyzing antigenic relationships of SARS-CoV-2 variants using naïve animal sera and human sera following vaccination and/or infection;

4. Preliminary preclinical data on immune responses in animal models, following infection with XBB.1 descendent lineages;

5. Preliminary preclinical immunogenicity data on the performance of candidate vaccines with updated antigens (data not shown); and

6. B cell memory responses following vaccination and/or infection.

1. SARS-CoV-2 evolution, including genetic and antigenic characteristics of earlier and current SARS-CoV-2 variants, including XBB.1 descendent lineages, and its impact on cross-neutralization and cross-protection following vaccination and/or infection

There continues to be substantial genetic and antigenic evolution in the virus (Figure 1).1 The spike proteins of XBB.1 descendent lineages, such as XBB.1.5, have more than 40 mutations (including substitutions, insertions and deletions) compared to the index virus. XBB.1 descendent lineages, including XBB.1.5 and XBB.1.16, are dominant globally (Figure 2) and exhibit a high degree of immune evasion, with XBB.1.5 being one of the SARS-CoV-2 variants with the greatest magnitude of immune escape to date.

Several studies, including the excerpted data below, demonstrate that sera from individuals who have received two, three or four doses of index virus-based vaccines, a booster dose of a bivalent (BA.1.1 or BA.4/5-containing) mRNA vaccine, or had breakthrough infection post vaccination show substantial reductions in neutralizing antibody titers against XBB.1 descendent lineages, as compared to titers specific for the antigens included in the vaccine (Figures 3-4).2,3 Individuals with hybrid immunity from any SARS-CoV-2 infection show higher neutralizing antibody titers against XBB.1 descendent lineages compared to responses from vaccinated individuals who had no evidence of infection. (Figure 5-6).2,4

Collectively, the published and unpublished data reviewed indicates that SARS-CoV-2 has evolved to escape humoral immunity induced by prior infection(s) and/or vaccination with currently approved COVID-19 vaccines and that the antigen composition of currently-approved vaccines may no longer elicit meaningful neutralization titers against currently circulating variants, including XBB.1 descendent lineages.
Figure 1. Simplified illustration of phylogenetic relationships of SARS-CoV-2 clades, as defined by Nextstrain

Figure 2: Number (top) and percentage (bottom) of SARS-CoV-2 sequences from 1 Oct 2022 – 16 April 2023. Analysis conducted by WHO using data extracted from GISAID.org on 1 May 2023. * indicates descendent lineages are included.
Figure 3: Neutralization titers of human sera following 1 (A), 2 (B), or 3 (C) doses of index-virus containing mRNA vaccines against 614G, Delta and several Omicron descendant lineages (x axis). Geometric mean is displayed above each graph. Dotted line indicates lower limit of detection. Trends in neutralizing titers per variant is depicted by connected lines for each individual serum.

Figure 4: Serum neutralization of Omicron descendant lineages BQ.1, BQ.1.1, XBB, and XBB.1. Neutralization of pseudotyped D614G and Omicron descendant lineages by sera from five different clinical cohorts. The limit of detection is 100 (dotted line). Error bars represent geometric mean ± geometric SD. Values above the symbols denote the geometric mean ID50 values, and values beneath the symbols denote the numbers of samples that lost neutralization activity. Values on the lower left show the sample size (n) for each group. The fold reduction in geometric mean ID50 value for each variant compared to D614G is also shown above the symbols. Comparisons were made by two-tailed Wilcoxon matched-pairs signed-rank tests. ***p < 0.001; ****p < 0.0001.
Figure 5: Neutralization profiles after boosting with a fourth dose of bivalent mRNA vaccines in individuals with (right) or without (left) evidence of prior infection. Plasma was collected from individuals that received three doses of an index-based monovalent mRNA vaccine followed by a fourth dose of a bivalent mRNA vaccine. Antibodies against SARS-CoV-2 nucleocapsid (N) were determined using ELISA and samples were grouped accordingly: fourth dose of index+BA.1 mRNA vaccine, without detectable N antibodies (BA.1 biv./N-), n=12; or with positive N ELISA (BA.1 biv./N+), n=5; fourth dose of index+BA.4/5 mRNA vaccine without detectable N antibodies (BA.4/5 biv./N-), n=16; or with positive N ELISA (BA.4/5 biv./N+), n=15. Titers of neutralizing antibodies against indicated variants are shown for individual patients as symbols connected by lines. Mean titers are shown as bars. Titers below 16 were treated as negative (dotted line) and titers below 1 were set to 1.

