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Published in:
Clinical Chemistry and Laboratory Medicine

DOI:
10.1515/cclm-2024-0919

Publication date:
2025

Document Version
Publisher's PDF, also known as Version of record

Letter to the Editor

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Neutralizing antibodies against KP.2 and KP.3: why the current vaccine needs an update

https://doi.org/10.1515/cclm-2024-0919
Received August 8, 2024; accepted August 9, 2024;
published online August 16, 2024

Keywords: SARS-CoV-2; KP.2; KP.3; humoral response; vaccination

To the Editor,

The emergence of new SARS-CoV-2 variants continues to challenge global efforts to control the COVID-19 pandemic. In the early of 2024, the JN.1 variant that presented a Leu455Ser substitution in the spike (S) protein became dominant over XBB.1.5 [1]. More recently, JN.1 evolved into JN.1 subvariants including KP.2 (JN.1.11.1.2) and KP.3 (JN.1.11.1.2). Amongst other, these two variants acquired additional substitutions in S including Arg346Thr, Phe456-Leu, and Gln493Glu [1]. These key mutations are associated with increased binding affinity to the ACE2 receptor and potential immune escape [2–4]. Theses JN.1 subvariants have spread rapidly throughout the world and have become the dominant variants replacing JN.1. Despite this, they remain on the WHO watch list and are not yet considered variants of concern [5]. Understanding the duration and efficacy of neutralizing antibody (NAb) responses elicited by vaccine formulations is crucial in predicting long-term protection and guiding public health strategies [6, 7]. The BNT162b2 bivalent booster, designed to target both the original strain and Omicron BA.1 or BA.4-5 variant, represents a pivotal advancement in vaccine technology aimed at enhancing immune responses and mitigating the impact of variant-driven surges [8, 9]. Previous studies have already raised the alarm about the lack of effectiveness of the bivalent booster on the latest variants of concern (BA.2.86, FL.1.5.1 and JN.1) [1, 10, 11]. It is therefore crucial to document the efficacy of the vaccination against these new emerging variants. These data may indicate the importance of adapting future.

This study aims to evaluate the 6-month NAb response against KP.2 and KP.3 as compared to previously circulating variants in individuals who received the BNT162b2 bivalent booster. The population of this study participated in the CRO-VAX-HCP study, a Belgian multicenter, prospective, and interventional study that aimed at evaluating the humoral response in healthcare workers. Participants received two doses of the BNT162b2 mRNA COVID-19 vaccine, followed by a homologous booster (third dose) and a bivalent booster (fourth dose, either BA.1 or BA.4/5) (ethical number: 2020-006149-21). The population of this study was composed of 9 males and 21 females with median age of 54 years (inter-quartile range [IQR]=41–60) and 55 years (IQR=44–59) respectively. Among the participants, six developed a breakthrough infection (BTI) in the 6 months after bivalent booster administration. A pseudovirus neutralization test was used to evaluate the antibody neutralization potency against XBB.1.5, BA.2.86, FL.1.5.1, JN.1, KP.2 and KP.3. The antibody titer was determined as the serum dilution at which 50 % infectivity was inhibited (IC_{50}), using a non-linear sigmoid regression model. Method details are described elsewhere [12]. The positivity cut-off was set at 20, and the detection limit at 10. The normality of the distribution was assessed using the Anderson–Darling test following log-transformation. Geometric mean titers

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(GMT) and 95 % confidence intervals (95 % CIs) were used to report the results. A multiple comparison test, specifically the two-stage linear step-up procedure of Benjamini, Krieger, and Yekutieli, was employed to evaluate potential differences between variant types. Statistical analyses were performed using GraphPad Prism 10.2.3 (GraphPad Software, Massachusetts, USA), with a significance level set at $p<0.05$.

Six months after the BNT162b2 bivalent booster dose administration, the GMT for XBB.1.5, BA.2.86, FL.1.5.1, JN.1, KP.2 and KP.3 were 29.5, 29.6, 25.2, 22.1, 16.0 and 13.4, respectively (Figure 1). The NAb titers of KP.2 and KP.3 were significantly lower compared to all other tested variants ($p<0.05$), and the decrease was mostly noticeable for KP.3. Compared to XBB.1.5, a 1.8 and 2.2-fold decrease was observed for KP.2 and KP.3, respectively. A 1.4 and 1.6-fold decrease was also identified for KP.2 and KP.3 compared to JN.1. The proportion of participants with a positive NAb titer was 67 , 67, 50, 47, 37, and 27 % for XBB.1.5, BA.2.86, FL.1.5.1, JN.1, KP.2, and KP.3, respectively (Figure 1).

The measurement of NAbs represents the best correlate of protection (CoP) against symptomatic disease. Therefore, the risk of developing the disease increased along with the decrease of NAbs [13, 14]. The results of this study highlighted a significant decrease in NAb titers against KP.2 and KP.3 as compared to former variants. The amount of literature dealing with the immune escape of these newer variants is still very limited. Li et al. have reported a global 1.41-fold decrease in NAbs titer for KP.2 compared to JN.1 [15]. Kaku et al. confirmed a reduced levels of NAbs against KP.2 and KP.3 compared to JN.1. The mean fold-decrease was 1.5 and 1.8 for KP.2 and KP.3, respectively [1]. These observations are in lines with our results and confirm a further escape of KP.3 over KP.2. Based on the increased immune escape of XBB.1.5 compared to previous variants, the CDC recommended the update of vaccines

