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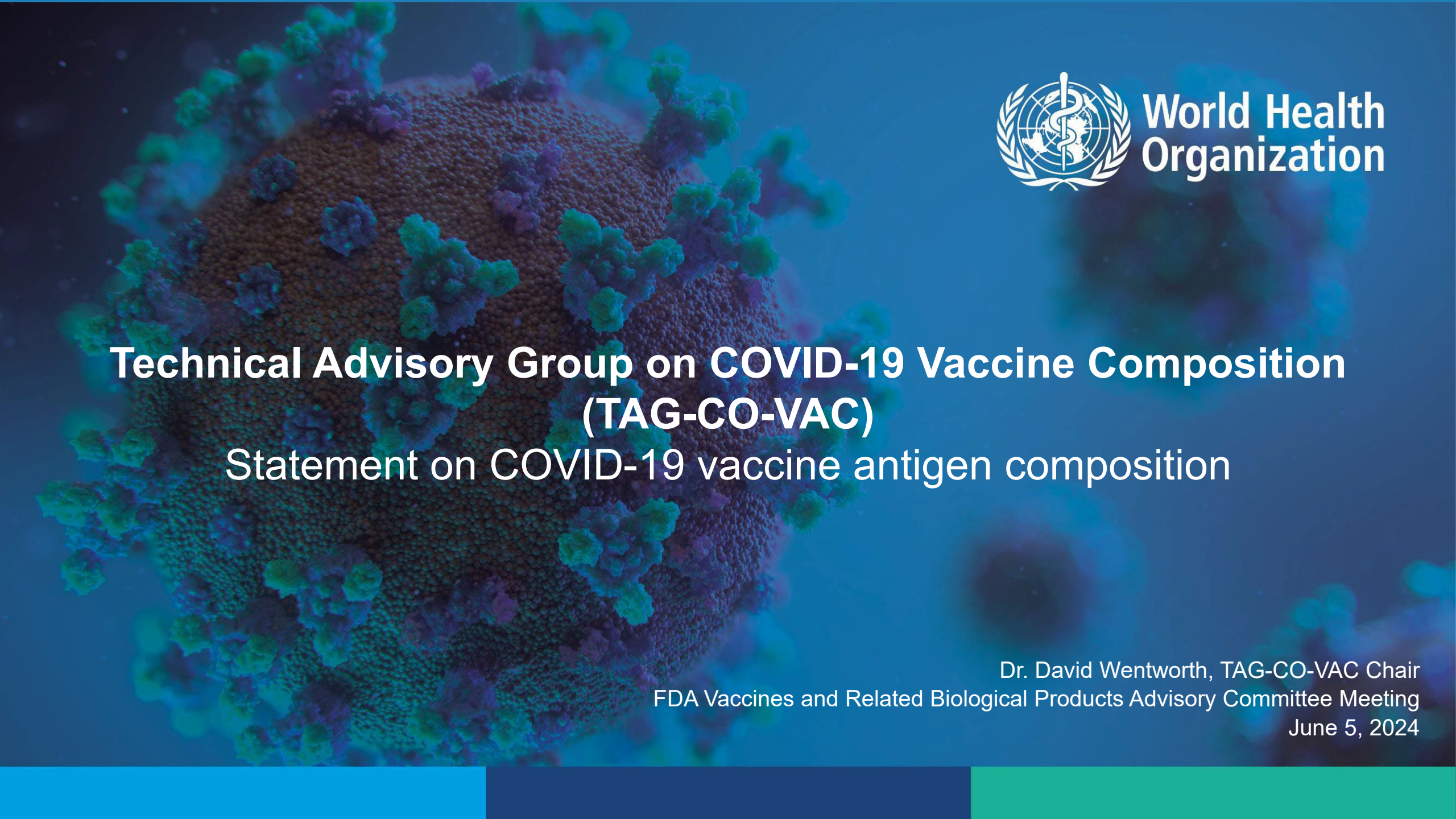

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Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC)

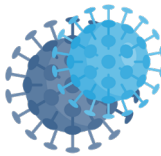
Statement on COVID-19 vaccine antigen composition

Dr. David Wentworth, TAG-CO-VAC Chair

FDA Vaccines and Related Biological Products Advisory Committee Meeting

June 5, 2024

Technical Advisory Group on COVID-19 Vaccine Composition



Functions of the TAG-CO-VAC

- Make recommendations to WHO on the **methods to assess the impact of SARS-CoV-2 variants** on COVID-19 vaccines;
- Provide **interpretation of available evidence on the effect of SARS-CoV-2 variants on COVID-19 vaccines**, including but not limited to vaccine effectiveness;
- **Recommend to WHO, for each COVID-19 vaccine platform, adaptations (if any) needed** so that vaccines continue to safely provide protection against SARS-CoV-2 variants.

Currently, the TAG-CO-VAC plans to make recommendations twice a year (April/November 2024)

- ~ 1 month earlier than in 2023, resulting from a workshop on: Global perspectives on COVID-19 vaccines strain update, jointly organized by International Coalition of Medicines Regulatory Authorities (ICMRA) and WHO on 26-27 February 2024; attended by ICMRA Members, WHO and vaccine manufacturers
  - Balance need for most recent epidemiological, immunological, and virological data with timeframes needed by manufacturers to update the composition of authorized vaccines to optimize vaccine distribution and availability.

TAG-CO-VAC website: https://www.who.int/groups/technical-advisory-group-on-covid-19-vaccine-composition-(tag-co-vac)
Also described in: Grant R, et al. Nat Med 2023

ICMRA/WHO report: https://www.icmra.info/drupal/en/covid-19/26_27february2024

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Recommendations for COVID-19 vaccine composition

Objective:

Achieve broadly cross-reactive vaccine-elicited immune responses in the context of continued SARS-CoV-2 evolution

Recommendation:

As SARS-CoV-2 virus evolution is expected to continue from JN.1, future formulations of COVID-19 vaccines should aim to induce enhanced neutralizing antibody responses to JN.1 and its descendent lineages.

- One approach recommended by TAG-CO-VAC is the use of a monovalent JN.1 lineage antigen in vaccines*.

- Other formulations and/or platforms that achieve robust neutralizing antibody responses against currently circulating variants, particularly JN.1 descendent lineages, can also be considered.

* JN.1 Accession numbers: GenBank: PP298019, GISAID: EPI_ISL_18872762 (as of May 14, 2024)

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Further considerations

- The continued use of the current monovalent XBB.1.5 formulation will offer protection given the neutralizing antibody responses to early JN.1 descendent lineages, and the evidence from early rVE studies against JN.1.

- However, it is expected that the ability for XBB.1.5 vaccination to protect against symptomatic disease may be less robust as SARS-CoV-2 evolution continues from JN.1.

- In accordance with WHO SAGE policy, vaccination programmes should continue to use any of the WHO emergency-use listed or prequalified COVID-19 vaccines and vaccination should not be delayed in anticipation of access to vaccines with an updated composition. WHO stresses the importance of access to and equity in the use of all available COVID-19 vaccines.

