

Vaccines and Related Biological Products Advisory Committee Meeting

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World Health Organization

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

Interim statement on current COVID-19 vaccine composition

Prof. Kanta Subbarao, TAG-CO-VAC Chair
Vaccines and Related Biological Products Advisory Committee Meeting
28 June 2022

Technical Advisory Group on COVID-19 Vaccine Composition

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Functions of the TAG-CO-VAC

- Make recommendations to WHO on the **methods to assess the impact of Variants of Concern (VOCs) 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.

Members

18 Members: [https://www.who.int/groups/technical-advisory-group-on-covid-19-vaccine-composition-\(tag-co-vac\)](https://www.who.int/groups/technical-advisory-group-on-covid-19-vaccine-composition-(tag-co-vac))

Previous interim statements

11 January 2022: <https://www.who.int/news/item/11-01-2022-interim-statement-on-covid-19-vaccines-in-the-context-of-the-circulation-of-the-omicron-sars-cov-2-variant-from-the-who-technical-advisory-group-on-covid-19-vaccine-composition>

8 March 2022: [https://www.who.int/news/item/08-03-2022-interim-statement-on-covid-19-vaccines-in-the-context-of-the-circulation-of-the-omicron-sars-cov-2-variant-from-the-who-technical-advisory-group-on-covid-19-vaccine-composition-\(tag-co-vac\)-08-march-2022](https://www.who.int/news/item/08-03-2022-interim-statement-on-covid-19-vaccines-in-the-context-of-the-circulation-of-the-omicron-sars-cov-2-variant-from-the-who-technical-advisory-group-on-covid-19-vaccine-composition-(tag-co-vac)-08-march-2022)

Overview of TAG-CO-VAC evidence base



Since the designation of Omicron as a SARS-CoV-2 Variant of Concern in November 2021, the TAG-CO-VAC has reviewed published and unpublished data on the antigenicity and cross-protection of Omicron specific responses following vaccination or infection with prior VOCs, as well as following Omicron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.

The data highlighted in the following slides are not exhaustive, but were specifically reviewed and considered to inform the interim statement on COVID-19 vaccine composition.

Overview of evidence base

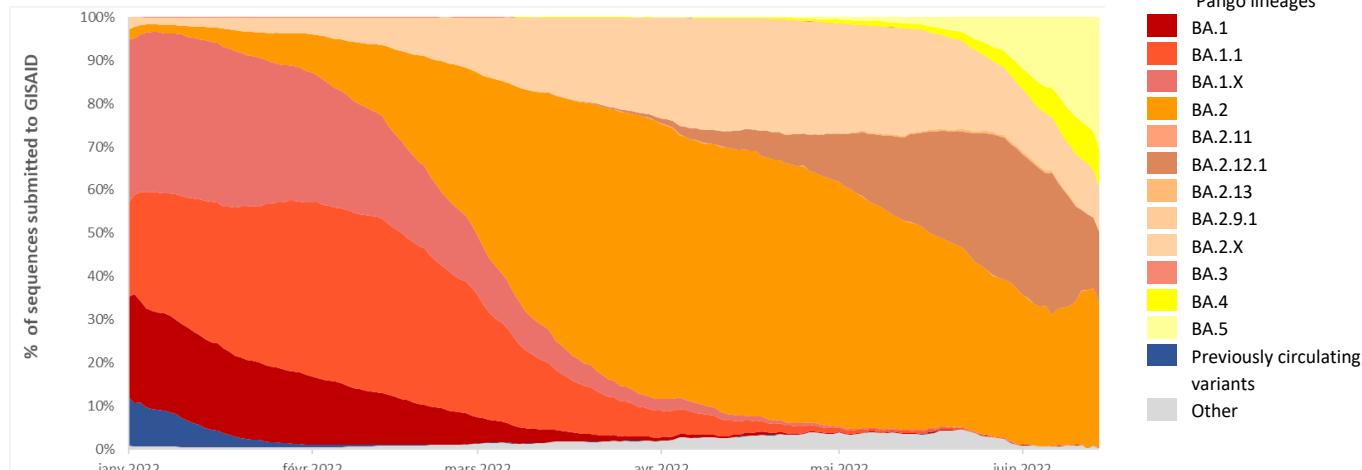
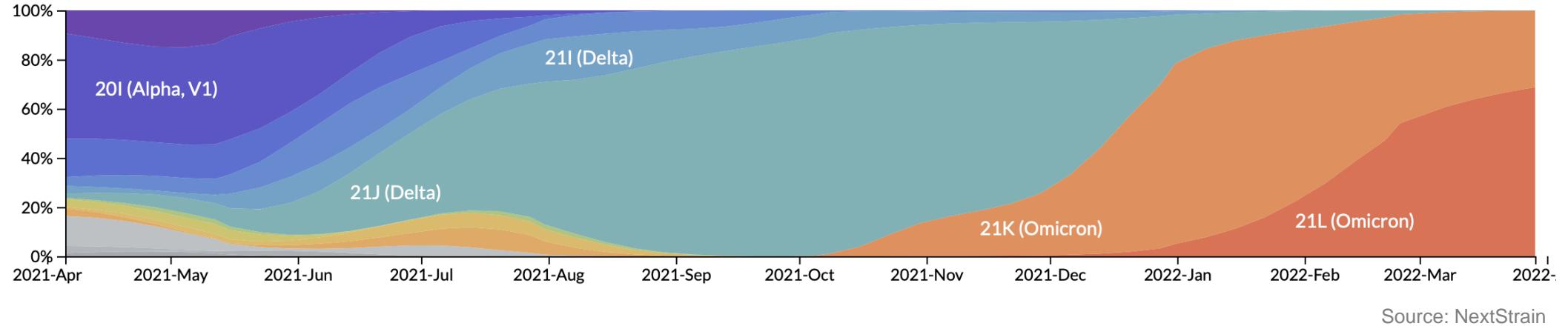
1. SARS-CoV-2 evolution and spread
2. Vaccine effectiveness against Omicron
3. Cross-neutralization and cross-protection data following infection with index virus or prior VOC or vaccination
4. Antigenic cartography
5. Preliminary data on Omicron infection
6. Preliminary data on candidate vaccines with updated composition

1. Evolution and spread: Omicron



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.

