

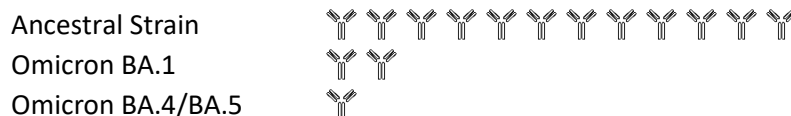
## COVID-19 Vaccine Performance Against Omicron Sub-Variants

**Few observational studies have evaluated COVID-19 vaccine effectiveness across different Omicron subvariants.** Observational studies have found reduced effectiveness of COVID-19 vaccines against the Omicron variant compared to earlier circulating variants of concern, with substantial reductions against infection and symptomatic disease and smaller reductions against severe disease.<sup>11</sup> Most of these studies were conducted during periods when the original Omicron BA.1 subvariant was dominant. However, BA.1 was subsequently replaced by BA.2 in many countries followed by BA.4 and/or BA.5. Whether vaccine effectiveness is further reduced against more recent Omicron sub-variants is an important question for vaccine policy, but few clinical studies have sufficient data to assess this.

**Laboratory studies can provide early evidence of vaccine performance against emerging variants and subvariants.** For example, studies measuring neutralizing antibodies in persons who received COVID-19 primary series vaccination showed only slightly lower antibody levels to the Alpha variant (1.5 times lower) relative to the original ancestral strain but much lower antibody levels to the Beta variant (5.1 times lower). These findings were confirmed subsequently by clinical studies showing no to little reduction in vaccine effectiveness against Alpha, but notable reductions against Beta.

**Laboratory evidence suggests vaccine performance may be reduced for Omicron subvariants BA.4 and BA.5 relative to subvariants BA.1 and BA.2.** A [recent systematic review](#) assessed neutralizing antibody response of COVID-19 vaccines between the different Omicron sub-variants as well as to the original strain. The authors compared reductions in neutralization capacity after a booster dose between BA.1 and each of the following later emerging Omicron subvariants: BA.1.1, BA.2, BA.2.12.1, BA.2.75, and BA.4/BA.5. Relative to the ancestral strain, there was a median 6-fold reduction in geometric mean antibody titers against BA.1 [interquartile range across 59 studies (IQR) was 4.6-9.4] compared to a 12.0-fold reduction for BA.4/BA.5 (IQR across 39 studies: 9.4-17.8). The review also compared BA.4/BA.5 directly to BA.1 across 33 studies that evaluated vaccine performance against both subvariants and found a median 2.1-fold reduction in geometric mean titers against BA.4/BA.5 relative to BA.1 [IQR: 1.5-3.1]. Evaluation for the primary vaccination series was not possible because vaccine performance against Omicron without a booster was too poor to enable accurate calculations.

**Figure. COVID-19 vaccines elicited 6 times fewer neutralizing antibodies against Omicron BA.1 and 12 times fewer antibodies against Omicron BA.4/BA.5 compared to the ancestral strain.**

