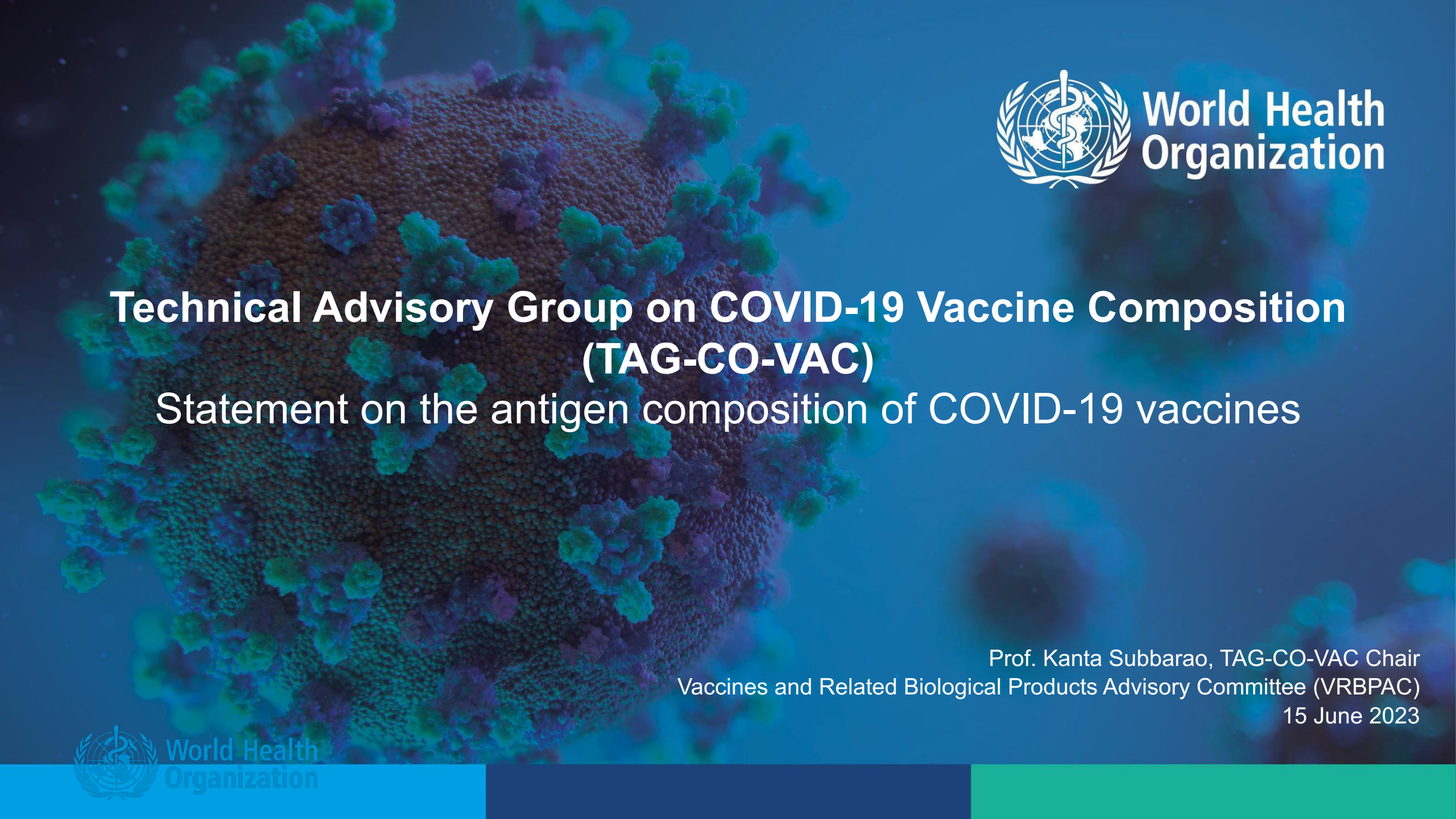
Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.



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

Statement on the antigen composition of COVID-19 vaccines

Prof. Kanta Subbarao, TAG-CO-VAC Chair

Vaccines and Related Biological Products Advisory Committee (VRBPAC)

15 June 2023

World Health Organization

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 Variants of Concern (VOC**s) on vaccines;
- Provide **interpretation of available evidence on the effect of VOCs on 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 WHO-recommended levels of protection against VOCs.

TAG-CO-VAC website: https://www.who.int/groups/technical-advisory-group-on-covid-19-vaccine-composition-(tag-co-vac)

Recommended levels of protection: WHO Target Product Profiles for COVID-19 Vaccines. Revised version April 2022.
Available at: https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines

World Health Organization

June 2022

World Health Organization

TAG-CO-VAC evidence base

June 2022

The TAG-CO-VAC and its Subgroup on Strain Selection reviewed published and unpublished data on the antigenicity and cross-protection of Omicron specific responses following vaccination or infection with prior VOCs, as well as following Omicron infection and/or Omicron-specific vaccine candidates, but acknowledge that the data are not exhaustive.

These data were used to inform the recommended vaccine composition update, published in June 2022.

Overview of evidence base

1. Cross-neutralization and cross-protection data following infection with index virus or prior VOC or vaccination
2. Antigenic cartography
3. Preliminary data on Omicron infection
4. Preliminary data on candidate vaccines with updated composition

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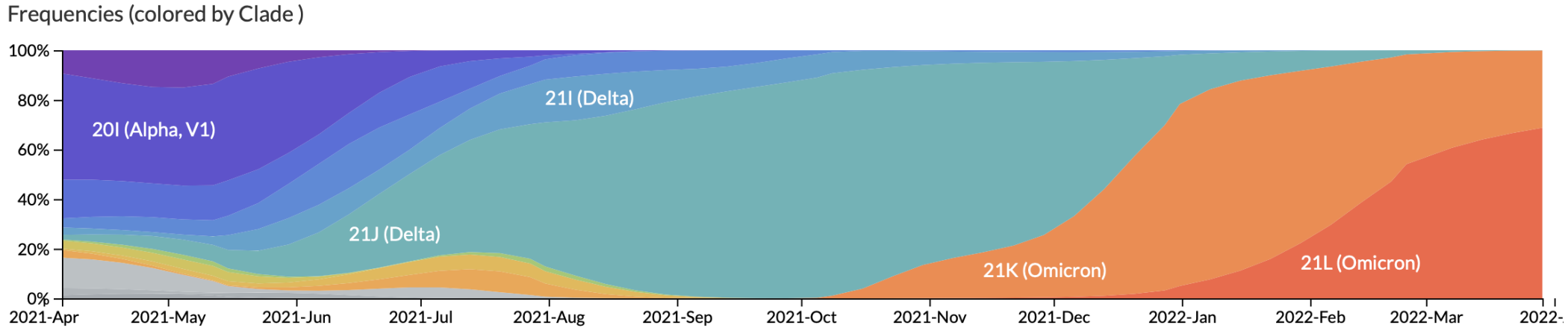
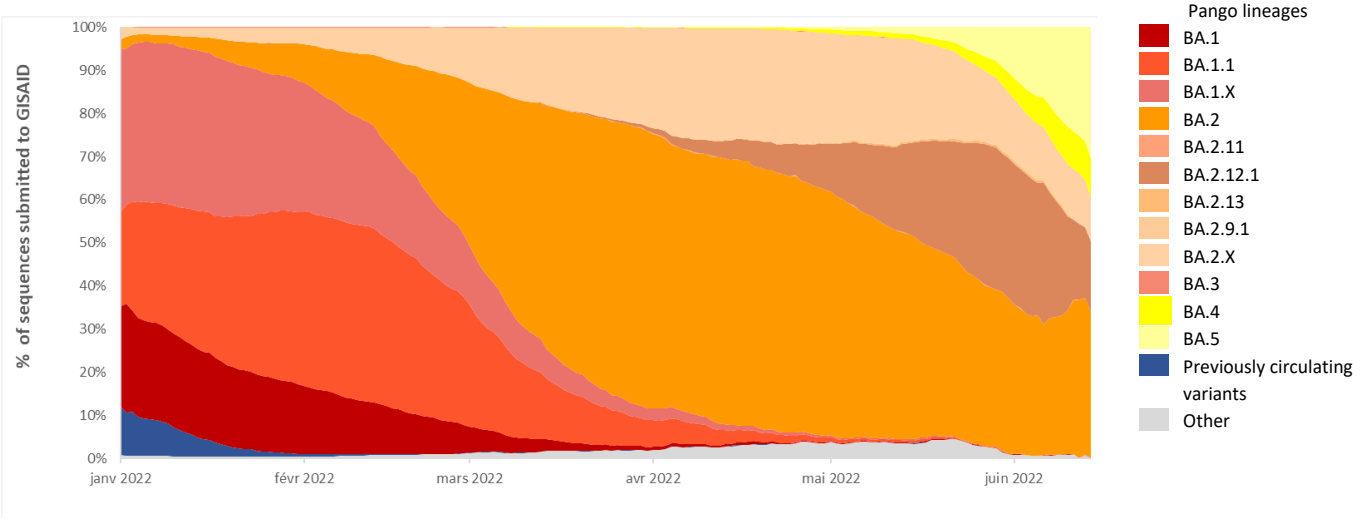
1. Evolution and spread: Omicron

June 2022

Since the classification of Omicron as a VOC, there has been rapid and relatively synchronous displacement of other circulating variants by Omicron in all six WHO regions.



Source: NextStrain



Proportion of sequences submitted to GISAID by Omicron descendent lineage and by epidemiological week

BA.2 remains the predominant Omicron descendent lineage globally.