Frequencies (colored by Clade)



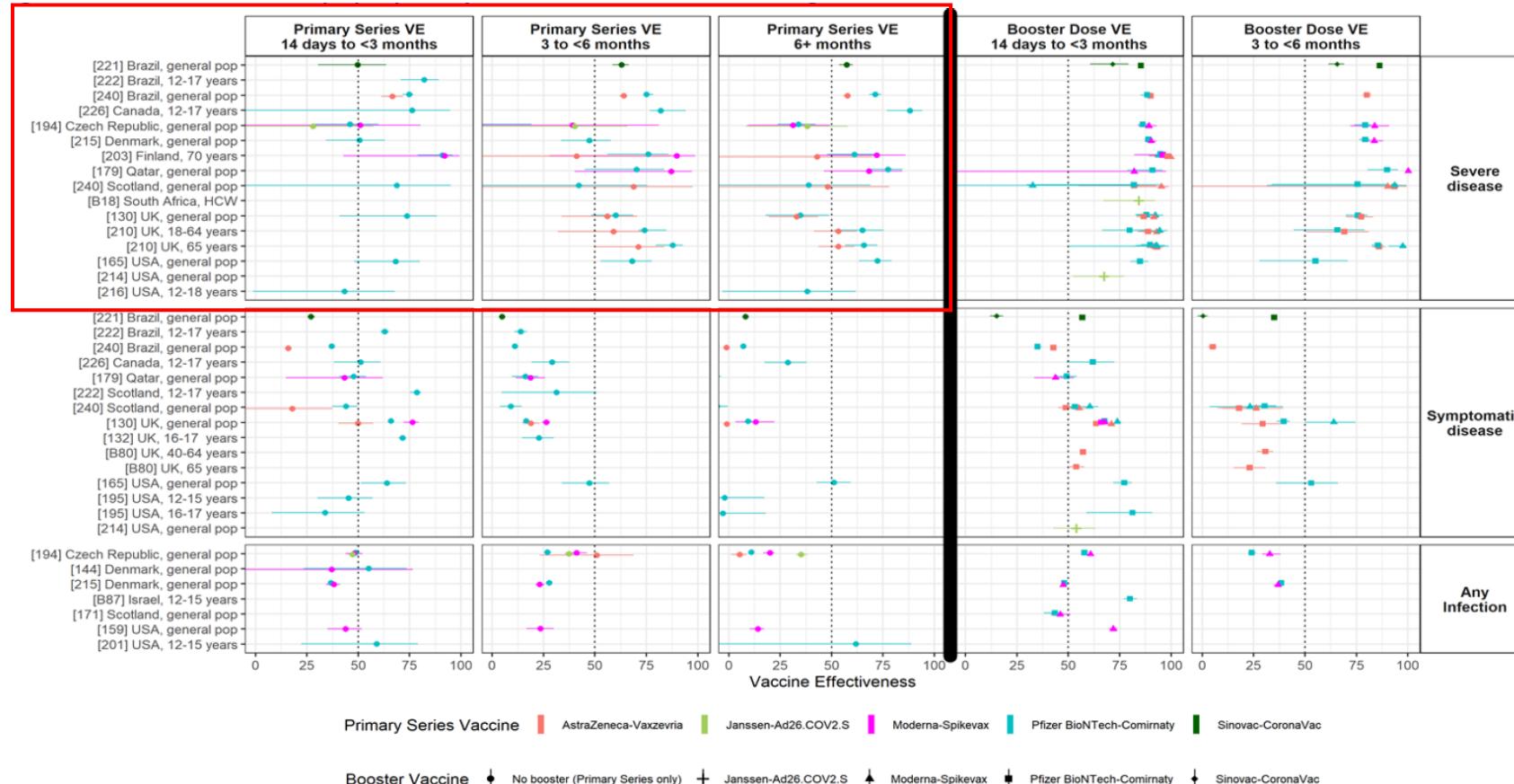
BA.2 remains the predominant Omicron descendant lineage globally.

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

2. Vaccine effectiveness: Omicron



Vaccine effectiveness (VE) of primary series and booster vaccination against Omicron



Omicron is first VOC with properties of immune evasion, resulting in lower vaccine effectiveness of the primary series of current COVID-19 vaccines, as compared to previous VOCs.

2. Vaccine effectiveness: Omicron



Vaccine effectiveness (VE) of primary series and booster vaccination against Omicron

