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

23 December 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 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; (4) Preliminary immunogenicity data on immune responses following infection with circulating SARS-CoV-2 variants; (5) Available vaccine effectiveness (VE) estimates of currently approved vaccines during periods of circulation of XBB.1 and JN.1 lineages; 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 Unpublished and/or confidential data reviewed by the TAG-CO-VAC and the Subgroup are not shown.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 continues to undergo sustained evolution since its emergence in humans, with important genetic and antigenic evolution of the spike protein.

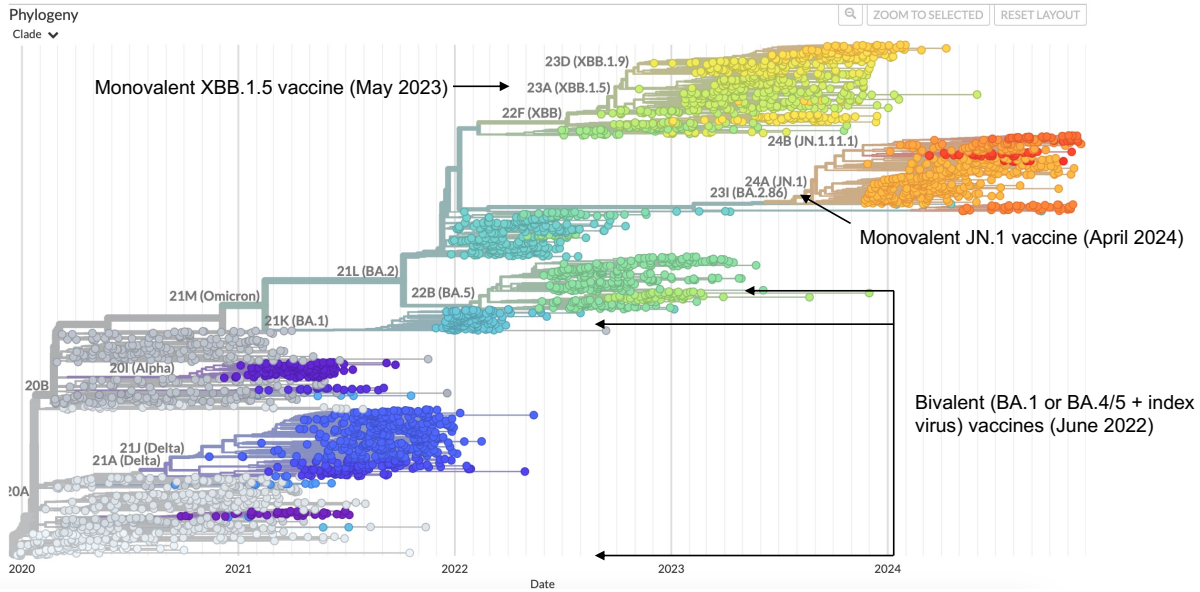

Figure 1: Phylogeny of SARS-CoV-2 variants since its introduction in humans illustrated using Nextsrain.[1]
The year is shown on the X axis and various clades labeled as Nextclade (Pango lineage) at the branches. Clades that included vaccine antigens are indicated with the date of the TAG-CO-VAC recommendation 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, and they rapidly displaced the 21J (Delta) clade.

All SARS-CoV-2 variants circulating in humans over the last six months are derived from 24A (JN.1). There is continued evolution from JN.1, with many variants within this clade having combinations of changes in the spike protein at epitopes targeted by neutralizing antibodies (e.g. F456L + R346T in KP.2; F456L + Q493E in KP.3; F456L + Q493E+ 31del in KP.3.1.1; F456L + R346T + Q183H + 31del in LB.1). These changes highlight the potential fitness advantages they confer in the human population.

XEC is a recombinant of KS.1.1 and KP.3.3.[2] It contains 10 nucleotide mutations/ 7 amino acid mutations relative to JN.1 of which 5 are nonsynonymous spike mutations compared to JN.1 (Figure 2).[3]

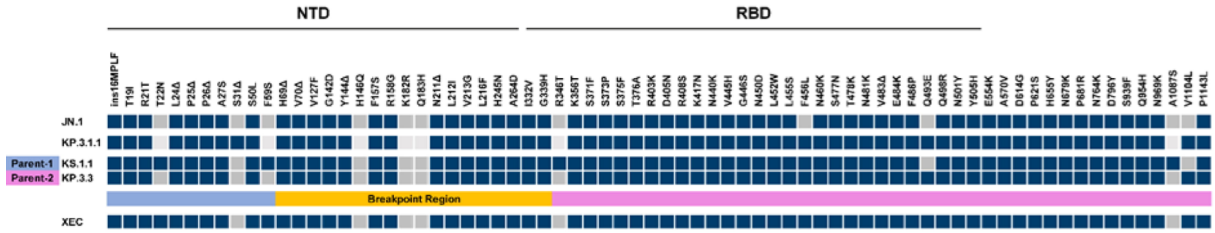

Figure 2: Schematic overview of the mutations found in the spike protein of the indicated sublineages (in comparison to the S protein of SARS-CoV-2 Wuhan-Hu-01).[3]
Parental lineages (KS.1.1 and KP.3.3) of the recombinant XEC lineage are indicated and the breakpoint region is highlighted in yellow. NTD = N-terminal domain; RBD = receptor-binding domain.

At the time of the previous COVID-19 vaccine antigen composition recommendation from TAG-CO-VAC in April 2024, nearly all (>94%) SARS-CoV-2 genetic sequences in publicly available databases were within the JN.1 clade. As of December 2024, no single variant has emerged as clearly displacing all other variants (Figure 3). However, the weekly proportion of XEC sequences among all SARS-CoV-2 sequences submitted to GISAID continues to increase, while the weekly proportions of all other Variants of Interest (JN.1) or Variants Under Monitoring (KP.2, KP.3, KP.3.1.1, JN.1.18 and LB.1) are now declining. The full list of Variants of Interest or Variants Under Monitoring is available on the WHO website.[3] This displacement of other variants by XEC indicates its greater fitness as compared to other currently circulating SARS-CoV-2 variants in the human population.

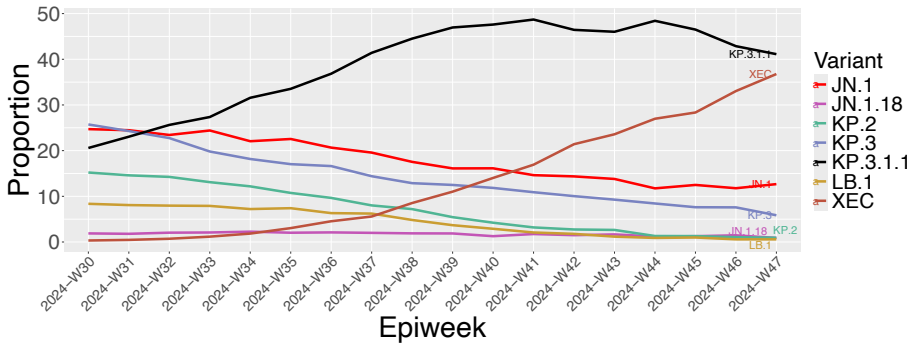

Figure 3: Proportion of SARS-CoV-2 sequences from July 2024 – December 2024.
Figure produced by WHO based on SARS-CoV-2 sequence data and metadata from GISAID, extracted on 7 December 2024. The variants shown here include descendent lineages, except those individually specified.

