

Annex: Interim statement on the composition of current COVID-19 vaccines

17 June 2022

Annex 1: Flowchart of TAG-CO-VAC decision making process

Annex 2: Evidence supporting consideration to update vaccine composition, in the context of Omicron

Annex 3: Evidence to support an Omicron-specific update of vaccine composition

Annex 1: Flowchart of TAG-CO-VAC decision making process

The flowchart below describes the current decision-making process of the TAG-CO-VAC, which is initiated following the designation of a VOC by the WHO, upon the advice of the Technical Advisory Group on SARS-CoV-2 Virus Evolution (TAG-VE).

A decision from TAG-CO-VAC on COVID-19 vaccine composition currently follows a two-step process:

- The first step involves an assessment of features of the newly designated VOC, including transmissibility/spread, clinical severity, mutations and antigenic changes, and vaccine effectiveness to decide whether an updated vaccine composition should be considered. See: [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.](#)
- The second step considers the antigenic characteristics of the VOC, including cross-neutralization and cross-protection following infection and vaccination to assess whether, in addition to retaining protection against severe disease and death, an updated vaccine composition is likely to broaden the immune response.

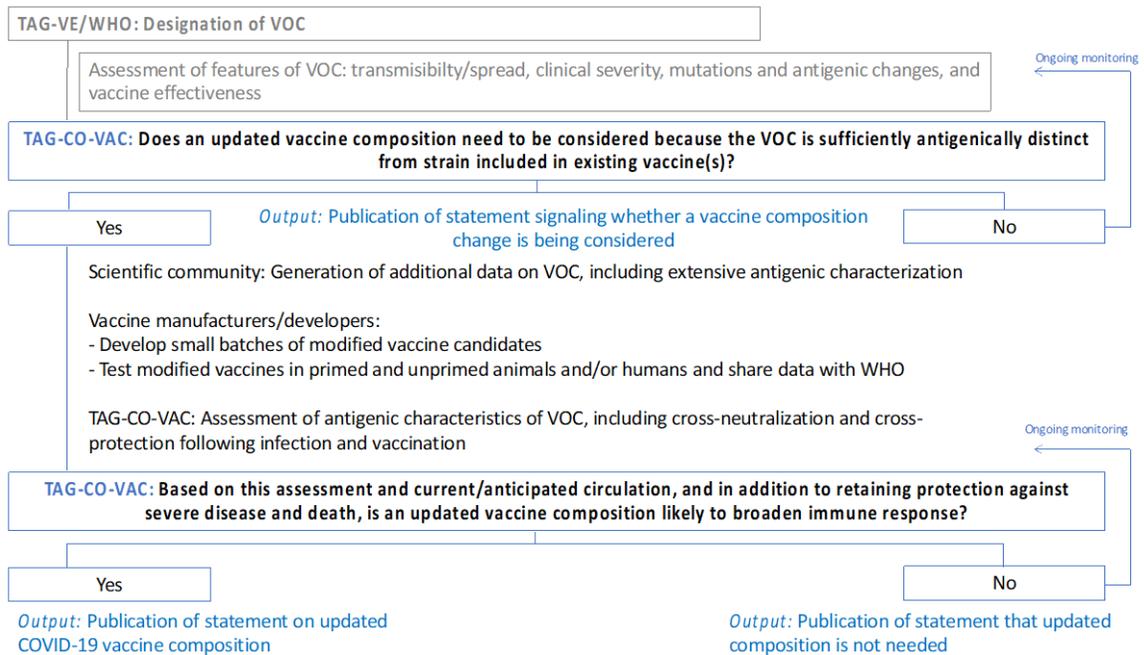


Figure 1. Overview of current TAG-CO-VAC decision-making process

Annex 2: Evidence supporting consideration to update vaccine composition, in the context of Omicron

Information below has been compiled from the [WHO COVID-19 Weekly Epidemiological Updates](#) up to 10 June 2022.

Mutational profile: Omicron is a highly divergent genetic variant with a large number of mutations, including 26-32 mutations in the spike protein, some of which are associated with potential for escape from humoral immunity and greater transmissibility. There are currently 5 main descendant lineages: BA.1, BA.2, BA.3, BA.4 and BA.5, which share some mutations in the Spike but have distinct mutational profiles within the Spike and across other regions of the genome.

Transmissibility and spread: The current global epidemiology of SARS-CoV-2 is characterized by declines in reported cases since a peak in new cases in January 2022, when the Omicron variant first became dominant. Omicron continues to be predominant globally, and among Omicron lineages, BA.2 and its descendent lineages account for 63% of all variants in the epidemiological week 20 of 2022. More recently, BA.4 and BA.5 are increasing in prevalence in certain regions, but these trends should be interpreted with caution as a result of changes to COVID-19 testing and sequencing strategies.