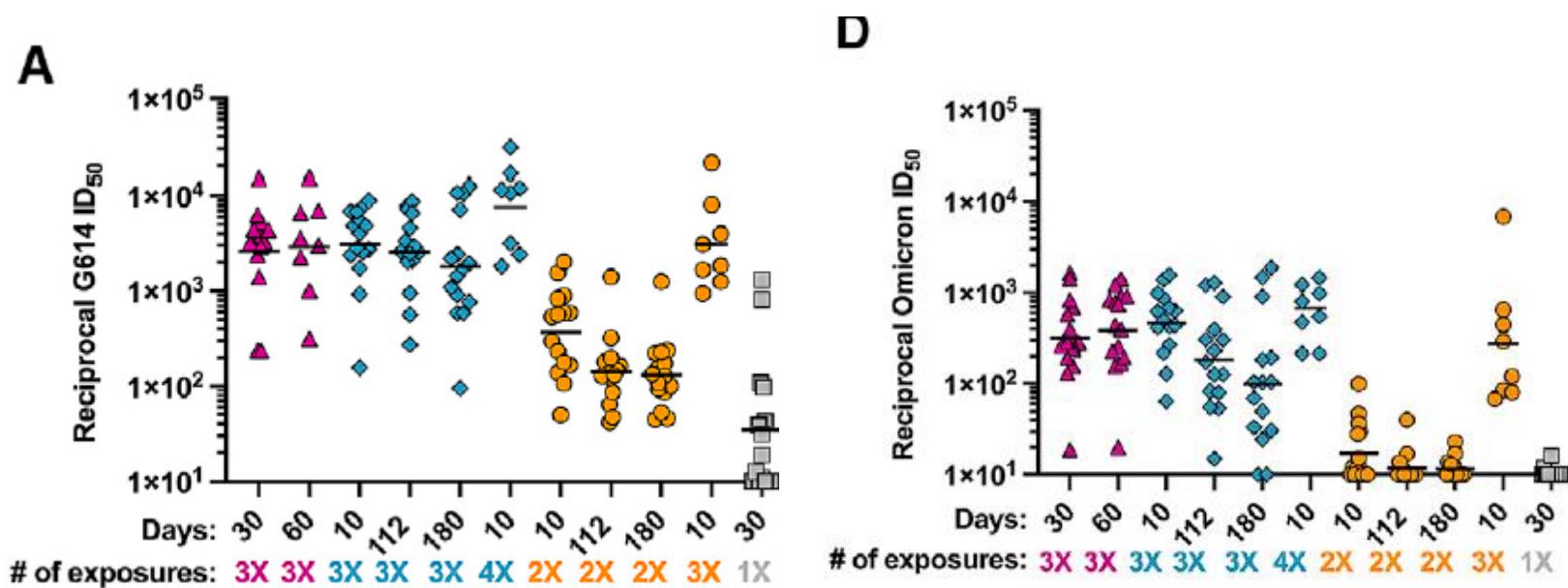


Currently licensed COVID-19 vaccines based on the index virus confer **high levels of protection against severe disease outcomes for all variants, including Omicron with a booster dose.**

3. Cross-neutralization and cross-protection data

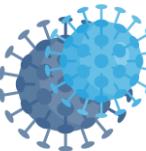


Repeated exposure to SARS-CoV-2 antigens, (either through breakthrough infection, vaccination post infection or at least 3 doses of vaccination) **enhances the magnitude and breadth of the antibody response.**

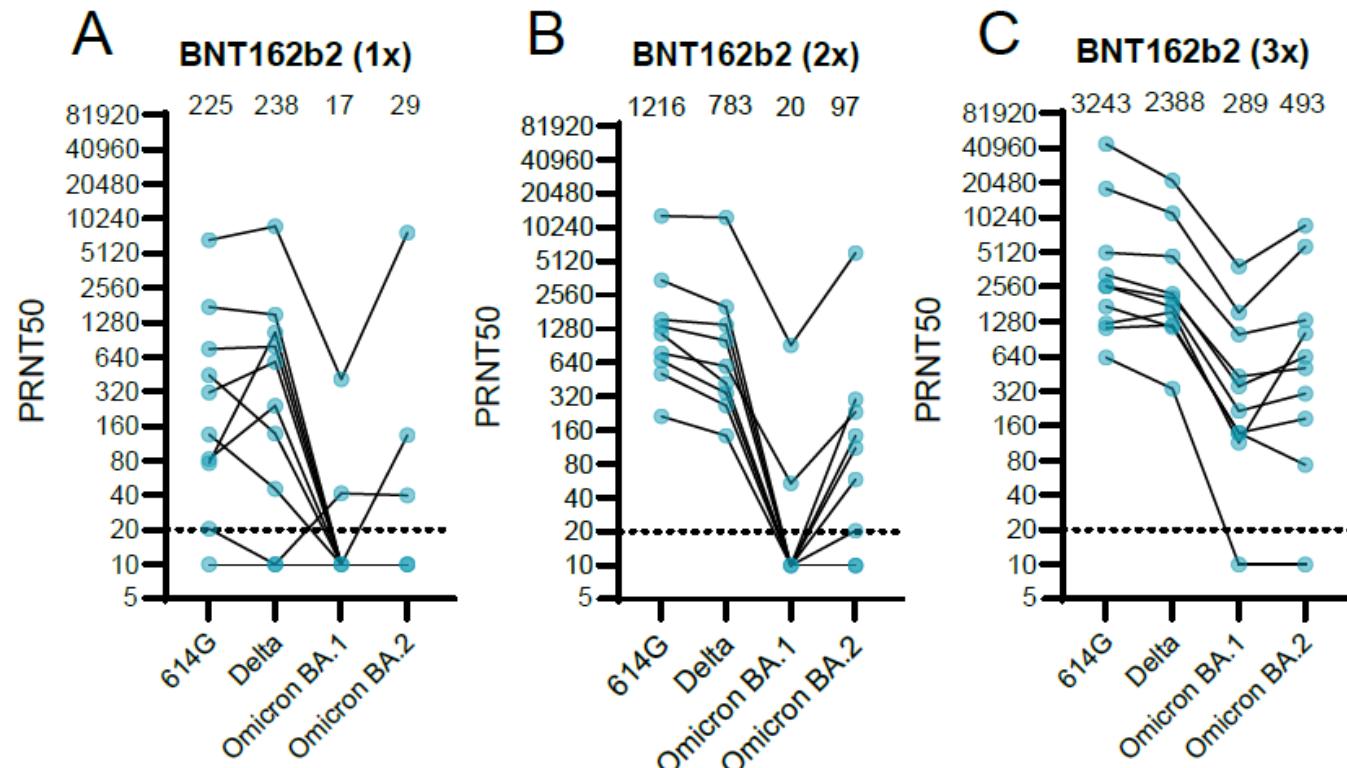


Pseudovirus neutralization activity against G614 (A) or Omicron (D) using serum samples from individuals with breakthrough infection (magenta triangles), who had been infected in 2020 and then vaccinated (blue diamonds), who had been vaccinated only (orange circles), or who were infected only in 2020 in Washington State, USA (gray squares)

3. Cross-neutralization and cross-protection data



Similarly, following 3 doses of index virus mRNA vaccine, there is **greater cross reactivity to Omicron strains** and to BA.2 than BA.1 than following one or two doses of mRNA vaccine.