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

Published and unpublished data on sera from naïve mice immunized with mRNA vaccine antigens derived from JN.1 showed increased neutralizing antibody titers to JN.1 descendent variants, including JN.1, JN.1.16.1, KP.2, KP.2.3, KP.3, KP.3.1.1, LB.1 and XEC (Figure 4). These data indicate that these descendent variants are antigenically closely related.

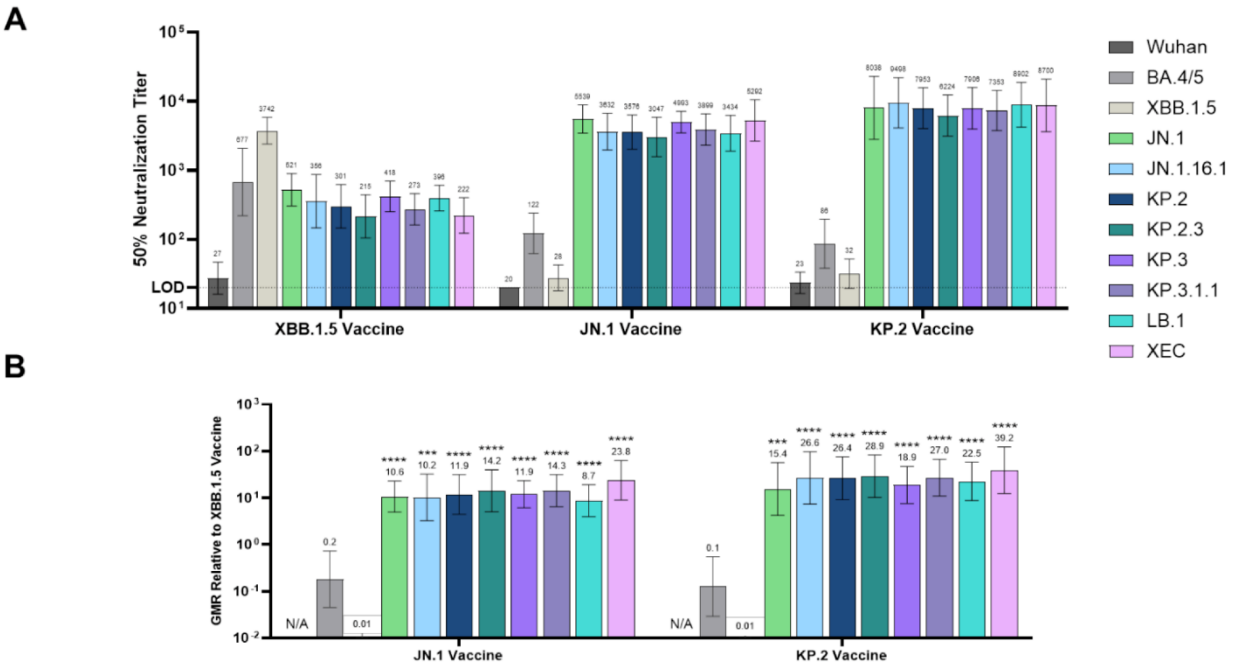

Figure 4: (A) Pseudovirus neutralizing antibody titers against index virus, BA.4/5, XBB.1.5, JN.1, JN.1.16.1, KP.2, KP.2.3, KP.3, KP.3.1.1, LB.1 and XEC in naïve mice sera immunized with monovalent XBB.1.5, JN.1 or KP.2 BNT162b2 mRNA vaccines.[4] The number above each bar indicates the 50% neutralizing geometric mean titer (GMT) with 95% CI of 10 mice per vaccine group. (B) The geometric mean ratio (GMR) is shown as the ratio of the BNT162b2 monovalent JN.1 or KP.2 vaccine GMT to the BNT162b2 monovalent XBB.1.5 vaccine GMT of the analogous pseudovirus. The number above each bar indicates the GMR with 95% CI.

Using sera from naïve vaccinated mice, JN.1 descendent variants remain antigenically distant from XBB lineage variants and form a distinct antigenic cluster (Figures 5 and 6). JN.1, KP.3.1.1, XEC are antigenically closely related to each other (approximately 1 antigenic unit in cartographic analysis, which corresponds to a two-fold-reduction in neutralization).[4]

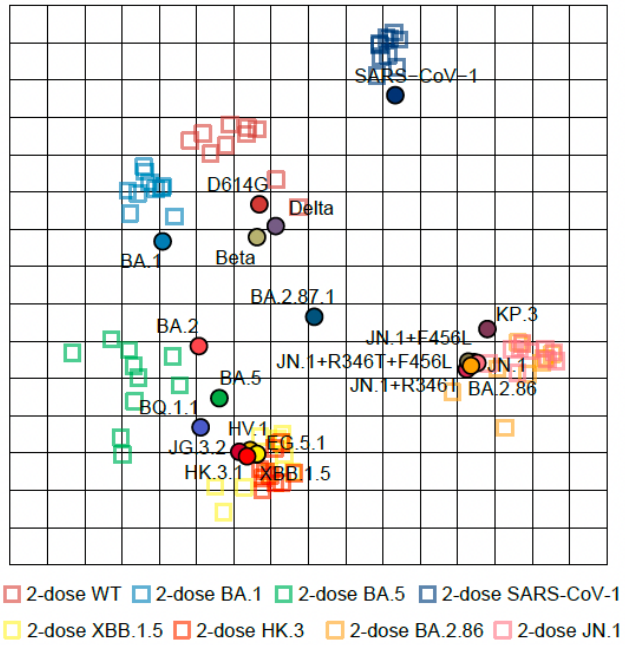

Figure 5: Antigenic cartography using sera from naïve mice immunized with 2-doses of 10μg spike mRNA vaccine.[5] Each square indicates a plasma sample and each circle indicates a SARS-CoV-2 variant.