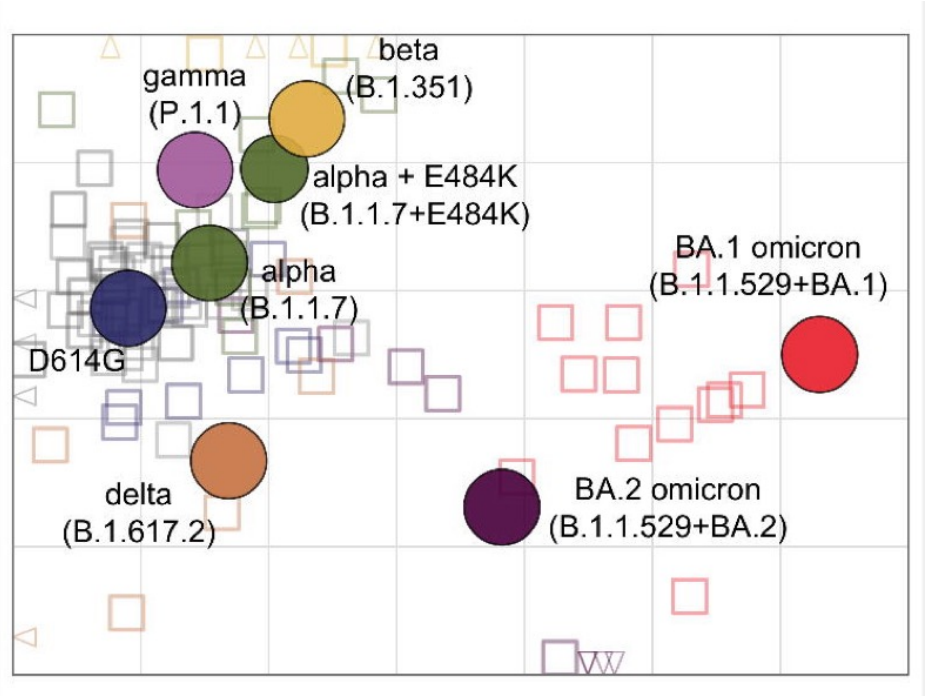
BA.4 and BA.5 have the same spike and are increasing in proportion.

World Health Organization

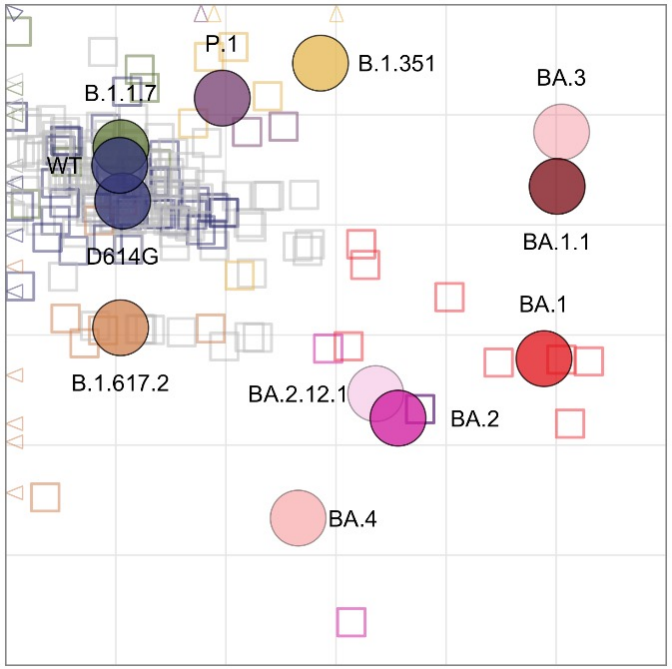
4. Antigenic cartography

June 2022

Neutralizing antibody data from human sera following infection with 614G or variants demonstrate that **Omicron lineages are antigenically distinct from the earlier VOCs** including 614G, Alpha, Beta, Gamma, Delta, Lambda, Mu and Zeta. The data also indicate that **BA.1 may be more antigenically distinct** from the index virus (D614G) than other sublineages.



Antigenic map of SARS-CoV-2 variants constructed from single exposure convalescent and double vaccinated sera.



Aggregated antigenic map of SARS-CoV-2 variants constructed using data from multiple preprint and published studies.

Rossler A, Netzl A, Knabl L, et al. BA.2 omicron differs immunologically from both BA.1 omicron and pre-omicron variants. Preprint. medRxiv. 2022; doi: 10.1101/2022.05.10.22274906

Netzl A, Turrelo, LeGresley E, et al. Aggregated incoming Omicron neutralization data. Last update 26 May 2022. Available from: https://docs.google.com/presentation/d/13NFT3GjMluTbDQZRSl7VIua6G3FvwSHYgbU9gMoWI4U/edit#slide=id.g12df13b5e55_4_0

World Health Organization

TAG-CO-VAC Statement

June 2022

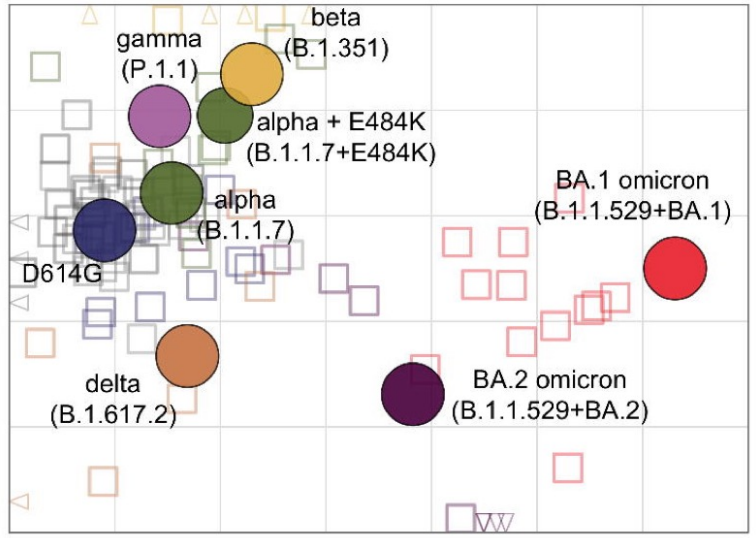
Summary of interim statement

Given the uncertainties in the trajectory of SARS-CoV-2 evolution and the characteristics of future variants, it may be prudent to pursue an additional objective of COVID-19 vaccination of **achieving broader immunity** against circulating and emerging variants while **retaining protection against severe disease and death.**

The inclusion of **Omicron**, as the most antigenically distinct SARS-CoV-2 VOC, as part of an updated vaccine composition may be beneficial if administered as a booster dose.

TAG-CO-VAC **does not advise the use of an Omicron-specific monovalent vaccine product as a standalone formulation for the primary series**.

The TAG-CO-VAC recognises **that viruses or viral genetic sequences very closely related to BA.1** are some of the most antigenically distant from the index virus to date and are likely to enhance the magnitude and breadth of the antibody response.



Antigenic map of SARS-CoV-2 variants constructed from single exposure convalescent and double vaccinated sera.

Full statement: https://www.who.int/news/item/17-06-2022-interim-statement-on--the-composition-of-current-COVID-19-vaccines
Accompanying SAGE statement: https://www.who.int/news/item/17-06-2022-interim-statement-on-decision-making-considerations-for-the-use-of-variant-updated-covid-19-vaccines

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Uncertainties in June 2022

- Trajectory of SARS-CoV-2 evolution: it was unclear whether future variants may evolve from previously circulating VOC (i.e. Alpha, Beta, Gamma, Delta etc.), or whether evolution would continue from Omicron.

- Performance of monovalent Omicron vaccines: it was not known whether an Omicron monovalent vaccine would offer similar cross-reactive immunity and cross-protection from severe illness caused by other VOCs in unprimed individuals as the index virus-based vaccines have done.

- Bi/multivalent products: it was unclear whether an Omicron-containing bi/multivalent product would elicit cross-reactive immune responses in humans that would be equivalent to those elicited with a sequential vaccine approach (i.e. primary vaccination using the index virus-based vaccines, followed by a booster dose of an Omicron-specific vaccine); there were no data on a bivalent product in naïve individuals.

- Potential performance of variant-specific vaccines: it was assumed that the safety and reactogenicity of any product with an updated vaccine composition would be comparable to those of the currently licensed vaccines based on the index virus.