TAG-CO-VAC evidence review: April 2024

TAG-CO-VAC and its subgroup held 8 meetings leading up to the recommendation meeting. Final recommendation meeting convened on 15-16 April 2024.

The key published and unpublished data reviewed by the TAG-CO-VAC included:

1. SARS-CoV-2 **genetic evolution**; (comprehensive analysis provided by WHO TAG-VE)
2. **Antigenic characterization** of representative SARS-CoV-2 variants using virus neutralization assays and animal antisera or human sera along with further analysis and visualization 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 or emerging** 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 (confidential; data not shown).

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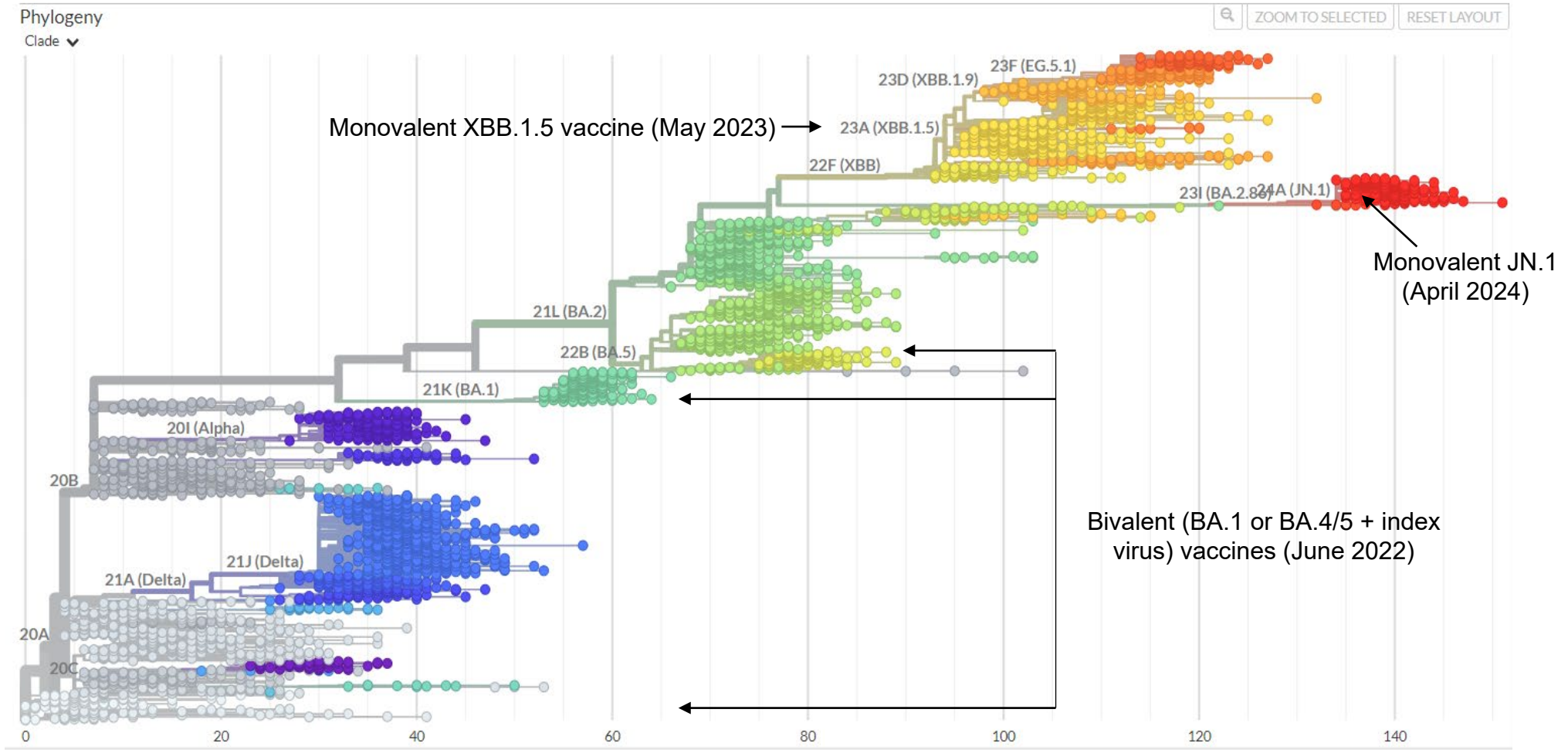
1. SARS-CoV-2 evolution: overview



Phylogeny of SARS-CoV-2 variants since its introduction in humans illustrated using Nextsrain.

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 previous TAG-CO-VAC recommendations for vaccine antigen composition

NextStrain: https://nextstrain.org/ncov

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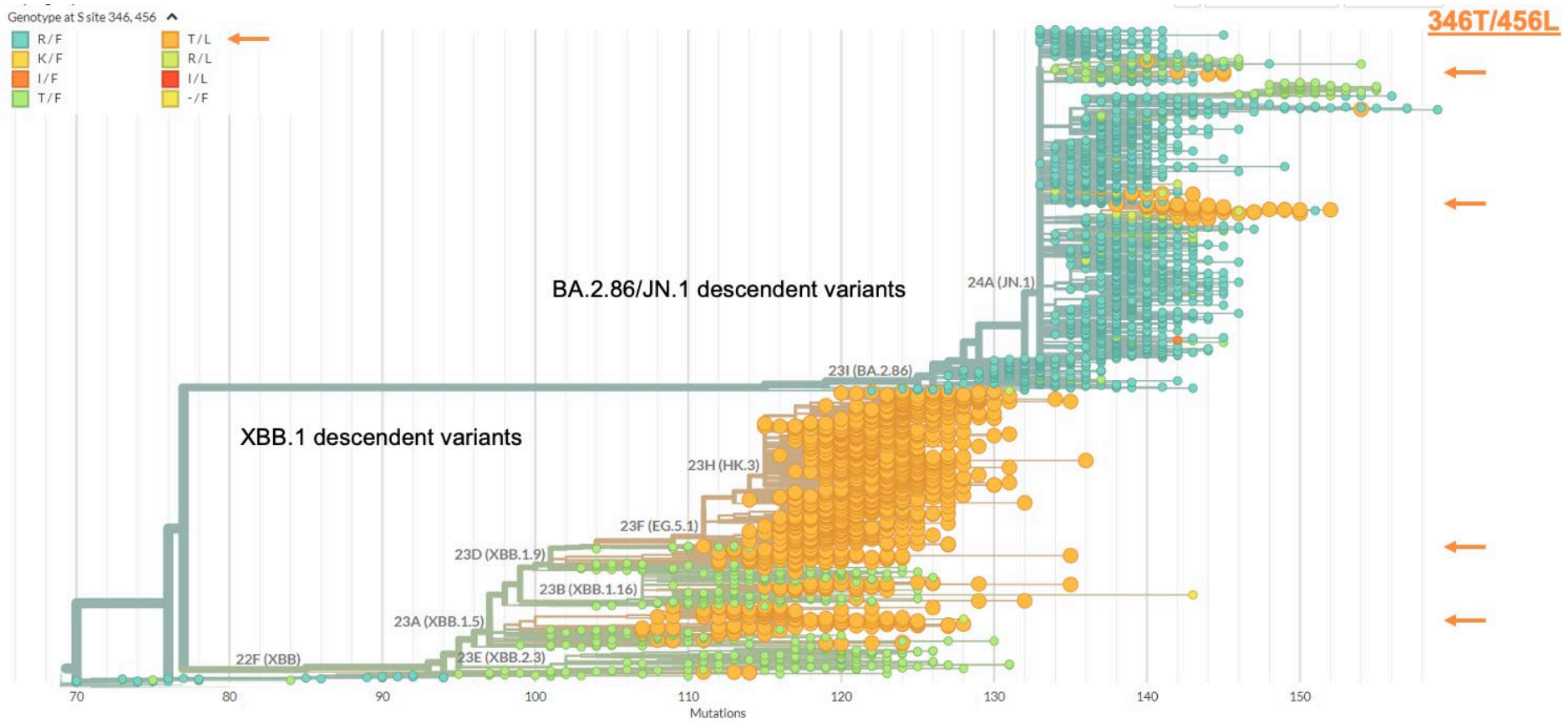
1. SARS-CoV-2 parallel evolution