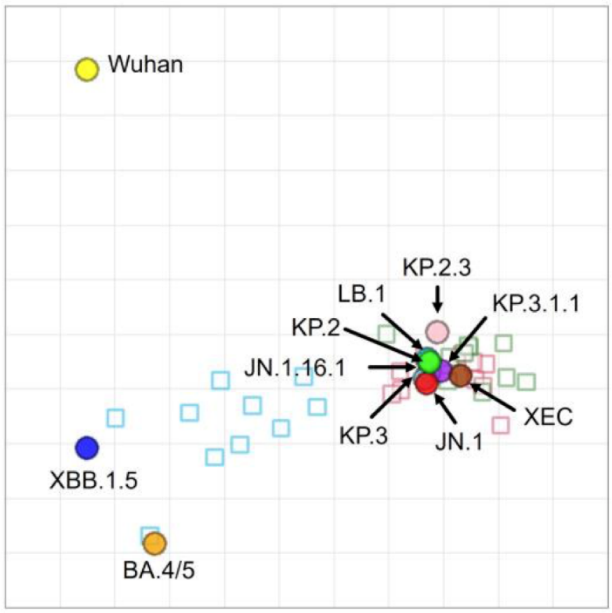

Figure 6: Antigenic cartography using sera from naïve mice immunized with BNT162b2 mRNA vaccines: monovalent XBB.1.5, JN.1, or KP.2.[4]
Each circle indicates a SARS-CoV-2 variant. Each square corresponds to serum from an individual mouse and is colored by the vaccine that mouse received (BNT162b2 monovalent XBB.1.5 (blue), JN.1 (magenta), or KP.2 (green)). Each square in the matrix represents 1 antigenic unit, which corresponds to a two-fold difference in neutralizing antibody titers.

Antisera from naïve hamsters infected with JN.1 showed greater cross-reactivity to SARS-CoV-2 variant KP.3.1.1, as compared to KP.2 antisera (Figure 7).

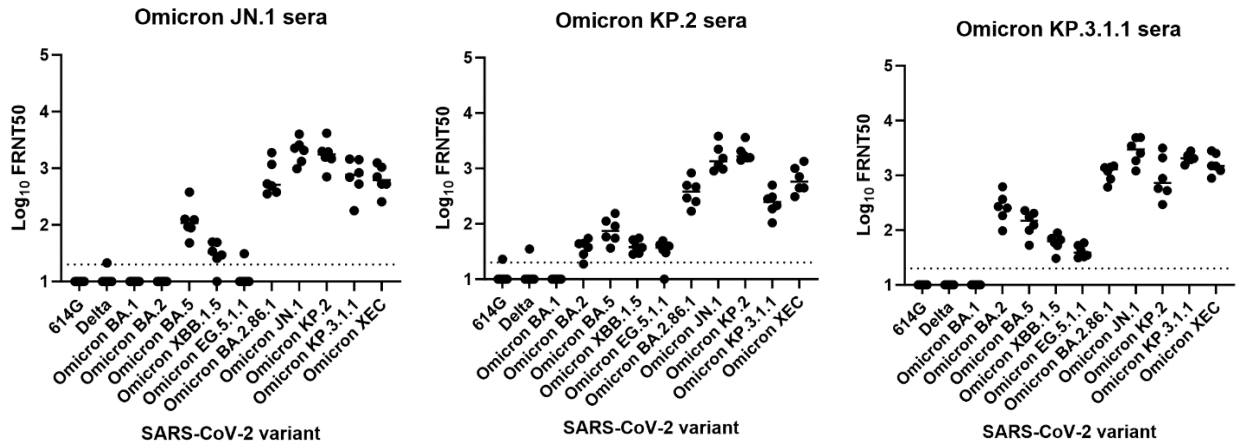

Figure 7: Neutralizing antibody titers of naïve hamsters infected with either JN.1 (left), KP.2 (middle) or KP.3.1.1 (right) against 614G, Delta, BA.1, BA.2, BA.5, XBB.1.5, EG.5.1.1, BA.2.86.1, JN.1, KP.2, KP.3.1.1, or XEC. Neutralization tests performed using infectious SARS-CoV-2 variants listed.
Unpublished data shared with permission from Dr. Bart Haagmans, Erasmus MC. The methodology has been previously described.[6]

As in naïve mice, antisera from single variant infected hamsters, KP.3.1.1 is antigenically closely related to JN.1 and to other circulating JN.1 descendent variants (approximately 1 antigenic unit in cartographic analysis) (Figure 8).

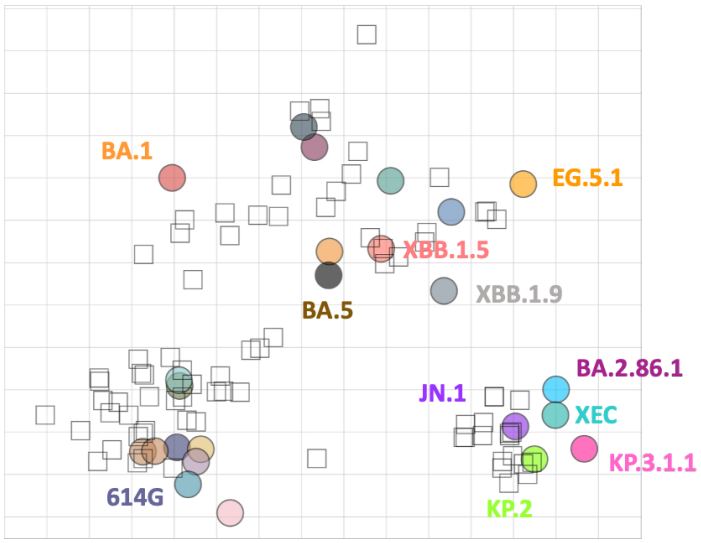

Figure 8: Antigenic cartography of hamster sera infected by SARS-CoV-2 variants: 641G, Delta, BA.1, BA.5, BM.1.1.1, XBB.1.5, JN.1, KP.2, KP.3.1.1.
Each square indicates a plasma sample and each circle indicates a SARS-CoV-2 variant.
Unpublished data shared with permission from Dr. Bart Haagmans, Erasmus MC. The methodology has been previously described.[6]

Similarly, in infectious SARS-CoV-2 neutralization data generated by the UK MRC ProVac consortium using antisera from single variant infected hamsters, there was a reduction in neutralizing antibody titers of approximately two-fold against KP.3.1.1 as compared to JN.1 (Figure 9).