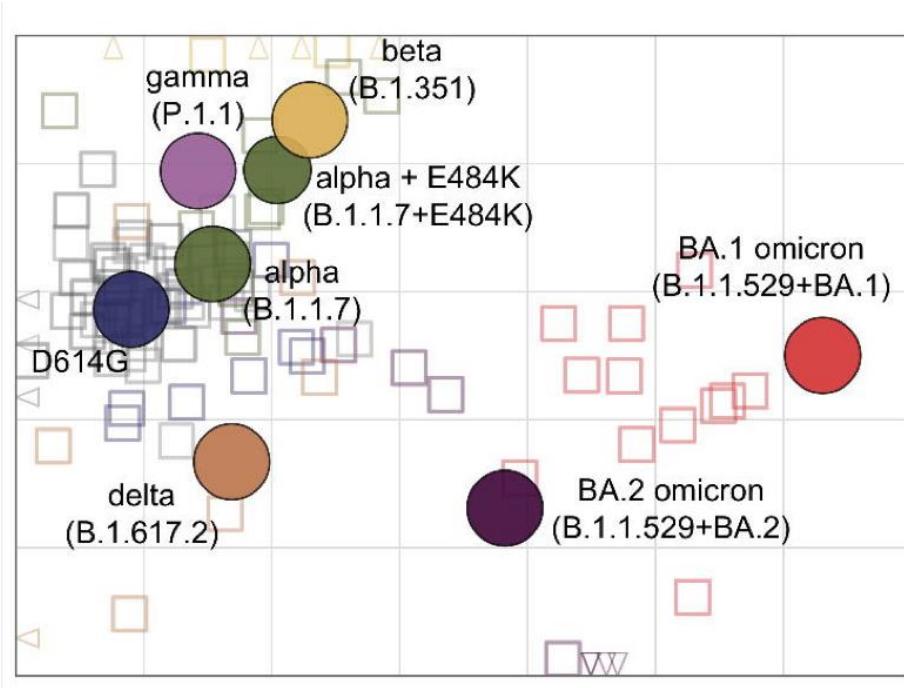


Pseudovirus neutralization activity against 614G, Delta, BA.1 or BA.2 using sera from individuals who had received 1 (A), 2 (B) or 3 (C) doses of BNT162b2. Dotted line indicates limit of detection.

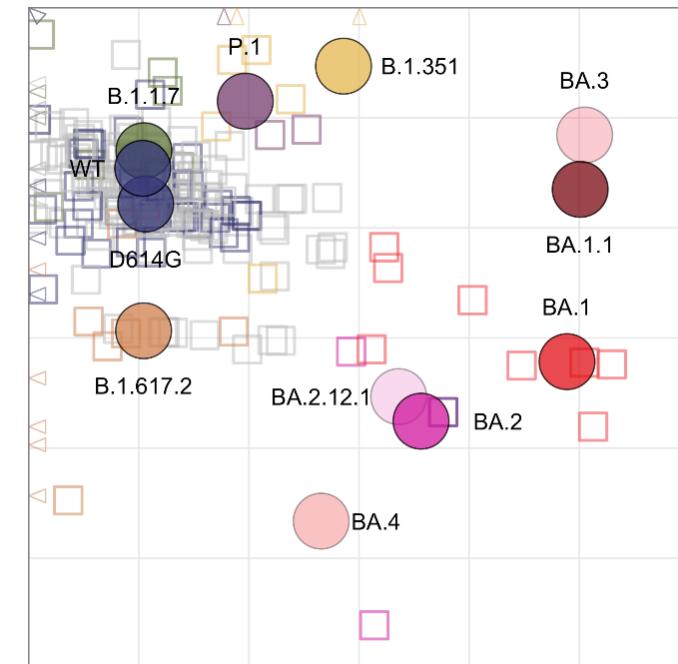
4. Antigenic cartography



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.

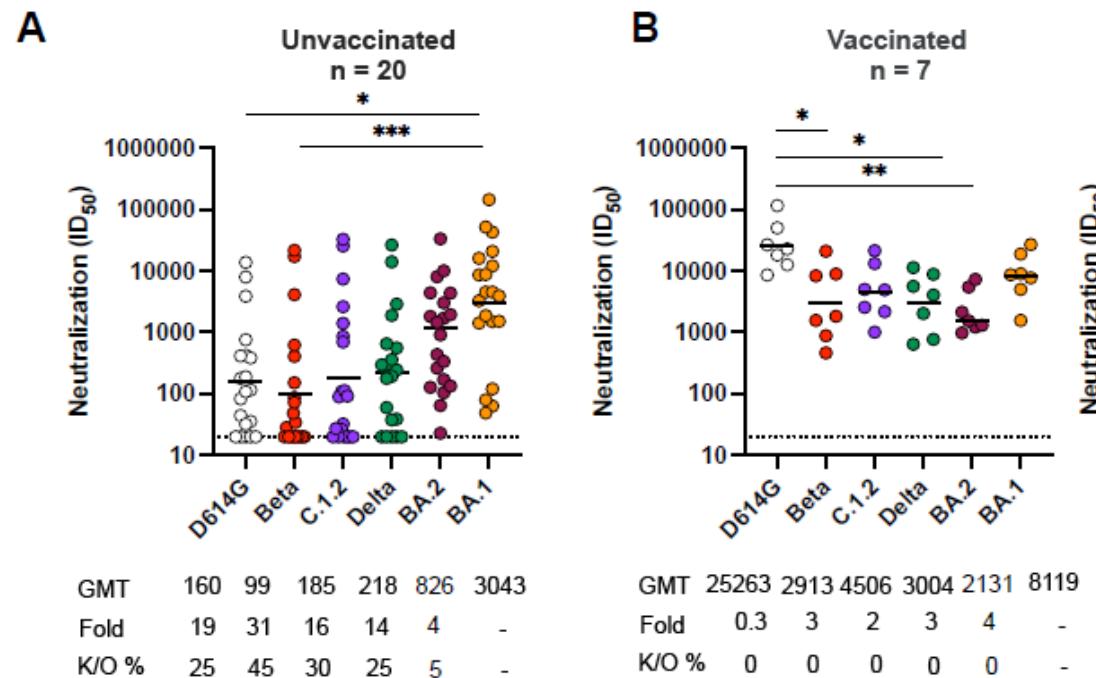
Rossler A, Netzl A, Knabl L, et al. BA.2 omicron differs immunologically from both BA.1 omicron and pre-omicron variants. Preprint. medRxiv. 2022; doi: 10.1101/2022.05.10.22274906

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/13NFT3GjMluTbDQZRSI7Vlua6G3FvwSHYgbU9gMoWI4U/edit#slide=id.g12df13b5e55_4_0

5. Data on Omicron infection



In naïve (unprimed) individuals who were infected with Omicron, the **immune response to Omicron (BA.1) infection is strong but not broadly cross-reactive against other VOCs**. However, in primed (vaccinated) individuals, the **breadth** of the neutralizing antibody response against other VOCs is **improved**.



