POSITION STATEMENTS OF THE PHILIPPINE SOCIETY OF ALLERGY, ASTHMA, AND IMMUNOLOGY ON COVID-19 BIVALENT VACCINES

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These statements were developed by the Vaccine Council of the Philippine Society of Allergy, Asthma, and Immunology (PSAAI)

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I. INTRODUCTION

RATIONALE

On November 26, 2021, the WHO declared Omicron (B.1.1.529) as a new SARS-CoV-2 variant of concern. By the end of 2022, the Omicron BA.5 sublineage accounted for most of the sequenced viral genomes worldwide.[1] In the Philippines from June 2023 onwards, the Omicron subvariant XBB and its sublineages were the most detected variants comprising 91.34% of samples sequenced with assigned lineages similar to the antigenic trajectory of the US and other countries.[2]

By September 1, 2022, the US CDC's Advisory Committee on Immunization Practices (ACIP) recommended a single bivalent mRNA COVID-19 booster dose, containing an ancestral SARS-CoV-2 strain component and an updated component of the omicron BA.4 and BA.5 sublineages.[3] In the Philippines, the same bivalent vaccines were launched only on June 21, 2023 and initially targeting healthcare workers and senior citizens who had received their 2nd monovalent booster at least 4 to 6 months prior.[4]

In this review, the authors aim to analyze currently available data to gain insights in selecting the most beneficial type of vaccine for the eligible Filipino population. This document will assess the immunogenicity, relative effectiveness and durability of the bivalent vaccines based on real-world data. The possible effects of hybrid immunity, the predominating variants of the virus as well as the emergence of new variants and its sublineages and vaccine safety profile were likewise reviewed in this document.

On May 18, 2023, the WHO Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) released a recommendation to use a monovalent XBB.1 descendent lineage in future formulations of COVID-19 vaccines instead of including the index virus and strongly related variants at a time when they are no longer circulating in humans.[9] In light of such a statement coming from an authoritative source this document will examine evidence that support such a recommendation. As such, the utility of the bivalent vaccine at a time when the Omicron BA.4 and BA.5 sublineages have now been replaced by the XBB subvariant and its sublineages will be evaluated**.**

Disclaimer: This document is intended for physicians' use only, and should not be interpreted out of context. Note that the recommendations are based on current evidence and may change as more studies become available.

BIVALENT COVID-19 VACCINES

The U.S. Food and Drug Administration (FDA) initially authorized the distribution of 2 bivalent COVID-19 vaccines in August 31, 2022. Both the Moderna and Pfizer bivalent vaccines are updated formulations of the original messenger RNA (mRNA) vaccines and contain two mRNA components of SARS-CoV-2, one of the ancestral strain of SARS-CoV-2 and the other one a common component between the BA.4 and BA.5 lineages of the omicron variant of SARS-CoV-2.[3] The recommended bivalent COVID-19 booster dose is 0.5ml given intramuscularly at least 2 months from receipt of the primary series or the most recent monovalent booster.[5]

The Comirnaty bivalent (Original/Omicron BA.4, BA.5) vaccine from Pfizer contains Tozinameran, a mRNA molecule with instructions for producing a protein from the original strain of SARS-CoV-2, and Famtozinameran which is another mRNA molecule with instructions for producing a protein from the Omicron BA.4 and BA.5 subvariants of SARS-CoV-2.[14] Likewise, the Spikevax bivalent (Original/Omicron BA.4, BA.5) vaccine from Moderna contains Elasomeran which is a mRNA molecule that codes for a protein from the original strain of SARS-CoV-2 and Davesomeran which codes for a protein from the Omicron BA.4 and BA.5 subvariants.[14]

In the Philippines, the Comirnaty bivalent (Original/Omicron BA.4, BA.5) vaccine was used during the initial roll of the bivalent boosters. This document will discuss studies involving the Comirnaty bivalent (Original/Omicron BA.4, BA.5) vaccine and the Spikevax bivalent (Original/Omicron BA.4, BA.5) vaccine.

EMERGENCE OF VARIANTS AND THE EVOLUTION OF SARS-COV-2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the COVID-19 pandemic, has been continuously spreading worldwide and undergoing rapid continuous evolutionary changes. Previously circulating variants of concern were the Alpha, Beta, Gamma, and Delta. The early part of 2022 witnessed the emergence of the Omicron BA.1/BA1.1 variant, which represented a crucial turning point in the pandemic due to its heightened transmissibility and enhanced ability to evade the immune response. Throughout 2022, the original Omicron variant has given rise to numerous subvariants, some of which exhibited increased pathogenicity while demonstrating even more pronounced immune evasion capabilities.

Since July 2022, different Omicron subvariants under monitoring that were previously and are currently being identified by the World Health Organization (WHO) or European Centre for Disease Prevention and Control (ECDC) (ie. BA.2.3.20, XBB and its sublineages) have been on a continuous increase starting September 2022. Pfizer and Moderna bivalent vaccines approved in September 2022 were approved and designed to target the BA.4 and BA.5 strains of omicron.[6]

In March 2023, ECDC removed Omicron BA.2, BA.4, and BA.5 from its list of variants of concern as these parental lineages were no longer circulating. From May 2023 onwards, XBB and its sublineages were the most detected variant, comprising 87.44% of samples sequenced, followed by the BA.2.3.20 and its sublineages at 11.79%. For the same time period, XBB.1.9.1 was the most detected XBB sublineage comprising 35.89 % of XBB cases sequenced.[7]

From May 2023, the XBB.1 descendent lineage has been predominant worldwide (i.e., XBB.1.5, XBB.1.16, XBB.1.9). In the Philippines, 117 samples sequenced by UP-PGC Visayas, SPMC, and BGHMC last July 11-12, 2023: 102 (87.18%) were classified as XBB (including four XBB.1.5 cases, 44 XBB.1.16 cases, 14 XBB.1.9.1 cases, 11 XBB.1.9.2 cases, 20 XBB.2.3 cases) and five (4.27%) as BA.2.3.20. The variants XBB.1.5

and XBB.1.16 are variants of interest (VOI) identified by the WHO, while variants under monitoring (VUM) include XBB, XBB.1.9.1 (a sublineage of XBB), XBB.1.9.2 (a sublineage of XBB), XBB.2.3 (a sublineage of XBB), BA.2.75, and CH.1.1 (a sublineage of BA.2.75). [6,9]

Recent studies have shown that the XBB Omicron subvariant exhibited increased infectivity in HEK293T-ACE2 cells, with 1.9- 2.2 times higher titers compared with D614G.[9] Currently, the vaccine booster roll-out provides the mRNA bivalent vaccine made by Pfizer, Comirnaty bivalent (Original/Omicron BA.4, BA.5) which contains the original strain plus the BA.4-5 Omicron subvariant.

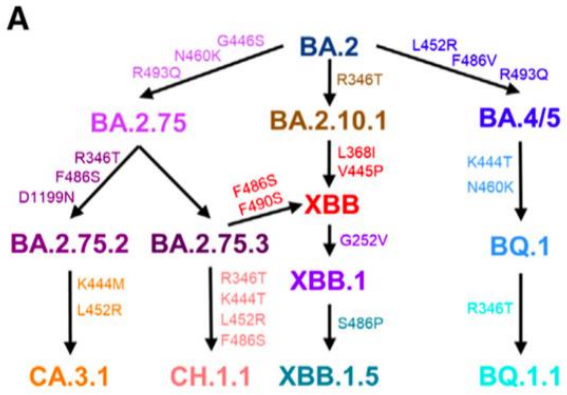

Figure 1: Schematic depiction of the relationships between different Omicron subvariants, with key lineage-defining amino acid mutations for each displayed.

In the study of Qu, it was noted that there was strong neutralization resistance exhibited by XBB.1.5, CH.1.1, and CA.3.1, with mean neutralizing antibody (nAb) titers 4.6–7.3 ($p < 0.0001$), 16.7–20.5 ($p < 0.0001$), and 17.7–23.2 times ($p < 0.0001$) lower than BA.4/5, respectively(1), among 14 healthcare workers (HCWs) who had received a bivalent booster in addition to 2–4 doses of monovalent mRNA vaccine. However, when compared to healthcare workers who only received 3 doses of the monovalent mRNA vaccine, dramatic reductions in neutralization sensitivity were observed for XBB.1.5, CH.1.1, and CA.3.1, which exhibited complete escape from nAbs, with mean nAb titers 3.3–4.5 ($p < 0.05$), 13.6–24.6 ($p < 0.0001$), and 15.4–21.9 times ($p < 0.0001$) lower than BA.4/5, respectively. Importantly, the overall trends for each subvariant in the 3-dose mRNA vaccine cohort remained similar to that of those who received the bivalent mRNA vaccination. When compared against sera of those who were infected during the Omicron B.4/5 wave, strong and almost complete neutralization resistance was observed for XBB.1.5, CH.1.1, and CA.3.1, with nAb titers 2.6 ($p > 0.05$), 3 ($p > 0.05$), and 4.1 times ($p < 0.05$) lower than BA.4/5, respectively. [10]

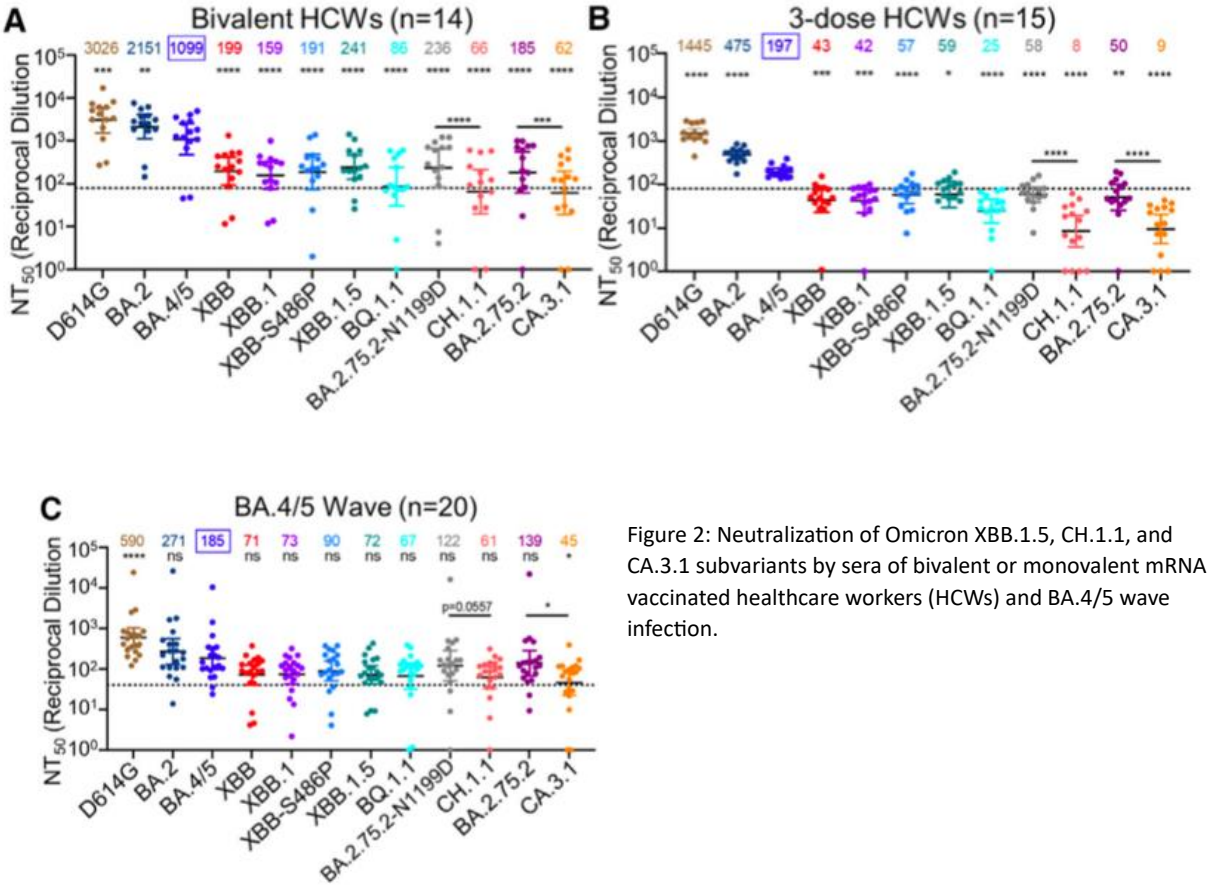

Figure 2: Neutralization of Omicron XBB.1.5, CH.1.1, and CA.3.1 subvariants by sera of bivalent or monovalent mRNA vaccinated healthcare workers (HCWs) and BA.4/5 wave infection.

