Letter to the Editor

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Assessment of the humoral response in Omicron breakthrough cases in healthcare workers who received the BNT162b2 booster

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To the Editor,

Since its identification in November 2021, the SARS-CoV-2 Omicron variant (B.1.1.529) demonstrated a considerable escape to antibody neutralization [1–4]. Immunization with two doses of BNT162b2 vaccine provided limited protection against symptomatic disease caused by Omicron with a vaccine efficacy 25 weeks post-second dose of only 8.8% [5]. This is consistent with the low proportion of individuals (i.e., 11%) still presenting a sufficient neutralizing capacity, defined as an ED_{50} of neutralization >30, 5 months after the second dose of BNT162b2 [4]. A BNT162b2 booster after the initial two-dose regimen substantially increased the vaccine efficacy to 66.0% after 1 week [5] and a strong increase in neutralizing capacity against Omicron was also identified (24.1–34.2-fold increase) [3, 4]. A higher protection was conferred against the delta variant (B.1.617.2), with a vaccine efficacy of 92.3 and 89.9% after 1 week and after more than 10 weeks, respectively [5]. Nevertheless, the protection against Omicron waned over time with a vaccine efficacy of 45.7% more than 10 weeks after the booster dose [5].

The aim of this study was to compare the humoral response in Omicron breakthrough cases in healthcare workers (HCWs) who received the BNT162b2 booster to a match-control group.

The CRO-VAX HCP study is a Belgian multicenter, prospective and interventional study designed to assess the antibody response in a cohort of HCWs having received the primary immunization with two doses of BNT162b2 vaccine followed by a booster dose of BNT162b2. All participants provided informed consent before collection of data and specimen. The study was approved by the ethic committee (approval number: 2020-006149-21). Participants received the first vaccine dose from 18 January 2021 to 17 February 2021. The second dose was administered 21 days after the first dose and the booster at the end of 2021, after a mean time of 299 days (min-max=265–369 days) since the first dose. All volunteers underwent a blood draw within 2 days before the first vaccine dose. Samples were collected at baseline and after 14, 28 (i.e., 7 days after the second dose), 56, 90, 180, before the third dose, after 7, 14, 28, 56, and 90 days.

In this interim report, a total of 70 HCWs received the third dose of BNT162b2 at the Clinique Saint-Luc (Bouge, Belgium). Fifty-three did not develop antibodies against SARS-CoV-2 nucleocapsid (anti-NCP) while 17 were seropositive at baseline (i.e., before the first dose). Fifty-eight subjects were followed up to 90 days (44 seronegative before the first vaccine dose and 14 seropositive).

Antibodies against SARS-CoV-2 nucleocapsid (anti-NCP; Elecsys Anti-SARS-CoV-2 NCP qualitative ECLIA, Roche Diagnostics, Machelen, Belgium) and the receptor binding domain (RBD) of the S1 subunit of the spike protein (anti-S; Elecsys anti-SARS-CoV-2 spike quantitative ECLIA, Roche Diagnostics) were measured at each time-point in all serum samples. Results above 0.80 BAU/mL for anti-S (manufacturer’s cut-off) or 0.165 COI (cut-off index) for anti-NCP antibodies were considered positives [6].
Breakthrough cases were defined as individuals that had a positive RT-PCR or antigenic test during the study, along with the development of anti-NCP antibodies in seronegative or significant increase in anti-NCP in seropositive participants. The breakthrough group was compared to a 1:2 matched control group. Controls received the three BNT162b2 vaccine doses and did not develop a breakthrough infection. They were matched on sex, age, time between sample collection, and anti-NCP serological status at baseline.

Means and 95% confidence intervals (CI) were used to present the data. Normality of distribution was tested using the D'Agostino-Pearson test with log transformation. A Mann-Whitney test was used to compare controls and breakthrough cases. Differences between more than two groups was assessed using an ordinary two-way ANOVA with multiple comparison tests. Data analysis was performed using GraphPad Prism 9.3.1 (San Diego, CA, USA), with p<0.05 considered significant.

The anti-S response in samples from seronegative subjects was higher after the third dose compared to samples collected after the first two doses. In seropositive subjects, samples obtained from day 7 since the third dose resulted in higher anti-S levels compared to samples collected before the first dose, 180 days after the first dose, and just before the third dose. After the third dose, the maximal antibody response was reached at day 14 with a mean anti-S titer of 21,426 BAU/mL (95% CI: 19,680–23,171 BAU/mL) and of 19,467 BAU/mL (95% CI: 15,404–23,529 BAU/mL) in seronegative and seropositive subjects, respectively. Anti-S levels were only significantly lower in seronegative compared to seropositive (788 vs. 3,314 BAU/mL) in samples collected just before the third dose. Afterward, a significant increase in anti-S levels was observed in both groups, and no significant differences at days 7, 14, 28, 56, and 90 were identified between seronegative and seropositive. Anti-S levels at day 90 (14,644 BAU/mL) were however significantly lower compared to days 14 (21,426 BAU/mL) and 28 (20,783 BAU/mL) in seronegative subjects. No significant decline was observed between days 7 and 90 in seropositive subjects.