Phylogeny of SARS-CoV-2 virus genomes from samples collected over the last six months highlighting parallel evolution at specific postions.

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.

NextStrain: https://nextstrain.org/ncov

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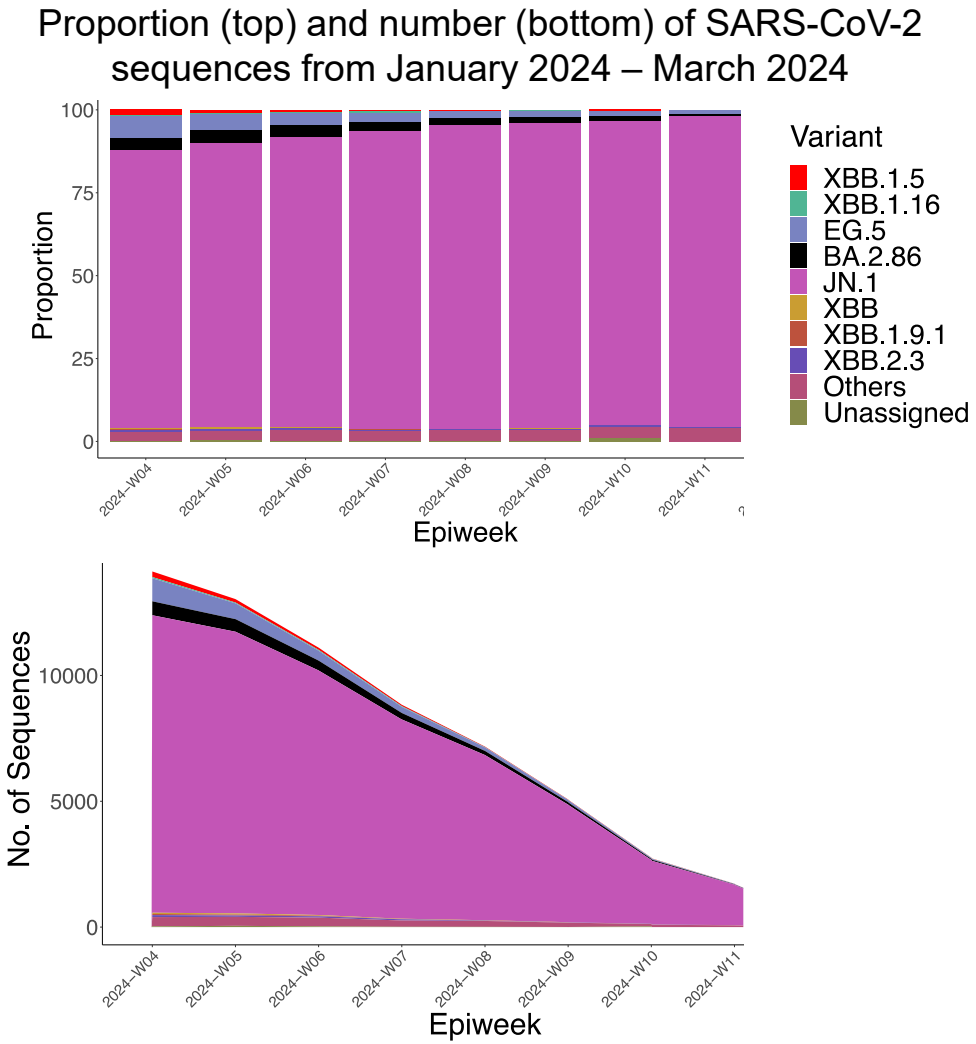
1. Global SARS-CoV-2 variant circulation



Nearly all (>94%) SARS-CoV-2 genetic sequences in publicly available databases fall within JN.1 clade;

JN.1 clade variants continue to displace existing XBB clade variants.

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.

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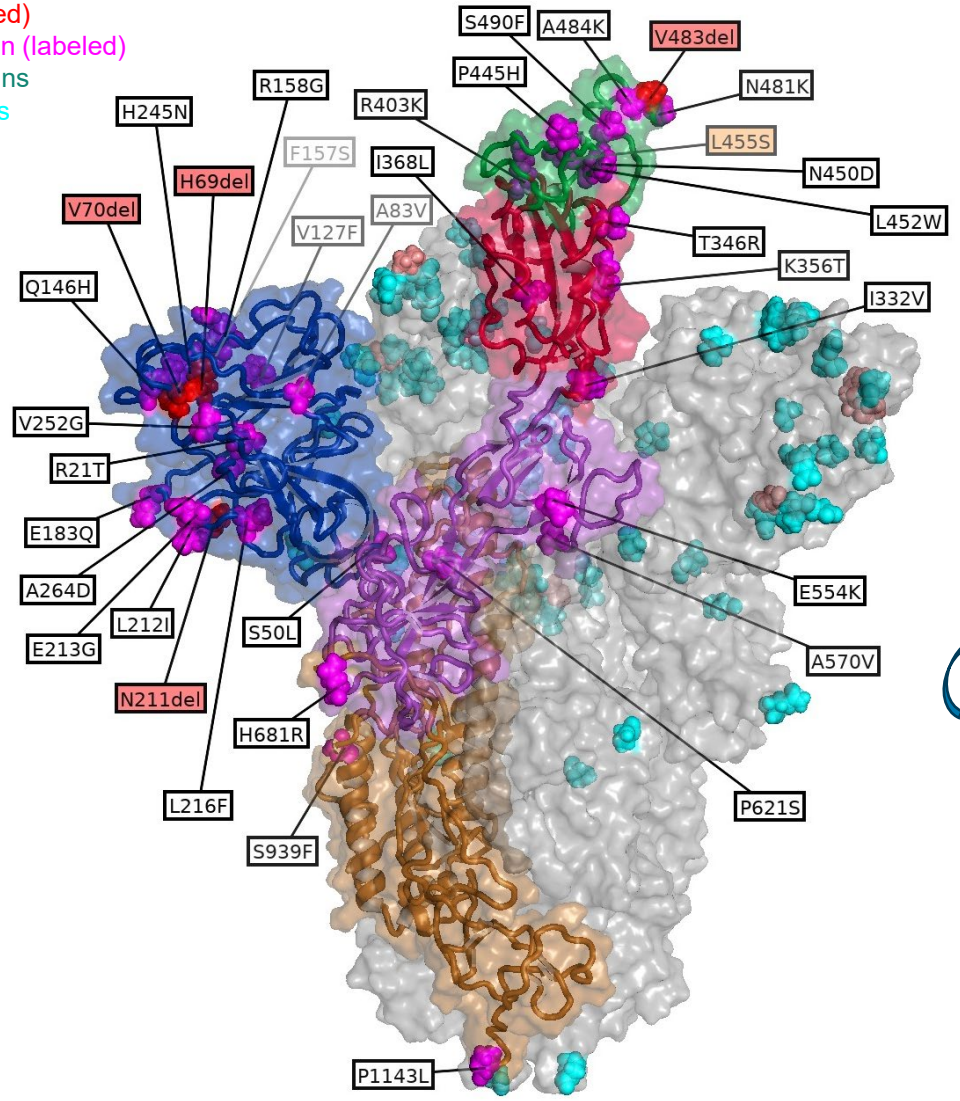
1. SARS-CoV-2 spike evolution: 3D crystal structure illustrating location of amino acid differences on S molecule