From this data, it can be seen that the bivalent mRNA vaccine recipients exhibit approximately 2- to 8-fold higher nAb titers, depending on variants tested, compared with those that only received a 3-dose monovalent mRNA vaccination. It is important to note, however, that infection with an Omicron subvariant, most especially one that confers hybrid immunity, increases the nAb significantly compared to vaccination alone.

In order to understand the antigenic relationships of the increasing number of variants, antigenic cartography or mapping has been used to analyze the antigenic variation of the different variants and their relative relationships from each other using a quantitative and visual summary of the antigenic differences present (Fig 3).[12]

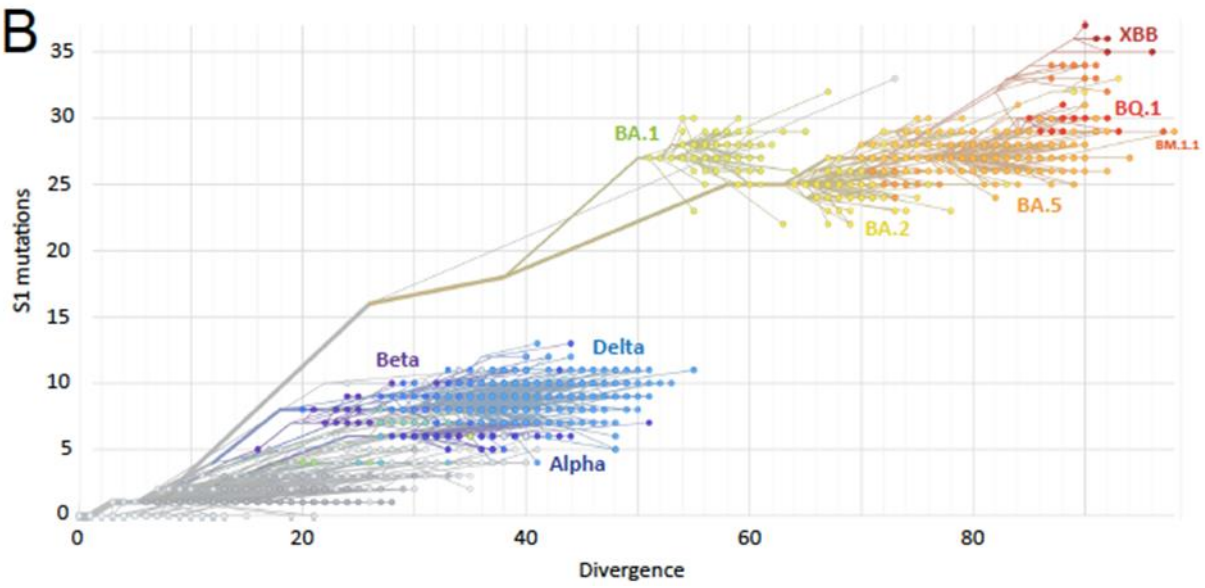

Figure 3: Phylogenetic scatter plot of all-time GISAID SARS-CoV-2 genomes in divergence (number of mutations in the genome relative to the root of the tree) and S1 mutations generated by Nextstrain.

Starting from July 2022, several Omicron subvariants have been closely monitored and flagged by the World Health Organization (WHO) and the European Centre for Disease Prevention and Control (ECDC). Notably, subvariants like BA.2.3.20, XBB, and its sublineages have seen a consistent rise since September 2022.[13]

The XBB lineage was first identified in India around mid-August 2022. It emerged as a result of a recombination event between two BA.2 lineages, namely BA.2.10.1 and BA.2.75.[11] This development caused significant concern due to the combination of various mutations in the spike (S) protein, which are known for their immune evasion capabilities, including R346T, G446S, and F486S (Fig 2).[12]

	T19I	Δ24-26	A27S	A67V	Δ69-70	V83A	T95I	G142D	Δ142-144	Δ144	Y145D	H146Q	K147E	W152R	F157L	Q183E	I210V	Δ211	L212I	V213	ins215EPE	G252V	G257S	G339	R346T	L368I	S371	T376A	D405N	R408S	K444T	V445P	G446S	L452R	N460K	F486	F490S	Q493R	G496S	T547K	N856K	L981F
Omicron BA.1																							D			L																
Omicron BA.2																				G			D			F																
Omicron BA.5																				G			D			F										V						
Omicron BQ.1.1																				G			D			F										V						
Omicron BM.1.1.1																				G			D			F										S						
Omicron XBB.1																				E			H			F										S						

Figure 4: **Genetic diversity in the Spike of Omicron BA.1, BA.2, BA.5, BQ.1.1, BM.1.1.1 and XBB.1 isolates.** Amino acid substitutions in S differentiating Omicron BA.1, BA.2, BA.5, BQ.1.1, BM.1.1.1 and XBB.1. In orange are indicated substitutions in the N-terminal domain, in green substitutions in the receptor binding domain and in black substitutions in the S2.

Recently, the XBB lineage has undergone further mutations in the S protein, G252V (XBB.1) and G252V + S486P (XBB.1.5). At present, the implications of these mutations on XBB.1 and XBB.1.5 remain unknown. However, it is worth noting that previous Omicron subvariants have frequently shown mutations at residue F486, such as F486V, F486I, and F486S, indicating a significant evolutionary hotspot.[11]

With the continuous evolution of SARS-CoV-2, the WHO Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) advises deviating from the inclusion of the index virus in future compositions of COVID-19 vaccines. Experts found out that the index virus and antigenically strongly

related variants no longer circulate in humans. The index virus antigen was found to generate undetectable or very low levels of neutralizing antibodies against currently circulating SARS-CoV-2 variants, that includes XBB descendent lineages. The inclusion of the index virus in bi- or multivalent vaccines reduces the concentration of the new target antigen as compared to monovalent vaccines. One approach recommended by TAG-CO-VAC is the use of a **monovalent XBB.1 descendent lineage, such as XBB.1.5 in the future formulations of COVID-19 vaccines.**[9]

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II. DEFINITION OF TERMS

Vaccine efficacy - the degree to which a vaccine prevents disease and transmission under ideal, controlled circumstances vs placebo (i.e., RCTs)

Vaccine effectiveness - the degree to which a vaccine prevents disease and transmission in the real world when given to a population

Absolute vaccine effectiveness - compares the frequency of the outcome (i.e., infection, hospitalization, death) in vaccinated (primary series or first booster) versus unvaccinated groups to estimate risk reduction for disease based on vaccination

Relative vaccine effectiveness - assesses the vaccine effectiveness of booster regimens by comparing disease incidence or frequency of the outcome between those receiving a booster dose and those receiving the primary series alone

Immunogenicity - the ability of a vaccine to induce an immune response (antibody- and/or cell-mediated immunity) in a vaccinated individual

Monovalent vaccine - contains a component of, or a component that corresponds to, the original strain of the virus eliciting an immune response against a single antigen

Bivalent vaccine – contains two components and thereby elicits an immune response against two different antigens

Hybrid immunity - the immune protection in individuals who have had one or more doses of a COVID-19 vaccine and experienced at least one SARS-CoV-2 infection before or after the initiation of vaccination

Immunologic imprinting - a phenomenon where prior exposure to a viral strain (an antigen) elicits B-cell memory which confers protection against related antigens in the future

Antigenic mapping / cartography – a method that allows for the calculation of antigenic distances between viruses/strains of viruses in sera and their positioning on a map, by quantifying raw data from hemagglutination inhibition assays

III. IMMUNOGENICITY AND EFFECTIVENESS

IMMUNOGENICITY

Statement 1: The bivalent vaccine elicited neutralizing antibody responses against different omicron variants and subvariants.

The currently available immunogenicity studies on omicron-containing bivalent booster vaccines are mainly focused on the assessment of humoral immune response post-immunization through neutralizing antibody and spike-binding antibody assays. Elevated titers of neutralizing and spike-binding antibodies may represent efficacy and potency of SARS-CoV-2 vaccines against the circulating omicron variants and their sublineages.[1,2]

At present, only few immunogenicity studies on bivalent booster vaccines are available. Two relevant studies are discussed in this review.

In an open-label clinical trial by Chalkias, et al,[3] neutralizing antibody and spike-binding antibody responses against ancestral SARS-CoV-2 (D614G), Omicron BA.1 variant, and BA.4/BA.5 subvariants were assessed after second booster vaccination. 53.7% of adult participants received a second booster dose of monovalent mRNA-1273 (Moderna), while the remaining 46.3% received the bivalent mRNA-1273.214 vaccine, containing ancestral SARS-CoV-2 and BA.1 omicron variant, at a median of 134 to 136 days after receipt of first booster dose of mRNA-1273. Immunogenicity assessment was done after 28 days of receiving the second booster vaccine. Interim results showed that among participants without previous SARS-CoV-2 infection, geometric mean titers (GMT) of neutralizing antibodies against omicron BA.1 variant was 2372.4 (95% confidence interval [CI], 2070.6 to 2718.2) and 1473.5 (95% CI, 1270.8 to 1708.4) 28 days after receipt of mRNA- 1273.214 and mRNA-1273 booster doses, respectively. Among participants with previous SARS-CoV-2 infection, GMT were higher after the mRNA-1273.214 booster than after the mRNA-1273 booster against both ancestral SARS-CoV-2 with GMT ratio of 1.27 (95% CI, 1.07 to 1.51) and omicron BA.1 with GMT ratio of 1.90 (95% CI, 1.50 to 2.40). Similarly, among participants with or without previous SARS-CoV-2 infection, a higher GMT of neutralizing antibodies against omicron BA.4/5 subvariants were observed after receipt of mRNA-1273.214 booster than after mRNA-1273 booster dose. Across all groups, a higher neutralizing antibody response was seen in the bivalent booster group compared to the monovalent booster group.

In the same study, spike-binding antibody response against SARS-CoV-2 variants was also assessed among participants with or without prior SARS-CoV-2 infection. The results showed that the GMT levels of spike-binding antibody against ancestral SARS-CoV-2 and omicron BA.1 were higher after the mRNA-1273.214 booster than after the mRNA-1273 booster.

A study by Wang, et al[4] assessed the neutralizing antibody response to Omicron BA.4-BA.5 bivalent booster. In this cohort study, adult participants were divided into four study groups, namely the three-dose and four-dose monovalent, convalescent (three-dose monovalent with breakthrough infection), and bivalent Pfizer or Moderna booster group. Elevated antibody titers were observed across all four groups against ancestral strain. However, evaluation of statistical significance using two-tailed Mann-Whitney test showed no

significant difference in the neutralization of any SARS-CoV-2 variant (ancestral SARS-CoV-2 strain, p=0.13; Omicron BA.1, p=0.97 and BA.4–BA.5, p=0.57) between the four-dose monovalent group and bivalent Moderna or Pfizer group.

Due to the fact that the above immunogenicity studies were conducted at the time when the predominant strains of SARS-CoV-2 were omicron BA.1, BA.2, and BA.5, there is still the lack of immunogenicity assessment on vaccines targeting the current predominant strain–the XBB and its sublineages.

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Statement 2: Patients with breakthrough infections and given booster vaccinations of any type produce the highest level of neutralizing antibodies.