Severity: Omicron has been associated with lower severity when compared to Delta across multiple studies and settings.²⁻⁷ However, data specifically from naïve populations infected with Omicron indicate that there may be no intrinsic difference in severity compared to prior VOCs.^{8,9} Finally, the high prevalence of Omicron infections in certain countries have nonetheless resulted in a large burden for health care systems, especially in some countries that had avoided the impact of earlier VOCs.

Immune response: Higher rates of reinfection (i.e. infection with Omicron in individuals who were previously infected with the index virus or earlier VOCs) have been reported for Omicron compared to other SARS-CoV-2 VOCs;¹⁰⁻¹³ but individuals who have recovered from infection with a prior SARS-CoV-2 variant have a reduced risk of Omicron infection and hospitalization compared to naïve individuals, indicating there is preserved cross-protection.¹⁴ Further, analysis from Qatar demonstrated that previous infection with BA.1 confers 94.9% (95% CI: 88.4-97.8%) protection against BA.2 and 85.6% (95% CI: 77.4-90.9%) protection against BA.1 was observed following infection with BA.2.¹⁵

Several studies have found lower neutralizing antibody titers to Omicron when compared to the index virus, in individuals previously infected with the index virus or prior variants, or post vaccination.^{16,17} Similarly, binding antibody responses to BA.1 and BA.2 have also been reported to be lower than to other VOCs or the index virus in vaccinated individuals, which tended to be more pronounced for BA.2; these reductions may be partially restored in the weeks following a third vaccine dose.^{18,19} Further, preliminary data demonstrate stronger homologous immune responses to specific Omicron sublineages, such that neutralizing antibody titres to BA.4 or BA.5 are decreased following BA.1 infection compared to BA.1 specific responses; these decreases are less substantial in individuals who had been vaccinated and had Omicron (BA.1) breakthrough infection.^{20,21} In summary, these results indicate lower humoral responses to Omicron following vaccination or prior infection with earlier VOCs, but the degree of difference across Omicron sublineages continues to be examined.

Vaccine effectiveness: To date, 21 studies²²⁻⁴² from ten countries (Brazil, Canada, Czech Republic, Denmark, Finland, Israel, Qatar, South Africa, the United Kingdom and the United States of America) have

assessed the duration of protection conferred by five vaccines against Omicron (six studies assessed VE of primary series vaccination only, six assessed VE of booster vaccination only, and 11 assessed both).

For *severe disease*, within the first three months of primary series vaccination: six of 12 (50%) VE estimates for the mRNA vaccines (Moderna-Spikevax and Pfizer BioNTech-Comirnaty) were $\geq 70\%$;^{22,29,34,35,37} Of the two studies available for vector vaccines, one reported a VE of $<70\%$ for AstraZeneca-Vaxzevria,³⁷ and the other reported a VE of $<50\%$ for Janssen-Ad26.COVID.2.S (one dose);²⁶ The one study available for inactivated vaccines (Sinovac-CoronaVac) reported a VE of 50% .³⁶ Beyond three months after vaccination, 13 of 28 (44%) VE estimates for the mRNA vaccines were $\geq 70\%$,^{22,29,30,35,37,42} while 19 (68%) were $\geq 50\%$, one of the 12 (8%) VE estimates for AstraZeneca-Vaxzevria was $\geq 70\%$ ²² while eight (67%) were $\geq 50\%$, and the two available VE estimates for Sinovac-CoronaVac were $\geq 50\%$;³⁶ both estimates for Janssen-Ad26.COVID.2.S beyond three months of vaccination were $<50\%$.

Booster vaccination improved VE against *severe disease* outcomes in all studies in which it was assessed.^{22,25-27,30,36,37,39,40} There were 33 estimates of an mRNA booster, two estimates of a booster dose of Janssen-Ad26.COVID.2.S, and one estimate of a booster dose of Sinovac-CoronaVac. Across the datasets, only one estimate for Pfizer BioNTech-Comirnaty as a booster dose³⁷ and one estimate for Janssen-Ad26.COVID.2.S as a booster dose³⁹ were below 70% between 14 days and three months of receipt of a booster dose. At three to six months post mRNA booster, 17 of 20 (85%) estimates showed VE $\geq 70\%$ ^{22,25,26,30,31,36,37} (an mRNA vaccine was given as the primary series in 13 of the 20 estimates while AstraZeneca-Vaxzevria and Sinovac-CoronaVac were given as the primary series for six and one of the twenty estimates, respectively).

