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SHORT COMMUNICATION

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Durability of humoral and cellular immunity six months after the BNT162b2 bivalent booster

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Abstract

Studies about the duration of the humoral and cellular response following the bivalent booster administration are still scarce. We aimed at assessing the humoral and cellular response in a cohort of healthcare workers that received this booster. Blood samples were collected before the administration of the bivalent booster from Pfizer-BioNTech and after 14, 28, 90, and 180 days. Neutralizing antibodies against either the D614G strain, the delta variant, the BA.5 variant, or the XBB.1.5 subvariant were measured. The cellular response was assessed by measurement of the release of interferon gamma from T cells in response to an in vitro SARS-CoV-2 stimulation. A substantial waning of neutralizing antibodies was observed after 6 months (23.1-fold decrease), especially considering the XBB.1.5 subvariant. The estimated $T_{1/2}$ of neutralizing antibodies was 16.1 days (95% CI = 10.2–38.4 days). Although most participants still present a robust cellular response after 6 months (i.e., 95%), a significant decrease was also observed compared to the peak response (0.95 vs. 0.41 UI/L, $p = 0.0083$). A significant waning of the humoral and cellular response was observed after 6 months. These data can also help competent national authorities in their recommendation regarding the administration of an additional booster.

KEYWORDS

BA.5, bivalent booster, cellular response, humoral response, omicron, SARS-CoV-2, XBB.1.5

1 | INTRODUCTION

Neutralizing antibodies against omicron variants and subvariants, which represents a strong correlate of protection from SARS-CoV-2 infection, have been shown to significantly increase after bivalent booster administrations.[1–4] Accumulating evidence suggests that T cell response, i.e. helper CD4+ and cytotoxic CD8 + T cells, plays a key role in the protection against severe disease.[5] In contrast to neutralizing antibodies, T cells are more resilient against highly mutated emerging variants, with >80% of epitopes conserved among T cells.[5,6] Currently, the long-term kinetics of the humoral and cellular immunity has been poorly explored.

2 | MATERIAL AND METHODS

In this study, we present the 6-month humoral and cellular results from the participants of the multicenter and prospective CRO-VAX HCP study who received the bivalent booster (ethical approval number: 2020-006149-21; Appendix). Thirty-six were females (median age = 51.0 years; IQR = 43.0–58.8) and fifteen were males (median age = 51.0 years; IQR = 35.0–59.0). Ages were non-significantly different between females and males ($p = 0.88$). The majority of the participants (45/51; 88.2%) had a history of SARS-CoV-2 (Appendix).

A pseudovirus-neutralization test was used to assess the neutralization potency of vaccine-elicited antibodies against either the D614G strain, the delta variant, the BA.5 omicron variant, or the XBB.1.5 omicron subvariant. The antibody titer is determined as the dilution of serum at which 50% of the infectivity is inhibited (IC_{50}) as determined by a nonlinear sigmoid regression model (Appendix). Neutralizing antibodies against BA.5 were measured at each time point but neutralizing antibodies against the D614G strain, the delta variant and the XBB.1.5 omicron subvariant were only measured at 6 months in a subset of 30 participants randomly selected.

Total antibodies against the NCP were measured using the Elecsys Anti-SARS-CoV-2 assay (Appendix).

The T cell-mediated immune response was assessed using the cobas IGRA SARS-COV-2 Tubes and the Elecsys IGRA SARS-CoV-2 assay. The test measures the release of interferon gamma (IFNγ) from T cells in response to an in vitro SARS-CoV-2 stimulation in whole blood samples which have been formerly in contact with the SARS-CoV-2 coated antigens. More than 180 different SARS-CoV-2 antigens (structural (spike, membrane and nucleocapsid) and non-structural) are coated on the antigen tube, enabling a substantial coverage of commonly occurring HLA subtypes for stimulation of both CD4+ and CD8 + T cells. The assay is therefore robust to detect different variants (Appendix).

The detailed statistical analysis process is presented in the Appendix.

3 | RESULTS

The highest measured neutralizing capacity against the BA.5 variant was reached at day 28 with a GMT of 1095 (95% CI = 903.4–1327), representing a significant 7.0 increase from baseline (i.e., 157; 95% CI = 112–219, $p < 0.0001$). A substantial decrease was then observed up to 180 days with an observed GMT of 47.4 (95% CI = 36.6–61.6, $p < 0.0001$), which represents a 23.1 decrease. The neutralizing capacity at 180 days was significantly lower compared to baseline ($p = 0.0004$). The proportion of detectable neutralizing antibodies (i.e. <1:20) was 93.6%, 100%, 100%, 98.0%, and 85.4% at baseline and 14, 28, 90, and 180 days after the administration of the vaccine (Figure 1A). The fold change in the neutralizing capacity against BA.5 was similar between participants who received the BA.1 or the BA.4/5 booster ($p > 0.05$) (Appendix). The estimated $T_{1/2}$ of neutralizing antibodies was 16.1 days (95% CI = 10.2–38.4 days). According to the model, a mean time of 137 days (95% CI = 76–170) would be needed to cross the dilution titer threshold of 1:20 (Figure 1B).

