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

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Evidence to support considerations of COVID-19 vaccine antigen composition

The data highlighted below, while not exhaustive, were specifically reviewed and considered by the TAG-CO-VAC to inform the recommendation on COVID-19 vaccine composition: (1) SARS-CoV-2 evolution, including genetic and antigenic characteristics of earlier and current SARS-CoV-2 variants, and the impact of SARS-CoV-2 evolution on cross-neutralization and cross-protection following vaccination and/or infection; (2) Vaccine effectiveness (VE) of currently approved vaccines during periods of XBB 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 immunogenicity data on the performance of currently approved vaccines against circulating SARS-CoV-2 variants using animal and human sera; and (5) Cellular (T and B cell) immune responses following vaccination and/or infection. The TAG-CO-VAC convenes a Subgroup comprised of Members and Advisors with virological and immunological expertise. The data highlighted below were also reviewed and considered by the Subgroup. Unpublished and/or confidential data reviewed by the TAG-CO-VAC and the Subgroup are not shown.

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

SARS-CoV-2 continues to circulate and evolve and there continues to be important genetic and antigenic evolution of the spike protein of SARS-CoV-2 (Figure 1).1

XBB descendent lineages, including XBB.1.5, XBB.1.16, EG.5, HK.3 and HV.1, are dominant globally (Figure 2).2 A SARS-CoV-2 variant of interest BA.2.86 with the earliest sample collected in July 2023 has 36 amino acid substitutions relative to XBB.1.5 (Figure 3).3 The proportion of BA.2.86 and its descendent lineages, including JN.1, among available sequences has been increasing steadily (Figure 2).2

Several studies, including the excerpted data below, demonstrate that sera from individuals who have received three or four doses of index virus-based vaccines or a booster dose of a bivalent (BA.1- or BA.4/5-containing) mRNA vaccine show lower neutralizing antibody titers against XBB descendent lineages and BA.2.86, as compared to titers against the antigens included in the vaccine (Figures 4).4 In contrast, sera from humans infected with an XBB descendent variant or vaccinated with a XBB.1.5 monovalent vaccine, neutralized XBB descendent lineages including EG.5, HK.3, HV.1, as well as BA.2.86 and JN.1 (Figure 4-6).4,5,6 Individuals with hybrid immunity, defined here as a recent infection, followed by XBB.1.5 monovalent vaccine, show higher geometric mean neutralizing antibody titers against XBB descendent lineages as compared to responses from individuals vaccinated with XBB.1.5 monovalent vaccine without recent infection (Figure 6).6

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. Nonetheless, the XBB.1.5 monovalent vaccines elicit broadly cross-reactive neutralizing antibody responses against XBB descendent lineages including EG.5, HK.3, HV.1, as well as BA.2.86 and JN.1.
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 April 2023 – October 2023. Analysis conducted by WHO using data extracted from GISAID.org on 31 October 2023. * indicates descendent lineages are included.  

Figure 3: Mutations on the spike glycoprotein of BA.2, XBB.1.5 and BA.2.86. Mutations are indicated in purple; absence of mutations is indicated in sky blue. The short grey lines indicate mutations at the same sites.
Figure 4: Neutralization titers of human sera following vaccination (F-I) or breakthrough infection (K) (F: 3rd-dose index virus-based monovalent vaccine sera; G: 4th-dose index virus-based monovalent vaccine sera; H: BA.1 bivalent vaccine; I: BA.5 bivalent vaccine; K: XBB breakthrough infection.

Post-vaccination sera were collected 1 month after the last vaccination. Assays were performed with pseudoviruses harboring the S proteins of B.1.1, BA.2, EG.5.1, or BA.2.86. 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 (40-fold).

Figure 5: Serum neutralization of XBB.1.5, EG.5.1, HV.1, JD.1.1 BA.2.86 and JN.1 in individuals who received three doses of CoronaVac inactivated vaccine and had breakthrough infection (BTI) with BA.5 or BF.7 followed by XBB infection.

Labels for geometric mean titers (GMT) are located above each group, with the fold changes and statistical significances indicated above the GMT labels. Below the dashed line are labels specifying the numbers of negative samples which are related to the limit of detection (NT50=20). Two-tailed Wilcoxon signed-rank tests of paired 200 samples were used. *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001.
Figure 6: Timeline of vaccine administration, SARS-CoV-2 infection, and serum collection for each cohort (a); and serum neutralization of D614G, BA.5, XBB.1.5, EG.5.1, HV.1, HK.3, JD.1.1 and JN.1 in recipients of XBB.1.5 monovalent vaccine (b); XBB.1.5 infection (c); and pre-XBB Omicron infection + XBB.1.5 monovalent vaccine (d). Fold changes in ID$_{50}$ titers of the indicated cohorts against D614G, BA.5, XBB.1.5, EG.5.1, HV.1, HK.3, JD.1.1 and JN.1 between pre and post vaccination or infection. Geometric mean fold changes in ID$_{50}$ titer are shown as black bars and denoted above the dots. Statistical analyses were performed by employing Wilcoxon matched-pairs signed-rank tests.6

2. Vaccine effectiveness of currently approved vaccines during periods of XBB descendent lineage circulation

Estimates of VE against currently circulating SARS-CoV-2 variants, including XBB descendent lineages, are limited in terms of the number of studies, vaccine platforms evaluated, populations assessed, duration of follow-up and comparative estimates for monovalent XBB.1.5 vaccines versus other formulations.

