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

26 April 2024

Evidence to support considerations of COVID-19 vaccine antigen composition

The data highlighted below are representative examples of the data reviewed and considered by the TAG-CO-VAC to inform the recommendation on COVID-19 vaccine composition and include: (1) SARS-CoV-2 genetic evolution; (2) Antigenic characterization of previous and emerging SARS-CoV-2 variants using virus neutralization tests with animal antisera or human sera and further analysis of antigenic relationships using antigenic cartography; (3) Immunogenicity data on the breadth of neutralizing antibody responses elicited by currently approved vaccine antigens against circulating SARS-CoV-2 variants using animal and human sera, including modelling data; (4) Vaccine effectiveness estimates (VE) of currently approved vaccines during periods of circulation of XBB.1 and JN.1 lineages; (5) Preliminary immunogenicity data on immune responses following infection with circulating SARS-CoV-2 variants; and (6) Preliminary preclinical and clinical immunogenicity data on the performance of candidate vaccines with updated antigens shared confidentially by vaccine manufacturers with TAG-CO-VAC (data not shown).

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 Unpublished and/or confidential data reviewed by the TAG-CO-VAC and the Subgroup are not shown.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 genetic evolution

SARS-CoV-2 has undergone sustained evolution since its emergence in humans.

*Figure 1.* Phylogeny of SARS-CoV-2 variants since its introduction in humans illustrated using Nextstrain.¹

The number of mutations is shown on the X axis and various clades labeled as Nextclade (Pango lineage) at the branches. Clades that included vaccine antigens are indicated with the date of the TAG-CO-VAC recommendation for this vaccine antigen composition.
Genetically closely related but distinguishable clades such as 20I (Alpha) and 21A (Delta) (Figure 1, purple and blue respectively) represented early clades that were also associated with epidemics and these clades displaced previously circulating clades. The first Omicron lineage clades (e.g., 21K (BA.1) and 21L (BA.2) were genetically very divergent from the progenitor as indicated by the long branch lengths (Figure 1), and they rapidly displaced the 21J (Delta) clade.

All SARS-CoV-2 variants circulating in humans over the last six months are derived from 21L (BA.2) (Figure 2). The 22F (XBB) and 23I (BA.2.86) represent genetically related (i.e., both are derived from BA.2) but evolutionary distinct clades (Figure 2). The earliest 23I (BA.2.86) sample collection was in July 2023, with 34 amino acid substitutions relative to BA.2 and 36 substitutions relative to 23A (XBB.1.5). JN.1 is a descendent lineage of BA.2.86, with 1 additional change in the spike (L455S). Since the emergence of JN.1 many variants that fall within this clade have evolved additional changes in the spike protein within epitopes known to be targeted by neutralizing antibodies (e.g., R346T in BQ.1 and XBB; R346T+F456L in EG.5). This highlights the fitness advantages conferred by these changes in the human population. These advantages may be due to many factors including improved replication, receptor interactions, and/or immune evasion.

Figure 2. Phylogeny of SARS-CoV-2 virus genomes from samples collected over the last six months highlighting parallel evolution at specific positions.\(^1\)

Sequences encoding specific residues at positions 346/456 are coloured differently (see legend). Sequences in orange encode R346T+F456L and arrows indicate subclades where this combination has evolved independently.
At the time of the last TAG-CO-VAC COVID-19 vaccine antigen composition recommendation in December 2023, the proportion of JN.1 genetic sequences was low but increasing.² As of April 2024, nearly all (>94%) SARS-CoV-2 genetic sequences in publicly available databases fall within JN.1 clade (Figure 3). JN.1 clade variants continue to displace existing XBB clade variants (e.g. EG.5, HK.3) in all four WHO regions with consistent sharing of SARS-CoV-2 sequences (Western Pacific region, South East Asia region, European region and the region of the Americas).³ This displacement indicates greater fitness of JN.1 derived variants as compared to other circulating SARS-CoV-2 variants in the human population.⁴

A. Proportion of SARS-CoV-2 sequences

![Proportion of SARS-CoV-2 sequences](image)

B. Number of SARS-CoV-2 sequences

![Number of SARS-CoV-2 sequences](image)

Figure 3. Proportion (A) and number (B) of SARS-CoV-2 sequences from January 2024 – March 2024⁵