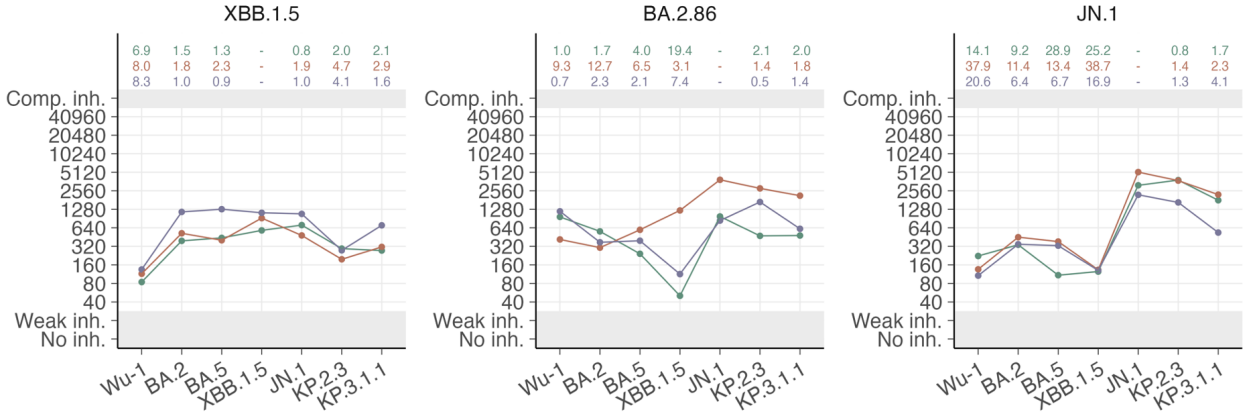

Figure 9: Neutralizing antibody titers of naïve hamsters infected with either XBB.1.5 (left), BA.2.86 (middle) or JN.1 (right) against Wu-1, Delta, BA.2, BA.5, XBB.1.5, BA.2.86, JN.1, or KP.3.1.1.
Unpublished data shared with permission from the UK MRC ProVac consortium.

KP.3.1.1 is approximately 1 antigenic unit from JN.1 in cartographic analysis (Figure 10).

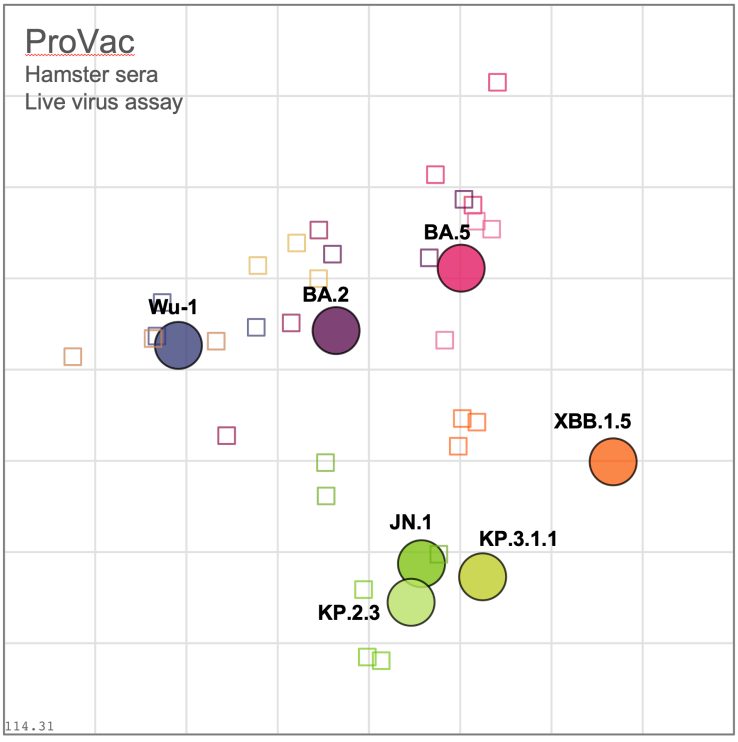

Figure 10: Antigenic cartography of hamster sera inoculated by SARS-CoV-2 variants.
Each square indicates a serum sample and each circle indicates a SARS-CoV-2 variant. Unpublished data shared with permission from the UK MRC ProVac consortium.

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

Published and unpublished data on sera from non-naïve animals and humans after XBB.1.5 immunization, with and without recent prior infection, neutralize well the homologous XBB.1.5 antigen, but show some drop against JN. 1 (Figures 11 and 12). However, there were greater reductions in cross-neutralization of emerging JN.1 lineage variants using post-monovalent XBB.1.5 vaccination sera, as compared to post-monovalent JN.1 or post-monovalent KP.2 vaccination sera.

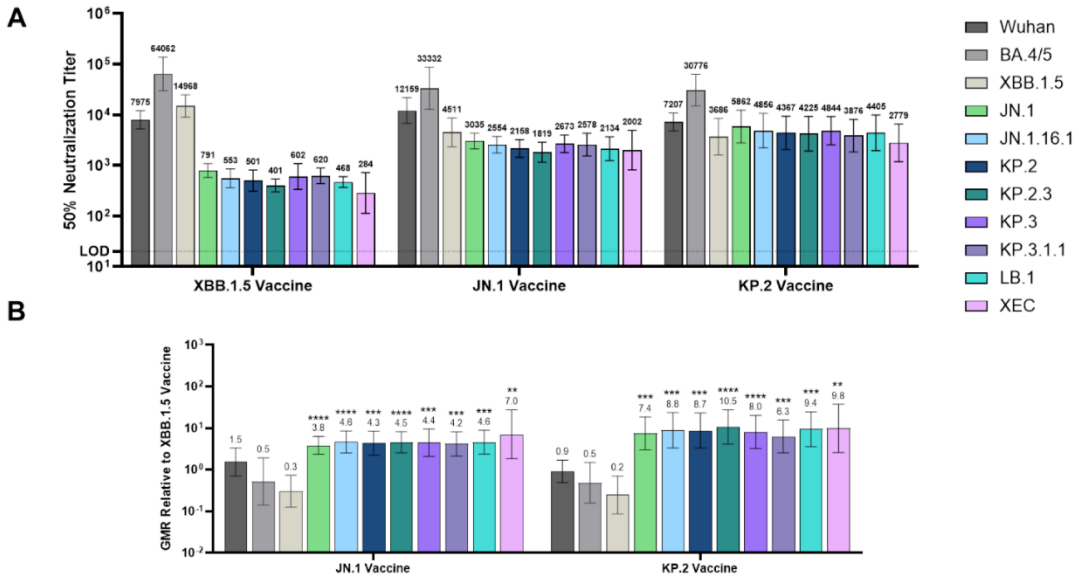

Figure 11: (A) Pseudovirus neutralizing antibody titers of mouse sera immunized with BNT162b2 mRNA vaccines: monovalent XBB.1.5, JN.1, or KP.2 against index virus, BA.4/5, XBB.1.5, JN.1, JN.1.16.1, KP.2, KP.2.3, KP.3, KP.3.1.1, LB.1 and XEC.[4] The number above each bar indicates the 50% neutralizing geometric mean titer (GMT) with 95% CI of 10 mice per vaccine group. (B) The geometric mean ratio (GMR) is shown as the ratio of the BNT162b2 monovalent JN.1 or KP.2 vaccine GMT to the BNT162b2 monovalent XBB.1.5 vaccine GMT of the analogous pseudovirus. The number above each bar indicates the GMR with 95% CI.