Sixteen subjects (27.6%) had a breakthrough infection after the administration of the booster dose. The mean age of breakthrough cases was 42.4 years (95% CI: 36.8–48.1 years, min-max: 29–60 years). Twelve (75%) were women and 4 (25%) were men. These were asymptomatic (n=3) or developed a mild form of the disease (n=13) (Supplementary Table 1). Two breakthrough cases (both seronegative at baseline) were observed 28 days after the third dose while 5 (4 seronegative and 1 seropositive) and 9 (6 seronegative and 3 seropositive) were identified after 56 and 90 days, respectively. Breakthrough cases occurred during a period where Omicron was highly dominant (>95%) between 16 January 2021 and 26 February 2022 [7]. The control group was composed of 32 individuals (23 women [71.8%] and 9 men [28.2%]). The mean age of 47.6 years (95% CI: 43.5–51.8 years, min-max: 27.0–63.0 years) was not significantly different compared to breakthrough cases (p=0.15).

In breakthrough cases, the peri-infection anti-S levels (i.e., values obtained at the timepoint just before the breakthrough infection) were significantly lower compared to the matched-control group (13,235 vs. 19,239 BAU/mL; ratio=0.69; p=0.0019) (Figure 1). Breakthrough cases all had anti-S <25,000 BAU/mL while 11 controls (34.4%) were >25,000 BAU/mL. The levels of anti-S increased to a mean titer of 19,239 BAU/mL after breakthrough infection, that was not significantly different from levels observed in the control group (p=0.68) (Supplementary Table 1).

We previously observed a continuous waning of total anti-S binding antibodies in both seronegative and seropositive subjects after the administration of two BNT162b2 doses. Additionally, total anti-S levels were systematically higher in seropositive compared to seronegative [8–10].

After the booster, a significant increase in anti-S levels was observed but a significant waning with time was already observed after 56 and 90 days in seronegative subjects (Table 1).
The first documented breakthrough infections in individuals that received the booster were reported on February 10, 2022 (n=7) [11]. In our study, we present 16 cases of breakthrough infection that mostly occurred 3 months after the booster dose (i.e., 56.3%). Most individuals presented mild symptoms (81.3%) and few were asymptomatic (18.7%). The peri-infection anti-S levels were significantly lower compared to the control group. Similar observations have been reported in the literature for other variants and before the booster dose [12–14]. Chau et al. found a lower mean neutralizing capacity in 10 Delta breakthrough cases 14 days after the second dose with the Oxford-AstraZeneca vaccine compared to a control group of 30 uninfected persons (p=0.005) [12]. In the study of Bergwerk et al., lower levels of NAbS were observed in a cohort of 22 Alpha breakthrough cases compared to a matched control group of 104 persons (192.8 vs. 533.7 AU). Samples were collected 4 months after the second dose. Additionally, lower IgG levels were also found (11.2 vs. 21.8 AU). The rate of breakthrough infections is however low (i.e., 3.2%) compared to the rate of breakthrough due to the Omicron variant observed in the present study (27.6%) [14].

Nevertheless, an optimal cut-off that might identify subjects at higher risk of developing a breakthrough infection could not be identified due to the anti-S overlap between groups. Our results also suggest that infections with the Omicron variant can occur despite high binding antibody concentrations. The presence of high levels of total antibodies cannot guarantee a protective effect against Omicron breakthrough infection.

After the Omicron breakthrough infection, no significant difference was observed compared to the control group. Contrariwise, Bates et al. found a substantial boosting of humoral immunity as measured by NAbS (FRNT50), anti-S IgG and IgA after Delta breakthrough infection in a population of 26 participants vaccinated with BNT162b2 compared to a group of 26 matched-controls [15].

Our study presents some limitations including the absence of NAbS measurement which should be complemented to assess if anti-SARS-CoV-2 spike and RBD antibodies are capable of predicting neutralizing activity in the era of Omicron [13]. The definitive confirmation of the variants represents another limitation. Nevertheless, it is most likely to be Omicron given the period of inclusion (>95% Omicron) and the high rate of breakthrough infections. The distinction between BA.1 and BA.2 was not possible as well.

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References


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