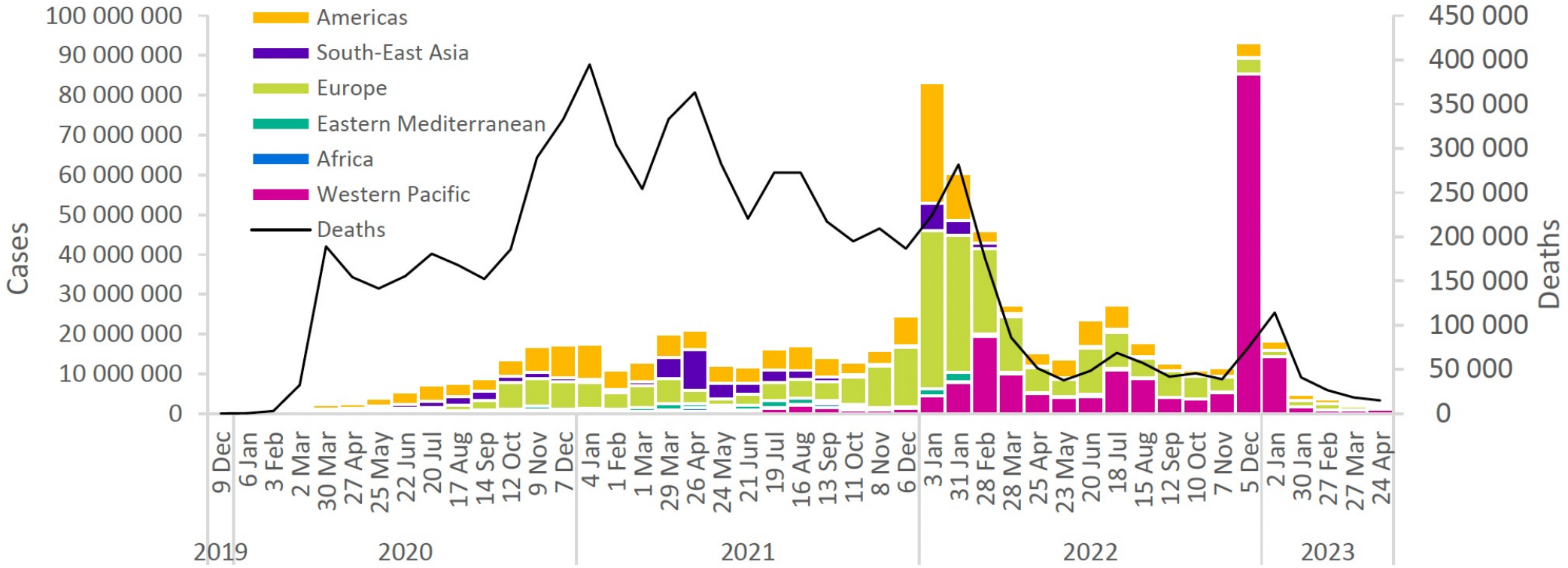
May 2023

World Health Organization

Current situation: May 2023

Cumulative:

- >766,000,000 confirmed cases
- >6,900,000 deaths



COVID-19 cases and deaths reported to WHO by WHO Region, January 2020 – May 2023

Cases are depicted by bars; deaths depicted by line

World Health Organization

Current situation: May 2023

Overall seroprevalence is high in all regions, as a result of vaccination and/or infection

WHO region	Aug 2021	Oct 2021	Dec 2021	Feb 2022	Apr 2022	Jun 2022
Americas (HIC)	84.4% [48.6%-96.9%]	93.5% [87.1%-96.8%]	95.4% [93.2%-97.0%]	97.7% [97.5%-97.9%]	99.8% [99.7%-99.8%]	100.0% [64.1%-100.0%]
Western Pacific	No data	34.0% [28.9%-39.5%]	30.0% [25.1%-35.4%]	97.2% [95.0%-98.5%]	No data	99.0% [98.7%-99.2%]
Europe (HIC)	81.1% [68.5%-89.4%]	88.7% [82.1%-93.1%]	94.1% [84.8%-97.9%]	94.0% [89.1%-96.7%]	95.2% [92.7%-96.8%]	96.1% [92.3%-98.1%]
South-East Asia	69.0% [65.6%-72.3%]	84.7% [81.4%-87.5%]	90.6% [90.3%-90.9%]	No data	No data	No data
Americas (LMIC)	85.0% [84.1%-85.8%]	No data	No data	No data	86.5% [84.0—88.7%]	No data
Africa	60.9% [50.7%-70.3%]	73.1% [72.0%-74.1%]	80.1% [71.8%-86.5%]	82.5% [62.6%-93.0%]	84.7% [72.6%-92.1%]	No data
Europe (LMIC)	No data	79.6% [77.9%-81.2%]	No data	No data	No data	No data
Eastern Med.	74.1% [73.2%-75.0%]	75.8% [72.9%-78.5%]	No data	No data	No data	No data
Global	45.8% [43.2%-48.5%]	70.0% [67.8%-72.2%]	72.4% [70.1%-74.7%]	89.5% [87.8%-91.0%]	89.8% [87.8%-91.4%]	

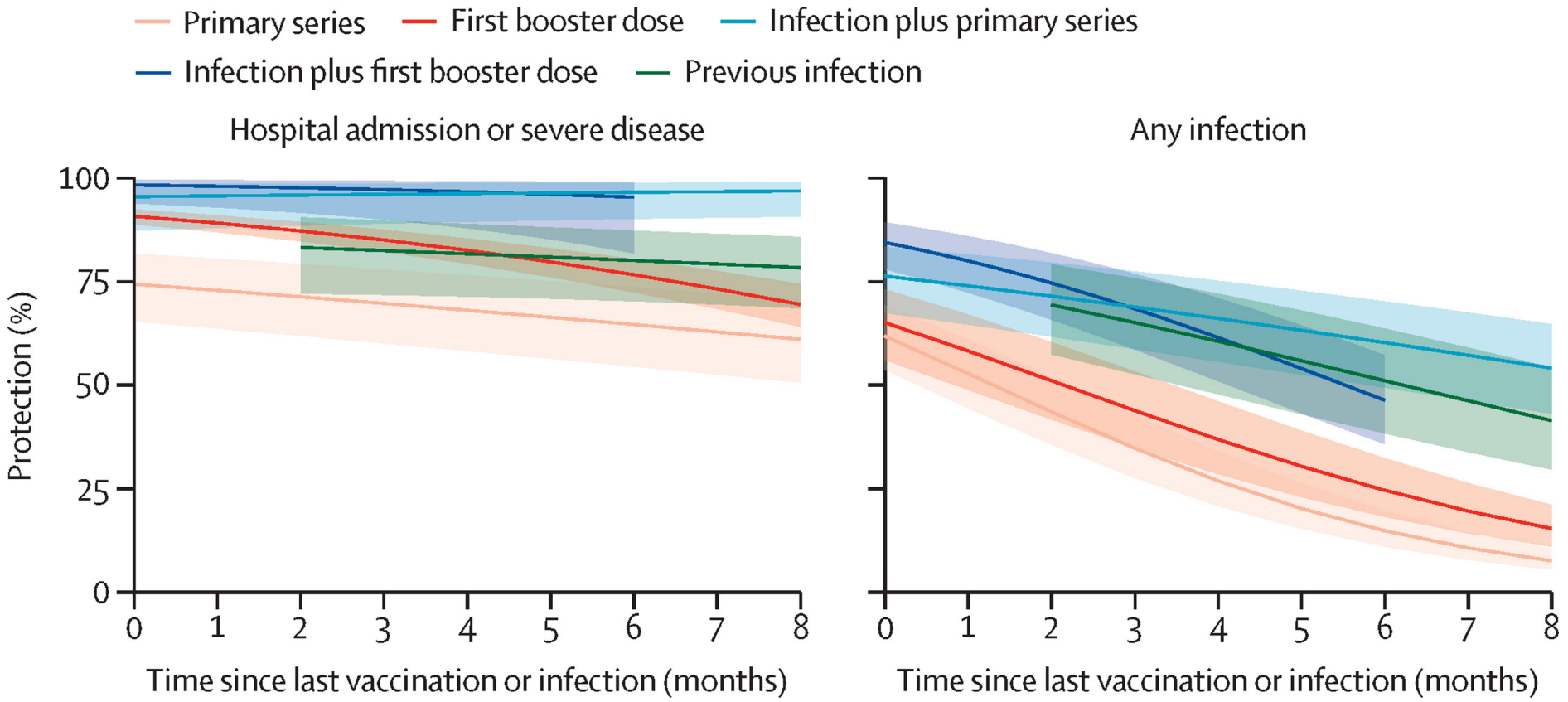
Seroprevalence varied by region, with many regions nearing 100% in 2022

Seroprevalence increased from Aug 2021 to Jun 2022 in all regions

Key: ≥ 80% ≥ 60% 80% ≥ 40%, ≥ 20%, ≥ 0%, White shading indicates n=1 study to analyze in month, region
No data: absence of general population study, or of low or moderate risk of bias studies, to analyze in month, region.

World Health Organization

Protective effectiveness of hybrid immunity



Protection against Omicron variant conferred by the primary series vaccine, first booster vaccine, previous infection, and hybrid immunity compared to immune-naive individuals over time

The shaded areas denote 95% CIs. Vaccine effectiveness data were procured from a separate systematic review

Bobrovitz N, et al. Lancet Infect Dis. 2023;23(5):556-567.

World Health Organization

TAG-CO-VAC evidence review: May 2023

The TAG-CO-VAC reconvened on 11-12 May 2023.

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

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 descendant 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.