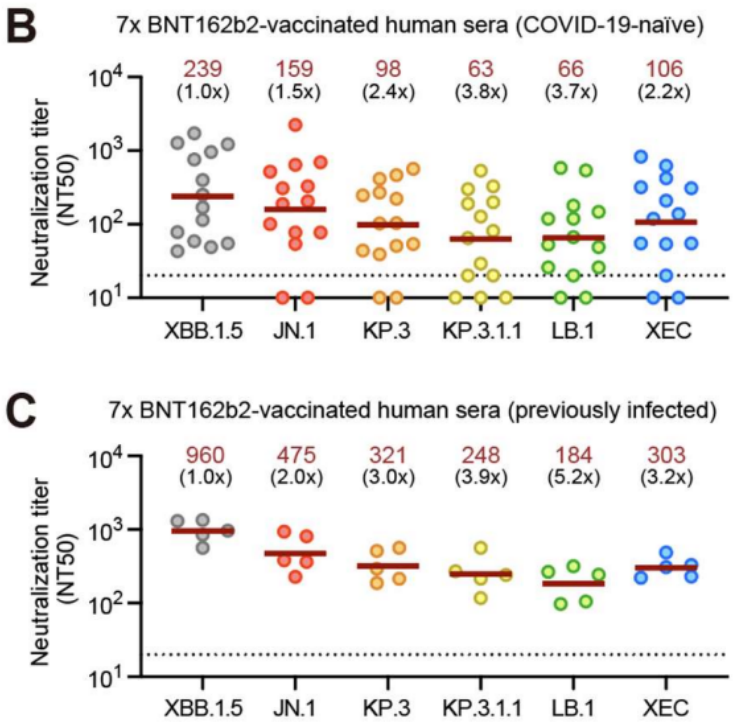

Figure 12: Neutralizing antibody titers (NT50) against SARS-CoV-2 variants XBB.1.5, JN.1, KP.3, KP.3.1.1, LB.1 and XEC in sera from 19 healthcare workers who received seven doses of BNT162b2 mRNA vaccine, with XBB.1.5 monovalent vaccine as their final dose in December 2023, stratified by prior SARS-CoV-2 infection status.[7]
Brown horizontal bars and numbers represent geometric mean titers. Black numbers indicate fold-changes in neutralization titer relative to XBB.1.5 (reference). The dotted line indicates the limit of detection for this assay.

In published and unpublished data from humans after vaccination with monovalent JN.1 or KP.2 antigens, neutralizing antibody titers that cross-reacted with all JN.1 descendent lineages tested were increased. Analysis of pre- and post-vaccination sera from JN.1 and KP.2 immunized individuals demonstrated strong rises in neutralization of JN.1 and descendent variants, including KP.2, KP.2.3, KP.3, KP.3.1.1 and XEC (Figures 13-15). Post-monovalent JN.1 or KP.2 vaccination neutralizing antibody titers against KP.3.1.1 and XEC were modestly lower (consistent 2-fold reductions in titers) than those against the homologous JN.1 or KP.2 antigens.

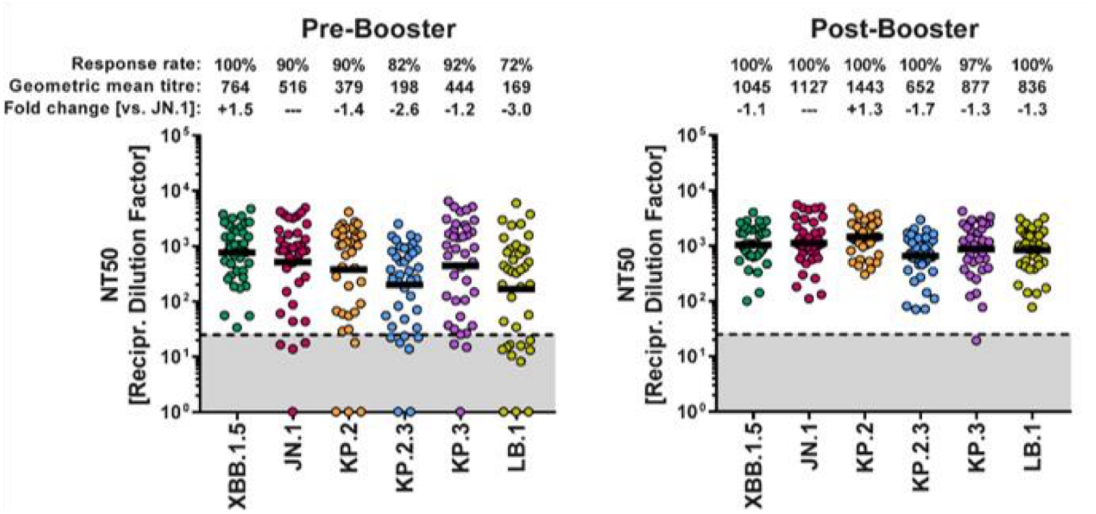

Figure 13: Neutralizing antibody titers (NT50) against XBB.1.5, JN.1, KP.2, KP.2.3, KP.3 and LB.1 pre- and post-monovalent JN.1 booster vaccination.[8]
The lowest plasma dilution tested (dashed lines) and the threshold (lower limit of detection; grey shaded areas) are indicated. Information on GMT (also indicated by horizontal lines) response rates, and median fold change in neutralizing antibody titers compared with JN.1 pseudovirus particles are indicated above the graphs.