Findings from these studies show reduced VE of COVID-19 primary series vaccines against the Omicron variant for all outcomes (*severe disease, symptomatic disease, and infection*) than has been observed for the other four VOCs. Importantly though, VE estimates against the Omicron variant remain high for *severe disease*, in the majority of studies. Booster vaccination substantially improves VE for all outcomes and for all combinations of schedules with estimates available for both primary series and booster vaccination, when assessed up to 6 months post boost. Studies that assess VE of booster vaccination beyond six months are needed to evaluate the longer duration of protection.

Summary

Based on the mutational profile showing substantial antigenic change, widespread replacement of other variants by Omicron globally, evidence of reduced immune responses and reduced VE of a primary vaccination series against severe disease, a strain update to COVID-19 vaccine composition may be warranted.

Annex 3: Evidence to support an Omicron-specific update of vaccine composition

The TAG-CO-VAC convenes a subgroup comprised of members and external advisors with virological and immunological expertise. The TAG-CO-VAC has reviewed published and unpublished data on the antigenicity and cross-protection following Omicron infection and/or Omicron-specific vaccine candidates. The data highlighted below, while not exhaustive, were specifically reviewed and considered by the subgroup, as well as by the full TAG-CO-VAC to inform the recommended vaccine composition update.

1. Cross-neutralization and cross-protection data following infection with index virus or prior VOC, or vaccination:

There are two important observations about cross-reactivity of the antibody responses to Omicron sublineages in people who have had prior infection or were vaccinated with index strains:

a. Several studies, including the study excerpted below (Figure 1), demonstrate that the **Omicron-specific immune response is reduced compared to that seen against the index virus in post vaccination (index virus) sera.**¹⁹ Sera from vaccinees who received different vaccines (see symbol legend) or had been infected with SARS-CoV-2 (1x Washington infected) were tested in pseudovirus neutralization assays against D614G, Omicron BA.1 and Omicron BA.2 pseudoviruses). Neutralizing antibody titres against Omicron strains BA.1 and BA.2 were consistently lower than against G614, that represents the index strain.

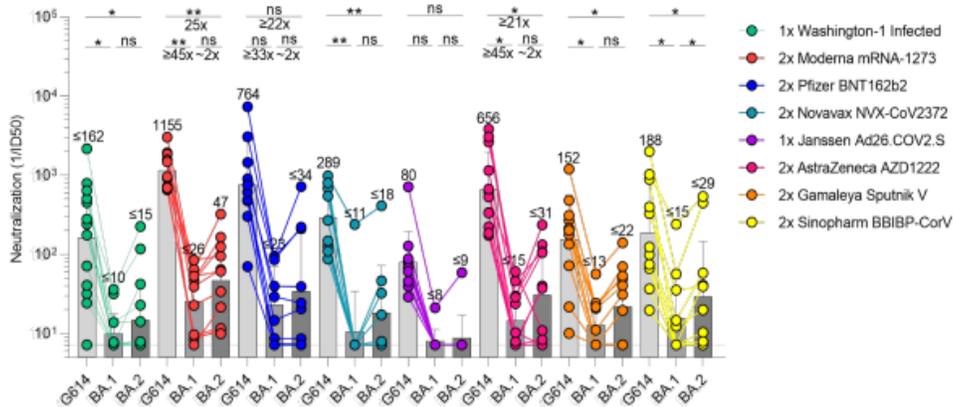


Figure 1: Neutralizing antibody titres in post-vaccination sera against G614, BA.1 and BA.2.¹⁹

b. **Repeated exposure** to SARS-CoV-2 antigens, (either through breakthrough infection, vaccination following natural infection or at least 3 doses of vaccination) **enhances the magnitude and breadth of the antibody response** (Figure 2-1).⁴³ 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 (Figure 2-2).⁴⁴

