

Annex: Report of the meeting of the WHO Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) held on 16-17 March 2023

14 April 2023

Overview of published evidence supporting the conclusions of the TAG-CO-VAC

On 16-17 March 2023, the TAG-CO-VAC met in Muscat, Oman. One of the objectives of the meeting was to review the evidence on the performance of updated COVID-19 vaccines that incorporate descendent lineages of Omicron as a booster dose. To this end, external epidemiological, virological and immunological experts were invited to present published and unpublished data up to 15 March 2023 that covered the following:

1. Observational epidemiological studies of estimates of absolute and relative vaccine effectiveness of BA.1- or BA.4/5-containing bivalent mRNA vaccines (i.e., index virus + BA.1 or BA.4/5), used as a booster dose against symptomatic and severe disease;
2. Laboratory-based data on the magnitude and breadth of cross-reactive immune responses against previous and circulating SARS-CoV-2 variants induced by BA.1- or BA.4/5- containing mRNA vaccines, as compared to index virus-based vaccines, used as a booster dose; and
3. Laboratory-based studies and observational data on immune memory responses to evaluate the impact of repeated antigen exposure on vaccine-induced immunity and protection.

A systematic review of published literature was not conducted, in order to take into account up-to-date unpublished findings. The data highlighted below, while not exhaustive, were specifically reviewed and considered by the TAG-CO-VAC in their assessment of the performance of updated COVID-19 vaccines that incorporate descendent lineages of Omicron, as compared to index virus based COVID-19 vaccines, when used as a booster dose.

1. Published observational epidemiological studies of estimates of absolute and relative vaccine effectiveness of BA.1- or BA.4/5-containing bivalent mRNA vaccines used as a booster dose against symptomatic and severe disease.

Collectively, the published data below indicate that booster doses of index virus-based vaccines continue to confer protection against severe disease and death caused by Omicron infection. Booster doses of BA.1- or BA.4/5-containing bivalent mRNA vaccines (i.e. the index virus + BA.1 or BA.4/5) modestly increase vaccine effectiveness against symptomatic disease, while the small number of studies assessing severe outcomes show similar vaccine effectiveness of the BA.1- or BA.4/5-containing bivalent mRNA vaccines compared to index-virus based vaccines. For both index virus-based and bivalent mRNA vaccines, protection from severe disease and symptomatic infection declines over time; protection from severe disease is maintained longer than protection from symptomatic infection.

Figure 1 shows that across 6 vaccine platforms, the administration of an index virus-based vaccine administered as a booster dose increases estimates of vaccine effectiveness (VE), as compared to pre-boost levels, against severe disease due to Omicron infection (data not shown for previously circulating VOCs, e.g. Alpha, Delta).