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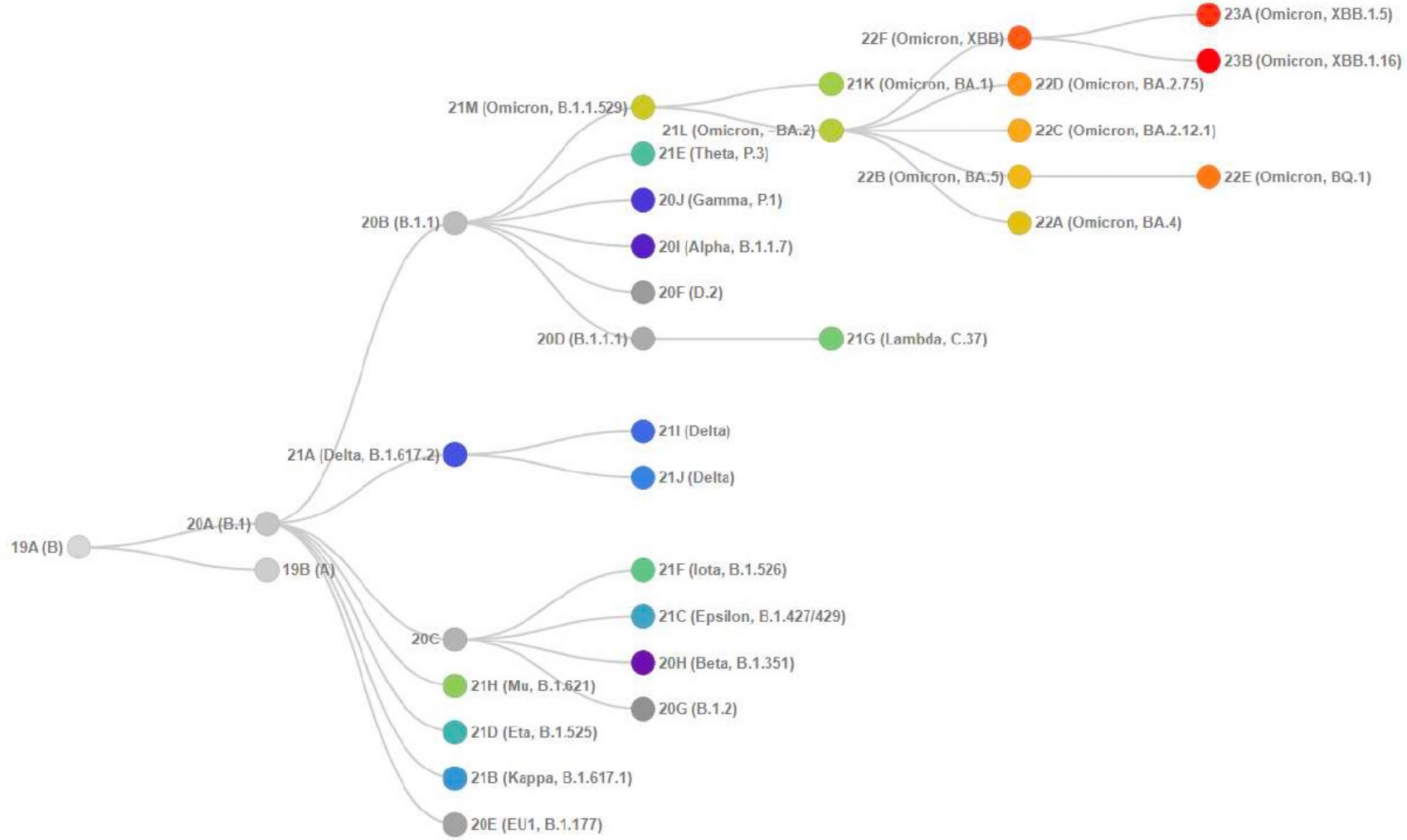
1. SARS-CoV-2 evolution



Simplified illustration of phylogenetic relationships of SARS-CoV-2 clades, as defined by Nextstrain

Nextstrain: https://clades.nextstrain.org

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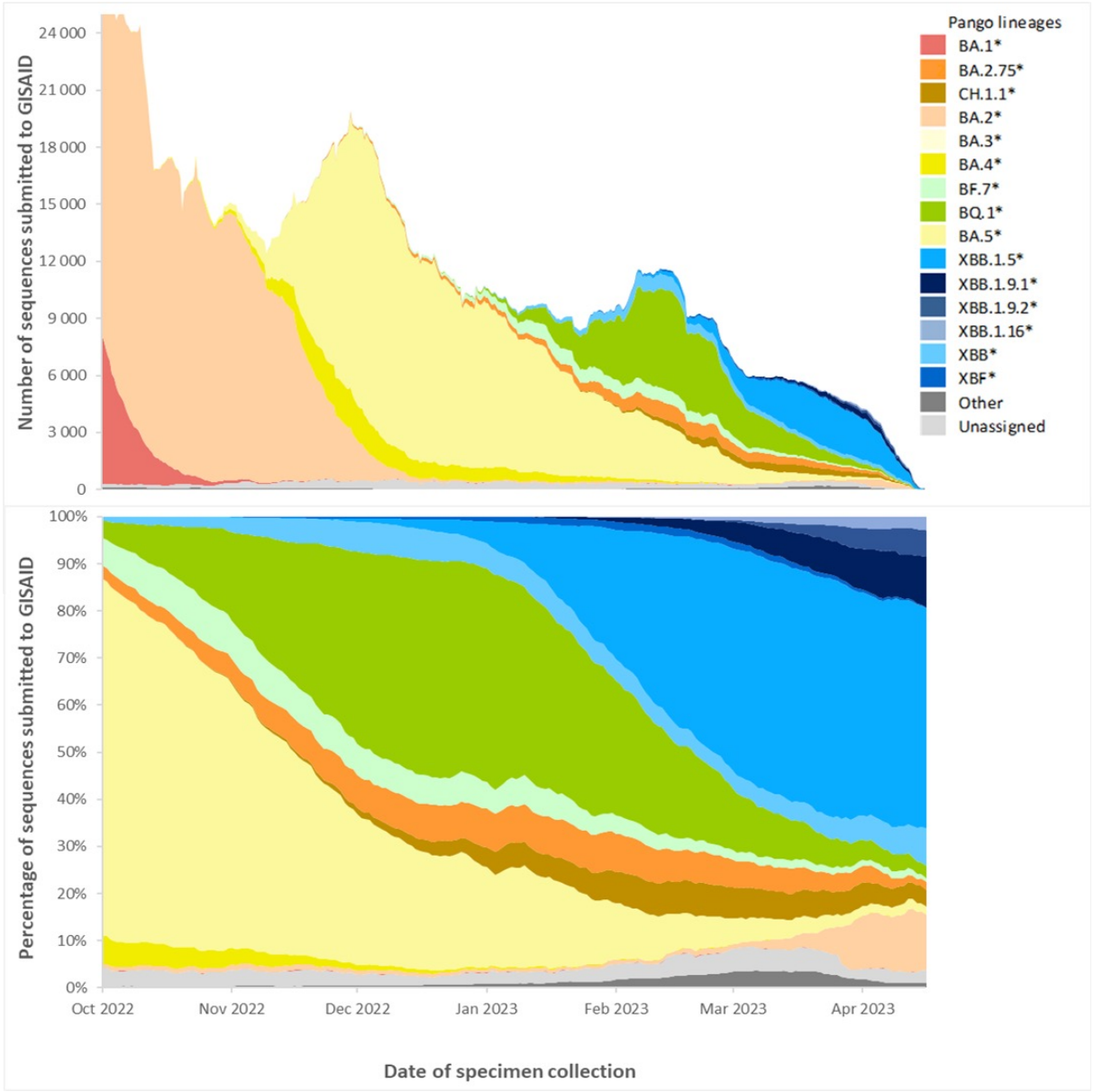
1. Global SARS-CoV-2 variant circulation



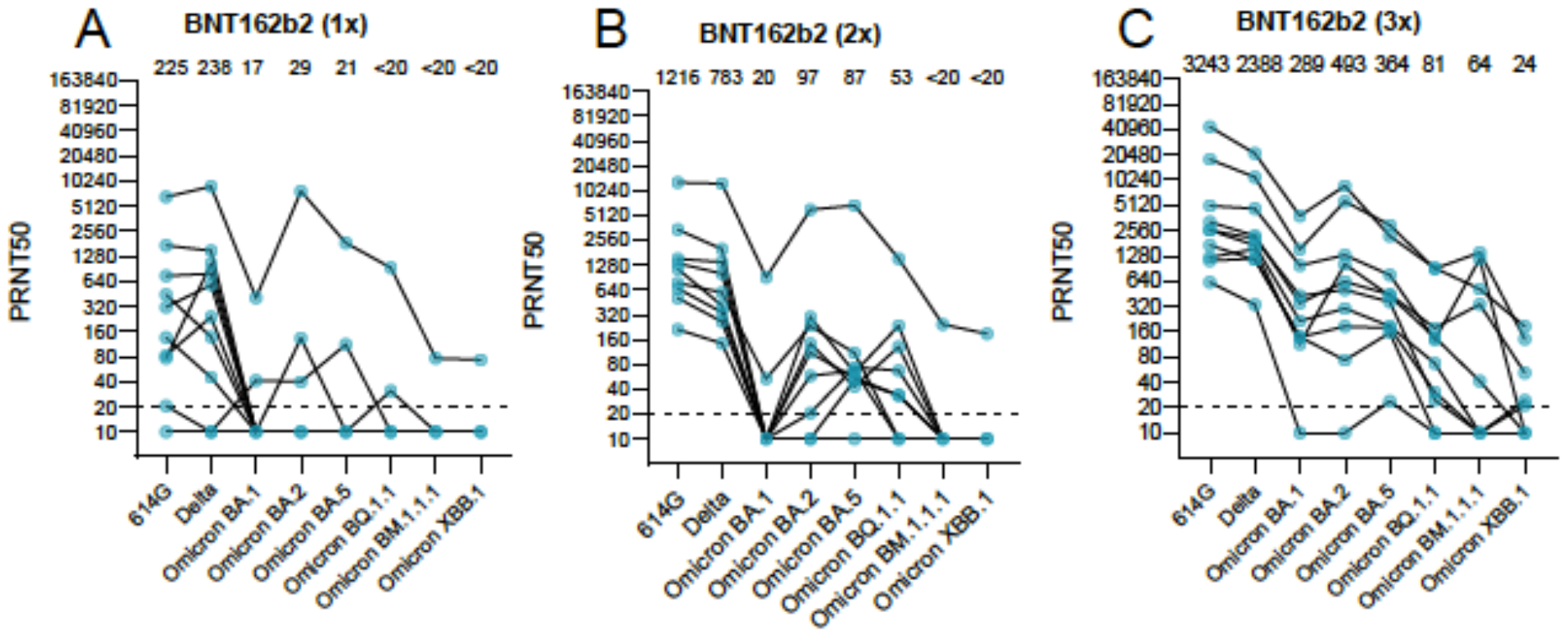
Number (top) and percentage (bottom) of SARS-CoV-2 sequences from 1 Oct 2022 – 16 April 2023