Hybrid immunity is achieved when immunity from actual infections is combined with vaccine-generated immunity to produce a higher antibody response.[1] While it is recognized that repeated natural infection will potentially stimulate polyclonal antibody production due to exposure to different parts of the virus, the extent by which neutralizing antibodies are produced will still depend on the type of infecting variant and the type of vaccine that the patient has received.

Studies on the effect of the bivalent vaccine on hybrid immunity is scarce. In one report, Hoffman et al. has shown that the highest omicron sublineage neutralization was observed in individuals who received triple vaccination and later developed BA.1 or BA.2 breakthrough infection and subsequently received a bivalent booster vaccination.[3]

It is important to note that hybrid immunity will likely depend on how close the infecting variant is to the viral strain incorporated in the vaccine. The bivalent booster was designed to protect from the original ancestral strain and the BA.5 omicron subvariant. The prevailing variant since December 2022 on the other hand is of the XBB type which is known to exhibit a high degree of immune evasiveness. The disparity between the prevailing variant and the vaccine strain may make the situation be subject to the phenomenon of immune imprinting. Immune imprinting occurs when high affinity and high specificity memory B cells produced by a vaccine designed for the primary viral strain prevent the production of new B cells with a different specificity in response to a unique but related virus.[4] Since the XBB variant lies graphically far from the ancestral variants in the bivalent booster when plotted on antigenic maps, it may be possible that such a phenomenon may be playing a role in determining the effectiveness of the bivalent vaccine against the XBB strain but more studies are needed to prove this.

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VACCINE EFFECTIVENESS

Statement 1: The bivalent mRNA booster was associated with a reduced risk of COVID-19 hospitalization and death in elderly adults aged 65 years or older for up to 120 days at the time period when Omicron subvariants BA.5 and BQ.1 were the predominant strains.

The first study by Arbel, et al., was a retrospective, population-based, cohort in Israel, which assessed the effectiveness of a bivalent mRNA vaccine booster dose to reduce COVID-19 hospitalizations and COVID-19 deaths among elderly population, aged 65 years and older, with various risk factors for severe COVID.[1] COVID-19 hospitalizations and deaths among bivalent vaccine recipients were compared with non-recipients. Eligible participants (n = 569,519) received Pfizer-BioNTech bivalent booster after they completed their primary series with two-dose monovalent mRNA vaccines, had a minimum of 3 months since last vaccination and had no less than 3 months since last COVID-19 infection. The study period lasted for 120 days, from Sept. 27, 2022 until Jan. 25, 2023, wherein the primary circulating variants were Omicron subvariants BA.5 and BQ.1. Among eligible participants, 134,215 (24%) received a bivalent booster. COVID-19 hospitalization occurred among 32 bivalent booster recipients compared to 541 bivalent booster non-recipients (adjusted HR 0.28, 95% CI 0.19–0.40, p<0.0001; Appendix A.1, Figure A.1), while COVID-19 death occurred among 13 bivalent booster recipients in contrast to 172 bivalent booster non-recipients (adjusted HR 0.32, 95% CI 0.18–0.58; p 0.0002). These results translate into vaccine effectiveness of a bivalent mRNA vaccine booster dose at 72% (95% CI 60–81) for COVID-19 hospitalization and 68% (95% CI 42–82) for COVID-19 death among adults aged 65 years or older. For COVID-19 hospitalizations, the absolute risk reduction in bivalent booster recipients versus non-recipients was 0.089% (95% CI 0.075–0.101), while for COVID-19 deaths, the absolute risk reduction in bivalent booster recipients versus non-recipients was 0.027% (95% CI 0.017–0.032). Furthermore, the number needed to vaccinate to prevent one COVID-19 hospitalization was 1,118 people (95% CI 993–1341), while for COVID-19 death, it was 3,722 people (95% CI 3086–6026).[1]

In this study, the main limitation was the low number of COVID-19 related hospitalizations and deaths during the observation period. [1] Next, there was no comparison between bivalent booster dose versus providing an additional monovalent booster dose. Third, vaccine effectiveness of the bivalent booster to reduce infection could not be determined since some infections were asymptomatic and self-diagnosed using home antigen kits and were not recorded in the database. Also, the possibility that some hospitalizations or deaths were due to another etiology, but was reported as COVID-19-related because the participants happened to have had SARS-CoV-2 infection when admitted could not be disregarded.[1]

In summary, bivalent mRNA booster dose was associated with a reduced risk of COVID-19 hospitalization and COVID-19 death in elderly adults aged 65 years or older, with various risk factors for severe COVID-19, for up to 120 days during the predominance of Omicron subvariants BA.5 and BQ.1. More studies with longer observation periods are needed.

Statement 2: Among healthcare workers, bivalent booster vaccination offered some protection while the BA.4/BA.5 lineages were the predominant strain, less protection when it was the BQ lineages, and no protective effect when it was the XBB strains that were predominant.

The second study from Ohio, United States was a retrospective cohort study by Shrestha, et al., which evaluated the effectiveness of a bivalent mRNA vaccine booster dose among employees of a healthcare system.[2] The study period lasted for 26 weeks, from September 12, 2022 to March 14, 2023, and was divided into 3 phases of virus dominance. Each phase depending on which SARS-CoV-2 strain accounted for more than half of all COVID-19 infections at the time. The dominant circulating strains shifted from initial Omicron subvariants BA.4 or BA.5 to BQ lineages in mid-December 2022 to XBB lineages by mid-January 2023. Among 51,982 eligible participants, 13,134 (26%) received the bivalent vaccine. And among those who received the vaccine, 87% (n = 11,397) were given the Pfizer vaccine and 13% (n = 1,700) were given the Moderna vaccine. The participants were relatively young, with a mean age of 42 years. During the study period, 8.7% (n = 4,424) employees contracted COVID-19, defined as a positive nucleic acid amplification test (NAAT) result for SARS-CoV-2.[2]

Among all study participants, bivalent booster vaccination offered some protection against COVID-19 while the BA.4/BA.5 lineages were predominating (HR, 0.71 [95% confidence interval (CI)], .63–.79; *P* <.001), less protection while the BQ lineages were the predominant strains (0.80 [.69–.94]; *P*= .005), and no protective effect while the XBB strains were dominant (HR, 0.96 [95% CI, .82–.1.12]; *P* = .59).[2]

Overall bivalent vaccine effectiveness was 29% (95% CI, 21%–37%), 20% (6%–31%) and 4% (−12% to 18%) during the BA.4/BA.5-dominant phase, BQ-dominant phase, and XBB-dominant phase, respectively. Among participants with prior COVID-19 infection or vaccination, bivalent vaccination protected against COVID-19 during the BA.4/BA.5-dominant phase (HR, 0.78 [95% CI, .70–.88; *P* <.001), but no significant protective effect could be demonstrated during the BQ-dominant phase (0.91 [.78–.1.07]; *P* = .25) or the XBB-dominant phase (1.05 [.85–.1.29]; *P*= .66).[2]

The authors also analyzed the cumulative incidence of COVID-19 stratified by the number of COVID vaccine doses previously received and found that the higher the number of vaccines previously received, the higher the risk of contracting COVID-19 (Appendix A.2).[2]

The authors enumerated several limitations such misclassification as previously uninfected among subjects with undetected prior infection, decreased detection of COVID-19 infection due to widespread use of home test kits, symptomatic and asymptomatic infections could not be distinguished, scarcity of severe illnesses for the study to determine if bivalent booster dose decreased the severity of COVID-19 and lastly, since the study was conducted among healthcare workers with few elderly subjects, majority of the participants were immunocompetent.[2]

In conclusion, the bivalent COVID-19 booster dose given to healthcare workers offered an overall modest protective effect against BA.4/BA.5 lineages at the time period that the same strains were circulating. However, the degree of protection provided by the bivalent booster diminished to low (BQ dominant-phase) and even to absence of protection (XBB dominant-phase) when the circulating strains were no longer represented in the vaccine.

Furthermore, COVID-19 risk increased with the number of vaccine doses previously received. Further studies are warranted to determine whether multiple doses of the vaccine may continue to have a beneficial effect.

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DURABILITY OF VACCINE IMMUNOGENICITY AND EFFECTIVENESS

Statement 1. The bivalent boosters provided a similar low magnitude immunogenic response as the monovalent booster, with a rapid waning of humoral immunity (neutralizing antibodies) for Omicron subvariants; however, T cell immunity appears to be preserved.

Wang et al evaluated 41 participants, mostly female, aged 24-63 years of age, who were divided into three cohorts – those who received 4 monovalent vaccines, those who received 3 monovalent + 1 bivalent vaccines, and those who received 3 monovalent vaccines then had a breakthrough infection with the Omicron BA.5 subvariant. They observed serum neutralizing antibody levels at nearly 1 month and approximately 3 months following the last vaccine dose or breakthrough infection, against the ancestral strain and a panel of omicron subvariants (BA.2, BA.5, BQ.1.1, and XBB.1.5). All three cohorts were seen to have the highest neutralizing antibody levels against the ancestral strain and much lower titers against the most recent omicron subvariants. (*Appendix C*) There was no significant difference of neutralizing antibody levels at 1 month after last booster for the cohorts who received either monovalent or bivalent booster. (*Appendix C.1*) At three months, mean neutralizing antibody titers in both cohorts who received monovalent/bivalent booster decreased approximately 50% against all tested viruses, with a trend toward higher titers (1.4 – 1.5x higher) in the bivalent booster cohort that was not statistically significant. The cohort that had a BA.5 breakthrough infection after 3 monovalent doses were seen to have significantly higher neutralizing antibody titers at 3 months against all tested omicron subvariants compared to those who received either monovalent or bivalent booster, and were infection naive. The same cohort did not show a discernable waning of antibody responses at 3 months.[8] (*Appendix C.2*)

The second study by Lasrado et al evaluated a group of 30 infection-naïve participants in the US, mostly female, with a median age of 42 years (24 – 77 years of age) for humoral and cellular immune responses following a bivalent booster with particular attention on the XBB.1.5 subvariant. Neutralizing antibody titers against the ancestral strain and against a panel of Omicron subvariants (BA.2, BA.5, BQ.1.1, XBB.1, and XBB.1.5) were measured prior to boosting, at 3 weeks after boosting and at 3 months after boosting. They found that levels of neutralizing antibodies peaked at 3 weeks after boosting, followed by a decline - with those against the BQ.1 and earlier XBB subvariants declining markedly at 3 months post-boosting by as much as 2-3 times. For the XBB.1 and XBB.1.5 subvariants, antibody levels declined to essentially baseline pre-bivalent booster levels. (*Appendix C.3*) Cellular immune response was measured via spike-specific interferon-gamma CD4+ and CD8+ T cell assays against ancestral, BQ.1.1 and XBB.1.5 peptides at baseline prior to boosting and at month 3 after boosting. Median CD4+ T cell responses were relatively preserved for the study period of 3 months, with a similar trend observed for CD8+ T cell response over the same period. (*Appendix C.4*) The authors' observation suggests that after bivalent mRNA boosting, a substantial immune escape from neutralizing antibodies occurs, but not from T cell responses. They concluded that the combination of low magnitude of increase in titers and rapid waning of neutralizing antibody titers will likely reduce efficacy of the bivalent mRNA boosters against infection, but that cross-reactive T cell responses present prior to boosting may continue to provide protection versus severe disease.

The two studies above provided useful insights on vaccine effectiveness according to the Omicron variant (BA.4/BA.5 up to XBB) predominating in each time period. However, they both involved small adult only populations, limited follow up duration to three months and no studies were done to establish clinical correlates of protection.

Statement 2: Bivalent vaccine effectiveness against hospitalization or death for age 65 and above was maintained at around 30-40% until 4 months after vaccination.