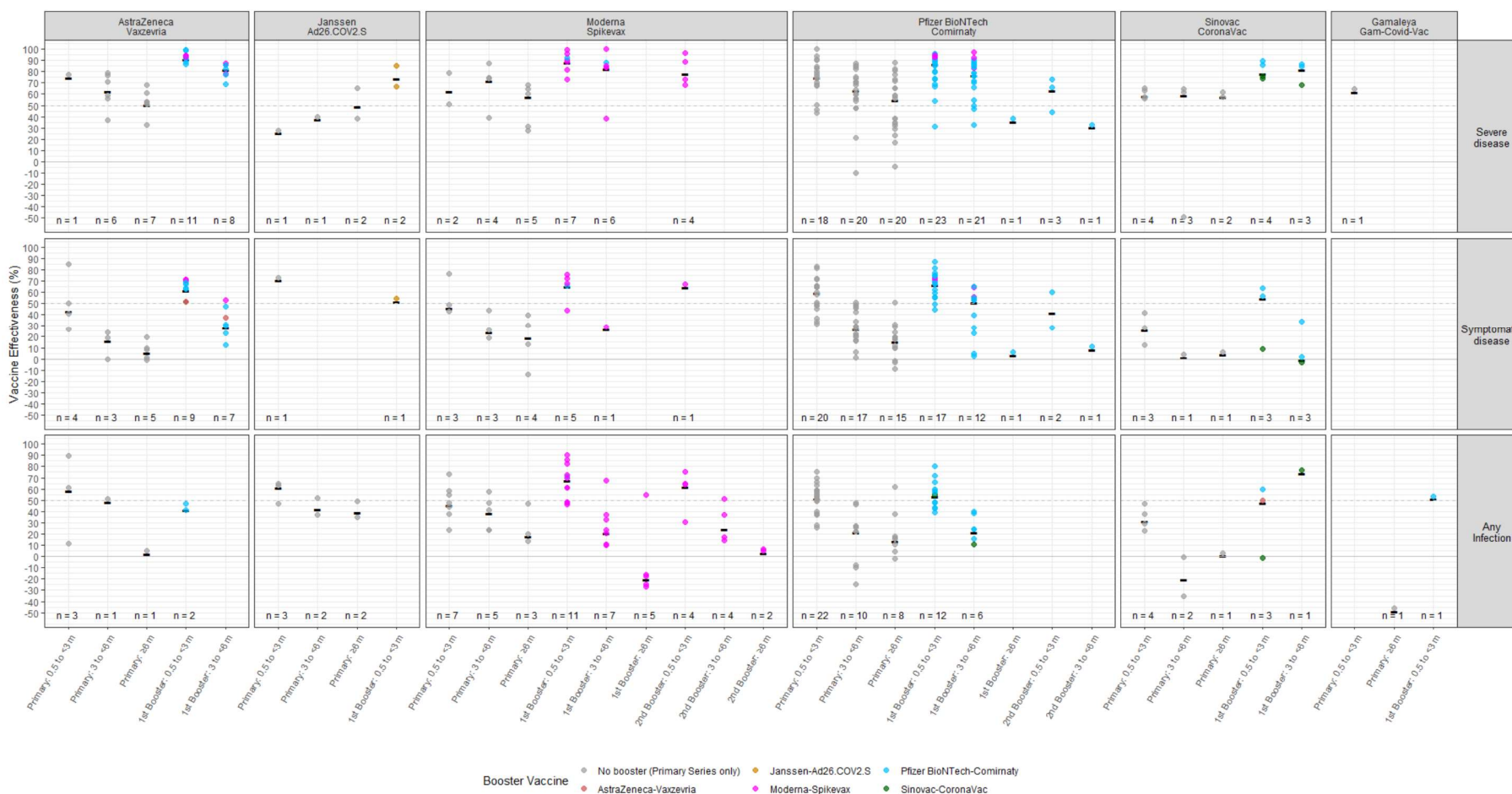


Figure 1. Collated vaccine effectiveness against any infection, symptomatic disease and severe disease over time across six vaccine platforms.¹ Dots represent point estimates of absolute VE from each study; dark black horizontal lines represent median VE across all studies in stratum. Vertical panels represent VE for full primary series (grey dots) and VE for homologous or heterologous booster vaccination (other colored dots) following completion of primary series vaccination with vaccine of primary series noted in panel header. Not shown in plot: VE against severe disease at 0.5-<3 month post primary series of Beijing CNBG-BBIBP-CorV (59%). VE studies included in the plot were identified from an ongoing systematic review of COVID-19 vaccine effectiveness studies. All studies were cohort or test-negative designs conducted when Omicron was the predominant circulating variant.

As of 9 March 2023, there have been 13 studies of vaccine effectiveness of BA.1- or BA.4/5-containing bivalent mRNA vaccines across 9 countries.²

Estimates of absolute vaccine effectiveness against severe disease for BA.4/5 containing bivalent vaccines administered as a booster dose range from 55-85% (Figure 2). Estimates of absolute vaccine effectiveness against symptomatic disease are lower than the estimates of absolute vaccine effectiveness against severe disease (Figure 2). However, at this stage in the pandemic, with high levels of infection- and/or vaccine-derived immunity in the population, using an unvaccinated population to calculate absolute vaccine effectiveness may introduce bias, as the unvaccinated population is likely to be quite different from the vaccinated population in terms of SARS-CoV-2 exposure and/or disease risk.