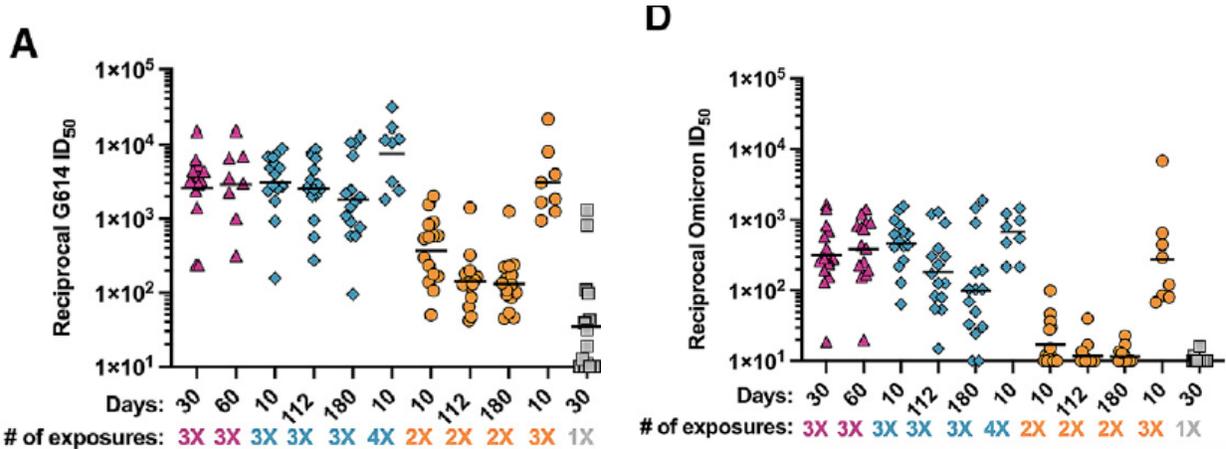


Figure 2-1: Pseudovirus neutralization activity against G614 (A) or Omicron (D) using Serum samples from individuals with breakthrough infection (magenta triangles), who had been infected in 2020 and then vaccinated (blue diamonds), who had been vaccinated only (orange circles), or who were infected only in Washington State, USA (gray squares).⁴³

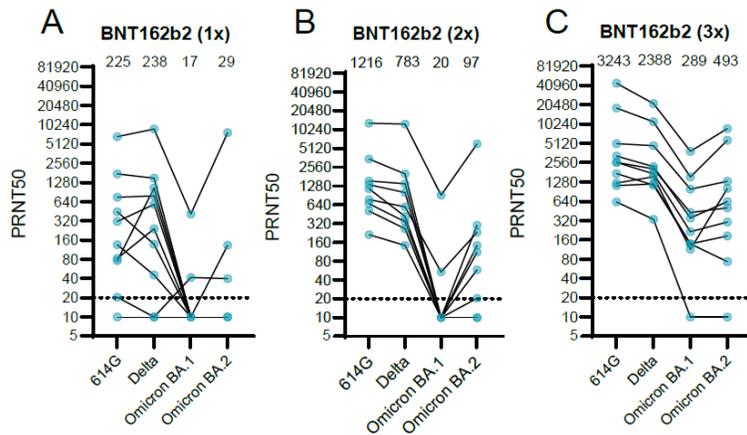


Figure 2-2: Pseudovirus neutralization activity against 614G, Delta, BA.1 or BA.2 using sera from individuals who had received 1 (A), 2 (B) or 3 (C) doses of BNT162b2. Dotted line indicates limit of detection.⁴⁴

2. Antigenic cartography

Antigenic cartography using neutralizing antibody data from human sera following vaccination or infection (Figure 3-1, Rossler et al⁴⁵ and aggregated in Figure 3-2 Netzl et al⁴⁶), as well as sera from hamsters infected

with SARS-CoV-2 VOCs (Figure 3-2, Mykytyk et al⁴⁴) demonstrate that Omicron viruses are antigenically distinct from the earlier VOCs including 614G, Alpha, Beta, Gamma, Delta, Lambda, Mu and Zeta. The data also indicate that **BA.1 is more antigenically distinct** from the index virus (D614G) than other sublineages.⁴⁴⁻⁴⁶

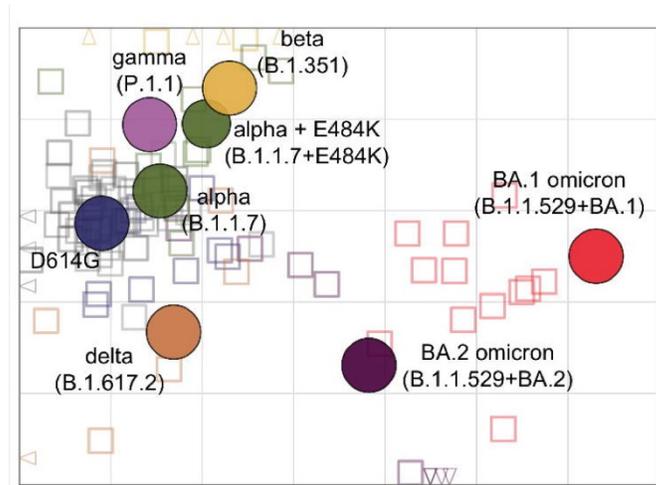


Figure 3-1: Antigenic map of SARS-CoV-2 variants constructed from single exposure convalescent and double vaccinated sera. Virus variants are shown as colored circles, sera as open squares with the color corresponding to the infecting variant. Vaccine sera are shown as grey tones. The x- and y-axis represent antigenic distances with one grid square corresponding to one two-fold serum dilution of the neutralization titer.⁴⁵