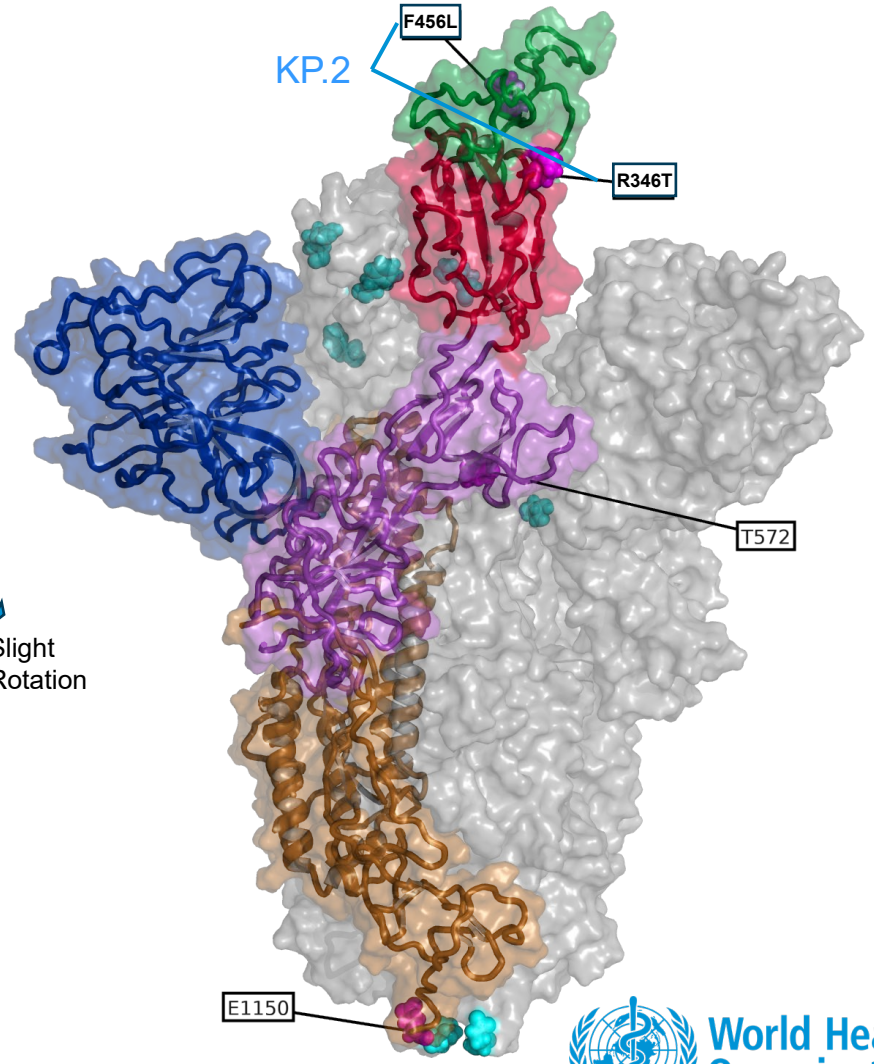
Red sphere – deletions in one chain (labeled)
Magenta sphere – substitutions in one chain (labeled)
Raspberry sphere – deletions in rest 2 chains
Cyan sphere – substitutions in rest 2 chains

Blue – NTD
Red – RBD
Green – RBM
Purple – S1
Gold – FCS
Brown – S2

XBB.1.5 compared to JN.1



JN.1 compared to some progeny



Slight Rotation

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

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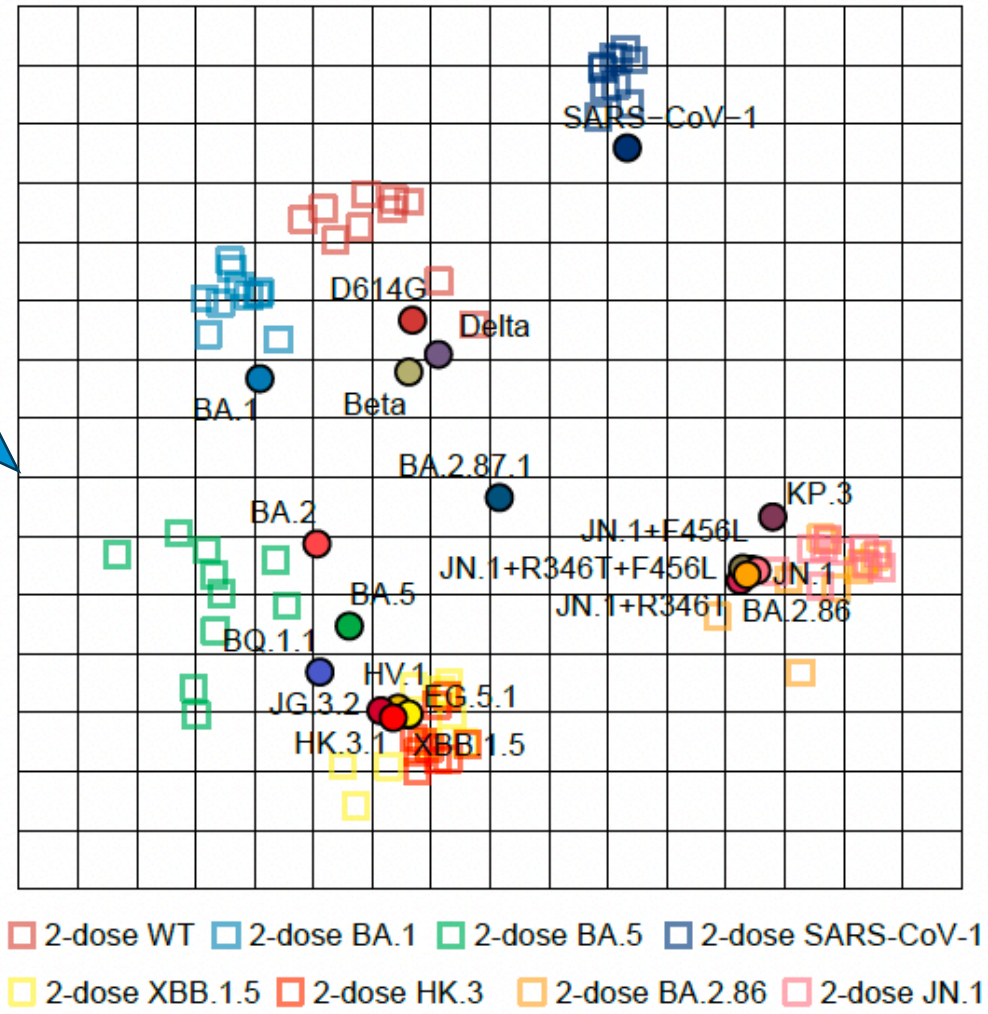
2. Antigenic characterization of SARS-CoV-2 variants (naïve mouse)