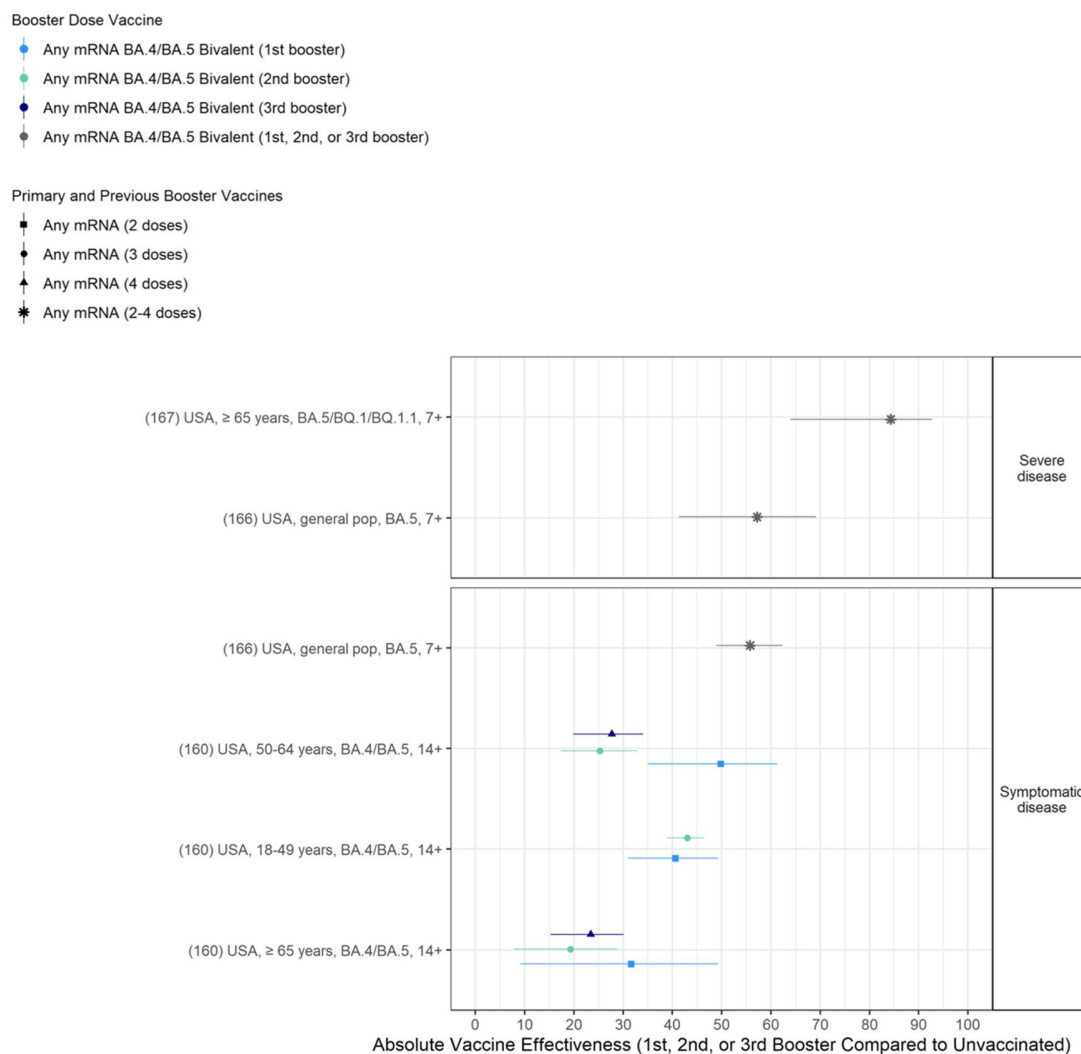


Figure 2. Forest plot of estimates (95%CI) of absolute vaccine effectiveness of BA.4/5 containing bivalent mRNA vaccines, administered as a first, second or third booster dose against severe disease and symptomatic disease during Omicron circulation.²

Country of study, population, Omicron descendent lineage (if specified), time since last booster dose (days) are indicated for each study on the y axis.

Estimates of relative vaccine effectiveness against severe disease and death conferred by BA.1 or BA.4/5-containing bivalent mRNA vaccines, as compared an index virus-based vaccine, administered a second booster dose, are shown in Figure 3. Estimates of relative vaccine effectiveness against symptomatic disease conferred by BA.4/5-containing bivalent mRNA vaccines, as compared an index virus-based vaccine, administered a first booster dose, are shown in Figure 4. Caution is needed when interpreting some studies that compare the performance of different vaccine products over different time periods, which may introduce potential biases.

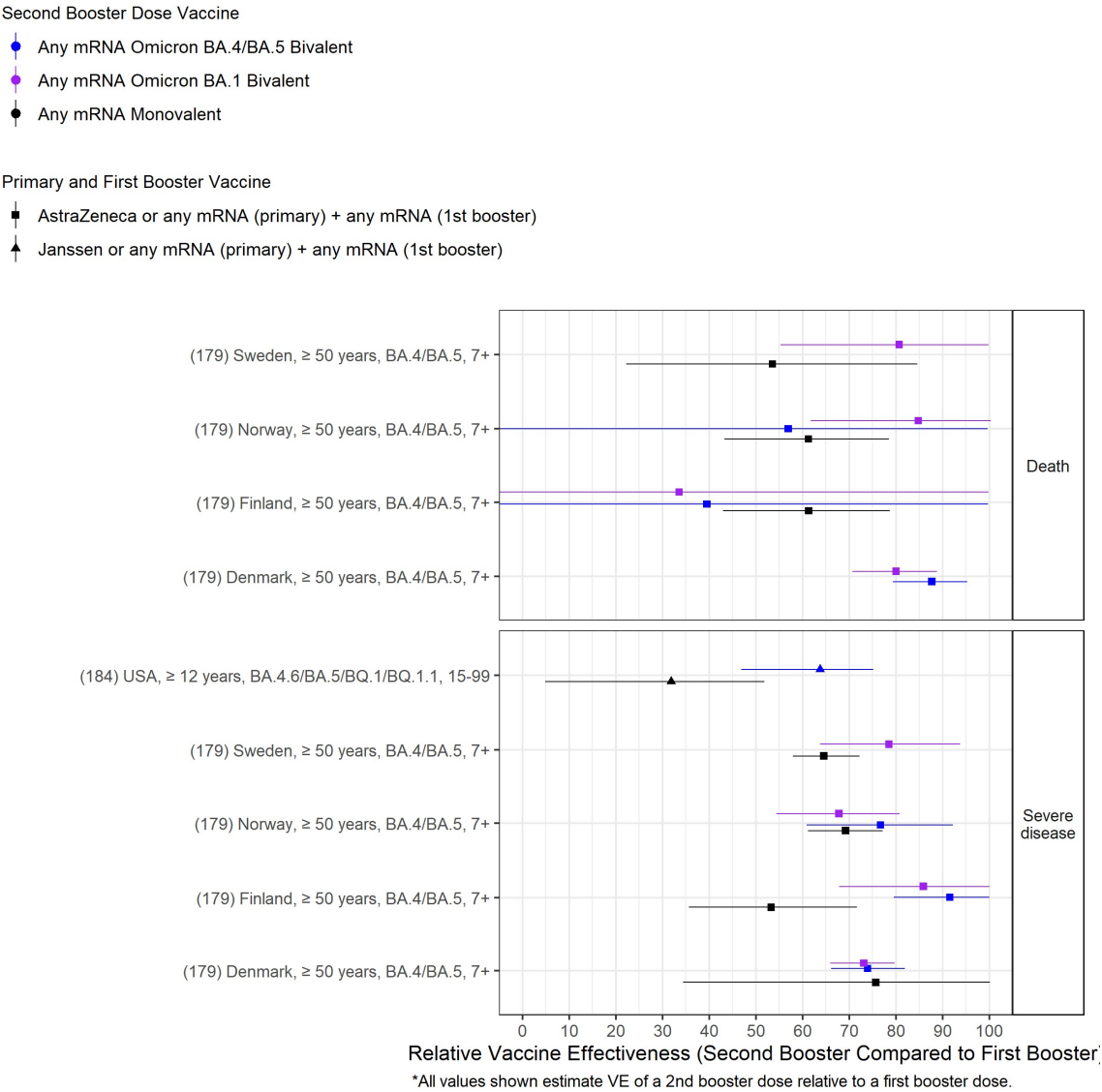


Figure 3. Forest plot of estimates (95% CI) of relative vaccine effectiveness of BA.1 or BA.4/5 containing bivalent mRNA vaccines, administered as a second booster dose, as compared to index virus-based mRNA vaccines, administered as a second booster dose, against severe disease and death during Omicron circulation.²

Country of study, population, Omicron descendent lineage (if specified), time since last booster dose (days) are indicated for each study on the y axis.