Two studies have so far described waning vaccine effectiveness of bivalent booster vaccines administered in 2022 to 2023 when the Omicron subvariants BA.4 thru XBB emerged and predominated. These studies described the bivalent vaccine's effect on serious outcomes such as hospitalization and/or death among patients with laboratory-confirmed or medically-attended symptomatic disease with a subgroup analyses by age. Vaccine effectiveness in terms of transmission or asymptomatic infection was not included in the analyses. Genomic sequencing to detect the specific Omicron subvariant was not done for each patient but instead, local epidemiologic data was relied upon to determine the predominant lineages that were relevant at the time when the studies were conducted.

The first study conducted by Lin et al involved the population of North Carolina (USA), aged 12 and above, who received the bivalent mRNA COVID-19 booster vaccine between September 2022 to February 2023 when the predominant subvariants (that were) circulating were the Omicron BA4, BA5, BQ.1, and BQ.1.1. Among the eligible public, only 20.2% availed of the bivalent vaccine. The association between bivalent booster and clinical outcomes such as infection, severe infection leading to hospitalization, severe infection leading to hospitalization/death, and severe infection leading to death were studied. (*Appendix C.5*) Overall, the vaccine effectiveness against laboratory-documented infection was at 28.9% at two weeks after bivalent booster vaccination, declining to 11.3% at 12 weeks. Vaccine effectiveness against severe infection leading to hospitalization was at 62.3% at 2 weeks, declining to 36.0% at ≥ 20 weeks. Against severe infection leading to hospitalization or death due to COVID-19, vaccine effectiveness was 67.4% at two weeks after bivalent booster vaccination, which then steadily declined to 38.4% at ≥ 20 weeks. Vaccine effectiveness against severe infection resulting in death was at 80.1% at two weeks after bivalent booster vaccination, declining to 43.1% at 16 weeks post bivalent booster vaccination. The study also compared vaccine effectiveness for those (participants) who received bivalent boosters at the time that the BA.4-BA.5 subvariants were predominant versus its effectiveness at the time that the BQ.1 subvariants became predominant and later on were supplanted by the XBB subvariants. The results were similar in terms of effectiveness and in waning between the two cohorts. (*Appendix C.6 and C.7*)

In the subgroup analysis of participants by age, the authors found that vaccine effectiveness against infection waned completely by 16 weeks post bivalent booster in adults aged 65 and above (*Appendix C.8*). On the other hand, effectiveness against severe infection resulting in hospitalization or death was maintained above 40% at around 20 weeks after receipt of bivalent booster in the same age group. (*Appendix C.9*)

This study may be limited by the low uptake of the bivalent booster among the eligible population (20.3%) during the study period thus findings may not be representative of the entire population. Furthermore, the study's outcome only included laboratory-documented COVID-19 infections and excluded at-home testing results.

Using data generated from the VISION network, the second study by Link-Gelles et al, specifically looked at bivalent mRNA vaccine durability in preventing severe outcomes from COVID-19 among adults with and without immunocompromising conditions from September 2022 to April 2023. It analyzed data from multiple states regarding hospitalizations/critical illness of persons aged 18 and above with COVID 19-like illness and their vaccination status. Among study participants, relative vaccine effectiveness against hospitalization at 60 days after receipt of bivalent vaccine decreased from 62% to 24% at 120 days. Relative vaccine effectiveness was more sustained against critical illness among immunocompetent adults aged 18 and above, registering at 69% by 60 days post receipt of bivalent booster, then decreasing to 50% by 120 days post bivalent booster. (*Appendix B*). In a subgroup analysis of adults aged 65 and above, the study found that the relative vaccine effectiveness against hospitalization was 64% at 60 days post receipt of bivalent booster, waning to 27% by 120 days post bivalent booster. The authors had surmised that the receipt of a bivalent dose afforded some protection in immunocompetent adults against COVID-19–associated hospitalization and critical illness that had waned since receipt of previous monovalent doses; however, protection waned in a similar pattern to that seen after receipt of a monovalent dose during Omicron predominance, with high initial vaccine effectiveness and a decrease over time since the last dose.

Statement 3: Bivalent vaccine effectiveness against hospitalization or death for age 18-64 rapidly declines 4 weeks after booster vaccination.

The study by Lin showed that for the young immunocompetent subgroup aged 18-64 years old, vaccine effectiveness against hospitalization or death peaked at two weeks post booster then showed a rapid decline, disappearing by the 15^{th}-16^{th} week after boosting. Protection from infection waned in a similar manner to the older subgroup and completely by the 16^{th}-17^{th} week after boosting. (*Appendix C.8* and C*.9*)

Meanwhile, in the study by Link-Gelles, the subgroup of younger adults aged 18 – 64 years had relative vaccine effectiveness against hospitalization of 61% at 60 days post receipt of bivalent booster, waning to 16% by 120 days post bivalent booster. *(Appendix B)*

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Statement 4: Vaccine Effectiveness (VE) for hospitalization was higher for immunocompetent patients versus immunocompromised patients 2 months after vaccination but for both groups, there was 50% VE for critical illness which lasted for 6 months after vaccination.

A multi-site VISION Network study in the United States which was published in May of 2023 analyzed 85,075 hospitalizations for COVID-19-like illness of persons 18 years old and older with and without immunocompromising conditions. They divided the population into cohorts by age, 18-64 years old and 65 and above. In this study, absolute vaccine effectiveness (VE) was estimated using a test-negative case-control design comparing the odds of vaccination (either bivalent booster or monovalent doses only versus being unvaccinated) among case (PCR positive) and control (PCR negative) patients. This means that they looked into the number of cases and controls who were vaccinated as well as unvaccinated and used the data to determine the relationship of vaccination with the likelihood of getting hospitalized and developing critical illness due to COVID-19. On the other hand, relative vaccine effectiveness was calculated by comparing those who received a bivalent booster with those who received monovalent doses only. Data gathering lasted from September 2022 to April 2023 during the period of predominance of the Omicron subvariants BA.4, BA.5 and XBB in the US.[1]

Among the 66,141 (77.7%) immunocompetent patients, 6,907 (10.4%) were case patients and 59,234 (89.6%) were control patients (Appendix B). The median age of case and control patients was 76 years and 71 years, respectively. Absolute vaccine effectiveness (VE) against COVID-19–associated hospitalization was similar across age groups, but waned over time, from 62% during the first 7–59 days vaccine to 24% by 120–179 days after receiving the bivalent vaccine. Among those who received monovalent doses only, VE was 21% at a median of 376 days (207 – 505 days) after the last dose.

18,934 (22.3%) were immunocompromised patients. 1,834 (9.7%) were case patients and 17,100 (90.3%) were control patients. Median age of case and control patients was 73 years and 70 years, respectively. VE against COVID-19–associated hospitalization was 28% during the first 7–59 days after receiving the bivalent dose and declined to 13% by 120–179 days. VE for those who received monovalent doses only was 3% at a median 355 days (235 - 474 days) after the last dose.

The estimates of relative and absolute VE against hospitalization were similar in both groups (Appendix B). Moreover, in immunocompetent adults, protection provided by a bivalent dose waned in a similar pattern to that seen after receiving a monovalent dose during Omicron predominance, with a high initial VE that decreased over time since the last dose.

Among both immunocompetent and immunocompromised individuals VE against critical illness (defined as ICU admission or death) were at 50% and 53% respectively.

There are several limitations listed in this study. First, previous SARS-CoV-2 infection was not considered in the analysis. Second, residual confounding is possible such as behavioral differences and use of COVID-19 medications like nirmatrelvir/ritonavir (Paxlovid). Third, sublineage-specific VE could not be computed. Fourth, there is failure to compare product-specific bivalent booster VE estimates. Fifth, although all case-patients included in the analysis had COVID-19–like illness and a positive SARS-CoV-2 test result at the time of the included hospitalization, some might have had relatively mild COVID-19 disease and been hospitalized because of reasons unrelated to COVID-19, which could lower measured VE. Lastly, the included participants might not be representative of the entire population of the United

States. The study period lasted only 179 days and the actual length of protection is still not known. Further vaccine effectiveness studies are needed.

References:

1. Link-Gelles R, Weber ZA, Reese SE, et al. Estimates of Bivalent mRNA Vaccine Durability in Preventing COVID-19-Associated Hospitalization and Critical Illness Among Adults with and Without Immunocompromising Conditions - VISION Network, September 2022-April 2023. MMWR Morb Mortal Wkly Rep. 2023;72(21):579-588. Published 2023 May 26. doi:10.15585/mmwr.mm7221a3

IV. SAFETY

Statement 1: There was no evidence for safety concerns found in the use of either the Pfizer or the Moderna mRNA COVID 19 bivalent boosters.

There were major updates by different reporting systems presented during the Advisory Committee on Immunization Practices (ACIP) meeting on April 19, 2023. CDC's Vaccine safety Datalink (VSD) and Rapid Cycle Analysis (RCA) initially detected a statistical signal for ischemic stroke after Pfizer-BioNTech bivalent booster vaccination in the age group 65 years and older, but a 10 week follow up analysis using an unboosted group for comparison showed attenuation of the RR to 1.26 which are lower than the previously reported RR of 1.92. [1]

In the same meeting, The Vaccine Adverse Event Reporting System (VAERS) reports and chart verified reports showed no significant or unusual signal of ischemic stroke/TIA in the 3 weeks after mRNA COVID-19 bivalent vaccination among the three age groups (ages 18–39, 40–64, and ≥65 years) of the population studied. Likewise, there was no evidence of safety concerns detected for ischemic stroke with the primary series or monovalent boosters for Pfizer-BioNtech or Moderna COVID-19 Vaccines in the US and global monitoring.[1]

A study In Denmark, looking at 2.2M individuals >50 years old who received at least 3 monovalent vaccine from January 2021 to December 2022 was done to compare potential risks of adverse events from the bivalent booster. 1,740,417 out of the total study population received bivalent booster dose as the fourth dose using BNT162b2 with BA.4-5, BNT162b2 with BA.1 and mRNA-1273 with BA.1. The main risk period (1-21 days after the fourth dose) and the three reference periods were evaluated. The three reference periods refer to the following: For the unboosted population 1.) 29 days onwards after the third dose until the end of the study, for the boosted population 2.) 29 days after the third dose until the bivalent vaccine (fourth dose) and 3.) 29 days after the fourth dose until the end of the study. Outcomes measured are hospital visits due to post vaccination concerns. They noted that the risk of adverse events was not elevated in the risk period nor in the 3 reference periods stated, when analyzed according to age, sex, vaccine type or using other analytical approaches. However, post hoc analysis detected signals on more hospital visits due to myocarditis (9 cases) among females within 28 days post bivalent vaccination. This however, represents only 5.3 cases per 1,000,000 vaccinated individuals which was considered a very small number to be of major concern. Indeed, in a VAERS report involving 22.6M boosted individuals, only 5 reports of myocarditis were received.[2]

Hannawi et al in a phase 2 clinical trial between January 27 and April 28, 2022 on safety and immunogenicity of the bivalent covid 19 booster vaccine, randomly assigned 234 adults to receive bivalent vaccine or placebo. They found out that the most common solicited adverse events (AEs) were Grade 1 injection-site pain (10.7%) and pyrexia (6.3%). There were no reports of Grade 3 or higher grade (solicited) AE, serious AEs or AEs of special interest.[3]

A study on safety monitoring after bivalent vaccinations in persons 12 years and older from August 31 to October 23, 2022, showed that out of 5,542 adverse events reported to the VAERS, 5,291 (95.5%) events were classified as nonserious, including 2,762 (94.3%) after Pfizer-BioNTech and 2,530 (96.8%) after Moderna bivalent booster vaccination. The most reported nonserious adverse events were headache (628; 11.9%), fatigue (575; 10.9%), fever (561; 10.6%), pain (524; 9.9%), and chills (459; 8.7%). [4]

Among children aged 5 to 11 years who received the bivalent covid 19 booster vaccine in United States, following a 11-week surveillance period, commonly reported non serious events included fever (21; 14.5%), syncope (20; 13.8%), vomiting (18; 12.4%), nausea (17; 11.7%), and dizziness (14; 9.7%). Two serious reports were for children who received Pfizer-BioNTech vaccine; one for a child who developed symptoms consistent with Miller Fisher syndrome, a rare acquired neurological condition thought to be a variant of Guillain-Barré syndrome; verification based on medical record review is still pending. No reports of myocarditis or death after bivalent booster vaccination were received. These reports, however, are subject to certain limitations. V-safe, is a voluntary reporting smart phone application that may not represent the entire vaccinated population. VAERS on the other hand, can be affected by report biases and underreporting of nonserious events. Lastly, a limited surveillance period may not be enough to come up with the most appropriate conclusions[5].

