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Letter to the Editor

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Update on Bimervax® immunogenicity amplitude. Insights on humoral response against XBB.1.5 from an extension study (NTC05142553)

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Sir,

The World Health Organization (WHO) [1], in May 2023, and the European Medicines Agency (EMA) [2], in June 2023, published their recommendations on the composition of COVID-19 vaccines for the 2023-24 season. These recommendations, published after the acceptance of the manuscript, oblige the authors to produce a brief update and reinforce the Bimervax® vaccine positioning based on new evidence from the pivotal clinical trial (HIPRA-HH-2 extension, NCT05142553).

In 2023, COVID-19 cases have been mainly associated with the BQ and XBB.1.5 lineage variants, causing mostly mild cases, albeit also boosting hybrid immunity throughout the population. In early 2023, the XBB subvariant emerged and became predominant during the first semester of the year, accounting for around 90% of all variants in the winter period. Although in June XBB.1.5 still represented 75% of prevalent circulating sublineages, XBB.1.16 and XBB.2.3 appear to have been replacing it since April 2023.

The WHO Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) postulates that new COVID-19 vaccine formulations should seek to induce antibody responses that neutralize XBB Omicron descendent lineages [1]. One recommended approach is the use of a monovalent XBB.1 descendent lineage, such as XBB.1.5, as the vaccine antigen, although other formulations and/or platforms that achieve robust neutralizing antibody responses against XBB descendent lineages can be considered [1]. They also recommend moving away from the inclusion of the index virus in future COVID-19 vaccine formulations [1]. The EMA's Emergency Task Force recommends updating vaccines to target XBB strains, which have become dominant in Europe and other parts of the world [2]. The EMA and ECDC have also noted that monovalent vaccines (vaccines targeting a single strain, such as XBB.1.5) are a reasonable choice for providing protection against current dominant and emerging strains [2].

The HIPRA-HH-2 extension trial started in September 2022 (vaccination period up until December 2022), and data from 288 individuals vaccinated with a fourth dose of Bimervax® (PHH-1V) up until May 30, 2023, have been collected, coinciding with the period of maximum prevalence of the BQ and XBB.1.5 subvariants. On the cut-off date, only 34 (11.8%) individuals reported COVID-19, and no cases of severe disease, hospitalizations or death due to COVID-19 were recorded. Neutralizing antibody titers against XBB.1.5 were analyzed 14 days after the booster in all participants and at 3 months in individuals reporting mild infection during the study period.

The preliminary results (Figure 1; Table 1) show that a fourth dose of PHH-1V elicited a significant neutralizing antibody response against XBB.1.5 14 days after the booster (GMT= 284.32, GMFR=5.45). Compared to the humoral response induced by PHH-1V vaccination against previous variants [3], the XBB.1.5 neutralizing antibody levels are lower, which is in line with the results obtained with boosters with other vaccines against the XBB.1.5 subvariant [4-6]. However, in the same extension study, natural infection with the virus

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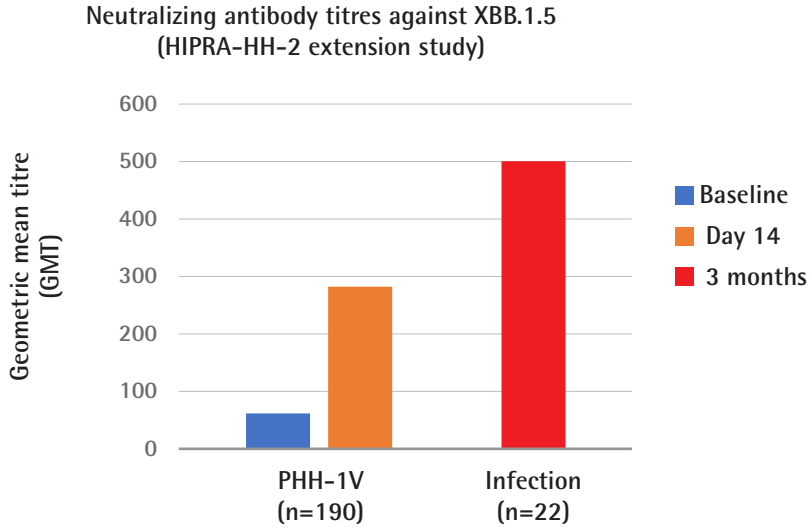

Figure 1 Geometric mean titer (GMT) of neutralizing antibodies against XBB.1.5 subvariant at baseline (blue bar) and day 14 (orange bar) after a boost with PHH-1V or after mild infection (red bar).

Table 1 Geometric mean titer (GMT) and Geometric Mean Fold Rise (GMFR) of neutralizing antibodies against the XBB.1.5 subvariant at baseline and 14 days after the 4th dose of PHH-1V. Neutralizing antibody levels (GMT) against the XBB.1.5 subvariant at 3 months in individuals reporting COVID-19 during the study period.

	HIPRA-HH-2 extension study (NCT05142553)		
	GMT at baseline (95% CI)	GMT at day 14 (95% CI)	GMFR (95% CI)
Study population (N=190)	52.18 (38.305, 71.078)	284.32 (208.685, 387.376)	5.45 (4.51, 6.58)
	GMT at 3 months (95% CI)		
Infected during study period (N=22)	500.11 (322.973, 774.386)		

CI: confidence interval

was also seen to elicit low XBB.1.5 neutralizing antibody levels (GMT=500.11, Figure 1; Table 1). In conclusion, both the Bimervax® vaccine (PHH-1V) and natural infection elicit a more discrete response compared to other variants, although considering the low percentage of individuals reporting infection (all mild), the response appears to be sufficient for protection from severe disease.

With the aforementioned results, this panel agrees on the capacity of PHH-1V booster immunization to induce a broad humoral response against emerging variants, including the 2023 circulating subvariants (XBB.1.5), as well as to provide protection from severe disease. Future strains for the 2023-2024 are not currently foreseeable, although based on the existing evidence on current and incoming vaccines, the HIPRA PHH-1V is still a robust option for COVID-19 vaccination boosting.

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