1st Booster Dose Vaccine

- Any mRNA Omicron BA.4/BA.5 Bivalent
- Any mRNA Monovalent

Primary Series Vaccine

- Any mRNA
- ▲ Janssen or any mRNA

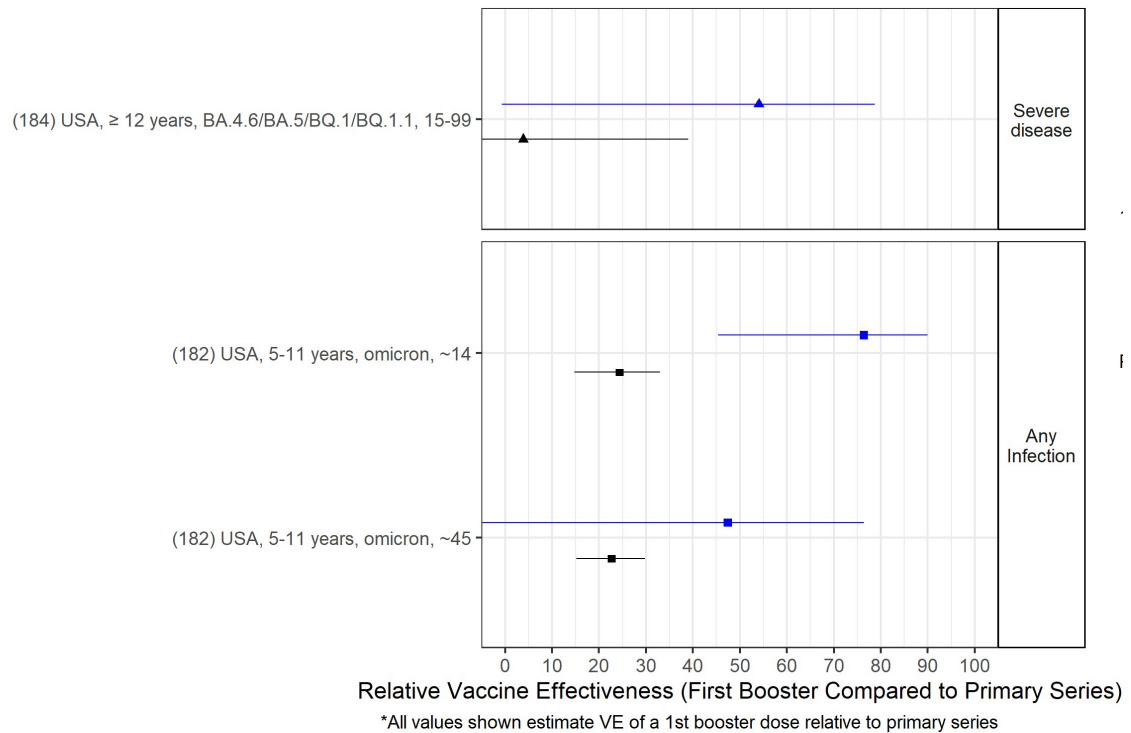


Figure 4. Forest plot of estimates (95% CI) of relative vaccine effectiveness of BA.4/5 containing bivalent mRNA vaccines, administered as a first booster dose, as compared to index virus-based mRNA vaccines, administered as a first booster dose, against severe disease and any infection during Omicron circulation.²

Country of study, population, Omicron descendent lineage (if specified), time since last booster dose (days) are indicated for each study on the y axis.

Estimates of protection from symptomatic disease (assessed by RT-PCR and paired serology) using the Moderna BA.1-containing bivalent mRNA vaccine as a booster dose, as compared to the index virus-based mRNA vaccine, administered as a booster dose, have been derived from two randomized controlled trials conducted by Moderna in the United States of America (Table 1) and the United Kingdom (Figure 5). Neither study found significant differences in the incidence of SARS-CoV-2 infection in individuals randomized to receive the index-virus based mRNA vaccine as compared to those randomized to receive the BA.1-containing bivalent mRNA vaccine.

Table 1. Incidence of COVID-19 and SARS-CoV-2 infection in phase 2–3 randomized controlled trial, comparing the Moderna BA.1 containing bivalent mRNA vaccine (mRNA-1273.214) with the Moderna index virus-based vaccine (mRNA-1273), administered as a booster dose.³

n (%)	Per-protocol Efficacy Set No Prior SARS-CoV-2 Infection	
	mRNA-1273.214 50 µg N=339	mRNA-1273 50 µg N=266
Covid-19 (COVE definition)* Cases	4 (1.2)	1 (0.4)
Covid-19 (CDC definition)* Cases	5 (1.5)	1 (0.4)
SARS-CoV-2 infection (regardless of symptoms) Cases	11 (3.2)	5 (1.9)
Asymptomatic SARS-CoV-2 infection Cases	6 (1.8)	4 (1.5)