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.

Naïve mouse model

- XBB.1.5 and BA.2.86 lineages form antigenically related clusters that are each antigenically distinct from BA.2 progenitor
  - XBB.1 clade variants are antigenically closely related to each other (i.e., well neutralized by XBB.1.5 antisera)
  - BA.2.86/JN.1 clade variants are antigenically closely related
- XBB.1.5 and JN.1 are antigenically very different



Jian F, et al. bioRxiv 2024: doi: 10.1101/2024.04.19.590276

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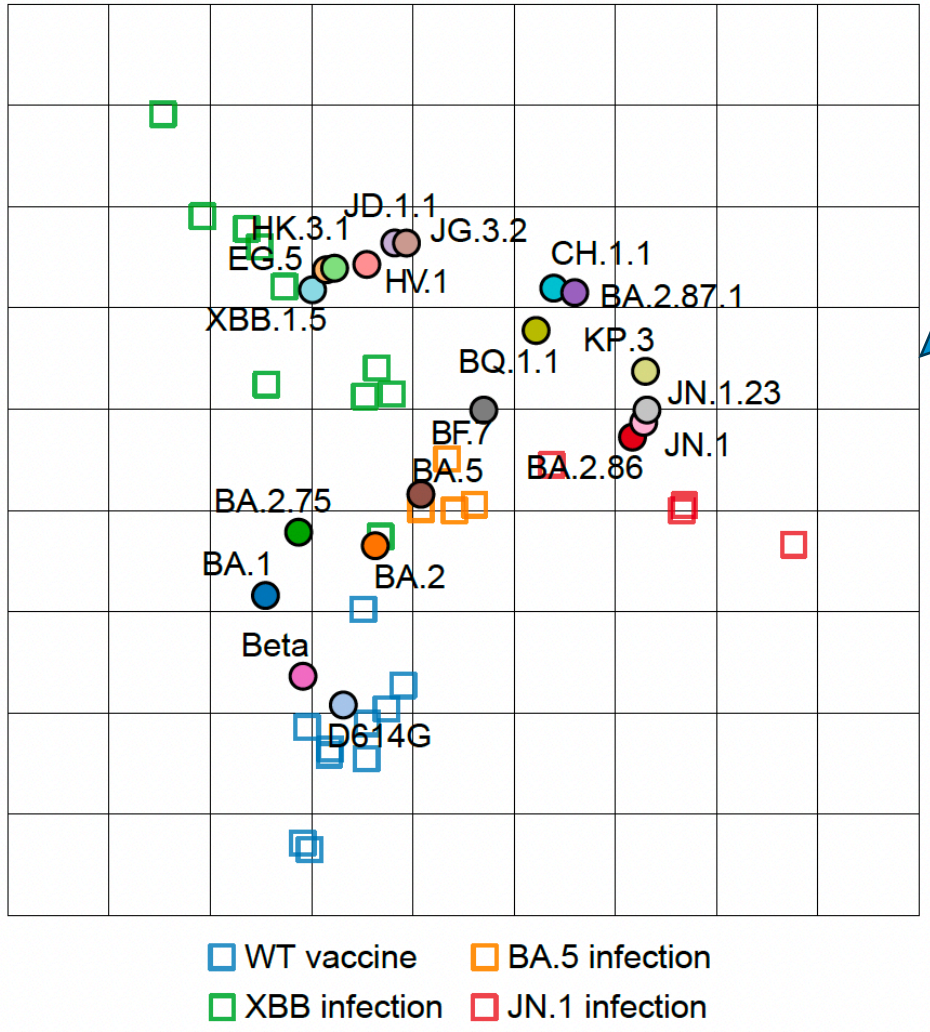
2. Antigenic characterization of SARS-CoV-2 variants (naïve human)

Antigenic cartography using human sera from single-exposure cohorts.
Each square indicates a plasma sample and each circle indicates a SARS-CoV-2 variant.



Naïve humans (similar to naïve animals)

- XBB.1 and BA.2.86 clades form antigenically related clusters that are each antigenically distinct from BA.2 progenitor
- XBB.1.5 and JN.1 are antigenically different

Jian F, et al. bioRxiv 2024: doi: 10.1101/2024.04.19.590276

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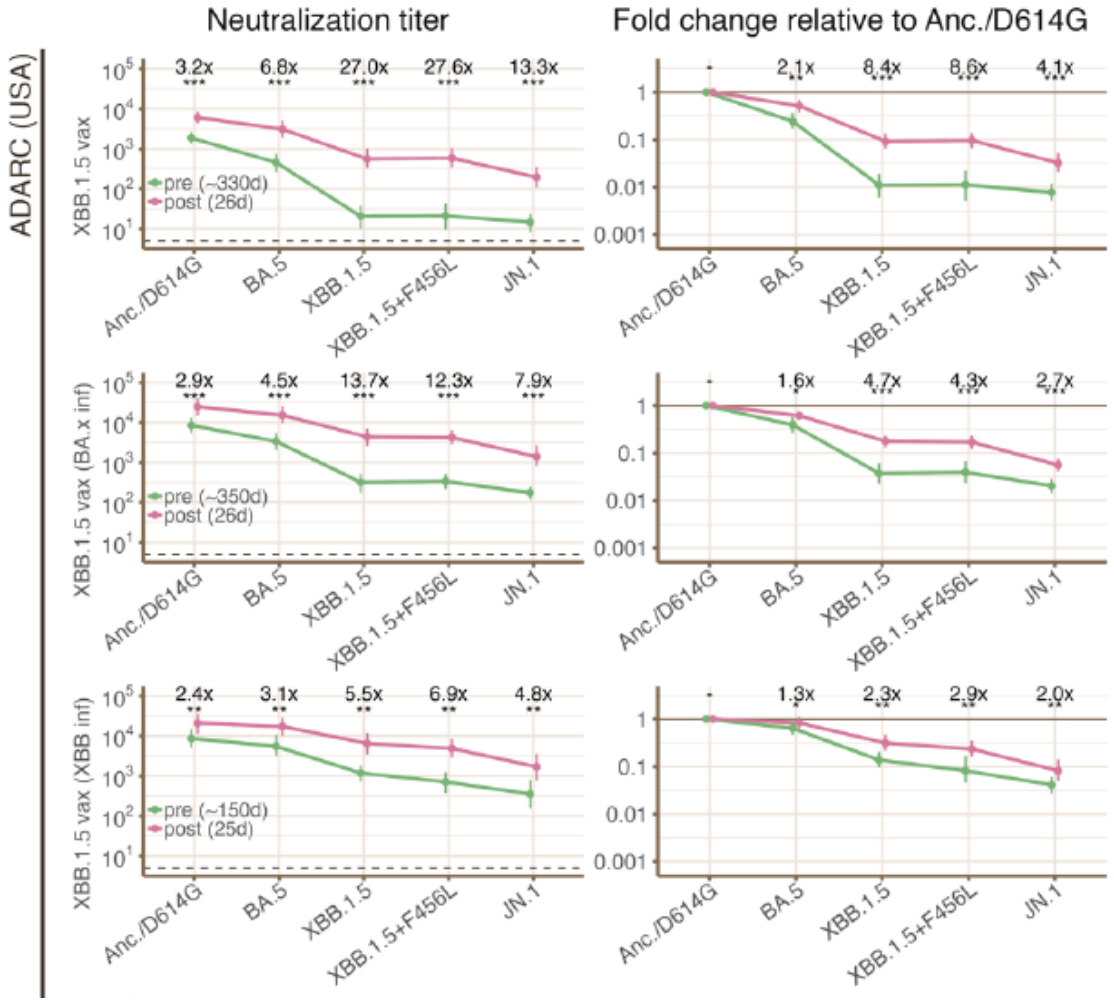
3. Breadth of neutralizing antibody responses (humans)