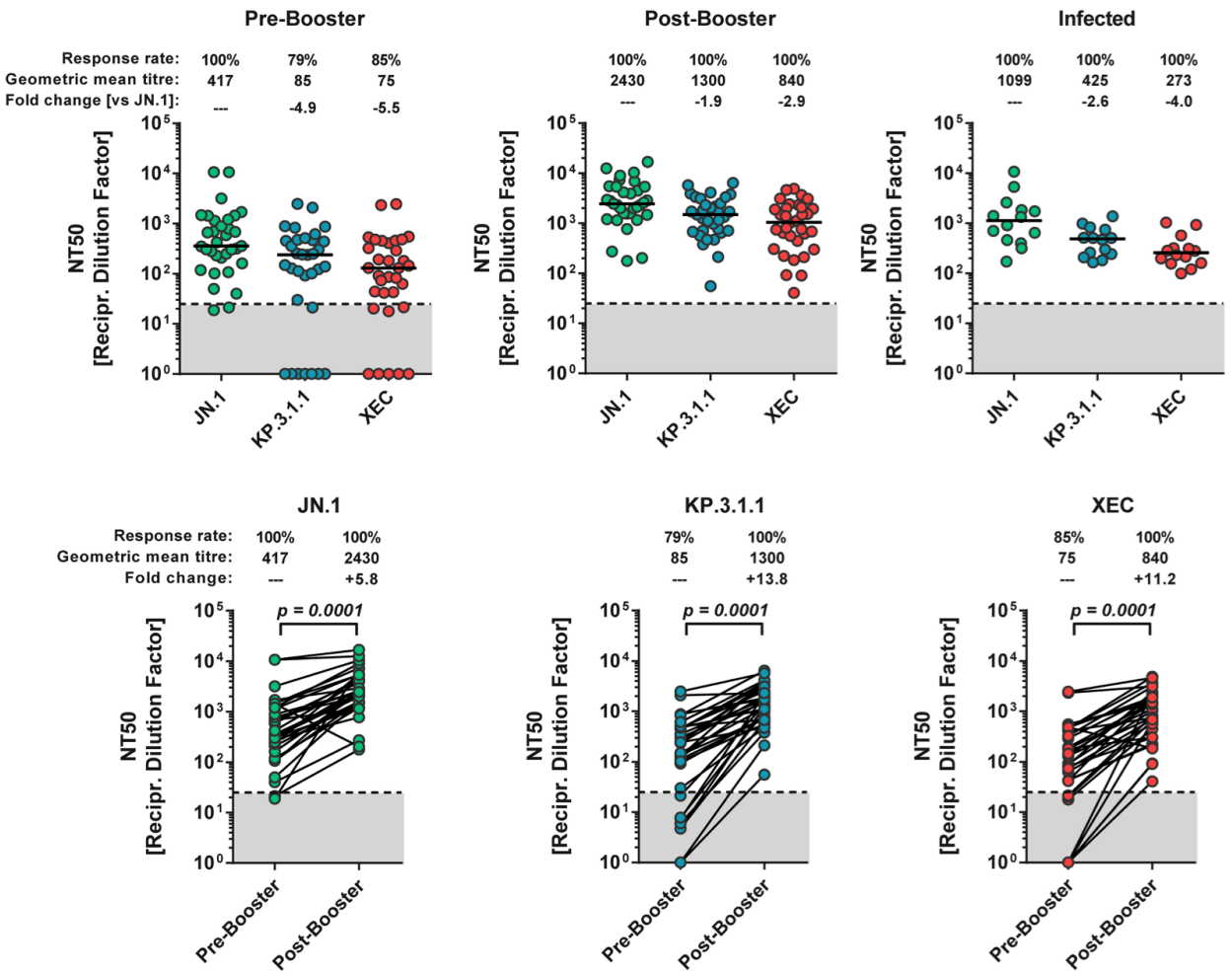

Figure 14: (Top) Neutralizing antibody titers against JN.1, KP.3.1.1 and XEC pre- and post-JN.1 booster vaccination or in individuals with recent SARS-CoV-2 infection (summer 2024).[2] Individual NT50 values were determined for each plasma using a non-linear regression model and geometric mean titers (GMT) were calculated for the respective sample groups. The lowest plasma dilution tested (dashed lines) and the threshold (lower limit of detection, LLOD; grey shaded areas) are indicated. Samples that yielded NT50 values below 12.5 (LLOD) were considered negative and manually assigned a value of 1. Presented are the GMTs (indicated by horizontal black lines and numerical values), response rates and fold changes in neutralization compared to JN.1. (Bottom) Neutralizing antibody titers pre- and post-JN.1 booster vaccination against JN.1, KP.3.1.1 and XEC. Information above the graphs indicate GMTs and the mean fold change in neutralization between pre- and post-booster samples. Statistical significance was assessed by Wilcoxon matched-pairs signed rank test (p 0.0001; ****).

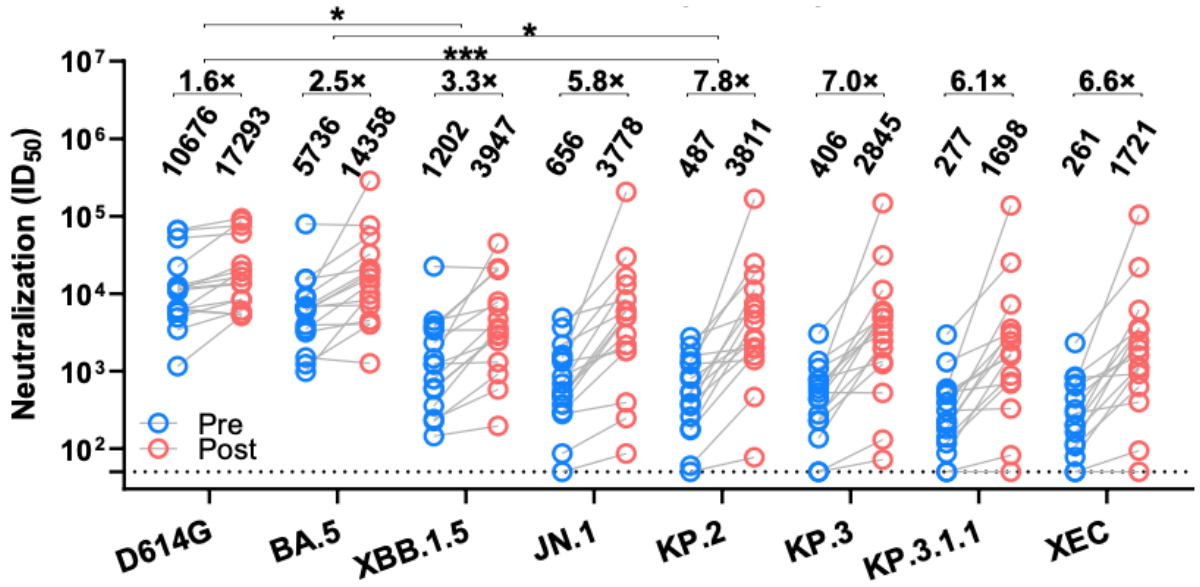

Figure 15: Neutralizing antibody titers against pseudoviruses D614G, BA.5, XBB.1.5, JN.1, KP.2, KP.3, KP.3.1.1 and XEC pre- and post-monovalent KP.2 vaccination among 16 vaccine recipients.[9]
The dotted line represents the assay limit of detection. Comparisons of fold increases in ID50 titers after KP.2 monovalent vaccine between KP.2 and other variants were analyzed using the Mann-Whitney U tests. *$p < 0.05$; ***$p < 0.001$

4. **Preliminary immunogenicity data on immune responses following infection with circulating SARS-CoV-2 variants**

In published and unpublished data from humans following re-infection with circulating SARS-CoV-2 variants increased neutralizing antibody titers that cross-reacted with all JN.1 descendent variants tested, including JN.1, KP.2, KP.3, KP.3.1.1 and XEC. (Figure 16). Neutralizing antibody titers against KP.3.1.1 and XEC were modestly lower than those against JN.1.