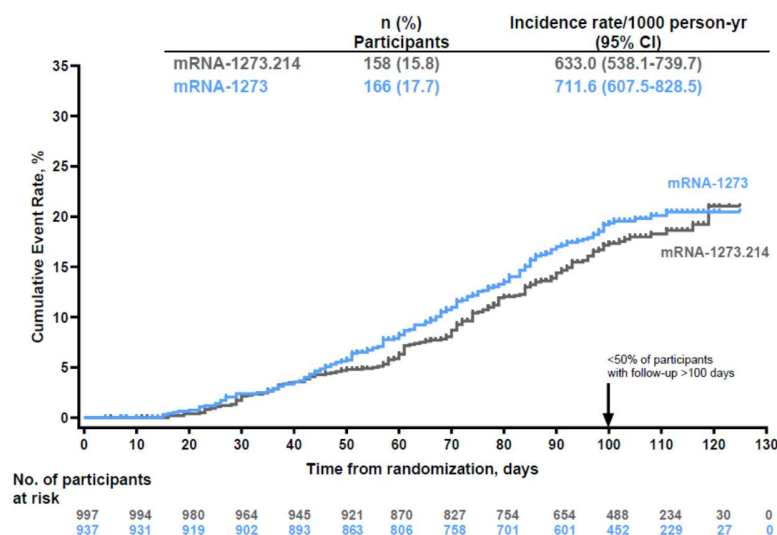
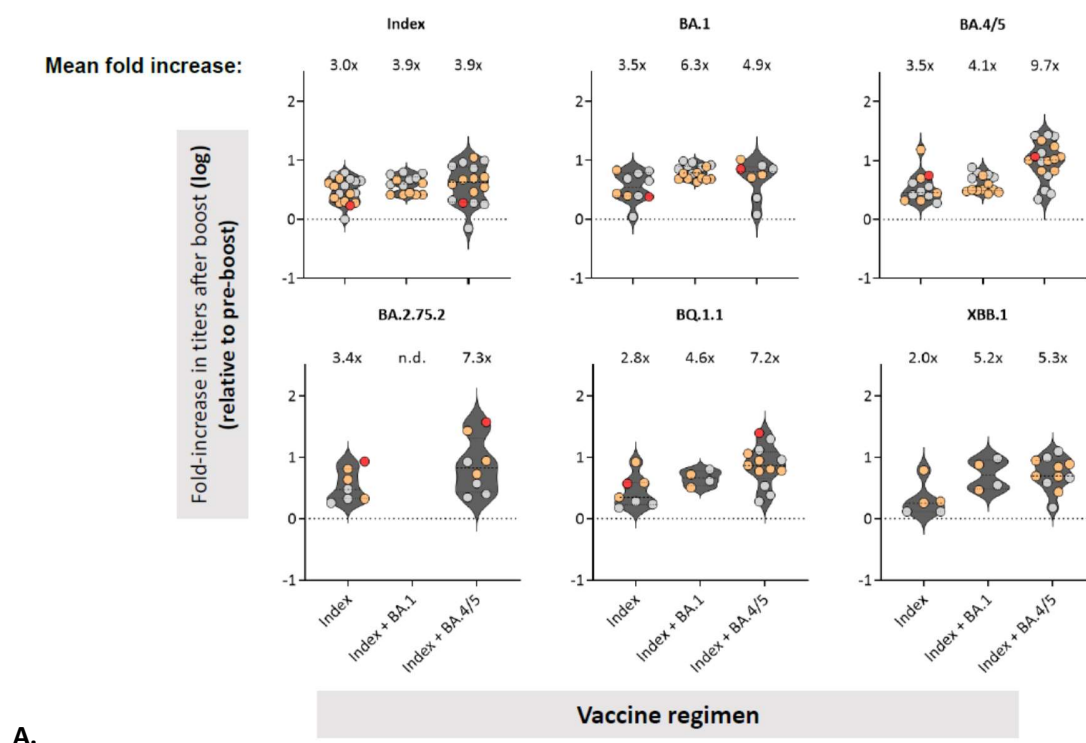


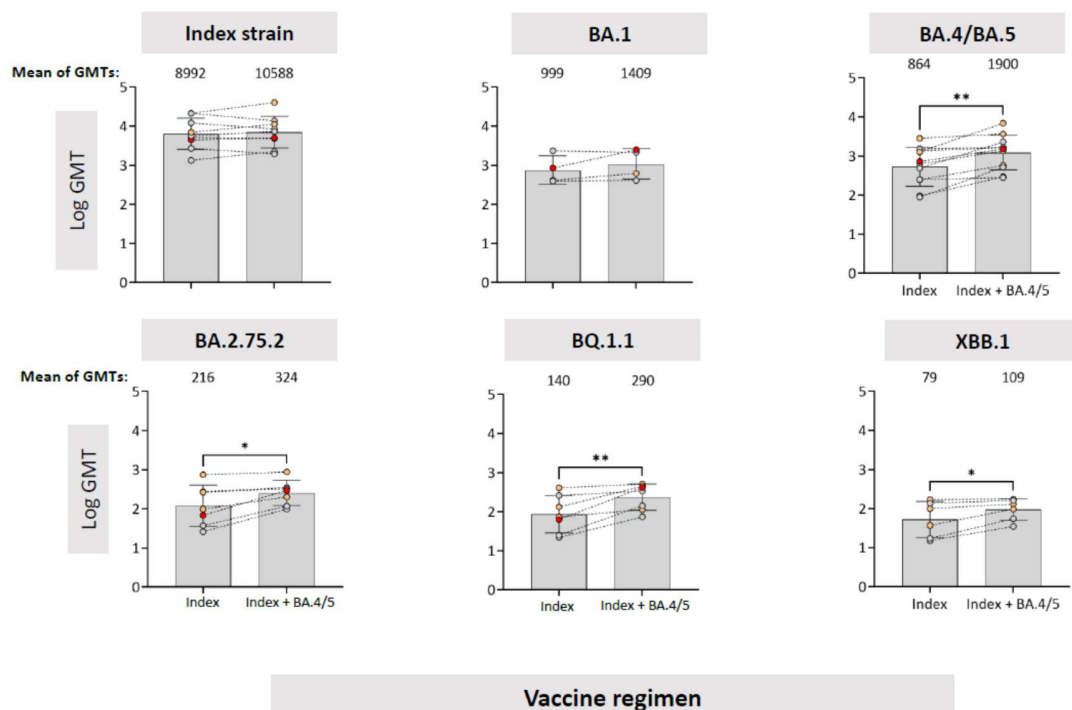
Figure 5. Cumulative event rates of COVID-19 up to 4 months post randomization to receive either the Moderna BA.1 containing bivalent mRNA vaccine (mRNA-1273.214) or the Moderna index virus-based vaccine (mRNA-1273) following a primary series of mostly AstraZeneca or Pfizer, at a time when the majority of infections were due to BA.5 infection, with some due to BA.4, and the remainder due to BA.2.⁴