- There continues to be substantial genetic and antigenic evolution in the virus
- The spike proteins of XBB.1 descendant 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
- Index virus and other early variants (e.g., Alpha, Beta, Gamma and Delta) are no longer detected in humans

Analysis conducted by WHO using data extracted from GISAID.org on 1 May 2023

World Health Organization

1. Impact of recent variants on cross-neutralization following vaccination



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

Rössler A, et al. medRxiv (pre-print). 2023; doi: 10.1101/2023.05.02.23289412

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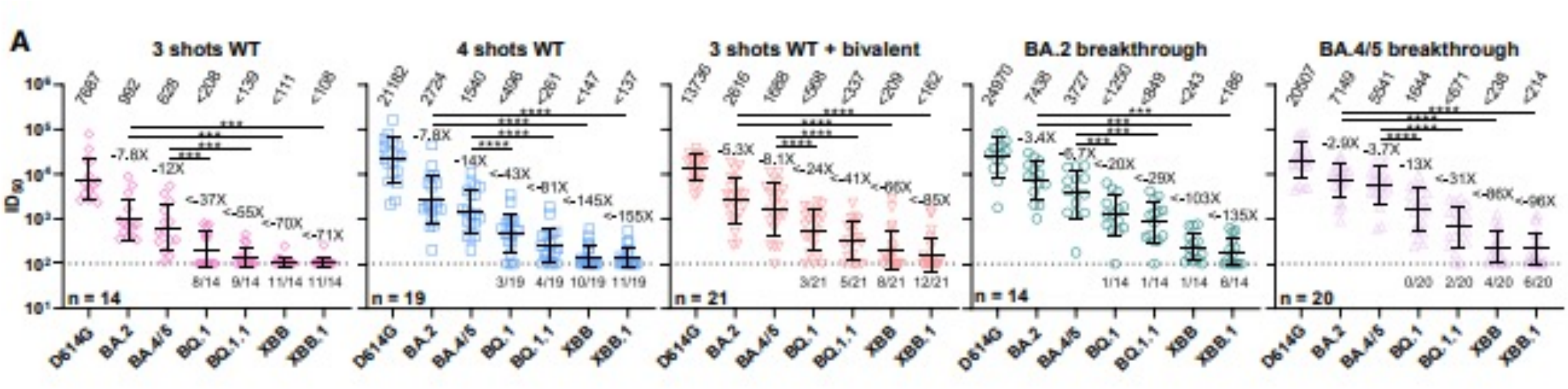
1. Impact on cross-neutralization following vaccination and infection



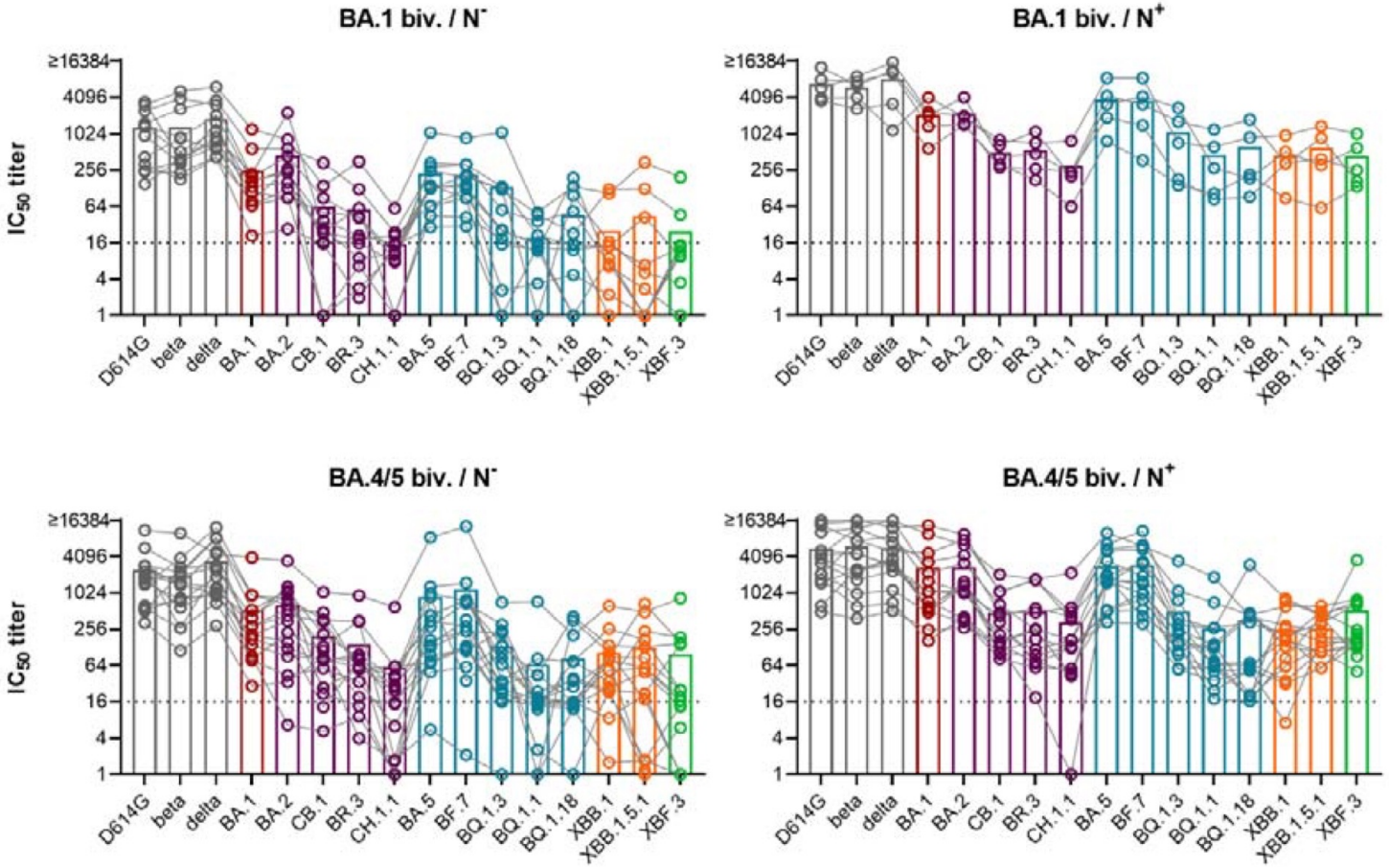
Serum neutralization of Omicron descendent lineages BQ.1, BQ.1.1, XBB, and XBB.1

Neutralization of pseudotyped D614G and Omicron descendent 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

Wang Q, et al. Cell. 2023;186(2):279-286.e8

World Health Organization

1. Impact on cross-neutralization following vaccination and infection



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

Rössler A, et al. medRxiv (pre-print). 2023; doi: 10.1101/2023.05.02.23289412

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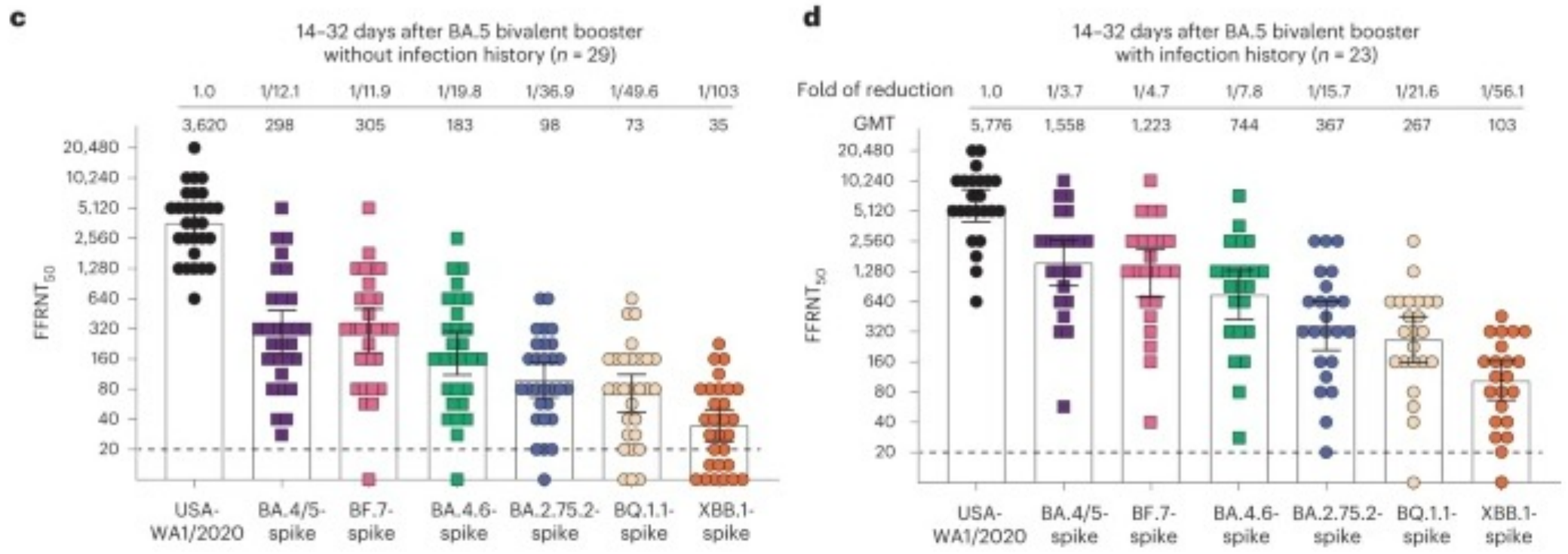
1. Impact on cross-neutralization following vaccination and infection