Figure produced by WHO based on SARS-CoV-2 sequence data and metadata from GISAID, from 5 February to 3 March 2024 (as of 20 April 2024). The variants shown here include descendent lineages, except for the descendent lineage(s) listed here. The Unassigned category includes lineages pending for a PANGO lineage name designation, whereas the Other category includes lineages that are assigned but not listed here.
SARS-CoV-2 continues evolve. There are genetic changes in important regions of the spike protein of JN.1 as compared to XBB.1.5. A comparison of SARS-CoV-2 spike glycoproteins of XBB.1.5 with JN.1 illustrates many substitutions in the receptor binding domain (RBD), a target of potent neutralizing antibodies, and the N-terminal domain (NTD) which is also bound by neutralizing antibodies (Figure 4).

Figure 4. Schrodinger homology model of JN.1, using 7YR2 (BA.2.75) structure.
Source U.S. CDC: M. Aggarwal, C. Paden, D. Wentworth

2. Antigenic characterization of previous and emerging SARS-CoV-2 variants using virus neutralization tests with animal antisera or human sera and further analysis of antigenic relationships using antigenic cartography

Multiple studies illustrate that representative XBB.1 lineage variants are antigenically closely related and cluster together with XBB.1.5 (Figures 5 and 6).\(^5\) The data also indicate representative JN.1 variants (Figures 5 and 6) are antigenically distant from XBB lineage variants and from a distinct antigenic cluster.\(^5\)
Figure 5. Antigenic cartography of mouse sera immunized by 2-dose 10µg spike mRNA vaccine. Each square indicates a plasma sample and each circle indicates a SARS-CoV-2 variant.
Figure 6. Antigenic cartography using human sera from single-exposure cohorts (A) or cohorts with index virus vaccine immunization (B). Each square indicates a plasma sample and each circle indicates a SARS-CoV-2 variant.
3. **Immunogenicity data on the breadth of neutralizing antibody responses elicited by currently approved vaccine antigens against circulating SARS-CoV-2 variants using animal and human sera, including modelling data.**

Published and unpublished data on sera from non-naïve animals and humans after XBB.1.5 immunization with or without recent prior infection, neutralize representative pre-Omicron and early Omicron variants (Figure 8). Post XBB.1.5 immunization sera neutralize XBB.1.5 and its derivatives, including EG.5, HK.3, HV.1, as well as BA.2.86 and JN.1. In a cohort of recipients of a fifth COVID-19 vaccine, the monovalent XBB.1.5 mRNA vaccine elicited higher neutralizing antibody titres against JN.1 than the bivalent (index virus + BA.4/5) mRNA vaccine (Figure 7). However, population immunity against JN.1 was ~2-4-fold lower than against the homologous XBB.1.5 immunizing antigen across different studies (Figures 8 and 9).6,8

![Figure 7](image_url)

*Figure 7. (A) Comparison of neutralization titres against SARS-CoV-2 variants in human sera who received either bivalent (index virus + BA.4/5) mRNA (top row) or monovalent XBB.1.5 mRNA vaccine (bottom row) as a fifth dose against SARS-CoV-2 index virus, BA.2.86, and JN.1. (B) Stratification of neutralizing antibody titres by pre-vaccination (top row) and post-vaccination (bottom row). P values shown are from unpaired, two-tailed Wilcoxon tests, or McNemar’s χ² tests if the median of one group was more or less than the quantitative range of the assay (40–2560). FC = fold change increase of neutralizing antibody titres with 95% CIs in brackets. IC₅₀ = 50% inhibitory concentration.*
Figure 8. Comparison of neutralization titres against SARS-CoV-2 variants in human sera collected pre- and post-XBB.1.5 vaccination and/or infection from participants in the United States of America. Geometric mean titres and 95% confidence intervals are shown. Numbers indicate fold change between sera pre- and post-vaccination.
Figure 9. Comparison of neutralization titres to SARS-CoV-2 variants, Germany, September 2023 (n = 39) with recent studies assessing geometric mean titres and fold change measured in different studies, including those using pseudoviruses, that presented titrations of BA.2.86 and/or JN.1.8
There are further subtle reductions in neutralization titres of JN.1 variants with F456L and/or R346T substitutions when compared to neutralization titers of XBB.1.5 (Figure 10).  