Based on analysis of findings from preclinical and clinical studies and ongoing post-vaccination safety assessments, expected adverse effects of the Bivalent Covid-19 booster appear to be not different from those seen with the monovalent Covid-19 vaccines. Nevertheless, surveillance programs such as VAERS and Vsafe are constantly monitoring potential adverse reactions based on signaling criteria and available monitoring data.

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V. SUMMARY OF STATEMENTS

IMMUNOGENICITY AND EFFECTIVENESS	**IMMUNOGENICITY** ***Statement 1:*** *The bivalent vaccine elicited neutralizing antibody responses against different omicron variants and subvariants.*
	Statement 2: *Patients with breakthrough infections and given booster vaccinations of any type produce the highest level of neutralizing antibodies.*
	VACCINE EFFECTIVENESS ***Statement 1:*** *The bivalent mRNA booster was associated with a reduced risk of COVID-19 hospitalization and death in elderly adults aged 65 years or older for up to 120 days at the time period when Omicron subvariants BA.5 and BQ.1 were the predominant strains.*
	Statement 2: *Among healthcare workers, bivalent booster vaccination offered some protection while the BA.4/BA.5 lineages were the predominant strain, less protection when it was the BQ lineages, and no protective effect when it was the XBB strains that were predominant.*
	DURABILITY OF VACCINE IMMUNOGENICITY AND EFFECTIVENESS ***Statement 1:*** *The bivalent boosters provided a similar low magnitude immunogenic response as the monovalent booster, with a rapid waning of humoral immunity (neutralizing antibodies) for Omicron subvariants; however, T cell immunity appears to be preserved.* ∞
	Statement 2: *Bivalent vaccine effectiveness against hospitalization or death for age 65 and above was maintained at around 30-40% until 4 months after vaccination.* ♦
	Statement 3: *Bivalent vaccine effectiveness against hospitalization or death for age 18-64 rapidly declines 4 weeks after booster vaccination.* ♦
	Statement 4: *Vaccine Effectiveness (VE) for hospitalization was higher for immunocompetent patients versus immunocompromised patients 2 months after vaccination but for both groups, there was 50% VE for critical illness which lasted for 6 months after vaccination.* ♦
SAFETY	***Statement 1:*** *There was no evidence for safety concerns found in the use of either the Pfizer or the Moderna mRNA COVID 19 bivalent boosters.*

♦ *Based on data from study of Link-Gelles et al and Tenforde et al with the following limitations: previous SARS-CoV-2 infection not considered in the analyses; residual confounding possible including behavioral differences and the use of COVID-19 medications like nirmatrelvir/ritonavir (Paxlovid); sublineage-specific VE could not be computed; product-specific bivalent booster VE estimates could not be compared; although all case-patients included in the analysis of Link-Gelles had COVID-19–like illness and a positive SARS-CoV-2 test result at the time of the included hospitalization, some might have had relatively mild COVID-19 disease and been hospitalized because of reasons unrelated to COVID-19, which could lower measured VE.*

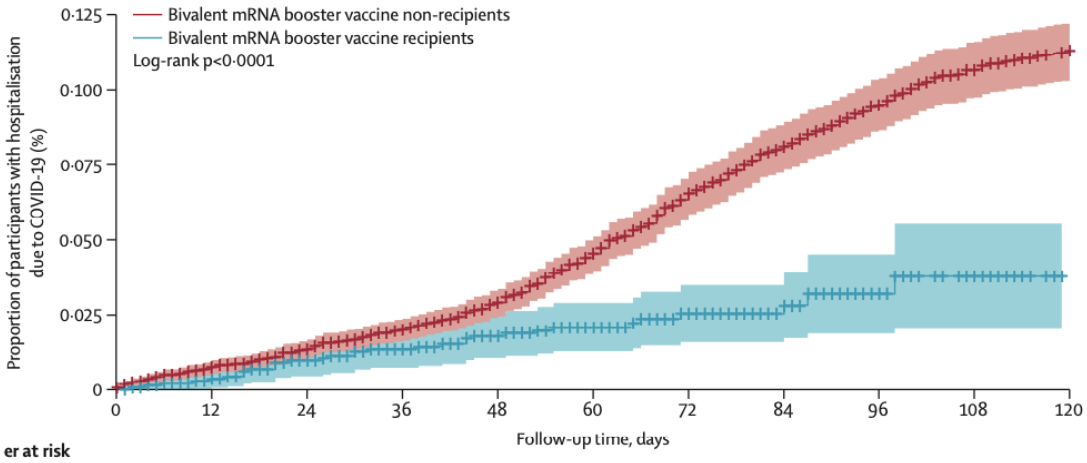
∞ *Based on two small studies (Wang et al and Lasrado et al) limited to only 3 months follow up.*

APPENDIX A.

Appendix A.1.

Authors/ Title/ Journal/ Country Hyperlink	**Study Design/ Population/ Sample size/ Booster Uptake**	**Vaccine**	**Study Observation Period**	**Variants Involved**	**Results**
Arbel R, Peretz A, Sergienko R, Friger M, Beckenstein T, Duskin-Bitan H, Yaron S, Hammerman A, Bilenko N, Netzer D. Effectiveness of a bivalent mRNA vaccine booster dose to prevent severe COVID-19 outcomes: a retrospective cohort study Lancet Infect Dis. 2023 Apr 13:S1473-3099(23)00122-6. Israel https://www.thelancet.com/action/showPdf?pii=S1473-3099%2823%2900122-6	Retrospective, population-based, cohort study Elderly population (65 years and older) with various risk factors for severe COVID (BMI, smoking status, history of diabetes, chronic obstructive pulmonary disease, asthma, chronic renal failure, lung cancer, hypertension, ischaemic heart disease, chronic heart failure, obesity, stroke, and transient ischaemic attack) 569,519 eligible participants 134,215 (24%) participants received bivalent mRNA booster	Pfizer-BioNTech COVID-19 vaccine	Sept. 27, 2022 to Jan. 25, 2023 120 days (or 4 months)	Omicron subvariants **BA.5** and **BQ.1**	• COVID-19 hospitalization occurred among 32 bivalent booster recipients compared to 541 bivalent booster non-recipients (adjusted HR 0.28, 95% CI 0.19–0.40, p<0.0001; Figure A.1 below), while COVID-19 death occurred among 13 bivalent booster recipients in contrast to 172 bivalent booster non-recipients (adjusted HR 0.32, 95% CI 0.18–0.58; p 0.0002). • Vaccine effectiveness of a bivalent mRNA vaccine booster dose was 72% (95% CI 60–81) for COVID-19 hospitalization and 68% (95% CI 42–82) for COVID-19 death among adults aged 65 years or older. • For COVID-19 hospitalizations, the absolute risk reduction in bivalent booster recipients versus non-recipients was 0.089% (95% CI 0.075–0.101), while for COVID-19 deaths, the absolute risk reduction in bivalent booster recipients versus non-recipients was 0.027% (95% CI 0.017–0.032). • The number needed to vaccinate to prevent one COVID-19 hospitalization was 1,118 people (95% CI 993–1341), while for COVID-19 death, it was 3,722 people (95% CI 3086–6026).

Figure A.1: Cumulative risk of hospitalisation due to COVID-19 by bivalent mRNA booster vaccination status. Shaded areas indicate 95% CIs.

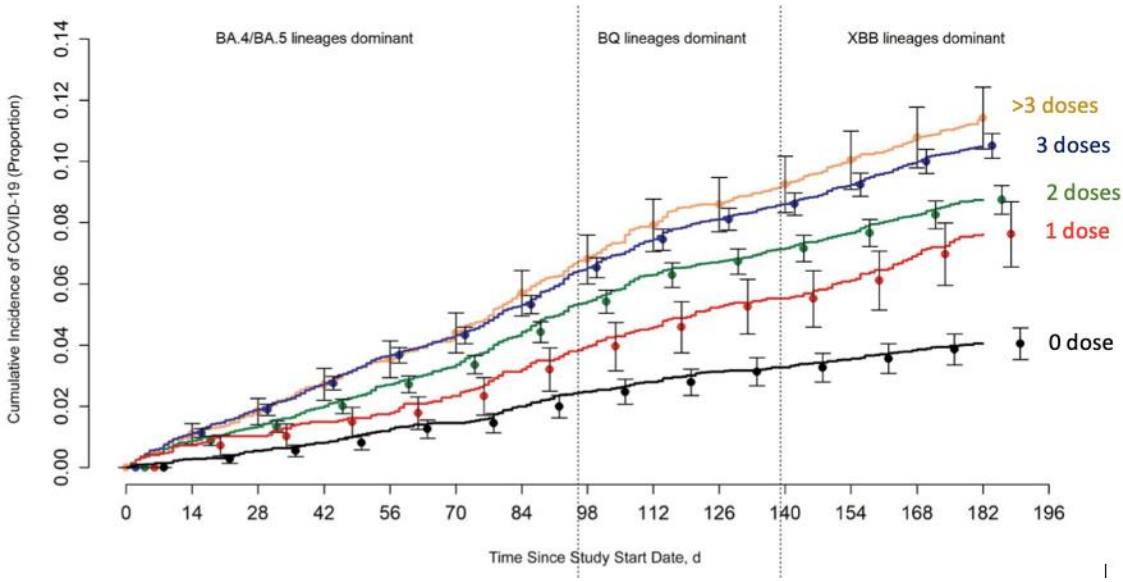


Appendix A.2.

Authors/ Title/ Journal/ Country Hyperlink	**Study Design/ Population/ Sample size/ Booster Uptake**	**Vaccine**	**Study Observation Period**	**Variants Involved**	**Results**
Shrestha NK, Burke PC, Nowacki AS, Simon JF, Hagen A, Gordon SM. Effectiveness of the Coronavirus Disease 2019 Bivalent Vaccine.	Retrospective cohort Healthcare employees (relatively young, with a mean age of 42 years)	Pfizer vaccine (n = 11,397, 87%) Moderna vaccine (n = 1,700. 13%)	Sept. 12, 2022 to Mar. 14, 2023 26 weeks (6 months and 2 weeks)	**BA.4** or **BA.5** Omicron subvariant (initially) **BQ** lineages (mid-Dec. 2022)	• 8.7% (n = 4,424) employees contracted COVID-19 (positive nucleic acid amplification test result) • Bivalent booster vaccination offered some protection against COVID-19 while the BA.4/BA.5 lineages were predominating (HR, 0.71 [95% confidence interval (CI)], .63–.79; *P* <.001), less protection while the BQ lineages were the

Open Forum Infect Dis. 2023 Apr 19;10(6):ofad209. USA (Ohio) https://pubmed.ncbi.nlm.nih.gov/37274183/	51,982 eligible participants 13,134 (26%) received the bivalent vaccine			**XBB** lineages (mid-Jan. 2023)	predominant strains (0.80 [.69–.94]; *P*= .005), and no protective effect while the XBB strains were dominant (HR, 0.96 [95% CI, .82–.1.12]; *P* = .59). • Overall bivalent vaccine effectiveness was 29% (95% CI, 21%–37%), 20% (6%–31%) and 4% (−12% to 18%) during the BA.4/BA.5-dominant phase, BQ-dominant phase, and XBB-dominant phase, respectively. • Among participants with prior COVID-19 infection or vaccination, bivalent vaccination protected against COVID-19 during the BA.4/BA.5-dominant phase (HR, 0.78 [95% CI, .70–.88; *P* <.001), but no significant protective effect could be demonstrated during the BQ-dominant phase (0.91 [.78–.1.07]; *P* = .25) or the XBB-dominant phase (1.05 [.85–.1.29]; *P*= .66). • The higher the number of vaccines previously received, the higher the risk of contracting COVID-19 (Figure A.2 below).