Comparison of neutralization titres against SARS-CoV-2 variants in human sera collected pre- (green) and post (pink) -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.



Turner S, et al. bioRxiv 2024: doi: 10.1101/2024.03.27.586820

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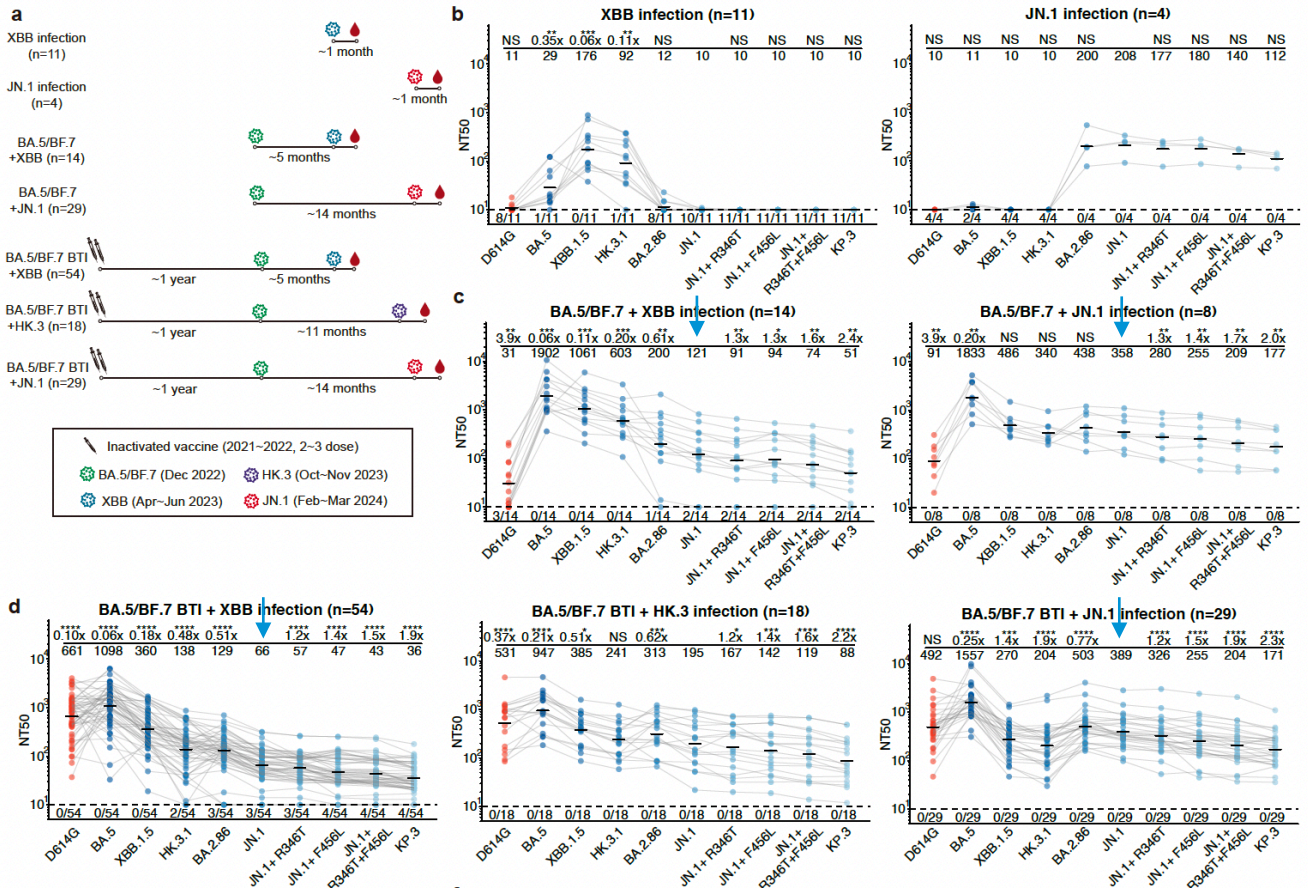
3. Breadth of neutralizing antibody responses (humans)



(A) Schematic of the SARS-CoV-2-related immune histories of the seven cohorts involved in this study. (B-D) 50% neutralization titers (NT_{50}) 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;