Figure 6: Pseudoneutralization profiles after boosting with a bivalent mRNA vaccine in individuals with (right) or without (left) evidence of prior infection. 50% fluorescent focus-reduction neutralization titers (FFRNT50) against omicron sublineages and WA-1/2020 were determined using human sera from BA.5 bivalent booster recipients with or without documented infection history. Bar heights and the numbers above indicate GMTs. Error bars indicate 95% confidence interval. The fold of GMT reduction against each Omicron sublineage, compared with the GMT against USA-WA1/2020, is shown in italic font. The dotted line indicates the limit of detection of FFRNT50. Statistical analyses were performed using the Wilcoxon matched-pairs signed-rank test for group comparison of GMTs.
2. Vaccine effectiveness of currently approved vaccines during periods of XBB.1 descendant lineage circulation

Estimates of VE against currently circulating SARS-CoV-2 variants, including XBB.1 descendant lineages, are very limited in terms of the number of studies, vaccine products evaluated, and populations assessed; some studies show similar VE against BA.5 descendant and XBB.1 descendant lineages, while others suggest reduced VE during periods of predominance of XBB.1 descendant lineages (Figure 7). Caution is needed in the interpretation of these findings as there may be differences in the characteristics of the vaccinated and comparator cohorts in terms of rates of infection, resulting in confounding through the infection-derived protection.

A recent study from Finland compared the risk of hospitalization and death due to COVID-19 in those who received a bivalent mRNA booster, as compared to those who did not receive a bivalent mRNA booster. The risks of hospitalization or death due to COVID-19 were found to be higher during a period of time during which XBB.1 descendant lineages circulated (Figure 8). However, in this ecological analysis of protection conferred by bivalent mRNA vaccines during a period of circulation of XBB.1 descendant lineages, other confounding factors may explain the observed increase in risk.

Figure 7. Estimates of relative vaccine effectiveness of a booster dose of any BA.1- or BA.4/5-containing mRNA vaccine (following three doses of index virus-based vaccine). Analysis conducted by WHO using data from published studies up to 10 May 2023.
Figure 8. Hazard ratios of hospitalization or death due to COVID-19 in adults who received bivalent mRNA vaccine as a booster dose in September – December 2022 (left) and January – March 2023 (right).

3. Antigenic cartography analyzing antigenic relationships of SARS-CoV-2 variants using naïve animal sera and human sera following vaccination and/or infection

Antigenic cartography using neutralizing antibody data from human convalescent sera (single infection, no vaccination) and sera from individuals who had received 2 doses of an index-virus based mRNA vaccine (BNT162b2, Pfizer/BioNTech) (Figure 9), as well as from hamsters inoculated using a variety of SARS-CoV-2 variants (Figure 10), demonstrates that Omicron-descendent lineages are very antigenically distant from the index virus (D614G) and pre-Omicron variants. Further, XBB.1-descendent lineages may be even further antigenically distinct from earlier Omicron descendent lineages, e.g. BA.1 or BA.5.
Figure 9: Antigenic map constructed from human single exposure and double vaccination sera. The antigenic map shows virus variants in colored circles and human sera as open squares in the color of their root variant, or grey for vaccine sera and light blue for CK.2.1.1 sera. Each grid in the map corresponds to one two-fold dilution of titers in the neutralization assay, making map distance a measure of antigenic similarity. Objects in the map are located relative to each other, x- and y-axis orientation is relative. Variants are labelled by Pango lineage and colloquial name. For recent variants, spike substitutions are listed in the upper right of the map.

Figure 10: Antigenic cartography of SARS-CoV-2 variants using hamster sera. Multidimensional scaling was used to generate an antigenic map from PRNT50 titres generated against 614G, Alpha, Beta, Gamma, Zeta, Delta, Delta AY.4.2, Lambda, Mu, Omicron BA.1, BA.2, BA.5, BQ.1.1, BM.1.1.1 and XBB.1. Viruses are shown as circles and anti-sera as squares of matching colour. All generated antisera are displayed; against all viruses except Delta AY.4.2, Lambda, Omicron BA.2, BQ.1.1, BM.1.1.1 and XBB.1. Distances between viruses and antisera in the map are inversely related to PRNT50 titres with minimized error. The grid represents two-fold dilutions in titrations. PRNT50 = plaque reduction neutralization titre resulting in 50% plaque reduction.