Figure A.2: Cumulative incidence of coronavirus disease 2019 (COVID-19) for study participants stratified by the number of COVID-19 vaccine doses previously received.



APPENDIX B.

Appendix B.1.

Authors/ Title/ Journal/ Country Hyperlink	Study Design/ Population/ Sample size/ Booster Uptake	Vaccine	Study Observation Period	Variants Involved	Results
Link-Gelles R., Weber Z., Reese S., et. al. Estimates of Bivalent mRNA Vaccine Durability in Preventing COVID-19–Associated Hospitalization and Critical Illness Among Adults with and Without Immunocompromising Conditions — VISION Network, September 2022–April 2023 US Department of Health and Human Services/Centers for Disease Control and Prevention MMWR / May 26, 2023 / Vol. 72 / No. 21 MMWR Morb Mortal Wkly Rep. 2023;72(21):579-588. USA (Multistate)	Case-Control, Test-Negative design Analysis of 85,075 hospitaliza-tions of persons with COVID-19-like illness 18 y/o and above with and without immunocompromising conditions hospitalized for COVID 19 like	All vaccines used for primary vaccination and monovalent boosters Pfizer or Moderna Bivalent Vaccine	September 13, 2022–April 21, 2023	**BA.4** or **BA.5** Omicron subvariant (initially) **BQ** lineages (mid-Dec. 2022) **XBB** lineages (mid-Jan. 2023)	• In this multistate analysis of 85,075 hospitalizations of persons with COVID-19–like illness: • bivalent doses were 62% effective among adults without immunocompromising conditions • 28% effective in those with immunocompromising conditions in preventing COVID-19–associated hospitalization during the first 7–59 days after vaccination. • Waning was evident in adults without immunocompromising conditions from 60–179 days (2–6 months) after vaccination. • VE was more sustained against critical illness in adults with (50% at 120–179 days after vaccination) and without (53% at 120–179 days after vaccination) immunocompromising

https://pubmed.ncbi.nlm.nih.gov/37227984/					conditions, which suggests that bivalent vaccines provide durable protection against the most severe outcomes from COVID-19.

TABLE 2. COVID-19 vaccine effectiveness* against laboratory-confirmed COVID-19–associated hospitalizations and critical illness† among adults aged ≥18 years, by age group and immunocompromise status — seven states,§ September 2022–April 2023

Clinical status/Age group, yrs/Vaccine type and doses received, interval since receipt of BV dose	Without documented immunocompromising conditions				With documented immunocompromising conditions			
	Total	Positive SARS-CoV-2 test result, no. (%)	Median interval since last dose, days (IQR)	VE, % (95% CI)	Total	Positive SARS-CoV-2 test result, no. (%)	Median interval since last dose, days (IQR)	VE, % (95% CI)
Hospitalization								
≥18								
Unvaccinated (Ref)	**15,514**	1,791 (11.5)	NA	Ref	**3,109**	314 (10.1)	NA	Ref
MV only	**37,269**	3,988 (10.7)	376 (270 to 505)	21 (16 to 26)	**11,140**	1,134 (10.2)	355 (237 to 474)	3 (–12 to 16)
BV, 7–59 days earlier	**4,857**	327 (6.7)	34 (21 to 47)	62 (57 to 67)	**1,612**	143 (8.9)	33 (19 to 46)	28 (10 to 42)
BV, 60–119 days earlier	**5,191**	486 (9.4)	87 (73 to 103)	47 (41 to 53)	**1,829**	140 (7.6)	88 (74 to 104)	41 (26 to 53)
BV, 120–179 days earlier	**3,310**	315 (9.5)	144 (132 to 159)	24 (12 to 33)	**1,244**	103 (8.3)	144 (131 to 159)	13 (–13 to 33)
18–64								
Unvaccinated (Ref)	**8,033**	591 (7.4)	NA	Ref	**NA**	NA	NA	NA
MV only	**12,368**	821 (6.6)	403 (306 to 534)	17 (7 to 26)	**NA**	NA	NA	NA
BV, 7–59 days earlier	**959**	38 (4.0)	33 (21 to 45)	61 (44 to 72)	**NA**	NA	NA	NA
BV, 60–119 days earlier	**935**	66 (7.1)	86 (72 to 101)	25 (1 to 43)	**NA**	NA	NA	NA
BV, 120–179 days earlier	**561**	31 (5.5)	143 (131 to 158)	16 (–24 to 43)¶	**NA**	NA	NA	NA
≥65								
Unvaccinated (Ref)	**7,481**	1,200 (16.0)	NA	Ref	**NA**	NA	NA	NA
MV only	**24,901**	3,167 (12.7)	362 (245 to 484)	24 (18 to 29)	**NA**	NA	NA	NA
BV, 7–59 days earlier	**3,898**	289 (7.4)	35 (21 to 48)	64 (58 to 68)	**NA**	NA	NA	NA
BV, 60–119 days earlier	**4,256**	420 (9.9)	87 (73 to 103)	51 (45 to 57)	**NA**	NA	NA	NA
BV, 120–179 days earlier	**2,749**	284 (10.3)	145 (132 to 159)	27 (15 to 37)	**NA**	NA	NA	NA
Critical illness**								
≥18								
Unvaccinated (Ref)	**14,090**	367 (2.6)	NA	Ref	**2,881**	86 (3.0)	NA	Ref
MV only	**33,925**	644 (1.9)	375 (269 to 505)	31 (21 to 40)	**10,263**	257 (2.5)	354 (235 to 474)	16 (–10 to 36)
BV, 7–59 days earlier	**4,579**	49 (1.1)	34 (21 to 47)	69 (57 to 77)	**1,501**	32 (2.1)	33 (19 to 46)	40 (7 to 61)¶
BV, 60–119 days earlier	**4,790**	85 (1.8)	86 (73 to 103)	46 (30 to 58)	**1,725**	36 (2.1)	88 (74 to 104)	43 (14 to 63)
BV, 120–179 days earlier	**3,028**	33 (1.1)	144 (132 to 159)	50 (26 to 66)	**1,155**	14 (1.2)	144 (131 to 159)	53 (13 to 75)¶

Abbreviations: BV = bivalent; MV = monovalent; NA = not applicable; Ref = referent group; VE = vaccine effectiveness.

* VE was calculated as (1 – odds ratio) x 100%, estimated using a test-negative case-control design, adjusted for age, sex, race and ethnicity, geographic region, and calendar time (days since January 1, 2021).

† Patients were considered to have critical illness if they were admitted to an intensive care unit or died. Death was identified at each individual site and was defined as a death while hospitalized or ≤28 days after admission.

§ California (September 13, 2022–April 21, 2023), Indiana (September 13, 2022–April 12, 2023), Minnesota and Wisconsin (September 13, 2022–April 21, 2023), Oregon and Washington (September 13, 2022–April 14, 2023), and Utah (September 13, 2022–April 21, 2023).

¶ These estimates are imprecise, which might be because of a relatively small number of persons in each level of vaccination or case status. This imprecision indicates the actual VE could be substantially different from the point estimate shown, and estimates should therefore be interpreted with caution. Additional data accrual could increase precision and allow appropriate interpretation.

** For VE against critical illness, case-patients were persons admitted to an intensive care unit or who experienced death associated with COVID-19, and control patients were persons hospitalized without COVID-19.

SUPPLEMENTARY TABLE. Relative COVID-19 vaccine effectiveness* against laboratory-confirmed COVID-19–associated hospitalizations and critical illness† among adults aged ≥18 years who received a bivalent vaccine dose compared with adults aged ≥18 years who received monovalent doses only, by age group and immunocompromise status — seven states,§ September 2022–April 2023

Clinical status/Age group, yrs/Vaccine type received, interval since receipt of BV dose	Without documented immunocompromising conditions				With documented immunocompromising conditions			
	Total	Positive SARS-CoV-2 test result, no. (%)	Median interval since last dose, days (IQR)	Relative VE, % (95% CI)	Total	Positive SARS-CoV-2 test result, no. (%)	Median interval since last dose, days (IQR)	Relative VE, % (95% CI)
Hospitalization								
≥18								
MV only (Ref)	**37,269**	3,988 (10.7)	376 (270 to 505)	Ref	**11,140**	1,134 (10.2)	355 (237 to 474)	Ref
BV, 7–59 days earlier	**4,857**	327 (6.7)	34 (21 to 47)	51 (45 to 57)	**1,612**	143 (8.9)	33 (19 to 46)	25 (9 to 38)
BV, 60–119 days earlier	**5,191**	486 (9.4)	87 (73 to 103)	33 (25 to 39)	**1,829**	140 (7.6)	88 (74 to 104)	39 (26 to 49)
BV, 120–179 days earlier	**3,310**	315 (9.5)	144 (132 to 159)	6 (–7 to 18)	**1,244**	103 (8.3)	144 (131 to 159)	11 (–13 to 29)
18–64								
MV only (Ref)	**12,368**	821 (6.6)	403 (306 to 534)	Ref	**NA**	NA	NA	NA
BV, 7–59 days earlier	**959**	38 (4.0)	33 (21 to 45)	51 (31 to 65)	**NA**	NA	NA	NA
BV, 60–119 days earlier	**935**	66 (7.1)	86 (72 to 101)	9 (–19 to 30)	**NA**	NA	NA	NA
BV, 120–179 days earlier	**561**	31 (5.5)	143 (131 to 158)	3 (–43 to 35)	**NA**	NA	NA	NA
≥65								
MV only (Ref)	**24,901**	3,167 (12.7)	362 (245 to 484)	Ref	**NA**	NA	NA	NA
BV, 7–59 days earlier	**3,898**	289 (7.4)	35 (21 to 48)	52 (45 to 58)	**NA**	NA	NA	NA
BV, 60–119 days earlier	**4,256**	420 (9.9)	87 (73 to 103)	36 (28 to 43)	**NA**	NA	NA	NA
BV, 120–179 days earlier	**2,749**	284 (10.3)	145 (132 to 159)	8 (–7 to 20)	**NA**	NA	NA	NA
Critical illness**								
≥18								
MV only (Ref)	**33,925**	644 (1.9)	375 (269 to 505)	Ref	**10,263**	257 (2.5)	354 (235 to 474)	Ref
BV, 7–59 days earlier	**4,579**	49 (1.1)	34 (21 to 47)	54 (38 to 66)	**1,501**	32 (2.1)	33 (19 to 46)	28 (–6 to 51)
BV, 60–119 days earlier	**4,790**	85 (1.8)	86 (73 to 103)	20 (–2 to 37)	**1,725**	36 (2.1)	88 (74 to 104)	32 (1 to 54)
BV, 120–179 days earlier	**3,028**	33 (1.1)	144 (132 to 159)	27 (–7 to 50)	**1,155**	14 (1.2)	144 (131 to 159)	45 (2 to 69)

Abbreviation: BV = bivalent; MV = monovalent; NA = not applicable; Ref = referent group; VE = vaccine effectiveness.

* Relative VE was calculated as (1 – odds ratio) x 100%, estimated using a test-negative case-control design. A combined model was generated including patients who had received a bivalent mRNA booster at 7–59, 60–119, or 120–179 days before their index date compared to those who received only monovalent vaccination. Odds ratios and 95% confidence intervals were estimated using multivariable logistic regression adjusting for age, sex, race and ethnicity, geographic region, and calendar time (days since January 1, 2021). Age and calendar time were modeled as natural cubic splines. VE was modeled separately for those with and without immunocompromising conditions, by age group (18–64 and ≥65 years), and for each outcome (hospitalization and critical illness).

† Patients were considered to have critical illness if they were admitted to the intensive care unit or died. Death was identified at each individual site and was defined as a death while hospitalized or ≤28 days after admission.