2. Laboratory-based data on the magnitude and breadth of cross-reactive immune responses against previous and circulating SARS-CoV-2 variants induced by BA.1- or BA.4/5- containing bivalent mRNA vaccines, as compared to index virus-based vaccines, used as a booster dose

Collectively, the data below indicate that the use of either index virus-based vaccines or BA.1- or BA.4/5- containing bivalent mRNA vaccines as a booster dose increases the magnitude of neutralizing antibody responses as compared to pre-boost levels. BA.1- or BA.4/5- containing bivalent mRNA vaccines administered as a booster dose enhance the magnitude and elicit greater breadth of cross-reactive immune responses as compared to index virus-based vaccines administered as a booster dose. There is limited evidence that BA.4/5- containing bivalent mRNA vaccines induce higher titres against recent Omicron-descendant lineages (e.g. BQ.1 and XBB.1) as compared to BA.1- containing bivalent mRNA vaccines.

An update to an ongoing systematic review assessing post-vaccination neutralizing antibody responses against SARS-CoV-2 variants was presented.⁵ At the time of analysis, data from 20 (out of 362) studies were included to assess the impact of BA.1- or BA.4/5- containing bivalent mRNA vaccines when administered as a fourth dose on the magnitude and breadth of the neutralizing antibody response. BA.1- or BA.4/5 containing bivalent mRNA vaccines elicit about two-fold increased neutralizing titres specific for Omicron-descendant lineages (BA.1, BA.4/5, BA.2.75.2, BQ.1 or XBB.1), as compared to index virus-based vaccines, when administered as a booster dose (Figure 6).





B. Figure 6. Compiled data on the fold increase in neutralizing antibody titres following an index virus-based vaccine, a BA.1-containing bivalent mRNA vaccine or BA.4/5-containing bivalent mRNA vaccine, administered as a fourth dose, as compared to pre-boost levels (A), and difference in absolute neutralizing antibody titres (Log GMT) in recipients of an index virus-based booster dose or a BA.4/5-containing bivalent mRNA booster dose (B).⁵

Each point represents one cohort (each study can contain multiple cohorts) and connected lines indicate paired observations from the same cohort. Infection status of the cohort is indicated by the color of the point: grey indicates no previously-documented infection, orange indicates cohorts with prior infection with a pre-Omicron variant, and red indicates cohorts infected with an Omicron variant. Numbers across the top of the plot represents mean fold change (A) or mean GMT (B).

In one example study, the neutralizing antibody responses against the index virus (WA1/2020), and multiple Omicron variants through fluorescence-based focus reduction neutralization test (FRNT) following a fourth dose of either BA.4/5 containing bivalent mRNA vaccine or index virus-based mRNA vaccine were compared (Figure 7).⁶ Although both the BA.4/5 containing bivalent mRNA vaccine and the index virus-based mRNA vaccine, administered as booster doses, increased neutralizing antibody titres, the enhancement was found to be greater in the recipients of the BA.4/5 containing bivalent mRNA vaccine. The enhancement is most notable against the more recently circulating descendent lineages of Omicron, e.g. BQ.1.1 or XBB.1. Figure 7 also shows that individual infection history impacts the overall magnitude of the neutralizing antibody response, but the trends observed below indicate that the BA.4/5 containing bivalent mRNA vaccine increases neutralizing antibody titres more than an equivalent dose of the index virus-based mRNA vaccine.