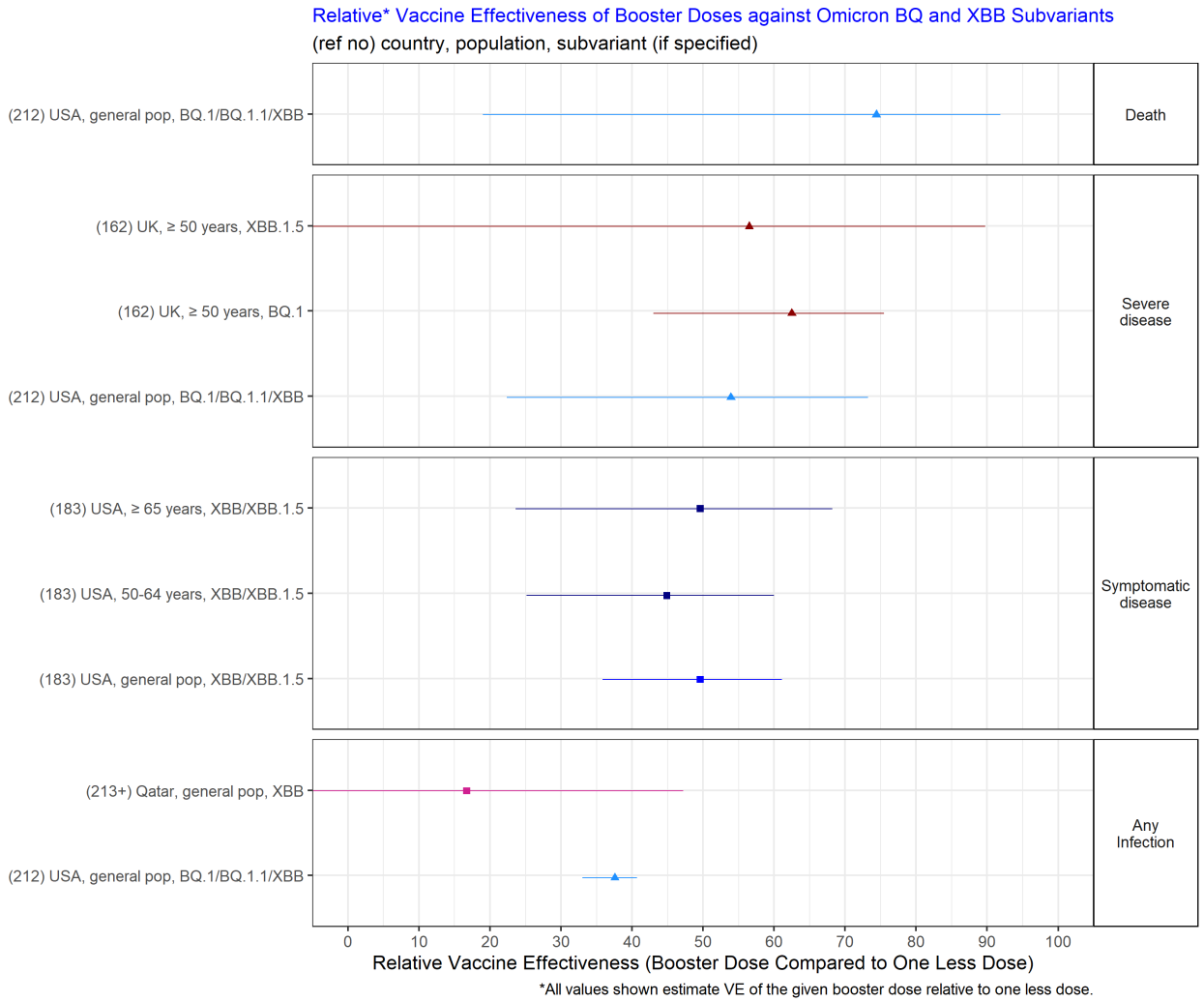
Pseudoneutralization profiles after boosting with a bivalent mRNA vaccine in individuals with (right) or without (left) evidence of prior infection

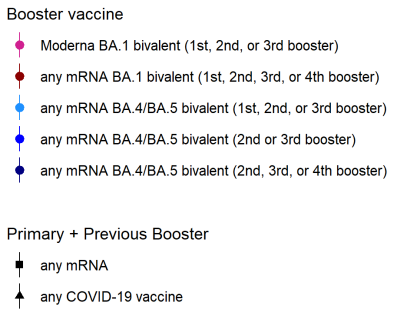
50% fluorescent focus-reduction neutralization titers (FFRNT50) against omicron sublineages and WA-1/2020 were determined using human sera from BA.5 bivalent booster recipients with or without documented infection history. Bar heights and the numbers above indicate GMTs. Error bars indicate 95% confidence 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

Kurhade C, et al. Nat Med. 2023;29(2):344-347

World Health Organization

2. VE of current vaccines during XBB.1 descendant lineage circulation



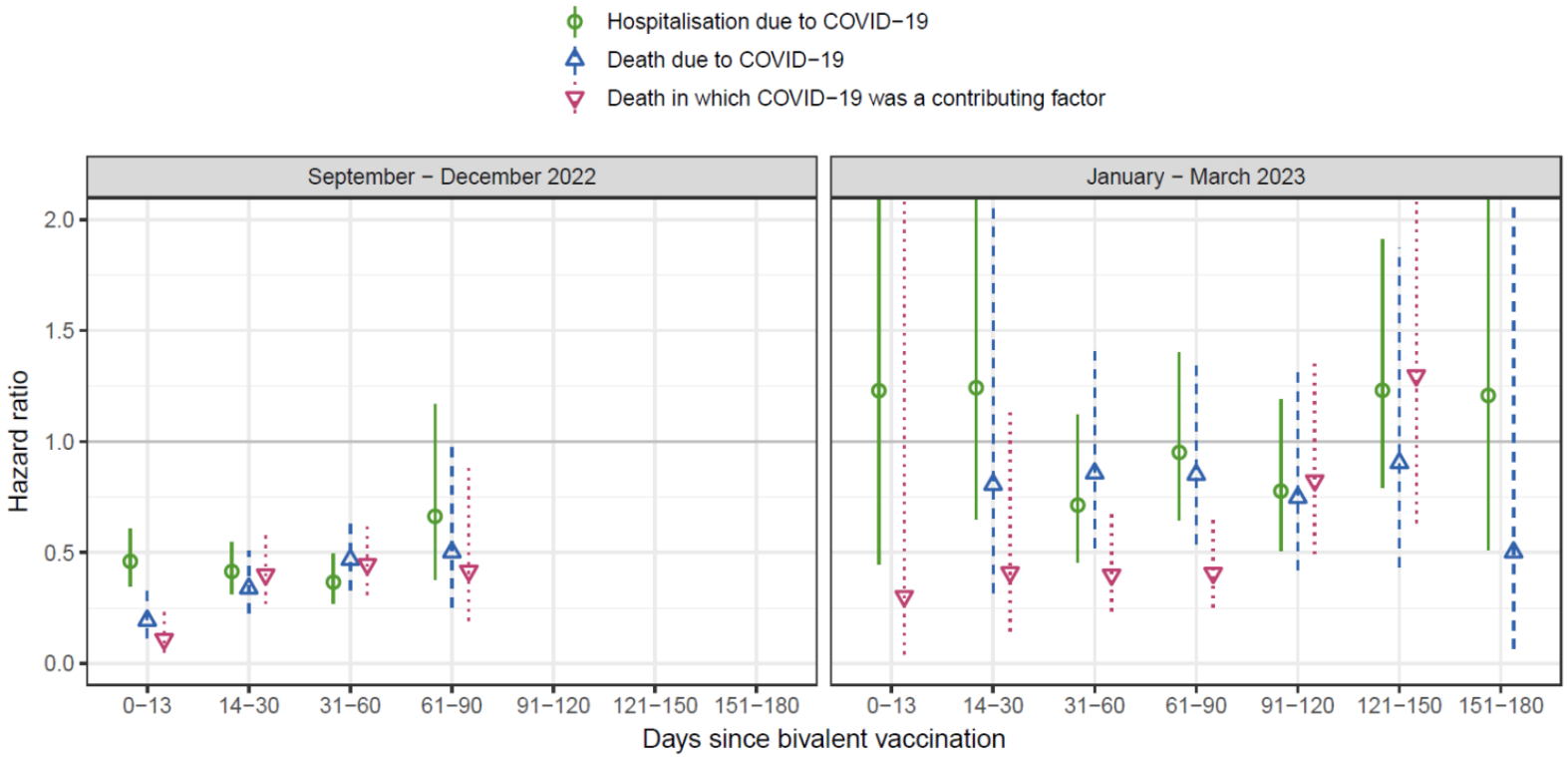


Estimates of relative vaccine effectiveness of a booster dose of any BA.1- or BA.4/5-containing mRNA vaccine (following three doses of index virus-based vaccine)

Lin DY, et al. N Engl J Med. 2023;388(19):1818-1820; Kirsebom FCM, et al. medRxiv (pre-print). 2023; doi: 10.1101/2023.03.31.23288018; Link-Gelles R, et al. MMWR Morb Mortal Wkly Rep. 2023;72(5):119-124; Chemaitelly H, et al. medRxiv (pre-print). 2023; doi: 10.1101/2023.04.15.23288612.

World Health Organization

2. HR of severe disease during XBB.1 descendant lineage circulation



Hazard ratios of hospitalization or death due to COVID-19 in adults who received bivalent mRNA vaccine as a booster dose

September – December 2022 (left) and January – March 2023 (right)

Poukka E, et al. medRxiv (pre-print). 2023; doi: 10.1101/2023.03.02.23286561.