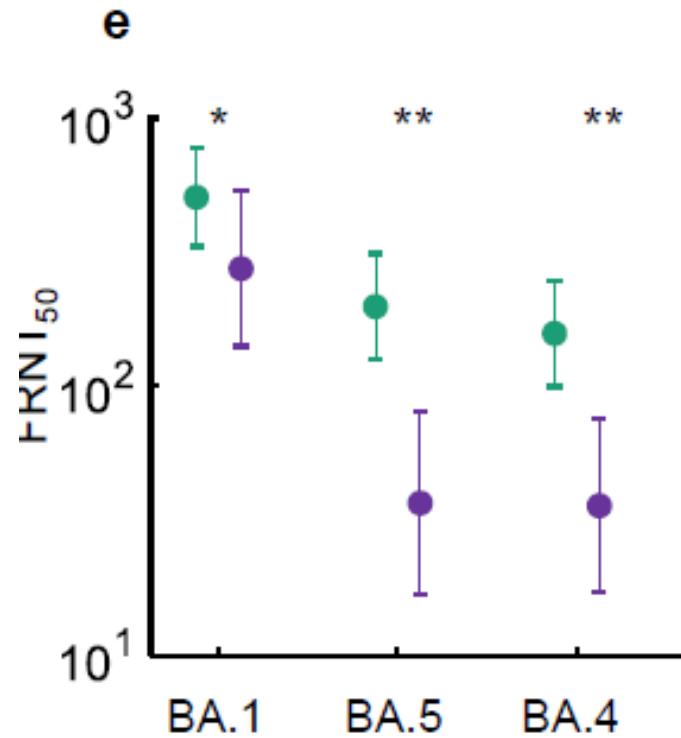
Pseudovirus neutralization activity against 614G, Beta, C.1.2, Delta, BA.1 and BA.2 of plasma from unvaccinated individuals (A) or those who had been vaccinated with either one dose of Ad26.Cov.2S or two doses of BNT162b2 (B), who were subsequently infected with Omicron. Dotted line indicates the limit of detection. Bar graphs compare responses in vaccinated and unvaccinated individuals.

5. Data on Omicron infection



Similarly, the neutralizing antibody response to BA.4 or BA.5 following BA.1 breakthrough infection is higher than in naïve individuals infected with BA.1.

Escape of BA.4 and BA.5 from Omicron/BA.1 elicited immunity

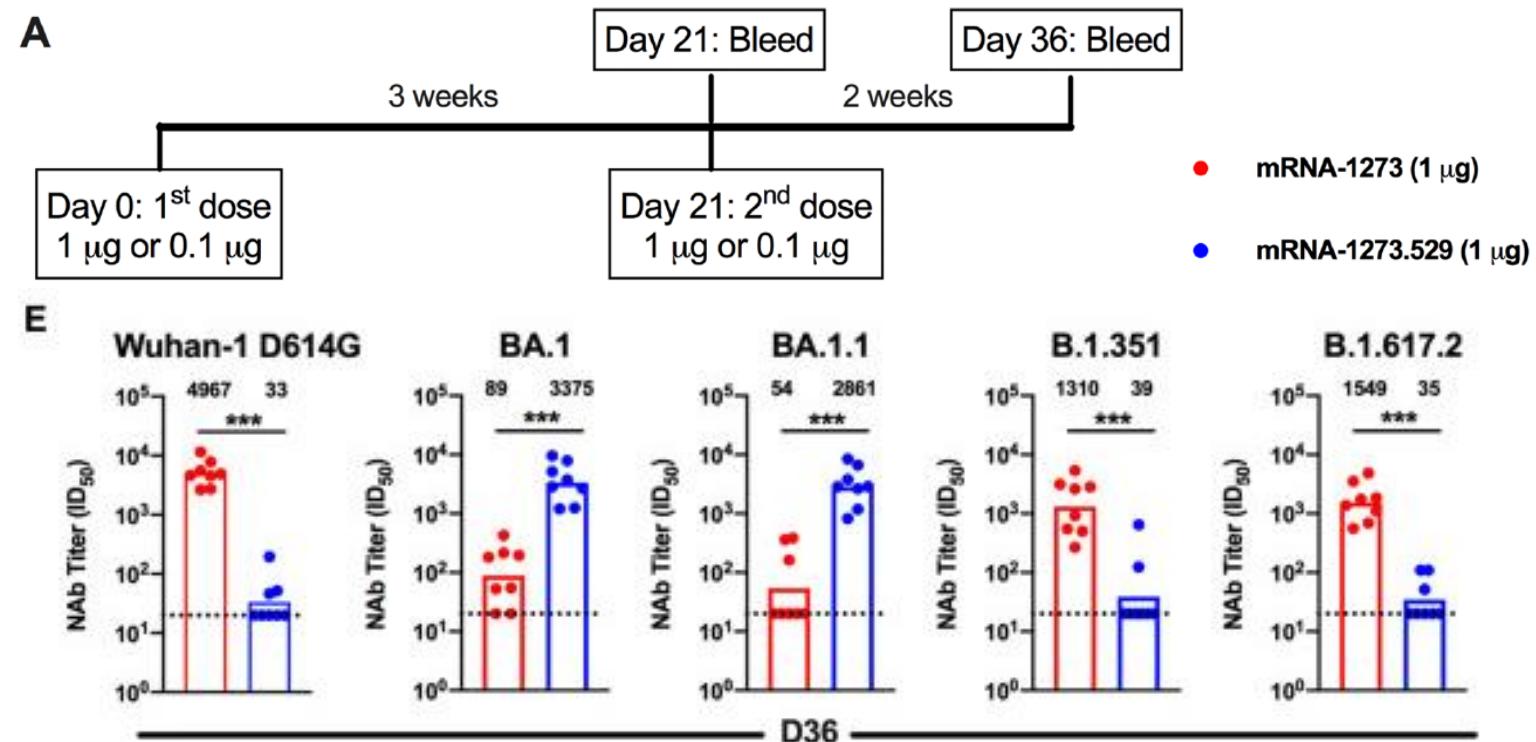


Pseudovirus neutralization of BA.1, BA.4 and BA.5 in individuals infected with BA.1 who had been previously vaccinated (n=15 in green) with BNT162b2 (n=8) or Ad26.Cov2.S (n=7) or unvaccinated (n=24 in purple).

6. Data on candidate vaccines with updated composition



In a mouse model, an Omicron-specific mRNA vaccine induces neutralising Ab against homologous virus, but the sera did not neutralise the index virus or other VOCs.