Jian F, et al. bioRxiv 2024: doi: 10.1101/2024.04.19.590276

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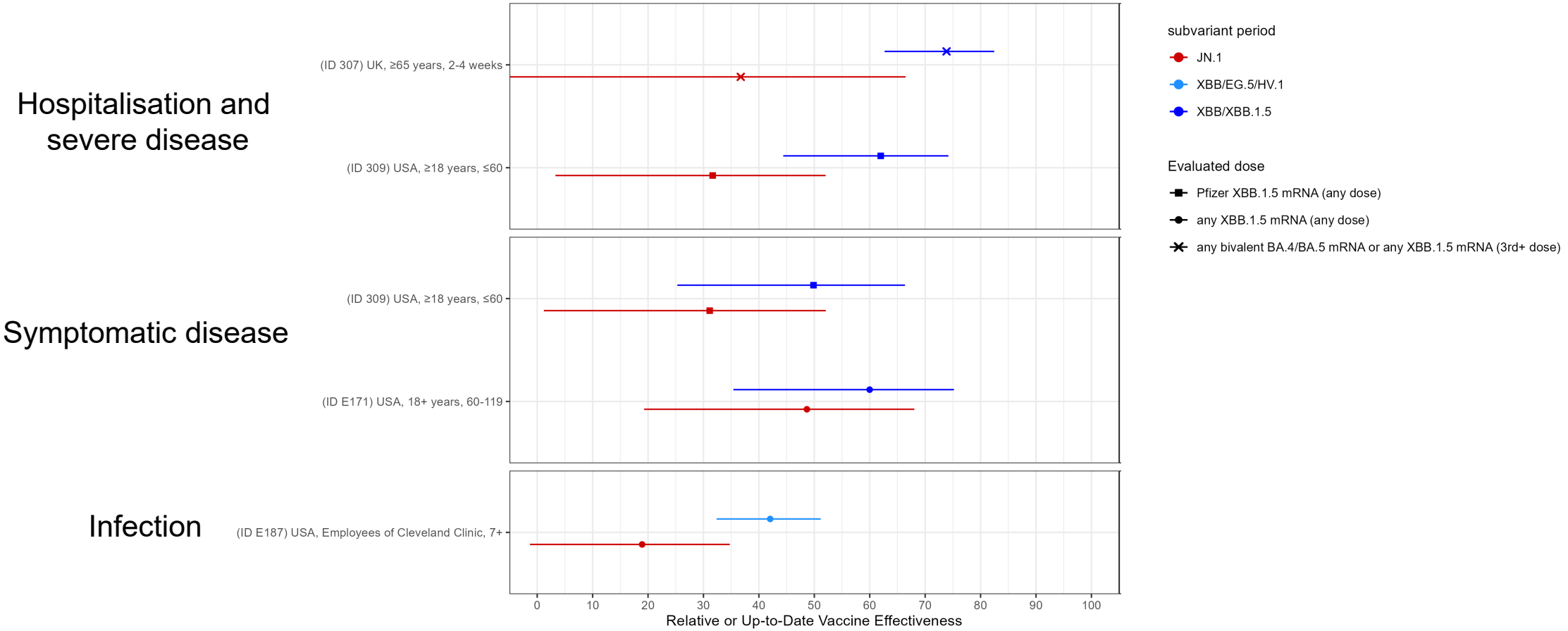
4. rVE estimates: XBB.1 / JN.1 circulation



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.

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.

https://view-hub.org/vaccine/covid/effectiveness-studies

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Summary of available evidence

Genetic analysis

- As of April 2024, nearly all (>94%) SARS-CoV-2 genetic sequences in publicly available databases are derived from JN.1, and these variants continue to displace existing XBB lineage variants (e.g. EG.5).
- Several JN.1 derived variants (e.g. JN.1.13.1, JN.1.11.1, KP.2) have independently evolved changes in the spike protein at epitopes involving amino acid residues 346 and/or 456. Substitutions at these amino acid residues have been identified in previous SARS-CoV-2 variants (e.g. R346T in BQ.1 and XBB; F456L in EG.5 and HK.3) and are within epitopes known to be targeted by neutralizing antibodies.
- Given the displacement of XBB lineage variants by JN.1 derived variants, it is likely that, in the near-term, future circulating SARS-CoV-2 viruses will be derived from JN.1.

Summary of available evidence (cont.)

Antigenic characterization and immunogenicity

- In immunologically naïve animal and human sera, XBB.1.5 and JN.1 lineage viruses are antigenically distinct from each other.
    - They form distinct clusters of antigenically closely related variants.
    - Naïve animal JN.1 antisera react well with many different co-circulating JN.1 progeny variants.
- In non-naïve animals and humans (with or without prior infection) monovalent XBB.1.5 vaccination sera neutralize XBB.1.5 and progeny including EG.5, HK.3, HV.1 (all had F456L) as well as BA.2.86/JN.1 lineage and progeny variants. However, neutralization titres against JN.1 in published and unpublished studies were typically lower (2-5-fold) than those against the homologous XBB.1.5 immunizing antigen.
    - There were additional small reductions in cross neutralization of JN.1 progeny with F456L and/or R346T substitutions in S. Similar reductions were also observed in limited studies with KP.3-like representative (S: F456L, Q493E).

Summary of available evidence (cont. II)

Vaccine effectiveness

- Studies focused on Monovalent XBB.1.5 vaccines showed protection against severe disease during periods of XBB descendent lineage circulation is high during the first three months after vaccination, but protection against symptomatic disease is lower.
- There were fewer studies estimating rVE for the monovalent XBB.1.5 vaccines during periods of JN.1 descendent lineage circulation. They show **additional protection offered during the first three months after vaccination, but point towards a slight reduction in rVE, as compared to rVE against XBB.1 lineage** variants, for protection against symptomatic disease and severe disease.
- 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 and its related emerging variants.

Summary of available evidence (cont. III)

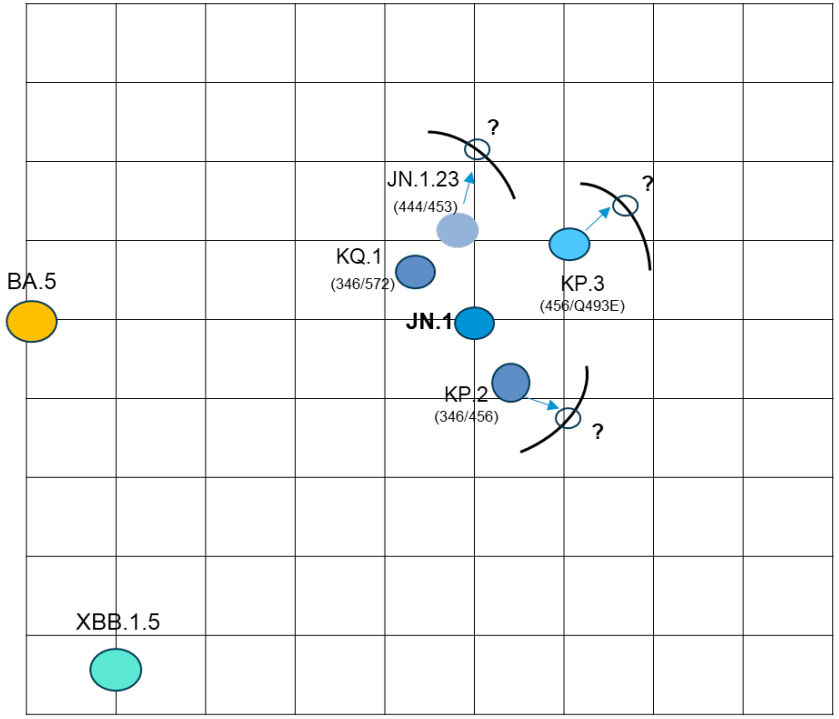
Preclinical data shared confidentially with the TAG-CO-VAC by vaccine manufacturers:

- Immunization of naïve mice, as well as mice previously immunized with representative SARS-CoV-2 variants, with monovalent JN.1-containing vaccine candidates elicits higher neutralizing antibody responses to JN.1 and its emerging descendent variants, as compared to responses elicited by currently approved vaccines.
- A single immunogenicity study in humans of a monovalent JN.1-containing vaccine candidate suggests that a JN.1 vaccine antigen is likely to produce higher neutralising antibodies to JN.1 and emerging decendents (e.g., KP.2) than an XBB.1.5 or related vaccine antigen.