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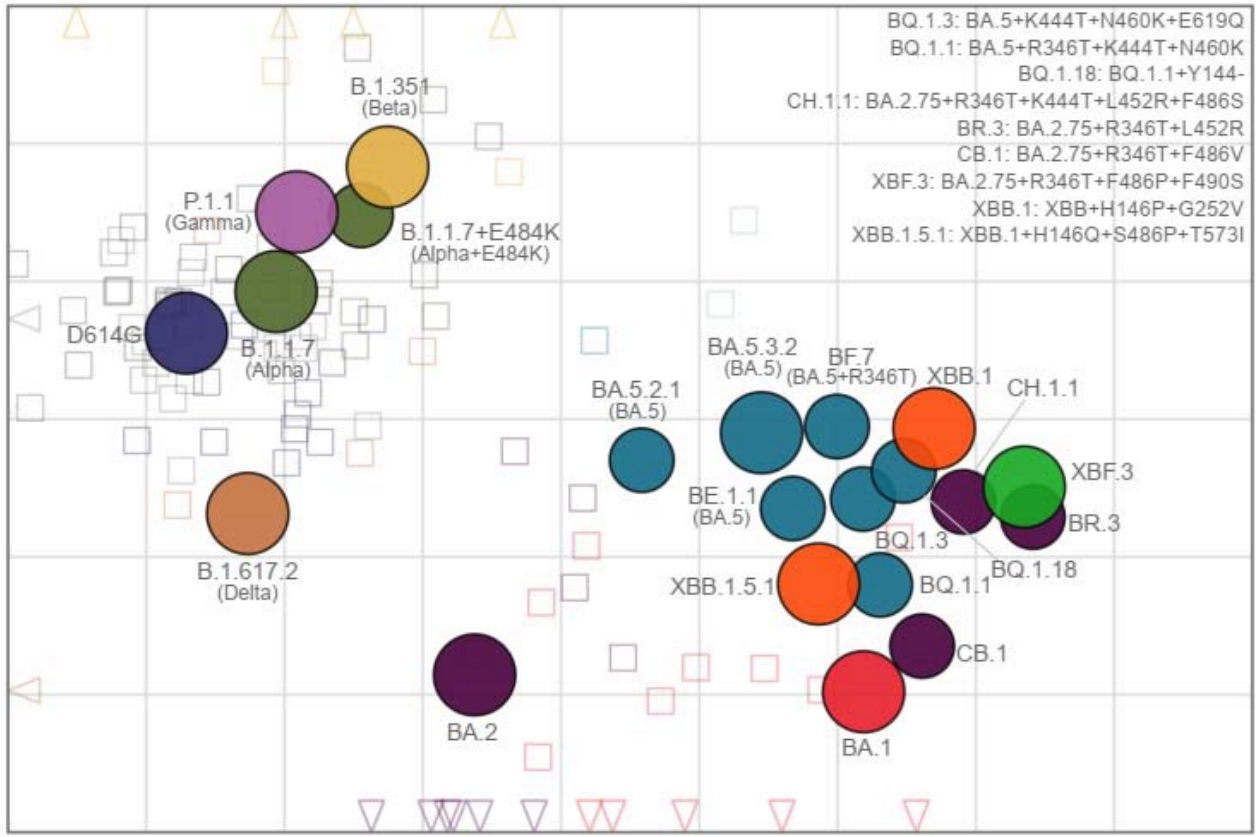
3. Antigenic cartography of SARS-CoV-2 variants using human sera



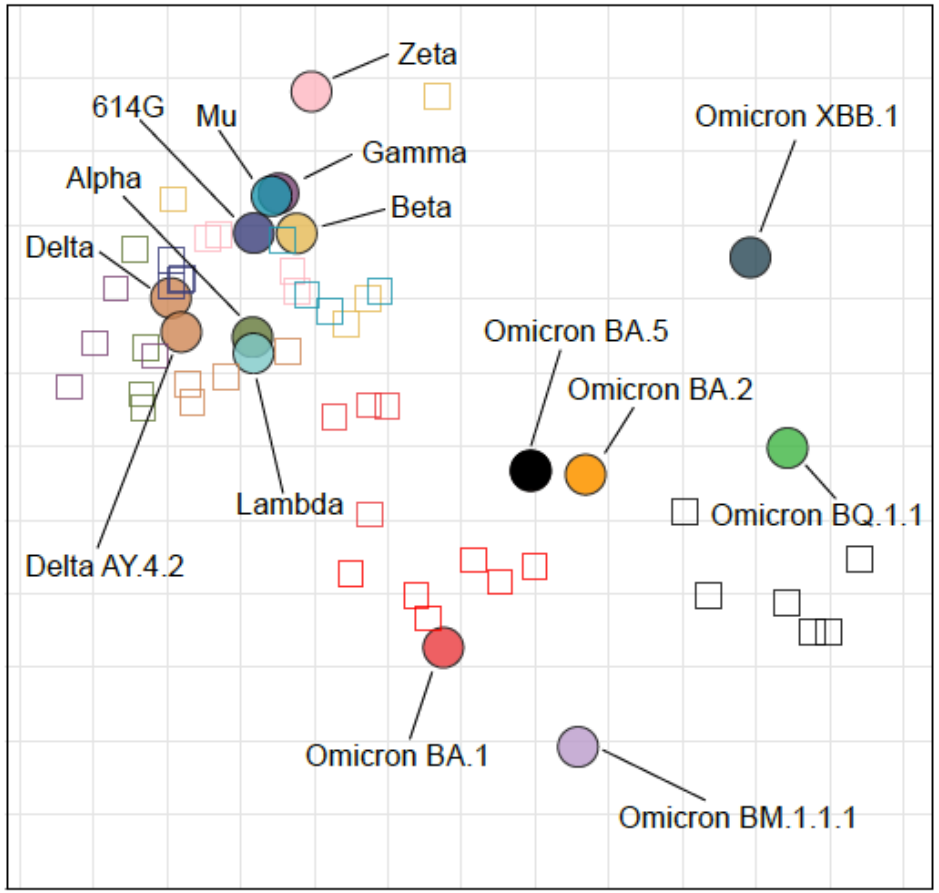
Antigenic map constructed from human single exposure and double vaccination sera

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

Rössler A, et al. medRxiv (pre-print). 2023; doi: 10.1101/2023.05.02.23289412

World Health Organization

3. Antigenic cartography of SARS-CoV-2 variants using naïve animal sera



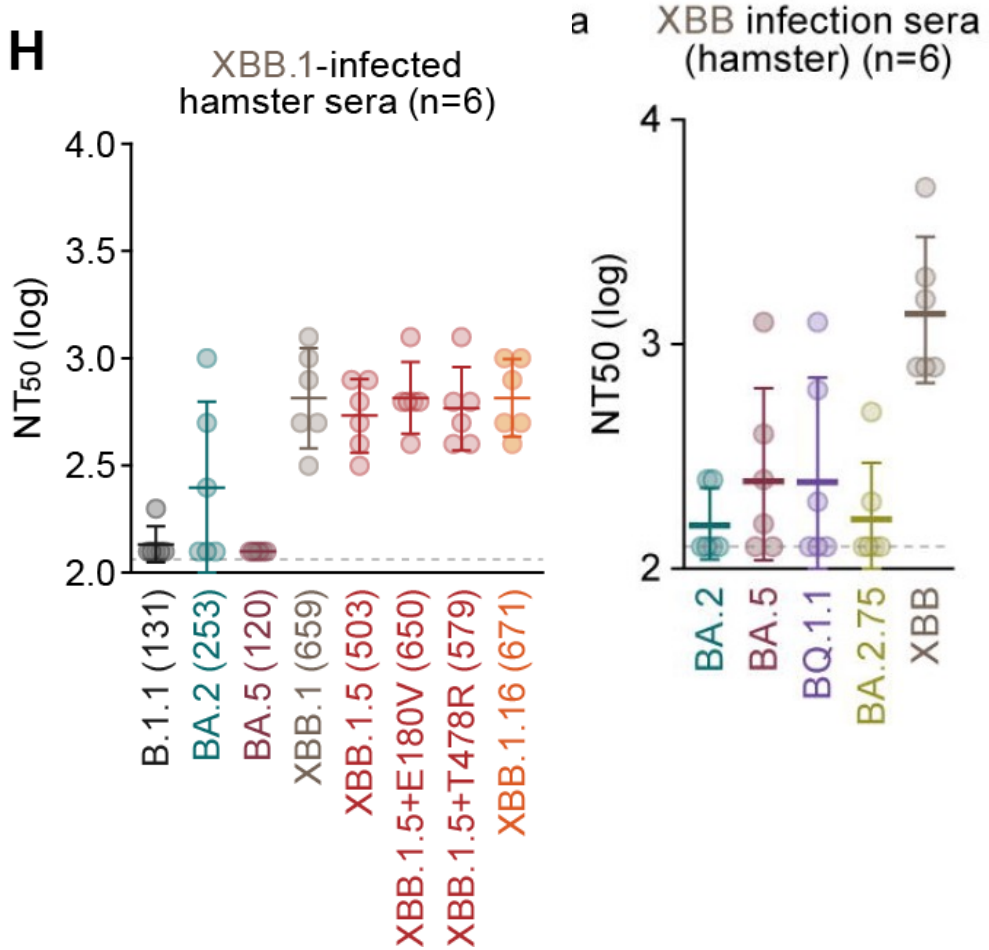
Antigenic cartography of SARS-CoV-2 variants using hamster sera

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

Mykytyn AZ, et al. Lancet Microbe. 2023;4(5):e294-e295

World Health Organization

4. Preclinical data following infection with XBB.1 descendent lineages



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)

Yamasoba D, et al. bioRxiv (pre-print). 2023; doi: 10.1101/2023.04.06.535883; Tamura T, et al. bioRxiv (pre-print). 2023; doi: 10.1101/2022.12.27.521986.