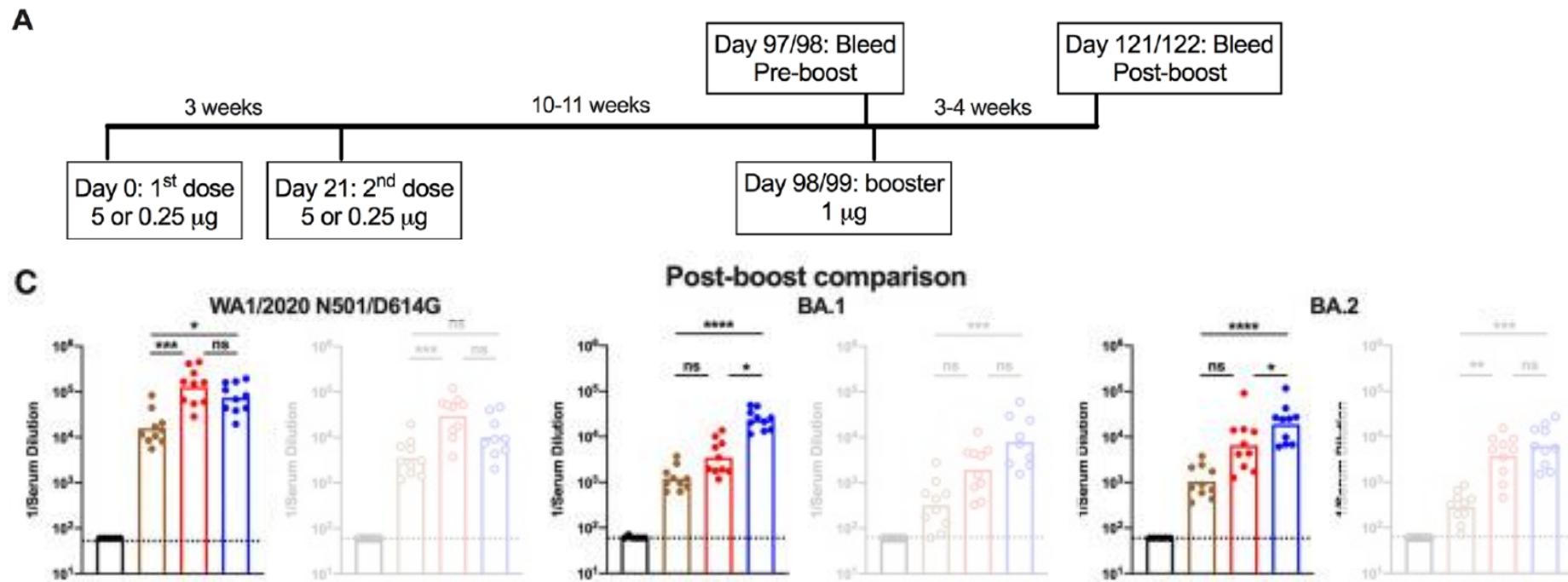


Pseudovirus neutralization activity of sera collected two weeks post vaccination (day 36) of BALB/c mice using 2 doses of either the mRNA-1273 vaccine (index-virus in red) or mRNA-1273.529 (Omicron-specific update in blue) against 614G, BA.1, BA.1.1, B.1.351, or B.1.617.2

6. Data on candidate vaccines with updated composition



In the same mouse model, two doses of mRNA-1273 followed by a **boost of mRNA-Omicron elicited higher titers of neutralizing antibodies against Omicron BA.1 and BA.2 while boosting neutralizing Abs vs index virus, compared to the mRNA-1273 boost alone.**

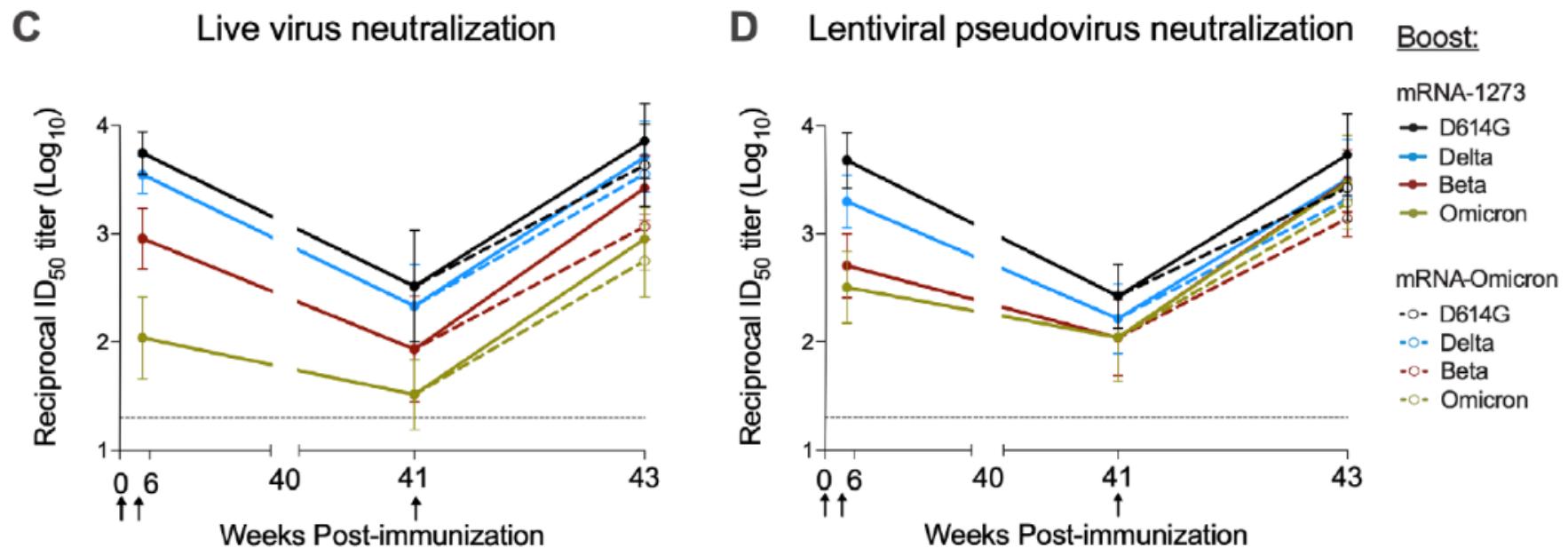


129S2 mice were immunized with mRNA vaccines (2 doses). Serum neutralizing antibody responses were analyzed in control animals (black), animals that only received the primary series (brown), those that received the mRNA-1273 vaccine booster (red) or those that received the mRNA-1273.529 vaccine (blue). Closed circles indicate the 5 µg dose and open circles indicate the 0.25 µg dose for the 1st and 2nd doses.