At 6 months, neutralizing antibodies against the delta variant, the BA.5 omicron variant and the XBB.1.5 omicron subvariant were 1.97, 5.20, and 10.81 lower compared to the D614G strain. The proportion of detectable neutralizing antibodies was 100%, 100%, 91.3%, and 66.6%, respectively (Figure 1C).

The highest T-cell response was observed after 14 days with a GMT of 0.95 UI/mL (95% CI = 0.72–1.24), representing a significant 1.97-fold increase from baseline (i.e., 0.48; 95% CI = 0.30–0.77, $p = 0.0306$). A significant decrease was then observed up to 180 days with an observed GMT of 0.41 (95% CI = 0.21–0.82, $p = 0.0083$), representing a 2.28-fold reduction compared to day 14 and a 1.17-fold decrease from baseline. The IFNγ responses at 90 and 180 days were not different from baseline ($p = 0.91$ and 0.95). The proportion of detectable levels of IFNγ was 98%, 100%, 100%, 100%, and 95% at baseline, 14, 28, 90, and 180 days (Figure 1D). The fold change in the IFNγ response against BA.5 was similar between participants who received the BA.1 or the BA.4/5 booster (Appendix).

Eleven participants (21.6%) developed a breakthrough infection between 90 and 180 days; which is consistent with the drop of neutralizing antibodies. The infection was associated with a significant rise in BA.5 neutralizing antibodies (fold increase of 2.55, $p = 0.0039$). The impact on the IFNγ release was not significant in these patients ($p = 0.4961$) (Appendix).

4 | DISCUSSION AND CONCLUSION

The increase of neutralizing antibodies following the administration of the bivalent booster we documented in our study (i.e., 7.0 increase) was consistent with the conclusions of other studies.[4,7] As for the humoral response following the first two doses of BNT162b2 and the homologous boosters,[8–11] a substantial waning of the humoral response was observed 6 months after the administration of the BNT162b2 bivalent booster. This decrease was especially important considering the XBB.1.5 subvariant. Moreover, the drop of neutralizing antibodies over time coincides with the decrease of bivalent booster effectiveness against infection in the recent report of Lin et al.[12]

Compared to the ancestral strain, the omicron variant is characterized by the presence of around 32 mutations in the spike protein.[13] The spike protein of BA.5 is identical to BA.2 except for 69–70 deletion, L452R, F486V and the wild-type amino acid at Q493.[14,15] For the recombinant XBB subvariants, the largest proportion of spike mutations is derived from the BA.2 with 10 new evolved mutations. The XBB.1.5 is characterized with a F486P substitution rather than the F486S substitution found in XBB.[16] The emergence of new omicron subvariants with substantial mutations is characterized by a considerable immune escape and a sharp increase in infectivity, especially considering the XBB.1.5. subvariant.[16]

A significant decay in the cellular response was also observed over time. Nevertheless, the proportion of samples still able to generate IFNγ in response to an in vitro SARS-CoV-2 stimulation remained high. This observation is consistent with the maintained and superior effectiveness against severe disease in the report of Lin et al.[12] The fact that the release of IFNγ could represent a good