Considerations of JN.1 antigen recommendation vs other sublineages (e.g., KP.2)
(TAG-CO-VAC April, 2024)

- Of potential candidates only JN.1 immunogenicity data available for TAG-CO-VAC analysis
  - Naïve and sequentially immunized animal JN.1 antisera react well with different co-circulating JN.1 progeny variants.
  - JN.1 post infection and post-vaccination human sera reacted well (within 2-fold) with different co-circulating JN.1 variants (e.g., KP.2, KP.3).
  - JN.1 genetically and antigenically central
    - Emerging variants react well with JN.1 antisera (within 2-fold)
    - Progeny variants can become antigenically farther apart from each other than from JN.1 parent.
- Cross reactivity of human sera against an emerging variant (e.g. KP.2) unknown.
  - May provide better reactivity with KP.2 or its descendants or have greater breadth.
  - May not provide as much breadth (i.e., reduced reactivity to other JN.1 variants)
    - Evolution may be driven by other fitness advantages that could negatively impact vaccine immunogenicity (e.g., spike stability, RBD position, hACE-2 binding).
- Earlier vaccine availability from multiple vaccine platforms are very important.

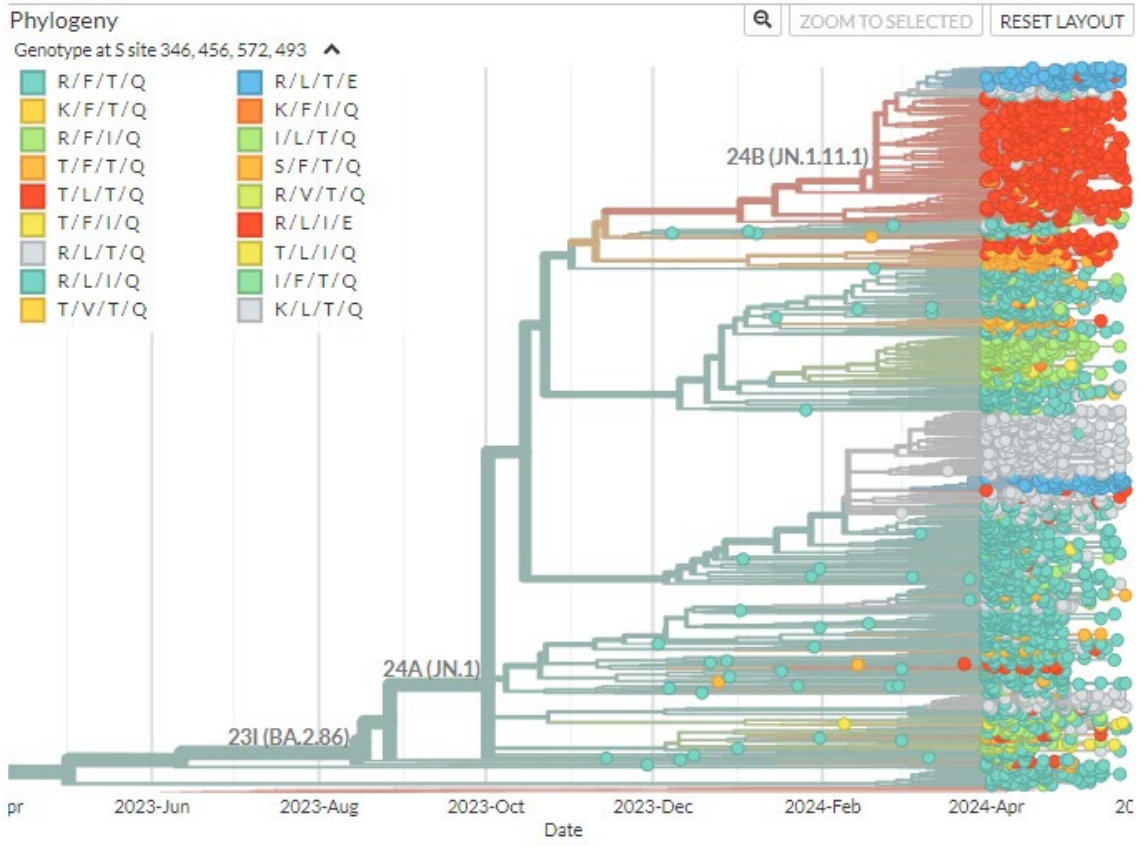
Artistic illustration of diversifying antigenic relationships



Drawn to show that emerging variants may be antigenically diverging from each other. Each square represents 2-fold antigenic distance.

Changes in viral lineages since TAG-CO- VAC meeting April 2024

- Continued JN.1 diversification
- Few countries with increasing SARS-CoV-2 activity
  - Thailand (JN.1 predominant)
  - Singapore (JN.1 and KP.2/KP.1)
  - New Zealand (JN.1> KP.3)
- Increases in KP.2 and **KP.3** proportions (WHO-TAG-VE as of Week 18)
  - KP.2 (F456L, R346T)
    - Global prevalence 14.7%
    - By WHO region comprised 17.5% in EUR , 14.0% in AMR, and 11.8% in WPR.
  - KP.3 (F456L and Q493E)
    - Global prevalence 16.5%
    - By WHO region comprised 20.3% in WPR, 17.3% in AMR, and 13.5% in EUR



Phylogeny of SARS-CoV-2 virus genomes from samples collected over the last two months highlighting parallel evolution at specific positions.
Showing 2250 of 3145 genomes sampled between Nov 2023 and May 2024. Sequences encoding specific residues at positions 346, 456, 572, 493 are coloured differently (see legend). Built with nextstrain/ncov. Maintained by the Nextstrain team. Data updated 2024-06-01.
Enabled by data from GISAID.

NextStrain: https://nextstrain.org/ncov

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Limitations of available evidence

- There are persistent and increasing **gaps in genetic/genomic surveillance** of SARS-CoV-2 globally, including low numbers of samples sequenced and limited geographic diversity.
- The trajectory of further SARS-CoV-2 evolution indicates that JN.1 will likely be the progenitor of SARS-CoV-2 variants, in the near term. However, the timing, specific mutations and antigenic characteristics, and the potential public health impact of newly emerged and future variants remain unknown.
- Data on the immune responses following XBB or JN.1 descendent lineage infection or XBB.1.5 vaccination are largely restricted to neutralizing antibodies and data on other aspects of the immune response, including cellular immunity, are limited.
- Immunogenicity data against currently circulating SARS-CoV-2 variants are not available for all COVID-19 vaccines.
- Estimates of rVE against recently circulating SARS-CoV-2 variants, including XBB or JN.1 descendent lineages, 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 during the same time period.

Acknowledgements and Thanks

World Health Organization

Chair

Dr David Wentworth

Chief of the Virology, Surveillance, and Diagnosis Branch (VSDB) of the Influenza Division at the U.S. Centers for Disease Control and Prevention (CDC)

Learn more ›

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