6. Data on candidate vaccines with updated composition



In macaques that received 2 doses of mRNA-1273 and were boosted at week 41 with mRNA-1273 or mRNA-Omicron had similar neutralizing antibody profiles 2 weeks later. In addition, 70-80% of B cells were cross-reactive against both index virus and Omicron.



Kinetics of the serum neutralizing antibody response (geometric mean titres) in Macaques against 614G, Delta, Beta or Omicron, following immunization using mRNA-1273 on day 0 and 6 and then boosted using either mRNA-1273 (solid lines) or mRNA-Omicron (dashed lines) on day 41 (indicated by arrows).

6. Data on candidate vaccines with updated composition



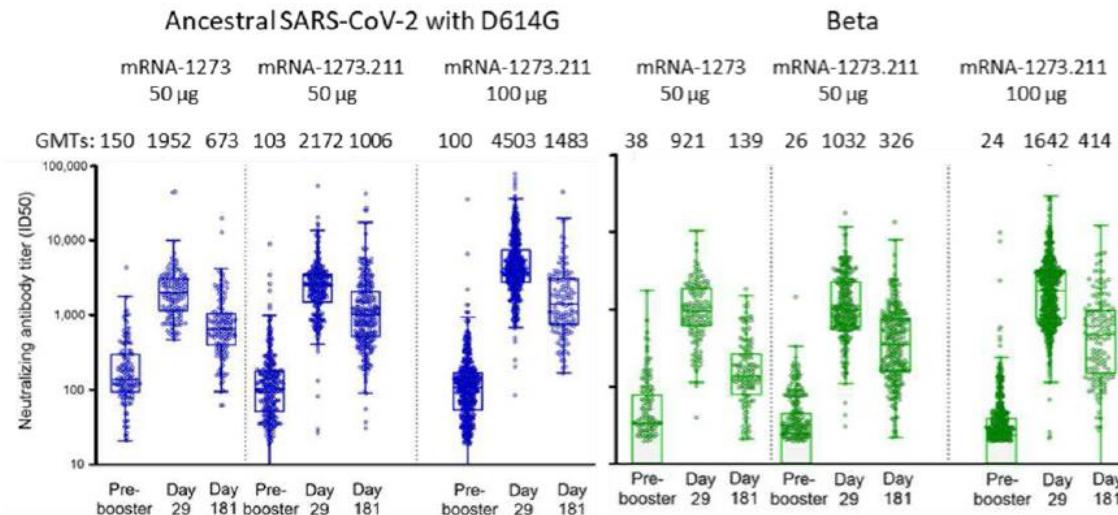
There are also preliminary data that a **bivalent booster composition** (index virus + Beta) can elicit similar, if not higher, titres of neutralizing antibodies, with more pronounced increases at later time points compared to the monovalent booster (index virus).

mRNA-1273 (index virus)

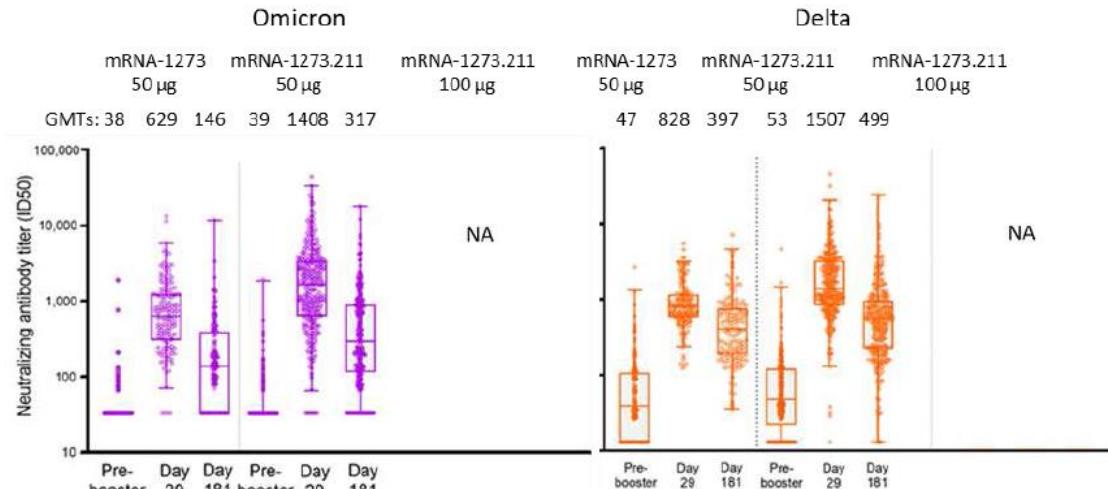
mRNA-1273.211 (25 μ g index virus + 25 μ g Beta)

These data may be indicative of the potential performance of a bivalent booster.

Pseudovirus neutralization against 614G, Beta, Omicron or Delta using serum samples collected from individuals who had received a primary series of mRNA-1273 (pre-booster) and then were boosted using either the mRNA-1273 (50 μ g dose) or mRNA-1273.211 (bivalent index virus + beta either 50 μ g or 100 μ g dose) vaccine