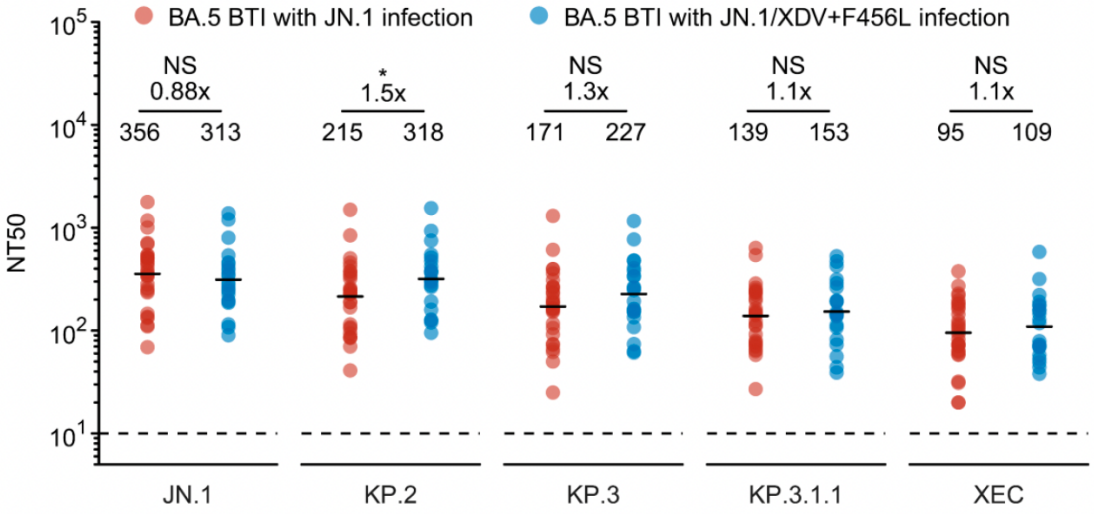

Figure 16: 50% neutralizing antibody titers (NT50) of convalescent plasma from individuals reinfected with JN.1 after BA.5 BTI (n = 29) and those reinfected with JN.1/XDV + F456L after BA.5 BTI (n = 21) against SARS-CoV-2 variants JN.1, KP.2, KP.3, KP.3.1.1, and XEC.[11]
Geometric mean titers (GMT) are labeled above each group, with fold changes and statistical significance indicated above the GMT labels. Paired samples were analyzed using a two-tailed Wilcoxon signed-rank test. *p<0.05.

5. Available vaccine effectiveness (VE) of currently approved vaccines during periods of XBB descendent lineage and JN.1 descendent lineage circulation

In a context of infection- and vaccine-derived immunity in the majority of the population, contemporary vaccine effectiveness (VE) estimates are relative (rVE) rather than absolute (comparing vaccinated to unvaccinated individuals). rVE, sometimes referred to as "up-to-date VE", demonstrate the added protection of most recent vaccination over and above pre-existing immunity derived from previous infections and/or vaccinations. There are currently no studies reporting VE or rVE estimates using monovalent JN.1 lineage (JN.1 or KP.2) vaccines.

Estimates of VE against recently circulating SARS-CoV-2 variants, including XBB or JN.1 descendent lineages, are limited in terms of the number and geographic diversity of studies, vaccine platforms evaluated, populations assessed, and duration of follow-up. Furthermore, the referent population for VE estimates varies substantially with respect to prior history of vaccination. There are currently no direct comparative estimates for monovalent JN.1, KP.2 or XBB.1.5 vaccines versus other antigen composition(s) delivered during the same time period. Finally, VE estimates may be confounded by differences in undocumented infection-derived immunity between groups, leading to potential underestimation of VE.

Approved monovalent XBB.1.5 mRNA COVID-19 vaccines continued to provide additional protection against severe disease and death during periods of XBB descendent lineage circulation in the first three months after vaccination; VE point estimates against symptomatic disease were typically lower. During periods of JN.1 descendent lineage circulation, monovalent XBB.1.5 mRNA vaccines continued to show additional protection in the first three months after vaccination (Figure 17),[12-25] however, available evidence points towards a reduction in rVE estimates against JN.1-derived variants, as compared to XBB.1 lineage variants, for protection against death, severe disease, symptomatic disease and infection (Figure 18).[15,17-21] The VE estimates for monovalent XBB.1.5 vaccines against JN.1-derived variants are consistent with reductions in neutralizing antibody titers observed in preclinical and clinical immunogenicity studies of post-monovalent XBB.1.5 vaccination sera against JN.1 descendent variants, as compared to XBB.1 lineage variants (described above).

Caution is needed in the interpretation of these findings (e.g., Figures 17 and 18) which are estimates of rVE (or up-to-date VE). There may be differences in infection rates between vaccinated and comparator groups, leading to confounding due to differential infection-derived protection, which would result in an underestimation of VE estimates. When comparing VE estimates during periods of different SARS-CoV-2 variant circulation, there may also be differences in calendar time and/or time since vaccination.