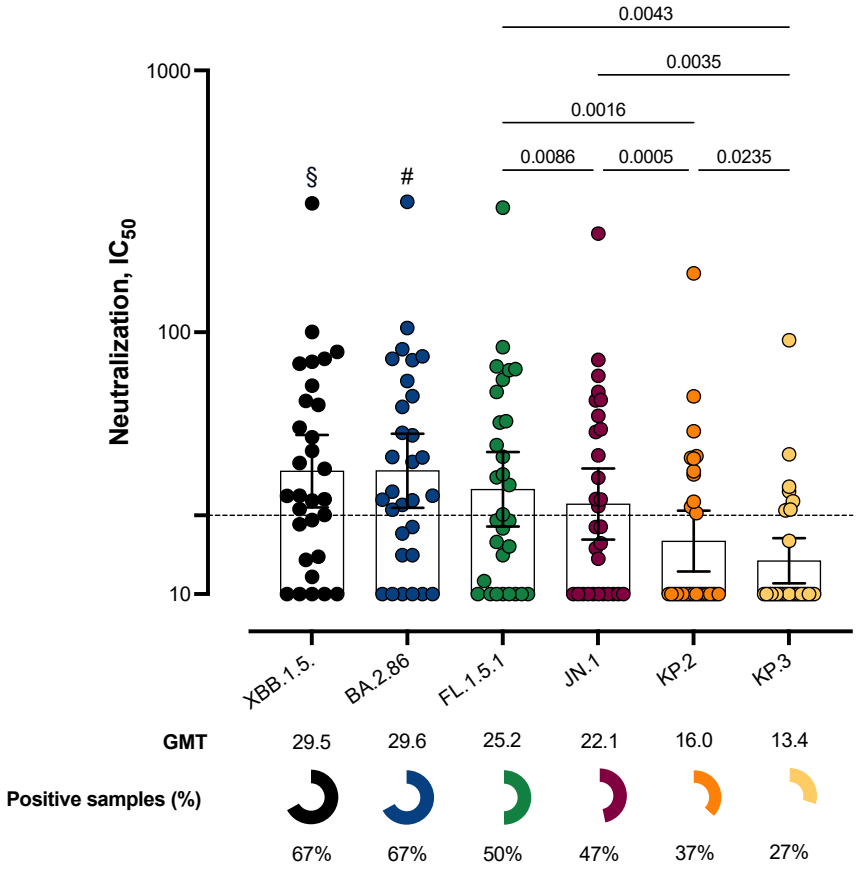

Figure 1: Comparison of the neutralizing capacity against XBB.1.5, BA.2.86, FL.1.5.1, JN.1, KP.2, and KP.3 in a population of 30 healthy volunteers 6 months after having received the bivalent booster. The proportion of detectable neutralizing antibodies was 67 , 67, 50, 47, 37, and 27 %, respectively. Geometric mean titers (GMT) (±95 % CI) and percentage of positive samples are represented. The black dotted line represents the positivity cut-offs for neutralizing antibodies (IC_{50} of 1:20). The grey dotted line represents the limit of detection of the assay (IC_{50} of 10). §, significantly higher compared to all other variants ($p<0.0001$). #, significantly higher compared to all other variants ($p<0.0001$) except for the XBB.1.5. Omicron subvariant ($p<0.0001$).

to contain a component from the Omicron XBB.1.5 lineage in September 2023. Although JN.1 presents an increased immune escape [1, 10, 11], the vaccine was not adapted at that time to contain its S sequence. Even if there is still some degree of cross-neutralizing activity of antibodies in individuals who received the XBB.1.5 monovalent booster or in individuals who developed XBB.1.5 BTI, the further immune escape of KP.2 and KP.3 will probably require at some point a vaccine adaptation. This adaptation should also be conditioned by the documentation of a reduced vaccine efficacy. Nevertheless, there is still very limited evidence to estimate effectiveness of current vaccines against KP.2 and KP.3, against symptomatic but also against severe diseases [16].

The FDA anticipates that the vaccine formulation would need to be adapted each year. The next monovalent vaccine formulation will probably be based on JN.1 or KP.2 and be available for fall 2024 [17].

While the adaptation of vaccine formulations is crucial for maintaining efficacy against evolving viral strains, it is important to consider the resilience of the T cell response against highly mutated variants, with more than 80 % of epitopes conserved [18, 19]. It has also been shown that the duration of the cellular response is longer compared to the humoral one [20, 21]. The cellular response might also be a better CoP against severe disease, meaning that a reduced level of NAbs will not always be related to poor outcomes.

In conclusion, our findings reinforce the need to readapt the vaccine formulation to be better prepared against sub-variants deriving from JN.1.

Research ethics: The research was in accordance with the declaration of Helsinki (ethical number: 2020-006149-21).
Informed consent: Informed consent was obtained from all individuals included in this study, or their legal guardians or wards.
Author contributions: Conceptualization: JF and JD; methodology: JF, CG, JC, CD and JD; software: JF, CG and JD; validation: JF and JD; formal analysis: JF, CG and JD; investigation: JF, CG, JC, and JD; resources: JMD, and JD; data curation: JF, CG and JC; writing–original draft preparation, JF; writing–review and editing, JF, CG, JC, CD, JMD, and JD; supervision: JD; project administration: JF and JD; funding acquisition: JF, JMD and JD. All authors have read and agreed to the published version of the manuscript.
Competing interests: The authors state no conflict of interest.
Research funding: None declared.
Data availability: Not applicable.

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