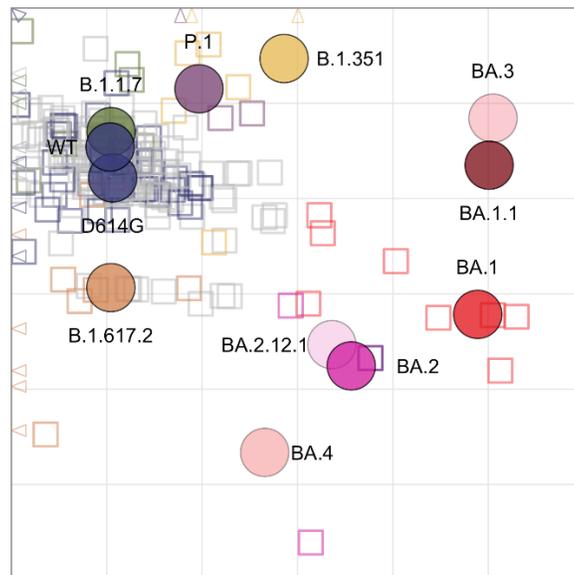


Figure 3-2: Aggregated antigenic map of SARS-CoV-2 variants constructed using data from multiple preprint and published studies. Virus variants are shown as colored circles, sera as open squares with the color corresponding to the infecting variant. The x- and y-axis represent antigenic distances with one grid square corresponding to one two-fold serum dilution of the neutralization titer⁴⁶

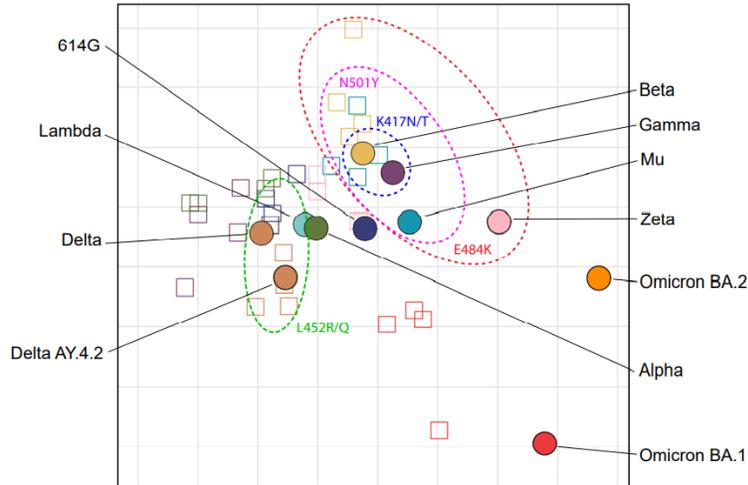


Figure 3-2: Antigenic map comparing neutralization of authentic SARS-CoV-2 using sera from hamsters who had been infected with various SARS-CoV-2 strains. Viruses are shown as colored circles and the antisera are squares, using the same color to match the viruses. Virus and antisera are positioned so that the distances between them are inversely related to the antibody titres. The grid in the background scales to a 2-fold dilatation of antisera in titrations.⁴⁴

3. Preliminary data on Omicron-infection:

a. In naïve (unprimed) individuals (humans) 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**.⁴⁷