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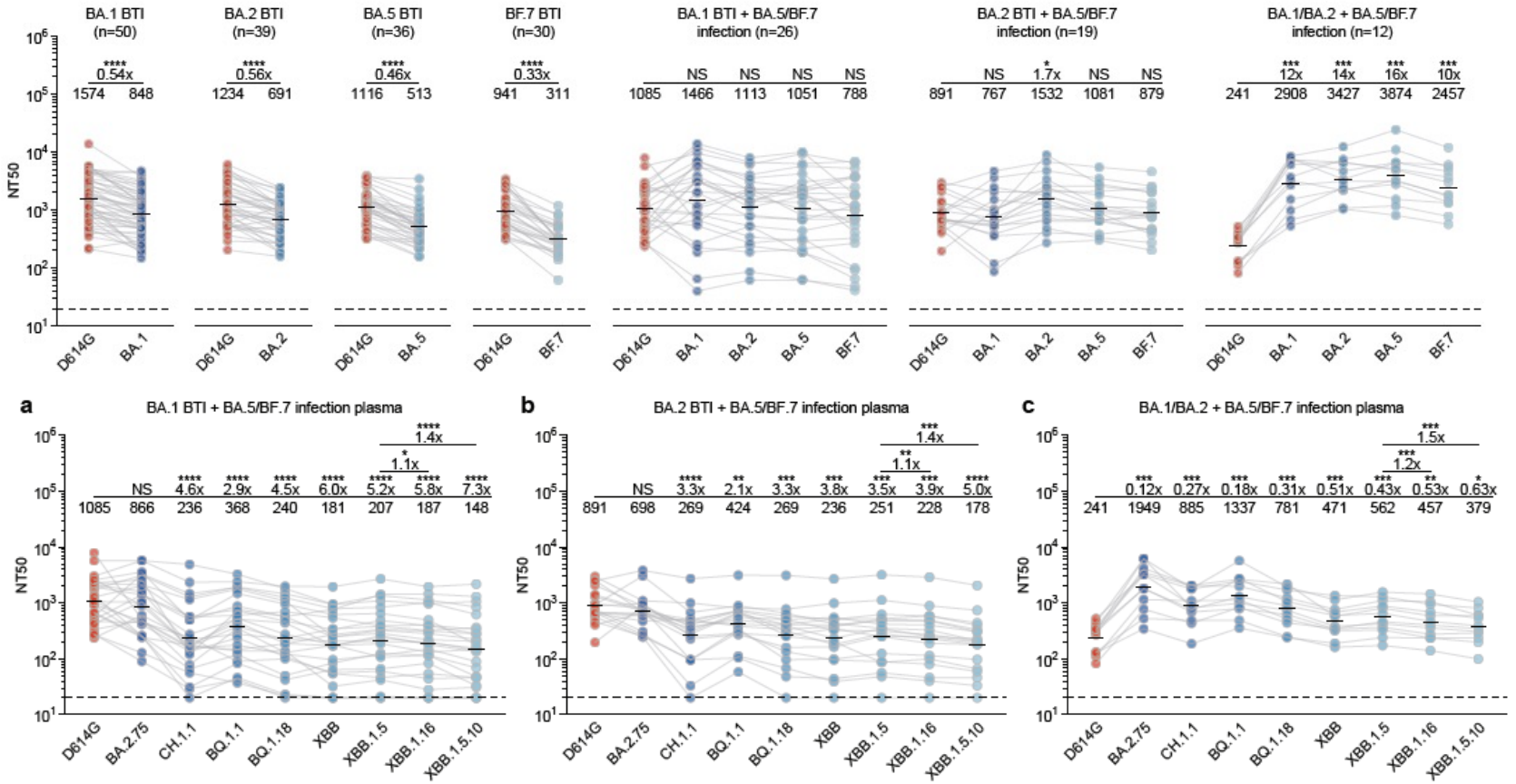
6. B cell memory responses following vaccination and/or infection



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.

Yisimayi A, et al. bioRxiv (pre-print). 2023; doi: 10.1101/2023.05.01.538516

World Health Organization

Summary of available evidence

May 2023

- In the fourth year of the pandemic, there is **high seroprevalence** in the global population as a result of vaccination and/or infection, and **immunological profiles against SARS-CoV-2 are highly heterogeneous** (i.e. individuals have been infected with different variants and/or vaccinated using a variety of vaccine platforms).

- There continues to be **substantial genetic and antigenic evolution of the spike protein of SARS-CoV-2**, and the evolutionary trajectory continues to diverge from the index virus. Despite increasing gaps in genomic surveillance globally, the available sequencing data indicates that the index virus and other early variants (e.g., Alpha, Beta, Gamma and Delta) are no longer detected in humans.

- As of May 2023, the **XBB.1 descendent lineages currently predominate** globally (i.e., XBB.1.5, XBB.1.16, XBB.1.9).

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Summary of available evidence (cont.)

- **XBB descendent lineages, including XBB.1.5 and XBB.1.16, are highly immune evasive**, with XBB.1.5 being one of the SARS-CoV-2 variants with the greatest magnitude of immune escape from neutralizing antibodies to date.

- Estimates of VE against currently circulating SARS-CoV-2 variants, including XBB.1 descendent 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 descendent and XBB.1 descendent lineages, while others suggest reduced VE during periods of predominance of XBB.1 descendent lineages.

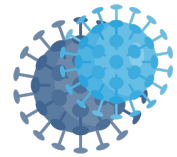
- Sera from individuals who have received two, three or four doses of index virus-based vaccines, or a booster dose of a bivalent (BA.1- or BA.4/5- containing) mRNA vaccine show **substantially lower neutralizing antibody titers against XBB.1 descendent lineages, as compared to titers specific for the antigens included in the vaccine**. Individuals with hybrid immunity due to any SARS-CoV-2 infection show higher neutralizing antibody titers against XBB.1 descendent lineages as compared to responses from vaccinated individuals who had no evidence of infection.

Summary of available evidence (cont.)

- There is *in vitro* evidence that **immune imprinting**, which is a phenomenon in which B cell memory recall responses towards previously encountered antigen reduce the response to new antigens, **may be occurring**. However, based on observational epidemiological studies to date, the clinical impact remains unclear.

- Preclinical data shared confidentially with the TAG-CO-VAC by vaccine manufacturers show that **vaccination with XBB.1 descendent lineage-containing candidate vaccines (including XBB.1.5) elicits higher neutralizing antibody responses to currently circulating SARS-CoV-2 variants**, compared to responses elicited by currently approved vaccines.

Limitations of available evidence



- The timing, specific mutations and antigenic characteristics, and the potential public health risks of future variants remain unknown;
- The majority of the available clinical and preclinical data of immune responses are on the recent variants XBB.1 or XBB.1.5, but there is minimal information on other current variants of interest or variants under monitoring;
- Data on immune responses over time following infection with currently circulating SARS-CoV-2 variants are limited;
- Data on the immune response specific for XBB.1 descendent lineages are largely restricted to neutralizing antibodies and are limited for other aspects of the immune response, including cellular immunity;
- Data on the protection conferred by hybrid immunity (i.e. combination of infection- and vaccination-induced immunity) are largely derived from populations that predominantly received an mRNA booster dose;
- Data on VE of current COVID-19 vaccines, including index-virus based and bivalent mRNA vaccines, against XBB descendent lineages are limited and estimates during periods of XBB.1 descendant lineage circulation are only available for mRNA vaccines;
- Data on candidate vaccines that include an XBB.1 descendent lineage are limited to animal models.

Full statement available: https://www.who.int/news/item/18-05-2023-statement-on-the-antigen-composition-of-covid-19-vaccines

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Recommendations for updates to COVID-19 vaccine composition

In order to improve protection, in particular against symptomatic disease, new formulations of COVID-19 vaccines should aim to induce antibody responses that neutralize XBB descendent lineages.

- One approach recommended by TAG-CO-VAC is the use of a **monovalent XBB.1 descendent lineage, such as XBB.1.5** as the vaccine antigen;
- Given the small genetic and antigenic differences from XBB.1.5, **XBB.1.16 may be an alternative**;
- Other formulations and/or platforms that achieve robust neutralizing antibody responses against XBB descendent lineages can also be considered.

Accession numbers:

XBB.1.5 (e.g., hCoV-19/USA/RI-CDC-2-6647173/2022, GenBank: OQ054680.1, GISAID: EPI_ISL_16134259, or WHO Biohub: 2023-WHO-LS-01, GenBank: OQ983940, GISAID EPI_ISL_16760602)

XBB.1.16 (e.g., hCoV-19/USA/MI-CDC-LC1038976/2023, GenBank: OQ931660 GISAID: EPI_ISL_17619088)

Full statement available: https://www.who.int/news/item/18-05-2023-statement-on-the-antigen-composition-of-covid-19-vaccines

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Recommendations for updates to COVID-19 vaccine composition (cont.)

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**.

- the index virus and antigenically closely related variants no longer circulate in humans;
- the index virus antigen elicits undetectable or very low levels of neutralizing antibodies against currently circulating SARS-CoV-2 variants, including XBB descendent lineages;
- inclusion of the index virus in bi- or multivalent vaccines reduces the concentration of the new target antigen(s) as compared to monovalent vaccines, which may decrease the magnitude of the humoral immune response; and
- immune imprinting due to repeated exposure to the index virus may reduce immune responses to new target antigen(s).

Full statement available: https://www.who.int/news/item/18-05-2023-statement-on-the-antigen-composition-of-covid-19-vaccines

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