§ California (September 13, 2022–April 21, 2023), Indiana (September 13, 2022–April 12, 2023), Minnesota and Wisconsin (September 13, 2022–April 21, 2023), Oregon and Washington (September 13, 2022–April 14, 2023), and Utah (September 13, 2022–April 21, 2023).

¶ These estimates are imprecise, which might be because of a relatively small number of persons in each level of vaccination or case status.

APPENDIX C

Appendix C.1.

Authors/ Title/ Journal/ Country Hyperlink	Study Design/ Population/ Sample size/ Booster Uptake	Vaccine	Study Observation Period	Variants Involved	Results
Wang Q, Bowen A, Tam AR, et al. SARS-CoV-2 neutralising antibodies after bivalent versus monovalent booster. The Lancet Infectious Diseases USA	Observational 3 clinical cohorts: a) monovalent: 4 doses monovalent mRNA vaccine, infection-naive b) bivalent: 3 doses monovalent mRNA + 1 dose bivalent mRNA vaccine, infection-naive	BNT162b2 or mRNA-1273 dose 1-3 BNT162b2 or Moderna bivalent for dose 4	Sera collected from large groups with ongoing cohort studies since 2020	D614G, BA.2, BA.5, BQ.1.1, and XBB.1.5	All three cohorts have the highest neutralizing antibody levels against the ancestral strain and much lower titers against the most recent omicron subvariants. 1 month after last booster (monovalent/bivalent): No significant difference of neutralizing antibody levels 3 months after last booster (monovalent/bivalent): Approximately 50% decrease in neutralizing antibody

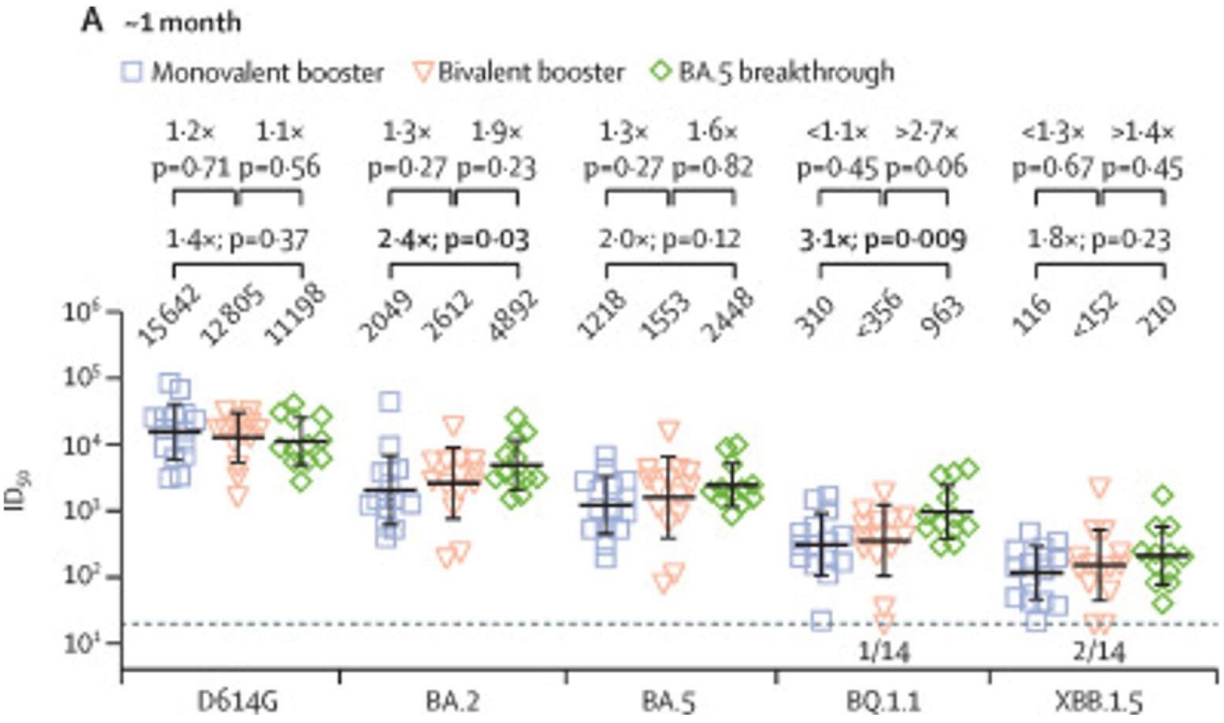
doi:10.1016/S1473-3099(23)00181-0 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10058662/	c) breakthrough: 3 doses monovalent mRNA followed by Omicron BA.5 infection N = 41 (a = 15, b = 14, c = 12) Age: 24 – 63				levels; trend toward higher titers (1.4 – 1.5x higher, not statistically significant) in the bivalent booster cohort 3 months after breakthrough infection: significantly higher neutralizing antibody titers compared to those who received either monovalent or bivalent booster; did not show a discernable waning of antibody responses

Mean Neutralizing Antibody Titers Across 3 Cohorts Against Ancestral Strain and Panel of Omicron Subvariants

	3 Monovalent + 1 Monovalent		3 Monovalent + 1 Bivalent		3 Monovalent + BA.5 Breakthrough Infection	
Strain	**1 month post booster**	**3 months post booster**	**1 month post booster**	**3 months post booster**	**1 month post booster**	**3 months post booster**
WA1/2020	15,642	6,601	12,085	6,438	11,198	11,419
BA.2	2,049	924	2,612	1,322	4,892	4,605
BA.5	1,218	509	1,553	835	2,448	2,482
BQ.1.1	310	<129	<356	<182	<152	1,011
XBB.1.5	116	<50	<152	<74	210	212

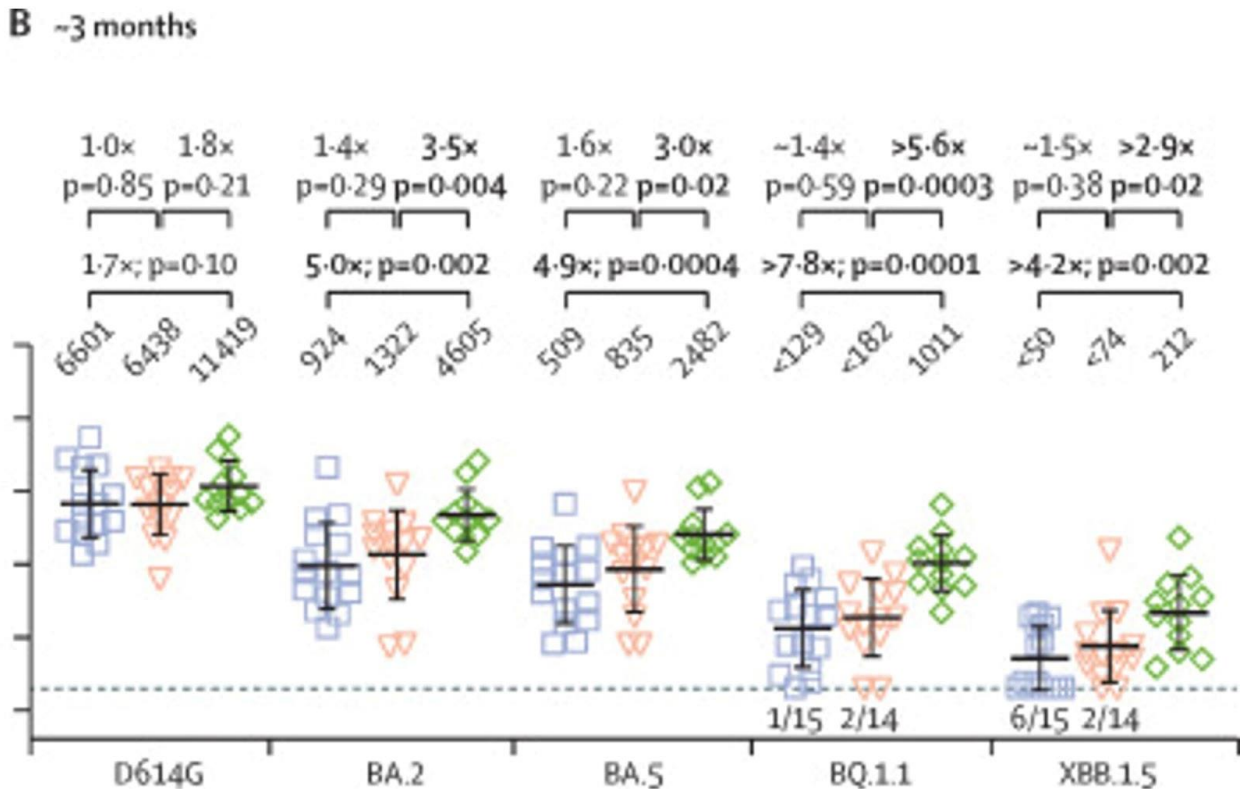
Appendix C.1

Serum neutralizing antibody levels against panel of SARS-CoV-2 variants/subvariants in 3 cohorts after 1 month from receipt of booster or breakthrough infection



Appendix C.2

Serum neutralizing antibody levels against panel of SARS-CoV-2 variants/subvariants in 3 cohorts after 3 months from receipt of booster or breakthrough infection



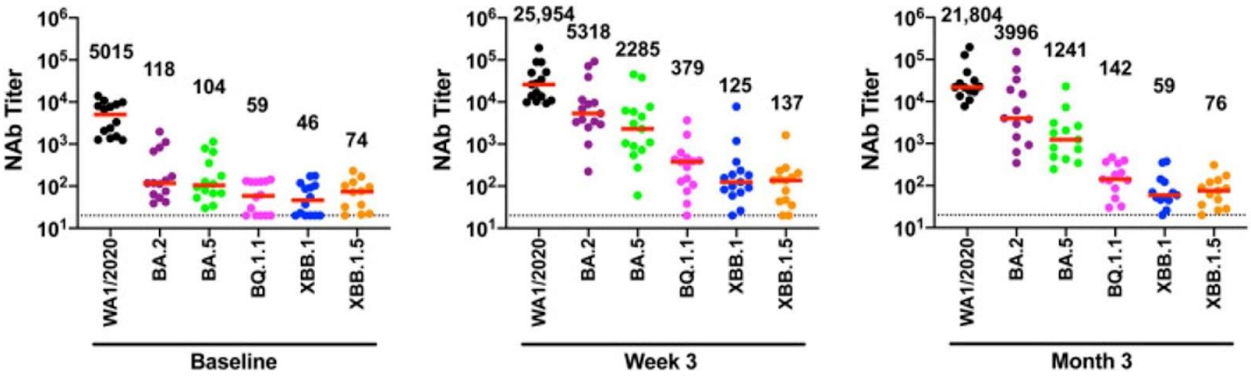
Appendix C.3
Mean Neutralizing Antibody Titers Baseline, 3 Weeks Post Bivalent Booster, And 3 Months Post Bivalent Booster

Appendix C.4.