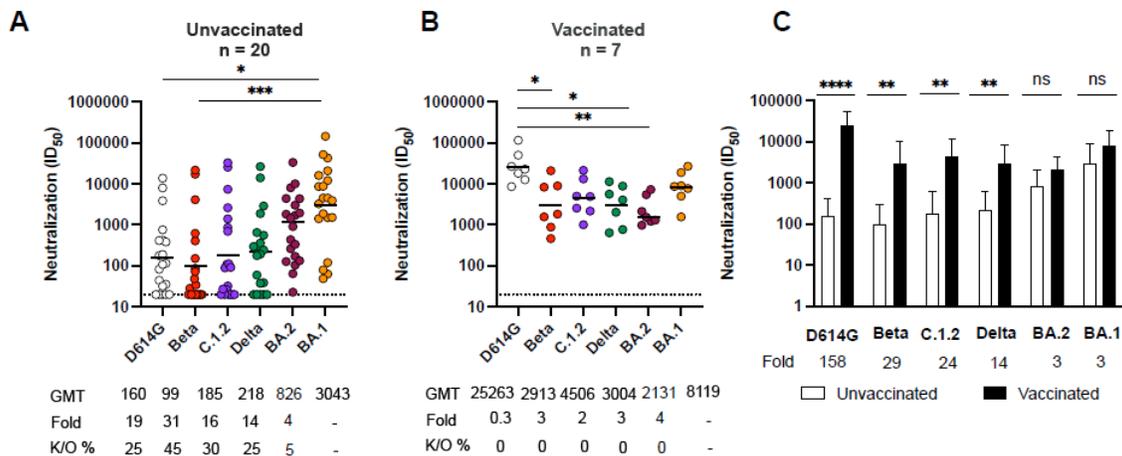


Figure 4-1: Pseudovirus neutralization activity against 614G, Beta, C.1.2, Delta, BA.1 and BA.2 of plasma from unvaccinated individuals (A) or those who had been vaccinated with either one dose of Ad26.CoV.2S or two doses of BNT162b2 (B), who were subsequently infected with Omicron. Dotted line indicates the limit of detection. Bar graphs compare responses in vaccinated and unvaccinated individuals.⁴⁷

b. 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.1.²⁰

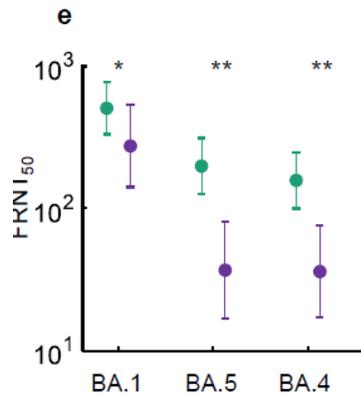


Figure 4-2: Pseudovirus neutralization of BA.1, BA.4 and BA.5 in individuals infected with BA.1 who had been previously vaccinated (n=15 in green) with BNT162b2 (n=8) or Ad26.CoV2.S (n=7) or unvaccinated (n=24 in purple). Error bars are GMT 95% confidence intervals. P values were determined by two-sided Wilcoxon rank sum test and represented as *0.05-0.01, **0.01-0.001).²⁰

4. Preliminary data on candidate vaccines with updated composition

a. Prototype Omicron-specific mRNA vaccines have been tested in animal models.

In a mouse model, it has been demonstrated that an Omicron-specific mRNA vaccine induces neutralizing Ab against the homologous virus, but the sera did not neutralize the index strain or other VOCs (Figure 5-1, Ying et al.).⁴⁸ 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** (Figure 5-2, Ying et al).⁴⁸ There are no data yet available on the immune response or effectiveness of an Omicron-specific vaccine in humans.

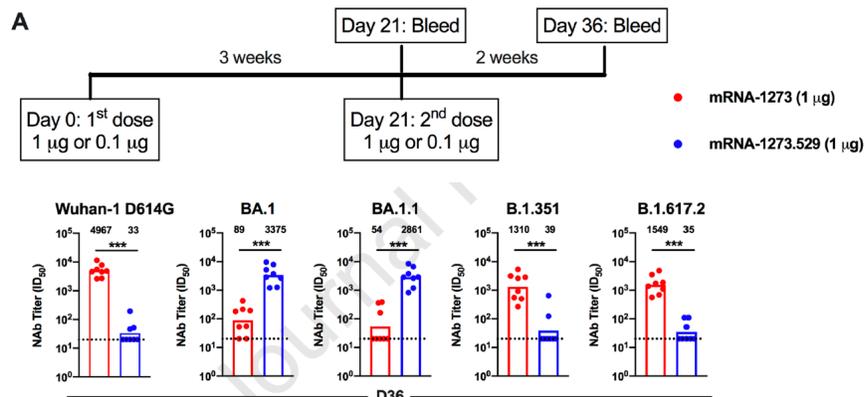


Figure 5-1: Pseudovirus neutralization activity of sera collected two weeks post vaccination (day 36) of BALB/c mice using 2 doses of either the mRNA-1273 vaccine (index-virus in red) or mRNA-1273-529 (Omicron-specific update in blue) against 614G, BA.1, BA.1.1, B.1.351, or B.1.617.2.⁴⁸