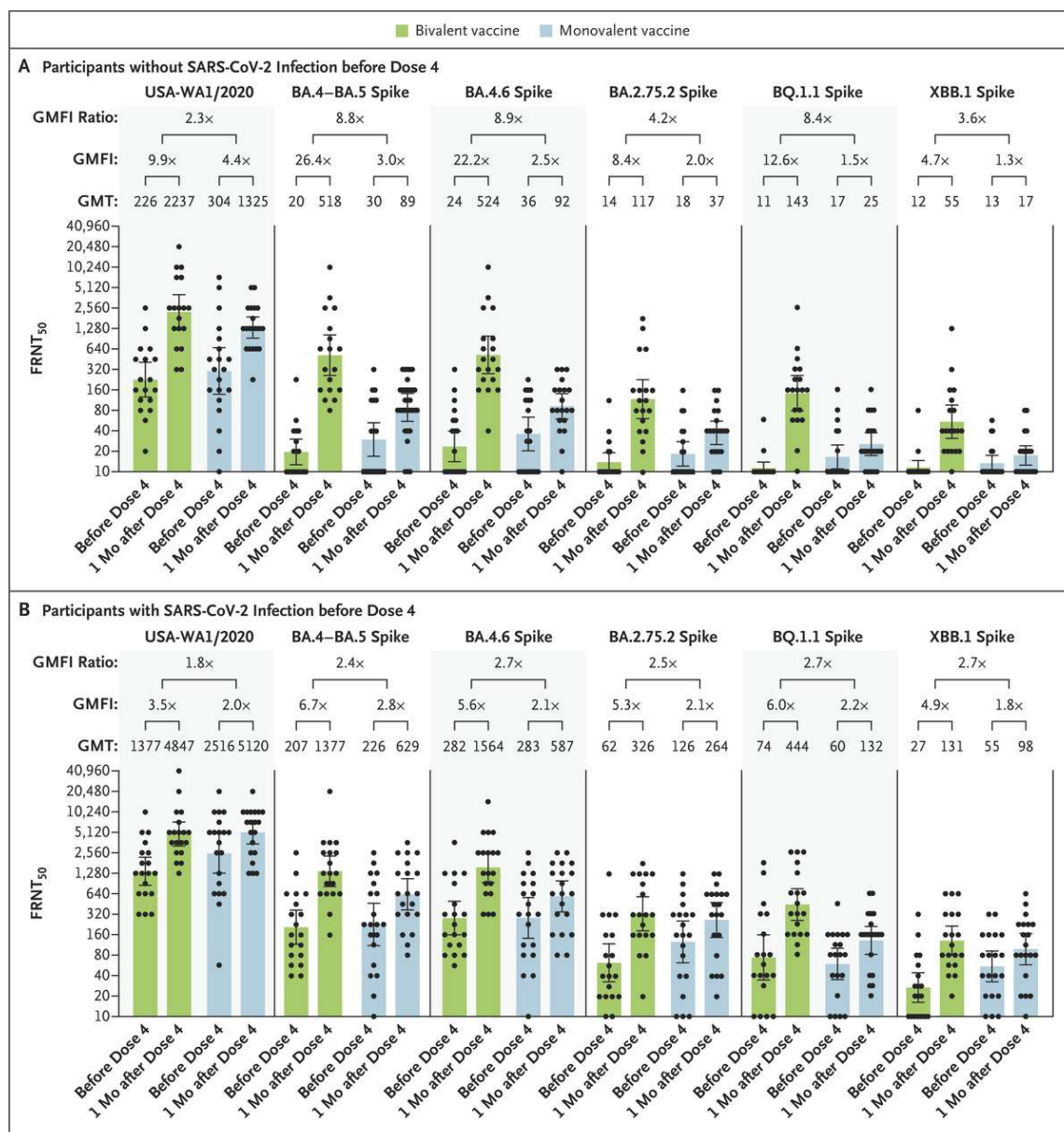


Figure 7. Neutralizing antibody responses with BA.4/BA.5-containing bivalent mRNA vaccine or index virus-based BNT162b2 vaccine administered as booster doses against the USA-WA1/2020 and Omicron descendent lineages BA.4/BA.5, BA.4.6, BA.2.75.2, BQ.1.1, and XBB.1 in all participants who did not have evidence of SARS-CoV-2 infection before the fourth dose of vaccine (A) and in those who had evidence of SARS-CoV-2 infection before the fourth dose of vaccine (B).

The heights of the bars and the numbers immediately above the bars indicate the geometric mean titers (GMTs) of neutralizing antibodies. The I bars indicate 95% confidence intervals. Each circle in the figure represents an individual participant. The geometric mean factor increases (GMFI [the increase in neutralizing titers in serum samples from the day of the fourth dose to 1 month after the fourth dose]) and GMFI ratios between GMFIs of bivalent vaccine and GMFIs of monovalent vaccine are shown.

3. Laboratory-based studies and observational data on immune memory responses

There is *in vitro* evidence indicating that repeated exposure to the same antigen preferentially recalls specific antibodies and memory B cells. The clinical impact of this phenomenon in observational studies to date is unclear, due to limited data and the possibility of bias.

Data were presented looking at serological responses in individuals who experienced breakthrough infection after receiving 3 doses of the CoronaVac index virus-based vaccine.⁷ The neutralizing antibody titres against the specific Omicron variant that caused the breakthrough infection (either BA.1, BA.2, BA.5 or BF.7) were lower than those to D614G, which is indicative of immune imprinting (data not shown).