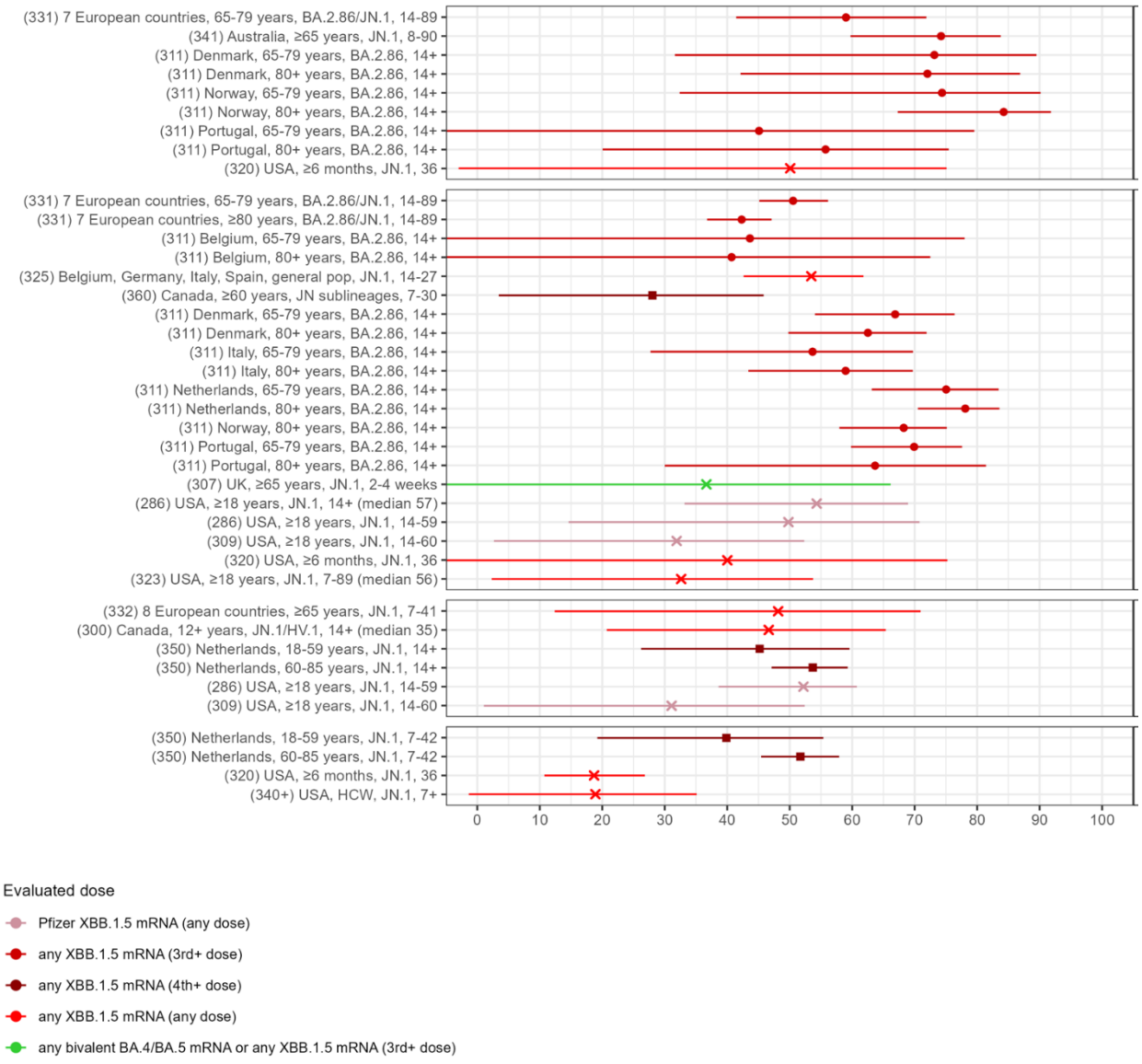

Figure 17: Estimates of relative or up-to-date vaccine effectiveness (VE) within three months of a dose of a bivalent BA.4/5 or monovalent XBB.1.5 mRNA vaccine during periods of JN.1 descendent lineage circulation.[15-25]
The top panel shows VE estimates against death, followed by hospitalization and severe disease, symptomatic disease and the bottom panel shows VE estimates against infection. Analysis conducted by WHO using data from www.view-hub.org with published VE studies up to 30 November 2024.

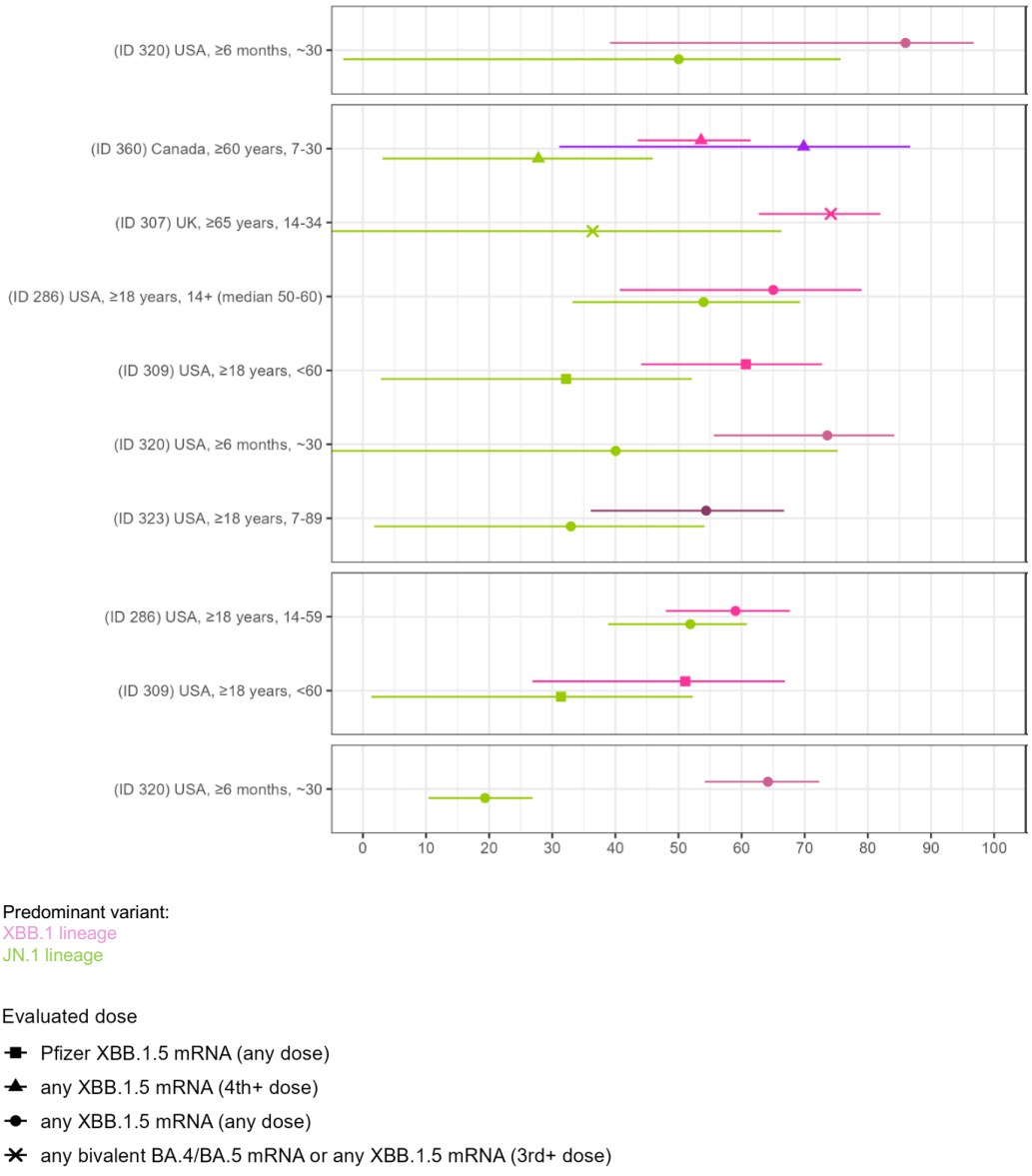

Figure 18. Estimates of relative or up-to-date vaccine effectiveness (VE) within three months of a dose of a bivalent BA.4/5 or a monovalent XBB.1.5 mRNA vaccine during periods of XBB.1 (magenta) or JN.1 (green) descendent lineage circulation.[15,17-21]

The top panel shows VE estimates against death, followed by hospitalization and severe disease, symptomatic disease and the bottom panel shows VE estimates against infection. Analysis conducted by WHO using data from www.view-hub.org with published studies up to 30 November 2024.

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