Figure 7 shows that additional protection conferred by bivalent (index virus and BA.1 or BA.4/5) mRNA boosters and a Beta-based protein booster within four months against severe disease during periods of XBB descendent lineage circulation remains high (Figure 7). VE against symptomatic disease is slightly lower than against severe disease and there is either no or low additional protection against infection during periods of XBB descendent lineage circulation.7-15 Protection wanes to some degree over time against severe disease and symptomatic disease, although waning is more rapid for symptomatic disease.13,16-17 Caution is needed in the interpretation of these findings as Figure 7 shows estimates of relative VE which compare a more vaccinated population to a less vaccinated population. Further, the comparator group varies across studies. There may also be differences in rates of infection between vaccinated and comparator groups, resulting in confounding through the infection-derived protection, which would tend to result in spuriously lower VE estimates.

Monovalent XBB.1.5 vaccines were recently introduced. Currently, there is only one study that has estimated real-world protection conferred by monovalent XBB.1.5 vaccine soon after vaccination. The study was conducted in Denmark among individuals over 65 years who received a booster dose with a
monovalent XBB.1.5 vaccine as compared to previously vaccinated individuals over 65 years who did not receive a booster dose of a monovalent XBB.1.5 vaccine. Those who had received a booster dose of a monovalent XBB.1.5 vaccine had a lower risk of being hospitalized for COVID-19 after vaccination than those who had received a BA.1 or BA.4/5 bivalent mRNA booster dose, but not a monovalent XBB.1.5 booster dose (HR=0.25, 95% CI: 0.16-0.39). However, this study only followed the XBB.1.5 monovalent vaccinees for an average of 10 days post-vaccination and a lower risk of being hospitalized for COVID-19 was also seen for a non-COVID-19 control outcome (HR 0.84, 95% CI 0.79-0.92), suggesting some bias in the study.

Figure 7. Estimates of relative vaccine effectiveness within four months of a booster dose of an index virus-based mRNA vaccine, bivalent (BA.1- or BA.4/5- containing) mRNA vaccine, or Beta-based protein vaccine in individuals who had received three, four or five doses of index virus-based vaccines or a booster dose of a bivalent (BA.1- or BA.4/5- containing) mRNA vaccine during periods of XBB descendent lineage circulation. Analysis conducted by WHO using data from published studies up to 30 November 2023.

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 naïve hamsters infected with different SARS-CoV-2 variants (confidential, data not shown), as well as mice immunized with an in-house spike mRNA vaccine demonstrates that XBB.1.5 and derived variants cluster antigenically and are distinct from earlier
Omicron variants. BA.2.86 is antigenically distant from XBB.1.5-derived variants and earlier Omicron variants.

![Antigenic cartography on pseudovirus neutralisation titres of naïve mice immunized by spike mRNA various SARS-CoV-2 variants](image)

*Figure 8:* Antigenic cartography on pseudovirus neutralisation titres of naïve mice immunized by spike mRNA various SARS-CoV-2 variants. Antigens are denoted as coloured circles whereas plasma are shown as squares with the outlines coloured by the corresponding antigens. The distances between plasma and an antigen are negatively correlated to the neutralisation ability.

4. **Preliminary immunogenicity data on the performance of currently approved vaccines against circulating SARS-CoV-2 variants using animal and human sera**

Preliminary clinical data demonstrate that sera from individuals vaccinated with XBB.1.5 monovalent vaccines elicit broadly cross-reactive neutralizing antibody responses against XBB descendent lineages including EG.5.1, as well as BA.2.86 (Figure 9) and JN.1 (confidential, data not shown). In contrast, sera from individuals vaccinated with bivalent BA.4/5 mRNA elicited reduced neutralizing antibody responses against BA.2.86 (confidential, data not shown).

Collectively, the available data indicate that XBB.1.5 monovalent vaccines elicit neutralizing antibody responses to currently circulating SARS-CoV-2 variants.
**Figure 9**: Neutralizing antibody titers pre-booster and day 15 post-booster dose against ancestral SARS-CoV-2 (D614G) and BA.4/BA.5, XBB.1.5, XBB.1.16, XBB.2.3.2, EG.5.1, FL.1.5.1 and BA.2.86 variants in individuals who received XBB.1.5-containing monovalent (mRNA-1273.8135) using a research grade VSV-based pseudovirus assay. **p < 0.01 and ****p<0.0001 by the Wilcoxon t-test. Dotted line denotes the limit of detection of the assay. 19
References