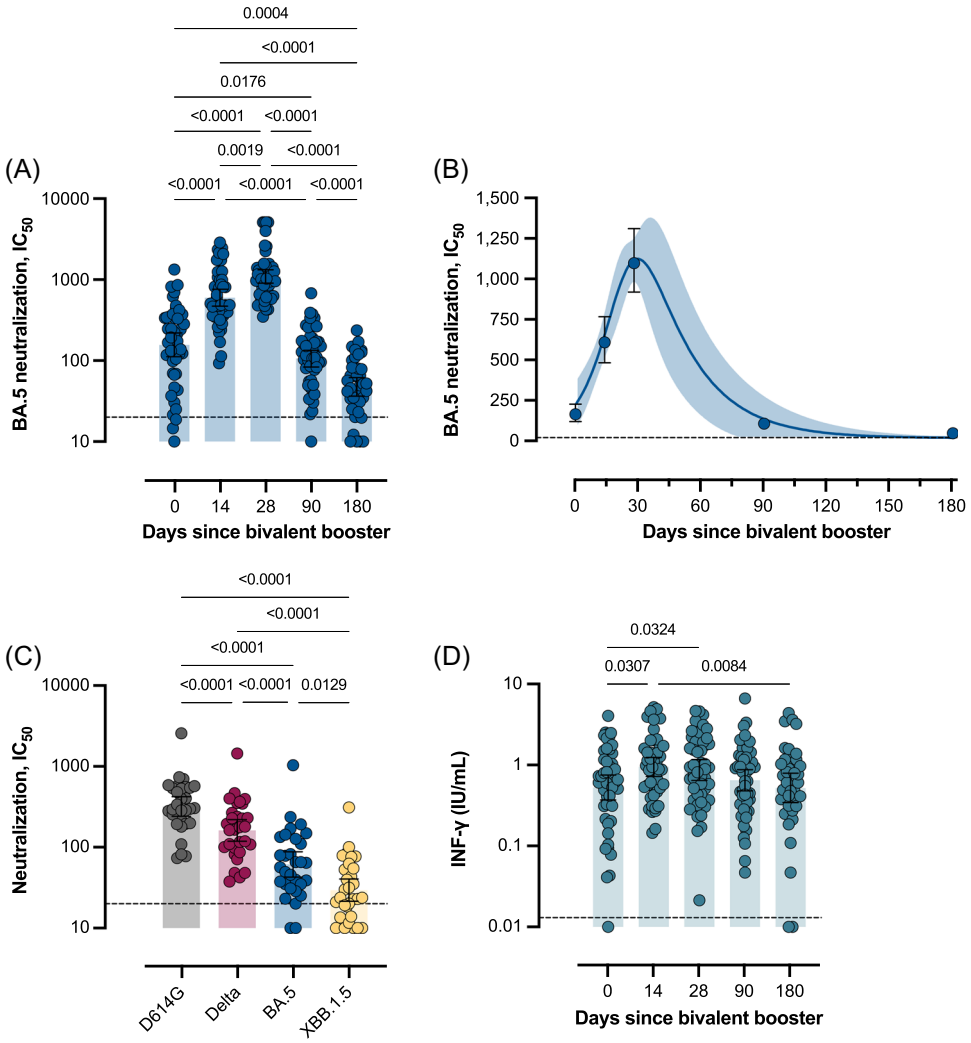

FIGURE 1 (A) Evolution of neutralizing antibodies against the BA.5 omicron variant before and after the bivalent booster with a 6-month follow-up in a population of 51 healthy volunteers. GMT were 157 (95% CI: 112–219), 598 (470–761), 1095 (903–1327), 106 (83.4–134), and 47.4 (36.6–61.6) at baseline and after 14, 28, 90, and 180 days. (B) Kinetic models of the neutralizing capacity against the BA.5 omicron variant. (C) Comparison of the neutralizing capacity against the D614G strain, the delta and BA.5 omicron variants, and the XBB.1.5 omicron subvariant in a population of 30 healthy volunteers 6 months after having received the bivalent booster. GMT were 319 (95% CI: 241–423), 162 (119–220), 61.4 (42.7–88.2), and 29.5 (21.4–40.6) for the D614G strain, the delta variant, the BA.5 omicron variant, and the XBB.1.5 omicron subvariant. The dotted line represents the positivity cut-offs for neutralizing antibodies (dilution titer of 1:20). (D) Evolution of the cellular response by means of the measurement of IFNγ. GMT were 0.53 UI/mL (95% CI: 0.37–0.75), 0.95 (0.72–1.24), 0.87 (0.65–1.17), 0.65 (0.48–0.87), and 0.52 (0.34–0.79) at baseline and after 14, 28, 90, and 180 days. The positivity cut-off for IFNγ was 0.013 IU/mL. Geometric means and 95% CIs are represented. Only $p < 0.05$ were graphically represented.

surrogate of the risk of severe infection still remains to be evaluated. Importantly, these data can also help competent national authorities in their recommendation regarding the administration of an additional booster.

AUTHOR CONTRIBUTION

Conceptualization: Julien Favresse and Jonathan Douxfils. *Methodology*: Julien Favresse, Constant Gillot, Mélanie Closset, Julien Cabo, Loris Wauthier, Clara David and Jonathan Douxfils. *Software*: Julien Favresse, Constant Gillot and Jonathan Douxfils. *Validation*: Julien Favresse and Jonathan Douxfils. *Formal analysis*: Julien Favresse, Constant Gillot and Jonathan Douxfils. *Investigation*: Julien Favresse, Constant Gillot, Mélanie Closset, Julien Cabo, Loris Wauthier, and Jonathan Douxfils. *Resources*: Marc Elsen, Jean-Michel Dogné, and Jonathan Douxfils. *Data curation*: Julien Favresse, Constant Gillot, Mélanie Closset, Julien Cabo, Loris Wauthier, and Marc Elsen. *Writing–original draft preparation*: Julien Favresse. *Writing–review and editing*: Julien Favresse, Constant Gillot, Mélanie Closset, Julien Cabo, Loris Wauthier, Clara David, Marc Elsen, Jean-Michel Dogné, and Jonathan Douxfils. *Supervision*: Jonathan Douxfils. *Project administration*: Julien Favresse, Mélanie Closset, Marc Elsen and Jonathan Douxfils. *Funding acquisition*: Julien Favresse, Mélanie Closset, Marc Elsen, Jean-Michel Dogné and Jonathan Douxfils.

All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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