Authors/ Title/ Journal/ Country Hyperlink	Study Design/ Population/ Sample size/ Booster Uptake	Vaccine	Study Observation Period	Variants Involved	Results
Lasrado N, Collier AY, Miller J, et al. Waning Immunity Against XBB.1.5 Following Bivalent mRNA Boosters. Preprint. bioRxiv. 2023;2023.01.22.525079. Published 2023 Jan 23. USA doi:10.1101/2023.01.22.525079 https://www.biorxiv.org/content/10.1101/2023.01.22.525079v1	Observational Infection naïve individuals N = 30 Age: 24-77 (Median 42)	BNT162b2 or mRNA-1273 or Ad26 for doses 1-2 BNT162b2, mRNA-1273 for doses 3-4 Pfizer bivalent or Moderna bivalent for most recent vaccine booster	Sera from individuals who received SARS-CoV-2 vaccines + bivalent mRNA boosters in the specimen biorepository of the Beth Israel Deaconess Medical Center 10/1/2022 - 1/7/2023	WA1/2020, BA.2, BA.4, BQ.1.1, XBB.1, XBB.1.5	At baseline, median NAb titers to WA1/2020, BA.2, BA.5, BQ.1.1, XBB.1, and XBB.1.5 were 5015, 118, 104, 59, 46, and 74, respectively. At week 3, (peak) median NAb titers to WA1/2020, BA.2, BA.5, BQ.1.1, XBB.1, and XBB.1.5 were 25,954, 5318, 2285, 379, 125, and 137, respectively. By month 3, median NAb titers to WA1/2020, BA.2, BA.5, BQ.1.1, XBB.1, and XBB.1.5 were 21,804, 3996, 1241, 142, 59, and 76, reflecting 1.2-, 1.3-, 1.8-, 2.7-, 2.1-, and 1.8-fold declines from week 3, respectively. (Marked decline against BQ.1 and earlier XBB subvariants; decline to essentially pre-bivalent booster levels against XBB.1 and XBB.1.5. Authors also noted that by month 3, 43% of participants had known COVID-19 infection.) Median CD4+ T cell responses to WA1/2020, BQ.1.1, and XBB.1.5 were 0.098%, 0.072%, and 0.065% at baseline and 0.099%, 0.073%, and 0.090% at month 3, respectively. (Relatively preserved in the study period) Median CD8+ T cell responses to WA1/2020, BQ.1.1, and XBB.1.5 were 0.080%, 0.060%, and 0.059% at baseline and 0.107%, 0.125%, and 0.106% at month 3, respectively. (Relatively preserved in the study period)

Humoral Immune Response: Median Neutralizing Antibody Titers

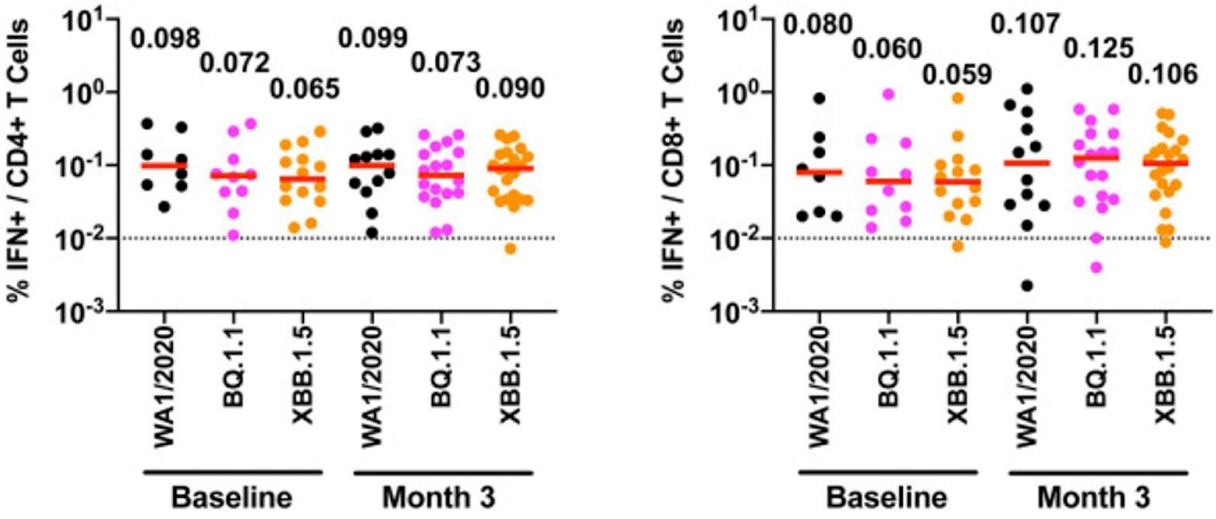
Strain	Baseline	3 weeks post bivalent booster	3 months post bivalent booster	Decline
WA1/2020	5,015	25,954	21,804	1.2x
BA.2	118	5,318	3,996	1.3x
BA.5	104	2,285	1,241	1.8x
BQ.1.1	59	379	142	2.7x
XBB.1	46	125	59	2.1x
XBB.1.5	74	137	76	1.8x



Appendix C.4
Cellular Immune Response At Baseline And At 3 Months Post Bivalent Booster

Cellular Immune Response: Intracellular Cytokine Staining Assay

	CD4+ T Cell Response		CD8+ T Cell Response	
Strain	**Baseline**	**3 months post bivalent booster**	**Baseline**	**3 months post bivalent booster**
WA1/2020	0.098 %	0.099 %	0.080 %	0.107 %
BQ.1.1	0.072 %	0.077 %	0.060 %	0.125 %
XBB.1.5	0.065 %	0.065 %	0.059 %	0.106%



Appendix C.5

Authors/ Title/ Journal/ Country Hyperlink	Study Design/ Population/ Sample size/ Booster Uptake	Vaccine	Study Observation Period	Variants Involved	Results

Lin D-Y et al.
 	
Durability of bivalent boosters against omicron subvariants.
 	
New England Journal of Medicine (May 2023)
 	
USA
 	
doi: 10.1056/NEJMc2302462
 	
https://www.nejm.org/doi/full/10.1056/NEJMc2302462
	Observational
	
	Individuals aged 12 and older who had received a primary vaccine series and booster dose before study; intervention was bivalent booster used as either first/second/third booster dose
	
	N = 6,306,311
	
	Booster uptake = 1,279,802 (20.29%)
	
	Association of Vaccination Histories beginning December 11 2020 to February 10 2023, with clinical outcomes (SARS-CoV-2 Infection, hospitalization, and death) from March 11 2020 to February 10 2023
		BNT162b2/mRNA-1273 or Ad26 as previous vaccine
		
		Bivalent BNT162b2 or mRNA-127 as bivalent booster
			September 01 2022 to February 10, 2023	BA.4, BA.5, BQ.1, BQ.1.1, XBB, XBB.1.5	Post-bivalent booster:
					
					Vaccine effectiveness against laboratory-documented infection
					2 weeks: 28.9%
					12 weeks: 11.3%
					
					Vaccine effectiveness against severe infection leading to hospitalization
					2 weeks: 62.3%
					12 weeks: 42.0%
					≥ 20 weeks: 36.0%
					
					Vaccine effectiveness against severe infection leading to hospitalization or death due to COVID-19
					2 weeks: 67.4%
					12 weeks: 43.1%
					≥ 20 weeks: 38.4%
					
					Vaccine effectiveness against death due to COVID-19
					2 weeks: 80.1%
					12 weeks: 45.7%
					16 weeks: 43.1%
					
					Similar vaccine effectiveness and waning for those (participants) who received bivalent boosters at the time that the BA.4-BA.5 subvariants were predominant (September 01 – October 31 2022) versus the time that the BQ.1 subvariants became predominant and later on were supplanted by the XBB subvariants (November 01 2022 to February 10, 2023)
					
					Subgroup Analysis by Age
					Vaccine Effectiveness against Infection Post Bivalent Booster
					• Age 12-64 years
					  ○ Peak: Week 2 (> 30%)
					  ○ Waned Completely: Week 17 (0%)
					• Age 65 and above
					  ○ Peak: Week 2 (~ 30%)
					  ○ Waned Completely: Week 16 (0%)
					
					Vaccine Effectiveness Against Severe Infection Resulting to Hospitalization or Death
					• Age 12-64 years
					  ○ Peak: Week 2 (> 65%)
					  ○ Waned Completely: Week 16 (0%)
					• Age 65 and above
					  ○ Peak: Week 2 (>65%)
					  ○ Maintained Above 40% at 20 weeks

Appendix C.5
Estimates (95% CI) for the Effectiveness of One Bivalent Booster Dose against Infection, Hospitalization, and Death, as a Function of Time since Receipt of the Booster.

Time Since Receipt of Booster (Weeks)	VE vs. Infection	VE vs. Hospitalization	VE vs. Hospitalization or Death	VE vs. Death
2	28.9% (24.7, 32.9)	62.3% (36.9, 77.5)	67.4% (46.2, 80.2)	80.1% (42.9, 93.0)
4	28.7% (26.5, 30.9)	47.4% (31.4, 59.7)	47.5% (32.6, 59.2)	50.5% (19.0, 69.8)
8	20.5% (18.9, 22.1)	44.8% (34.4, 53.6)	45.4% (35.8, 53.6)	48.2% (29.3, 62.0)
12	11.3% (9.7, 12.9)	42.0% (32.0, 50.5)	43.1% (33.8, 51.1)	45.7% (23.9, 61.3)
16	-	39.1% (22.7, 52.0)	40.8% (25.5, 52.9)	43.1% (2.1, 67.0)
20	-	36.0% (9.0, 55.0)	38.4% (13.4, 56.1)	-

Appendix C.6
Estimates (95% CI) for the Effectiveness of One Bivalent Booster Dose against Infection, Hospitalization, and Death, as a Function of Time since Receipt of the Booster, For the Cohort Receiving the Bivalent Vaccine During BA.4 and BA.5 Predominance (September 1 - October 31, 2022)

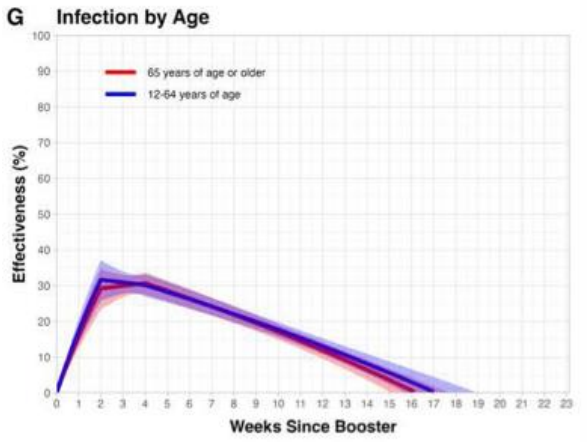
Time Since Receipt of Booster (Weeks)	VE vs. Infection	VE vs. Hospitalization	VE vs. Hospitalization or Death	VE vs. Death
2	25.5% (19.6, 31.0)	56.9% (18.5, 77.2)	61.6% (29.6, 79.0)	73.5% (14.5, 91.8)
4	22.5% (19.5, 25.5)	50.8% (31.5, 64.7)	49.0% (30.7, 62.5)	46.9% (6.9, 69.7)
8	16.3% (14.2, 18.4)	47.6% (35.3, 57.6)	46.9% (35.5, 56.3)	45.8% (23.6, 61.6)
12	9.6% (7.8, 11.3)	44.2% (34.0, 52.8)	44.8% (35.2, 52.9)	44.7% (22.4, 60.6)
16	-	40.5% (23.9, 53.5)	42.5% (27.1, 54.7)	43.6% (1.8, 67.6)
20	-	36.6% (7.6, 56.5)	40.2% (14.0, 58.4)	-

Appendix C.7
Estimates (95% CI) for the Effectiveness of One Bivalent Booster Dose against Infection, Hospitalization, and Death, as a Function of Time since Receipt of the Booster, For the Cohort Receiving the Bivalent Vaccine During BQ.1 and XBB Predominance (November 1, 2022 to February 10, 2023)

Time Since Receipt of Booster (Weeks)	VE vs. Infection	VE vs. Hospitalization	VE vs. Hospitalization or Death	VE vs. Death
2	31.6% (25.5, 37.3)	68.3% (24.1, 86.7)	74.2% (37.9, 89.3)	49.3% (10.1, 71.4)

4	37.4% (33.4, 41.1)	54.3% (22.5, 73.1)	57.0% (28.0, 74.3)	74.3% (19.1, 91.8)
8	27.8% (24.9, 30.6)	30.0% (4.5, 48.7)	33.3% (9.6, 50.8)	-
10	22.5% (17.9, 26.7)	-	-	-

Appendix C.8
Vaccine Effectiveness Against Infection by Age



Appendix C.9
Vaccine Effectiveness Against Severe Infection Leading to Hospitalization or Death by Age