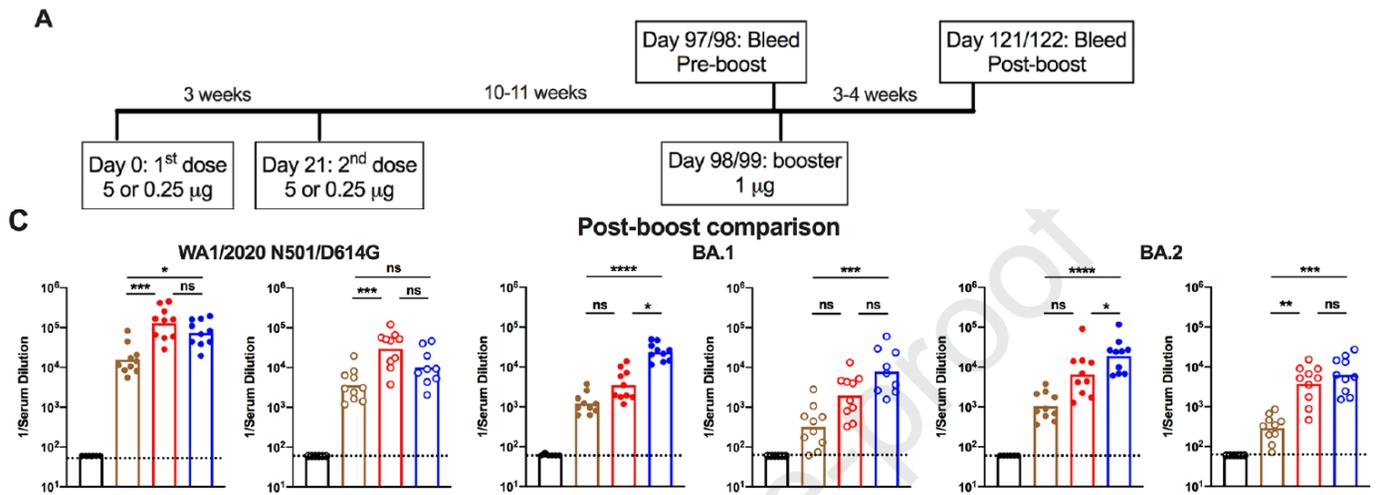


Figure 5-2: 129S2 mice were immunized with mRNA vaccines (2 doses). Serum neutralizing antibody responses were analyzed in control animals (black), animals that only received the primary series (brown), those that received the mRNA-1273 vaccine booster (red) or those that received the mRNA-1273.529 vaccine (blue). Closed circles indicate the 5ug dose and open circles indicate the 0.25ug dose for the 1st and 2nd doses.⁴⁸

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 (Figure 6, Gagne et al⁴⁹). And, 70-80% of B cells were cross-reactive against both the index virus and Omicron.⁴² The longevity of these antibody responses has not been reported.

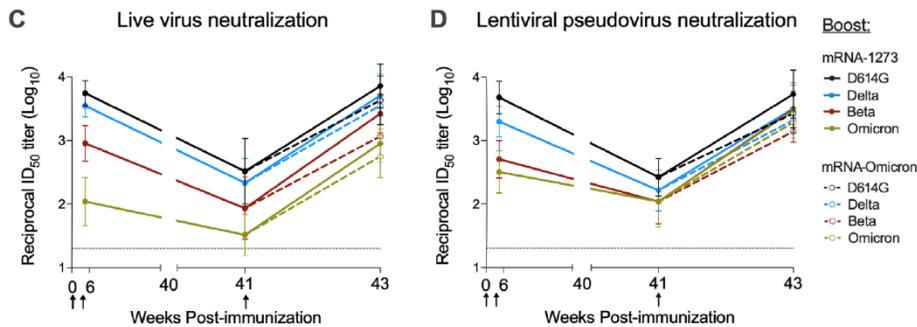
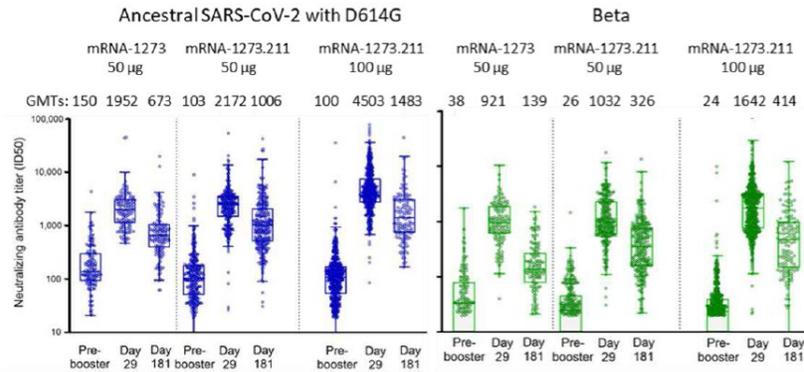


Figure 6: Kinetics of the serum neutralizing antibody response (geometric mean titres) in Macaques against 614G, Delta, Beta or Omicron, following immunization using mRNA-1273 on day 0 and 6 and then boosted using either mRNA-1273 (solid lines) or mRNA-Omicron (dashed lines) on day 41 (indicated by arrows).⁴⁹

b. There are also preliminary data that a **bivalent mRNA booster composition** (index virus + Beta; mRNA1273.211) can elicit similar, if not higher, titres of neutralizing antibodies against variants, with higher titres persisting at the 6-month time point compared to the monovalent booster containing the index virus alone, mRNA1273 (Figure 7).⁵⁰ These data may be indicative of the potential performance of a bivalent booster.