Similar data were reported in individuals who received repeated doses of index virus-based mRNA vaccine. Robust index virus-specific memory B cell responses were measured following a booster dose using either the monovalent index virus-based vaccine, a Beta/Delta-containing bivalent mRNA vaccine or a BA.1-containing monovalent vaccine, demonstrating that the memory response after boosting is predominantly imprinted by the index virus.⁸ A booster dose with the BA.1-containing monovalent vaccine, which is the most antigenically distant of the three booster vaccines, was able to induce *de novo* B cell responses to novel Omicron-specific spike.⁸

Finally, there is evidence from a matched, retrospective, observational cohort study in Qatar in which reinfection incidence was compared between individuals who received two doses versus three doses of index virus-based vaccines prior to Omicron infection. The adjusted hazard ratio for reinfection was 1.47 (95% CI: 1.23-1.76). Though confounders are addressed as part of the analysis, the possibility of residual bias remains and therefore these data have been interpreted with caution.⁹

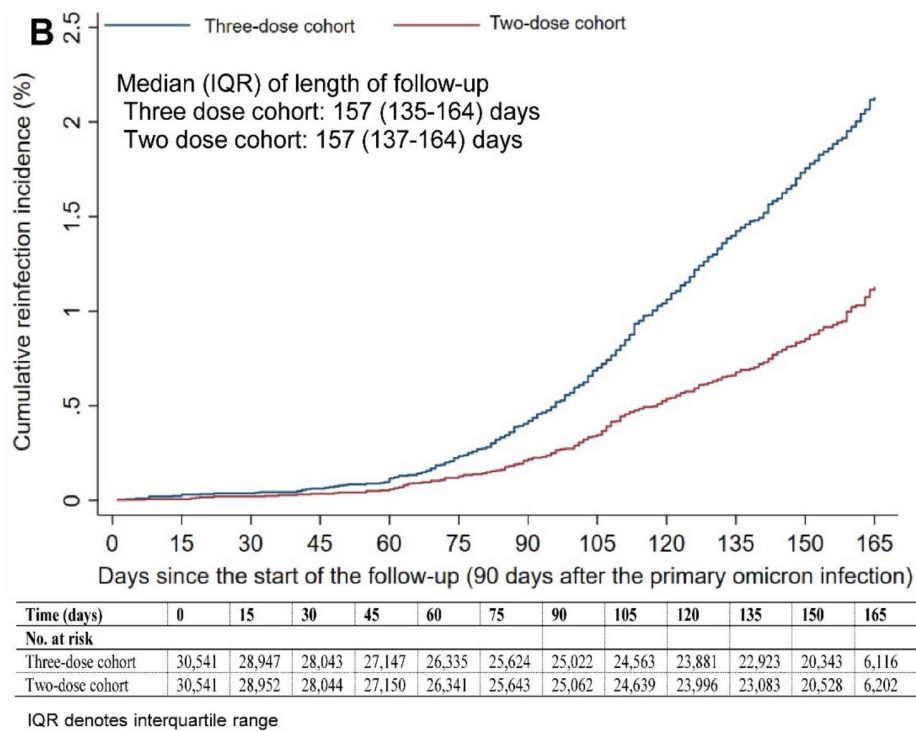


Figure 9. Cumulative incidence of reinfection using Kaplan-Meier estimator among those who had a primary infection with Omicron after receiving three doses of COVID-19 vaccination, as compared to receiving two doses of COVID-19 vaccination.⁹

References

1. International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, World Health Organization, Coalition for Epidemic Preparedness Innovations. Results of COVID-19 Vaccine Effectiveness Studies: An Ongoing Systematic Review
Forest Plots: Vaccine Effectiveness against Omicron Variant of Concern. Available from: https://view-hub.org/sites/default/files/2023-03/COVID19%20VE%20Studies_Forest%20Plots_Omicron_0.pdf
2. International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, World Health Organization, Coalition for Epidemic Preparedness Innovations. Results of COVID-19 Vaccine Effectiveness Studies: An Ongoing Systematic Review. Forest Plots: Vaccine Effectiveness of Bivalent Ancestral Strain/Omicron-based Vaccines. Available from: https://view-hub.org/sites/default/files/2023-03/COVID19%20VE%20Studies_Bivalent%20VE%20Plots.pdf
3. Chalkias S, Harper C, Vrbicky K, et al. A Bivalent Omicron-Containing Booster Vaccine against Covid-19. *N Engl J Med*. 2022;387(14):1279-1291.
4. Lee IT, Cosgrove CA, Moore P, et al. A Randomized Trial Comparing Omicron-Containing Boosters with the Original Covid-19 Vaccine mRNA-1273. *medRxiv* (pre-print). 2023; doi: 10.1101/2023.01.24.23284869
5. International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, World Health Organization, Coalition for Epidemic Preparedness Innovations. Results of Studies Evaluating the Impact of SARS-CoV-2 Variants of Concern on COVID-19 Vaccines: An Ongoing Systematic Review. Overview of neutralizing antibody responses in recipients of variant-containing vs. ancestral virus-based vaccines. Available from: <https://view-hub.org/sites/default/files/2023-03/Laboratory%20Evidence%20Bivalent%20Vaccines.pdf>
6. Zou J, Kurhade C, Patel S, et al. Neutralization of BA.4-BA.5, BA.4.6, BA.2.75.2, BQ.1.1, and XBB.1 with Bivalent Vaccine. *N Engl J Med*. 2023;388(9):854-857.
7. Yue C, Song W, Wang L et al. ACE2 binding and antibody evasion in enhanced transmissibility of XBB.1.5. *Lancet Infect Dis*. 2023;23(3):278-280
8. Alsoussi WB, Malladi SK, Zhou JQ, et al. SARS-CoV-2 Omicron boosting induces de novo B cell response in humans. *medRxiv* (preprint). 2022; doi: 10.1101/2022.09.22.509040
9. Chemaitelly H, Ayoub HH, Tang P, et al. COVID-19 primary series and booster vaccination and potential for immune imprinting. *medRxiv* (preprint) 2023; doi: 10.1101/2022.10.31.22281756.