4. Preliminary preclinical data on immune responses in animal models, following infection with XBB.1 descendent lineages and preliminary preclinical immunogenicity data on the performance of candidate vaccines with updated antigens

Limited preclinical data in hamsters show that infection of naïve animals with XBB descendent lineages induces higher titers to the homologous variant (Figure 11); these results are early post infection and it is likely the breadth of the response could expand overtime and would be increased in previously SARS-CoV-2 exposed individuals.

Further, preclinical data assessing vaccine candidates with an updated composition that include an XBB.1 descendent lineage across different platforms demonstrate that greater neutralizing antibody responses
to currently circulating SARS-CoV-2 variants, including XBB descendent lineages, are elicited compared to those following vaccination with index virus-based or earlier Omicron lineage-containing (i.e. BA.1 or BA.5) vaccines (confidential, data not shown).

Collectively, the data available to date indicate that inclusion of an XBB.1 descendent lineage in updated vaccines may enhance neutralizing antibody responses to circulating SARS-CoV-2 variants.

Figure 11: Pseudovirus neutralization assays using sera from hamsters (n=6) that had been infected with XBB.1 (left) or XBB (right). Each dot indicates the result of an individual replicate. Assays for each serum sample were performed in triplicate to determine the 50% neutralization titer (NT50). Each dot represents one NT50 value, and the geometric mean and 95% confidence interval are shown. The number in parenthesis indicates the geometric mean of NT50 values. The horizontal dashed line indicates the detection limit (120-fold).

5. B cell memory responses following vaccination and/or infection

B cell memory responses following vaccination and/or infection

Several studies, including the excerpted data below, have examined plasma neutralizing antibody titers in animal models and human sera in the context of repeated antigen exposure. As shown below in Figure 12, in individuals who had a breakthrough infection (BTI) following vaccination with Coronavac, plasma neutralizing titers to the corresponding variant were lower than those to the vaccine antigen (i.e. 614G). Compared to one-time BTIs, repeated Omicron infection led to an increase in the neutralizing titers of the corresponding variant as well as other related, earlier Omicron-descendent lineages. However, the neutralizing antibody titers of the vaccination-naïve reinfection group (far right, top) against Omicron variants were the highest among these cohorts. Collectively, these data illustrate that memory B cell responses, specific against 614G were recalled to a greater extent than the initial formation of novel Omicron-specific B cell responses, which is indicative of immune imprinting. Finally, in the reinfection cohort (bottom panels), relatively broad neutralizing antibody responses were detected, including to XBB descendent lineages, indicating that repeated antigen exposure may broaden the breadth of antibody responses. These observations and other similar data are informative when considering vaccine antigen composition.
Figure 12: Plasma neutralizing titers in convalescent human sera following Omicron infection in previously vaccinated and unvaccinated individuals.

Pseudoneutralization antibody titers in plasma. Fold changes between titers against variants and D614G were calculated and shown above the line. Statistical significance was determined using the Wilcoxon signed-rank test. BA.1, BA.2, BA.5, BF.7 BTI: post-vaccination Omicron breakthrough infection (BTI). BA.1, BA.2 BTI+ BA.5/BF.7 infection: post-vaccination Omicron breakthrough infection followed by BA.5/BF.7 reinfection. BA.1/BA.2+ BA.5/BF.7 infection: BA.1/BA.2 infection followed by BA.5/BF.7 reinfection with no vaccination history. Blood samples were collected 1-2 months after the last infection. Dashed lines indicate the limit of detection (LOD, NT50 = 20). *p < 0.05, **p < 0.01, ***p<0.001, ****p<0.0001, and not significant (NS) p > 0.05. All neutralization assays were conducted in at least two independent experiments.
Annex 2: Questions and answers related to the update to COVID-19 vaccine antigen composition

1. Should the index virus continue to be included in any new vaccine antigen formulations?

While currently approved COVID-19 vaccines, including those based on the index virus, continue to provide protection against severe disease, the TAG-CO-VAC advises moving away from the inclusion of the index virus in future formulations of COVID-19 vaccines. This is based on the following reasons: the index virus and antigenically closely related variants no longer circulate in humans; the index antigen elicits undetectable or very low levels of neutralizing antibodies against currently circulating SARS-CoV-2 variants; inclusion of the index virus in bi- or multivalent vaccines reduces the concentration of the new target antigen(s); and imprinting may reduce immune responses to new target antigen(s).