B. Omicron; Delta

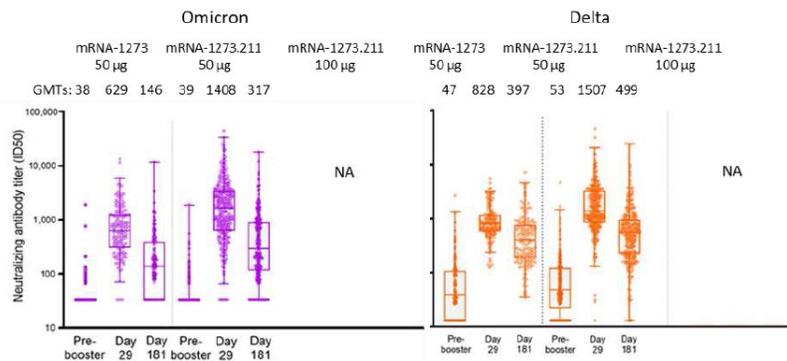


Figure 7: Pseudovirus neutralization against 614G, Beta, Omicron or Delta using serum samples collected from individuals who had received a primary series of two doses of mRNA-1273 (pre-booster) and then were boosted using either the mRNA-1273 (50ug dose) or mRNA-1273.211 (bivalent index virus + beta either 50ug or 100ug dose) vaccine. Sera were collected 29 or 181 following the booster dose.⁵⁰

c. **Preliminary data** on a candidate Omicron+index (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). This resulted in a geometric mean titre ratio (GMR) across all participants of 1.78 (97.5% CI: 1.56, 2.04) for the candidate bivalent vaccine. Further, a non-inferior neutralizing antibody response against the D614G virus was reported, with the GMT following the fourth dose of the mRNA-1273 booster estimated to be 5286.6 compared to 6422.3 following the candidate Omicron bivalent booster, resulting in a GMR of 1.22 (97.5% CI: 1.08, 1.37.)⁵¹

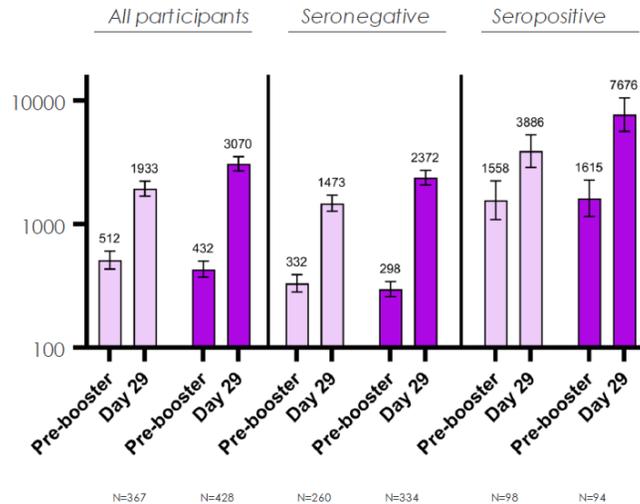


Figure 8: Pseudovirus neutralization against Omicron using serum samples collected from individuals who had received a primary series of two doses of mRNA-1273 followed by a 3rd dose of mRNA-1273. A 4th dose of either the mRNA-1273 (50ug, light purple) or mRNA-1273.214 (bivalent index virus + Omicron 50ug dose, dark purple) vaccine. Sera were collected 28 days post 4th dose (Day 29). Results are disaggregated according to whether the participants had experienced a breakthrough infection (sero-positive) or not (sero-negative).⁵¹

Summary

To date, Omicron is the most antigenically distinct SARS-CoV-2 VOC to have emerged, with BA.1 sequences as some of the most distant from the index virus. Antibody responses in previously naïve (unprimed) individuals exposed to Omicron are strong, but are limited (i.e. fairly high Omicron-specific neutralizing antibody titres are elicited, but 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 incorporation of an Omicron-specific vaccine product administered as a booster dose to achieve the objective of achieving broad immune responses against circulating and emerging variants, while retaining protection against severe disease and death.

The paucity of data must nonetheless be acknowledged. Specifically:

- Minimal / limited data on cross-reactivity (breadth) of humoral or cell-mediated immune responses in naïve individuals or in those who had breakthrough infection with 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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