Figure 10. (A) Schematic of the SARS-CoV-2-related immune histories of the seven cohorts involved in this study. (B-D) 50% neutralization titers (NT50) of plasma samples from seven different cohorts against SARS-CoV-2 variant pseudoviruses.  

Plasma source cohorts and corresponding number of samples are labeled above each panel. Dashed line indicates limit of detection (NT50 = 10). Numbers of negative samples are labeled below the dashed lines. Geometric mean titers (GMT) values are labeled as black bars and shown above each group of points, with fold-changes and significance compared to JN.1 labeled. Wilcoxon signed-rank tests are used to calculate the p-values. Wilcoxon rank-sum tests are used to determine p-values. *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; NS, not significant.

Secondary analysis of published immunogenicity data demonstrates that an additional vaccine dose with an updated vaccine antigen results in a greater increase in neutralizing antibodies against a future variant as compared to an additional dose of the same vaccine with a previous antigen composition (Figure 11). Using immunogenicity data from approximately 30 published studies and statistical modeling, the predicted additional effectiveness of an additional vaccine dose with an updated vaccine antigen may be about 23-33% against severe disease as compared to other vaccine antigen compositions and 11-25% against symptomatic disease. The data also demonstrate that if the vaccine antigen composition was not updated at all, the relative benefit of further doses with the same composition would become progressively smaller against future variants, resulting in vaccines becoming less effective.
Figure 11. Fold rise in neutralisation titres to the XBB lineage variants after boosting with vaccines containing different booster immunogens. Small numbers show the geometric mean of the fold rises for each immunogen. Comparisons across the top show p-values from unpaired t-tests.
4. Vaccine effectiveness (VE) of currently approved vaccines during periods of XBB descendent lineage and JN.1 descendent lineage circulation

In a context of high infection- and vaccine-derived immunity in the population, contemporary vaccine effectiveness (VE) estimates are mostly relative (rVE), rather than absolute (comparing vaccinated to unvaccinated individuals), and demonstrate the added protection of a vaccine over and above pre-existing infection- and vaccine-derived immunity. Estimates of rVE against currently circulating SARS-CoV-2 variants, including XBB or JN.1 descendent subclades, are limited in terms of the number of studies, geographic diversity, vaccine platforms evaluated, populations assessed, duration of follow-up, and comparative estimates for monovalent XBB.1.5 vaccines versus other formulations delivered at the same time.

Bivalent (index virus and BA.1 or BA.4/5) mRNA boosters and a Beta variant-based protein booster continue to offer protection against severe disease within three months since vaccination during periods of XBB descendent lineage circulation (Figure 12).11-24 rVE against symptomatic disease and infection is lower than against severe disease and wanes more rapidly over several months.13,14,20,22,24,25

Initial rVE estimates of monovalent XBB.1.5 vaccines during periods of JN.1 descendent lineage circulation are lower against all outcomes, as compared to periods of XBB.1 lineage variant circulation, although confidence intervals overlap (Figure 13).21,24,26,27 These observations are consistent with reductions in neutralizing antibody titres observed in preclinical and clinical immunogenicity studies of monovalent XBB.1.5 vaccinee sera against JN.1 derived variants (described above).

Caution is needed in the interpretation of these findings (e.g., Figures 12 and 13) which are estimates of rVE that 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 differential infection-derived protection between groups, which would tend to result in spuriously lower rVE estimates. When comparing rVE estimates during periods of different SARS-CoV-2 variant circulation, there may also be differences in time since vaccination.
Figure 12. Estimates of relative vaccine effectiveness (rVE) within three 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.13-25

The top panel shows rVE estimates against hospitalisation and severe disease; the middle panels show rVE estimates against symptomatic disease and the bottom panel shows rVE estimates against infection. Analysis conducted by WHO using data from published studies up to 11 April 2024. In the bottom panel, the study in Singapore had a rVE estimate: -24% (95%CI: -35;-15).13
Figure 13. Estimates of relative vaccine effectiveness (rVE) within three months of a dose of a bivalent (BA.4/5-containing) or a monovalent XBB.1.5 mRNA vaccine during periods of JN.1 or XBB.1 descendent lineage circulation.\textsuperscript{19,24,26,27}

The top panel shows rVE estimates against hospitalisation and severe disease; the middle panels show rVE estimates against symptomatic disease and the bottom panel shows rVE estimates against infection. Analysis conducted by WHO using data from published studies up to 11 April 2024.
References