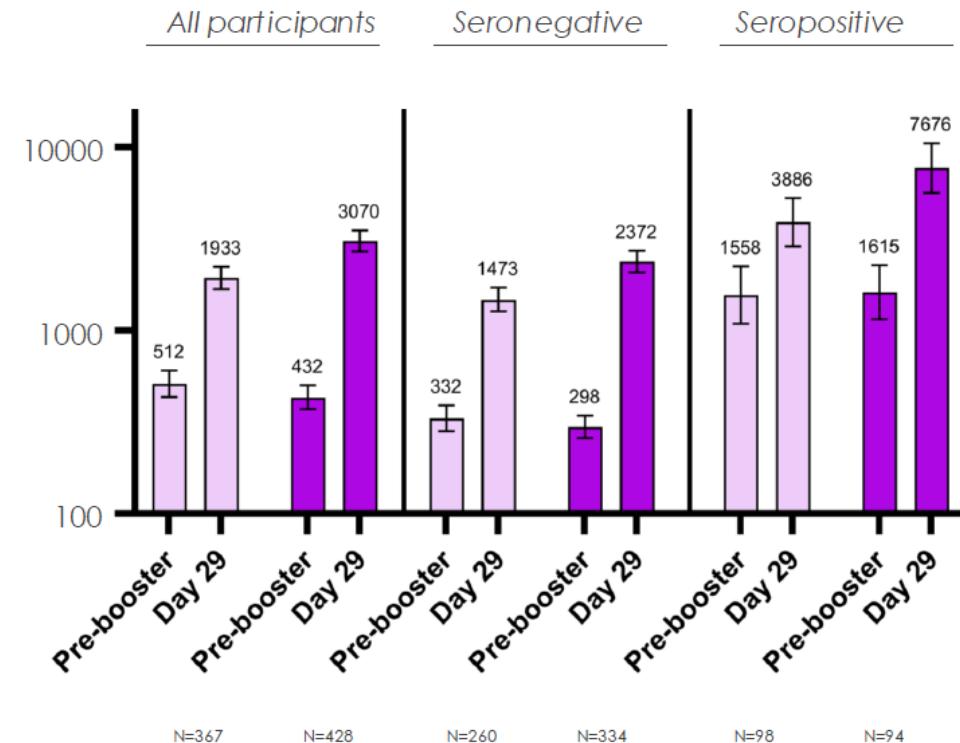
B. Omicron; Delta



6. Data on candidate vaccines with updated composition



In humans, preliminary data on a candidate Omicron + index virus (mRNA 1273.214) bivalent mRNA vaccine demonstrated **higher Omicron neutralizing antibody titres** when used as a fourth booster dose compared to a fourth booster dose of the index-virus (mRNA-1273). Further, a non-inferior neutralizing antibody response against the D614G virus was reported.



Pseudovirus neutralization against Omicron using serum samples collected from individuals who had received a primary series of two doses of mRNA-1273 followed by a 3rd dose of mRNA-1273. A 4th dose of either the mRNA-1273 (50ug, light purple) or mRNA-1273.214 (bivalent index virus + Omicron 50ug dose, dark purple) vaccine.

TAG-CO-VAC evidence base summary



- To date, **Omicron is the most antigenically distinct SARS-CoV-2 VOC to have emerged**, with BA.1 appearing to be the most distant from the index virus.
- Antibody responses **in previously naïve (unprimed) individuals exposed to Omicron are strong, but not broad** (i.e. fairly high Omicron-specific neutralizing antibody titres are elicited, with limited neutralizing activity against other VOCs or the index virus), indicating that a stand-alone Omicron-specific vaccine product will not suit the objectives of an update to COVID-19 vaccine composition.
- In contrast, in individuals who have been previously primed by SARS-CoV-2 infection or COVID-19 vaccination, **a broad immune response is elicited following Omicron infection**.
- **These data support a preference for the inclusion of Omicron in an updated vaccine composition, administered as a booster dose.**

TAG-CO-VAC evidence base limitations



Paucity of available data must be acknowledged:

- Minimal / limited data on cross-reactivity (breadth) of humoral or cell-mediated immune responses in unvaccinated individuals or vaccinated individuals with breakthrough BA.2, BA.4, BA.5 infection;
- Minimal / limited data on humoral and/or cell mediated immune responses over time following Omicron infection in naïve individuals or in those who had breakthrough infection;
- Data are only available for a BA.1-specific updated vaccine response in naïve or primed animals; no data on other Omicron sublineage-specific vaccines);
- Limited data on immune responses using an Omicron (BA.1)-specific vaccine used as a booster in humans;
- All of the limited data on variant-specific vaccine products in animal models and humans are using mRNA vaccines.



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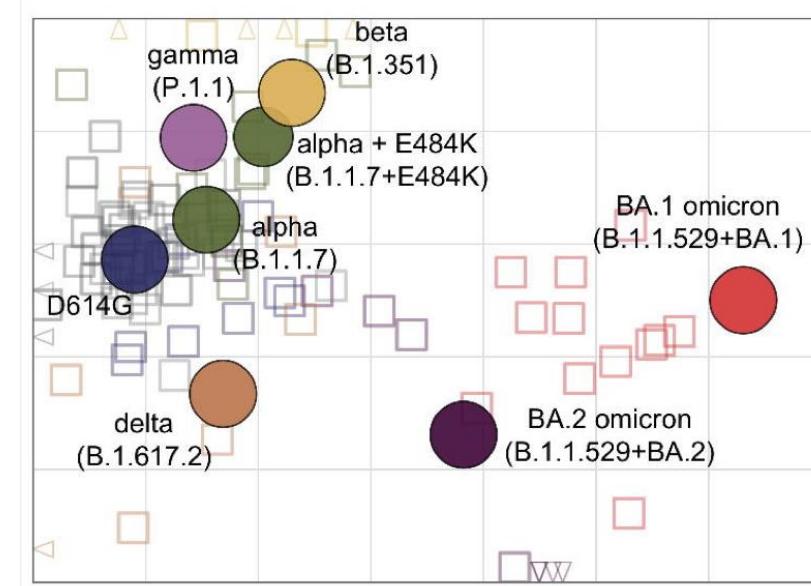
TAG-CO-VAC proposal for updated COVID-19 vaccine composition

TAG-CO-VAC Statement – 17 June 2022



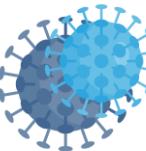
Summary of interim statement

- The continued use of **currently licensed vaccines** based on the index virus **confers high levels of protection against severe disease outcomes** for all variants, including Omicron with a booster dose, and is therefore appropriate to **achieve the primary goals of COVID-19 vaccination**.
- 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**.
- Available data indicate that 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 to those who have already received a COVID-19 vaccination primary series.



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

Further considerations in TAG-CO-VAC proposal



TAG-CO-VAC does not advise the use of an Omicron-specific monovalent vaccine product as a standalone formulation for the primary series because it is not yet known whether Omicron-specific vaccines will offer cross-reactive immunity and cross-protection from severe illness caused by other VOCs in naïve individuals as the index vaccines have done.

For the Omicron-specific vaccine product, 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.

While the TAG-CO-VAC recommends an Omicron-containing vaccine product, this does not preclude the consideration of other variant-specific formulations and/or bi/multivalent products by regulatory authorities, and that data support the fulfillment of the additional objective of achieving breadth of cross-reactive immunity to previous, currently circulating and/or emerging variants .