2. Should index virus-based vaccines continue to be used?

Yes. The TAG-CO-VAC recognizes and reiterates that currently approved COVID-19 vaccines, including those based on the index virus, continue to provide substantial protection against severe disease and death, which is the primary objective for COVID-19 vaccination. Currently approved COVID-19 vaccines should continue to be used in accordance with the current WHO SAGE Roadmap, published in March 2023.

Notwithstanding the protection against severe disease, protection against symptomatic disease is limited and less durable. New formulations of COVID-19 vaccines are needed to improve protection against symptomatic disease.

The development and production of COVID-19 vaccines with updated antigen composition requires time. Therefore, until vaccines with updated antigen composition are authorized and available, the best vaccine-induced protection against COVID-19 will be achieved by continued use of currently approved vaccines in accordance with the current SAGE Roadmap, accompanied by the practice of public health and social measures.

3. Why is TAG-CO-VAC recommending an update to the vaccine antigen composition?

The TAG-CO-VAC recognizes that currently approved COVID-19 vaccines, including those based on the index virus, provide protection against severe disease and death. Protection against symptomatic disease is limited and less durable for currently approved COVID-19 vaccines. Therefore, new formulations of COVID-19 vaccines should induce antibody responses that neutralize XBB descendent lineages, which is likely to be rapidly achieved through updates to the vaccine antigen composition.

4. Does the recommendation apply to all vaccine platforms?

Yes, the recommendation applies to all vaccine manufacturers considering update(s) to the antigen composition of any COVID-19 vaccine in their portfolio. The TAG-CO-VAC proposes that one approach to enhance vaccine-induced immune responses to circulating SARS-CoV-2 variants is through the use of a monovalent XBB.1 descendent lineage, such as XBB.1.5 as the vaccine antigen. However, this does not preclude the consideration by regulatory authorities of other formulations and/or platforms that demonstrate robust neutralizing antibody responses against XBB descendent lineages.
5. Why does the objective of an update to vaccine antigen composition focus on neutralizing antibody responses?

Neutralizing antibodies are antibodies that directly block infection of host cells and they are potent inhibitors of infection and subsequent disease. Most of the evolutionary changes in SARS-CoV-2, the virus that causes COVID-19, have occurred in the viral surface glycoprotein known as spike (S) and these are in sites (i.e., epitopes) targeted by neutralizing antibodies. Over the course of the pandemic the most successful variant lineages have evolved to escape these neutralizing antibodies. For example, many of the more than 40 amino acid substitutions, insertions or deletions between the spike glycoproteins of the index virus and current predominant variant XBB.1.5 are in neutralizing epitopes. While there are multiple layers of immune protection elicited by infection and/or vaccination, antibody neutralization titers have been shown to be important in protection from SARS-CoV-2 infection and in vaccine effectiveness.15-18

6. Will TAG-CO-VAC regularly recommend updates to vaccine antigen composition?

The TAG-CO-VAC will continue to meet regularly to assess the evidence to inform COVID-19 vaccine antigen composition updates. To this end, the TAG-CO-VAC plans to meet twice in 2023: the first meeting was from 11-12 May 2023 and a second meeting is planned for the second half of 2023, approximately 6 months after the first meeting. At each meeting the genetic and antigenic evolution of SARS-CoV-2 variants, the performance of vaccine products against circulating SARS-CoV-2 variants and the implications for COVID-19 vaccine antigen composition will be assessed. Based on this assessment, recommendations to either maintain current vaccine composition or to consider updates will be issued. This frequency of the evidence review by TAG-CO-VAC has been proposed given the kinetics of vaccine-derived immunity and the need for continued monitoring of the evolution of SARS-CoV-2, and will be adjusted if and as necessary.
References