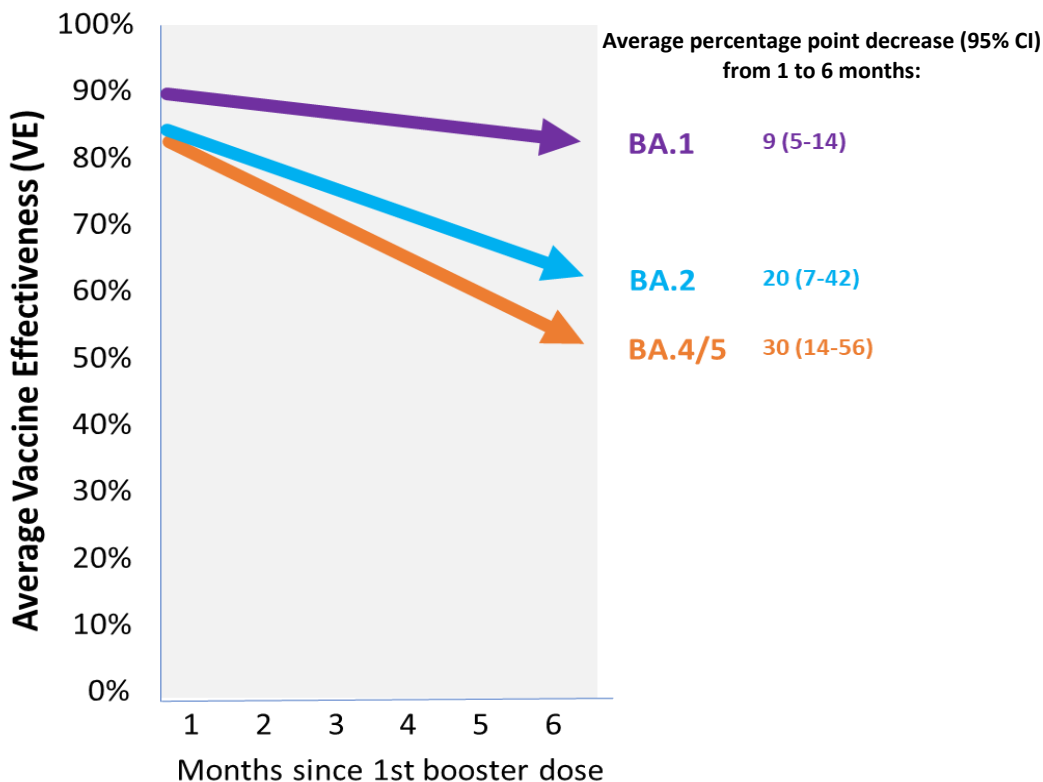


These laboratory findings suggest that the performance of booster vaccination in preventing clinical disease due to BA.1.1, BA.2, BA.2.12.1, and BA.3 will be similar to that of BA.1, but may be worse for BA.4/5. However, it is unclear if these antibody results will translate to reductions in ‘real-world’ vaccine effectiveness of booster doses. In addition, data for only a single booster dose was available and two booster doses may produce different effects.

<sup>1</sup> Higdon MM, Baidya A, Walter KK, et al. Duration of effectiveness of vaccination against COVID-19 caused by the omicron variant. *Lancet Infect Dis.* 2022 Aug;22(8):1114-1116. doi: 10.1016/S1473-3099(22)00409-1.

**Observational evidence hints at reduced vaccine effectiveness over time against BA.4/BA.5 compared to BA.1, but more evidence is needed.** As of March 2, 2023, 21 ‘real-world’ clinical studies have assessed vaccine effectiveness against severe disease due to Omicron over time (i.e. waning) following a booster dose of an mRNA COVID-19 vaccine.<sup>2</sup> The average decline in vaccine effectiveness from month 1 to month 6 after the booster dose was three times as steep when BA.4/BA.5 was dominant (30 percentage point decline) than when BA.1 was dominant (9 percentage point decline), and the average decline for BA.2 was twice as steep (20 percentage points) as that for BA.1 (Figure 2). However, more evidence is needed to determine if these differences are statistically significant. It is important to note that these observed differences in vaccine effectiveness between subvariants could be explained in part by methodological issues (e.g. the unvaccinated comparison group gaining more protection over time from prior infection with SARS-CoV-2), as described [by a recent report](#) of a meeting held by the World Health Organization. More studies are also needed to assess the impact of the latest Omicron sub-variants including BQ.1 and XBB, which evidence suggests are more immune evasive than BA.4/BA.5.

**Figure 2. Duration of protection of first booster dose vaccination against hospitalization/ severe disease by Omicron subvariant: results of a metaregression**



<sup>2</sup> Included studies are identified from an ongoing systematic literature review of COVID-19 VE studies and listed in Table 2 (Booster Dose Studies) of the COVID-19 Vaccine Effectiveness Results Summary Table updated weekly on the [VIEW-hub.org Resources Page](#). All studies providing estimates of VE against Omicron hospitalization or severe disease for at least two discrete time intervals since first booster dose are included in the metaregression.