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Peri-infection titers of neutralizing and binding antibodies as a predictor of COVID-19 breakthrough infections in vaccinated healthcare professionals: importance of the timing

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Abstract

Objectives: The BNT162b2 messenger RNA vaccine is highly effective in reducing COVID-19 infection, hospitalization and death. However, many subjects developed a breakthrough infection despite a full vaccination scheme. Since the waned efficacy of mRNA vaccines is correlated with the decrease of antibodies occurring over time, we aimed at evaluating whether lower levels of antibodies were associated with an increased risk of breakthrough infection in a cohort of breakthrough subjects that received three vaccine doses.

Methods: Total binding antibodies against the RBD of the S1 subunit (Roche Diagnostics, Machelen, Belgium) and neutralizing antibodies using the Omicron B.1.1.529 variant pseudovirus were measured. Based on individual kinetic curves, the antibody titer of each subject was interpolated just before the breakthrough infection and compared to a matched-control group that did not develop a breakthrough infection.

Results: Lower levels of total binding and neutralizing antibodies were observed compared to the control group (6.900 [95% CI; 5.101–9.470] vs. 11.395 BAU/mL [8.627–15.050] [p=0.0301] and 26.6 [18.0–39.3] vs. 59.5 dilution titer^{-1} [32.3–110] [p=0.0042], respectively). The difference between breakthrough and control subjects was mostly observed for neutralizing antibodies before three months after the homologous booster administration (46.5 [18.2–119] vs. 381 [285–509] [p=0.0156]). Considering the measurement of total binding antibodies before 3 months, there was no significant difference (p=0.4375).

Conclusions: In conclusion, our results showed that subjects that developed a breakthrough infection had lower levels of neutralizing and total binding antibodies compared to controls. The difference was mostly noticeable considering neutralizing antibodies, especially for infections occurring before 3 months after the booster administration.

Keywords: binding antibody; breakthrough; breakthrough; COVID-19; neutralizing antibody; SARS-CoV-2; vaccine efficacy.

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Introduction

The BNT162b2 messenger RNA (mRNA) vaccine is highly effective in reducing laboratory-confirmed infection, COVID-19 hospitalization and death [1–6].

Nevertheless, a gradual decline in vaccine efficacy (VE) over time has been observed within the first months after the initial two-dose and three-dose regimens [7–10]. Moreover, the VE of mRNA vaccines further decreased with the emergence of variants of concern, including the appearance of the Omicron variant on November 2021 [11, 12]. Many subjects who received two or three vaccine doses therefore developed a breakthrough (BK) infection despite a full vaccination scheme [13]. This also led to severe infections, especially in frail patients, and predictors of this lack or

reduced VE should be detected in order to adapt vaccination and/or protection strategies in these subjects [14]. There is therefore an interest in identifying vaccinated subjects at higher risk of developing an infection.

Since the waned efficacy of mRNA vaccines is correlated with the decrease of antibodies occurring over time [11, 15–21], a lower level of antibodies was hypothesized to be associated with a higher risk of BK infection [22, 23]. The aim of this study was to evaluate whether BK cases occurring after the administration of the homologous booster presented lower antibody levels before the BK event as compared to a matched-control group without BK infection. For that purpose, binding antibodies against the receptor binding domain (RBD) and neutralizing antibodies against the Omicron BA.1 variant were measured.

Materials and methods

Study design and participants

The CRO-VAX study is a Belgian prospective, interventional, multicenter study that was designed to assess the humoral response in a population of healthcare workers (HCW) from 18 to 65 years of age having received three doses of the BNT162b2 mRNA COVID-19 vaccine (Comirnaty®, Pfizer-BioNTech). The study was approved by a central Ethical Committee (approval number: 2020-006149-21) [24–28]. The homologous booster was administered between 8 November 2021 and 31 January 2022 and blood samples were collected at seven different time points, i.e., just before the booster injection and after 7, 14, 28, 56, 90, and 180 days.

Breakthrough cases were defined as individuals that had a positive reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) result during the study, along with the development of anti-nucleocapsid (NCP) antibodies in participants who were never infected or significant increase in anti-NCP in participants with a history of previous infection. The delay since vaccine administration and positive RT-qPCR was known for each BK case. The BK group was compared with a matched-control group. Controls received the three BNT162b2 vaccine doses and did not develop a BK infection, as confirmed by the absence of anti-NCP antibodies rise. They were matched on sex, age, timing (i.e., corresponding to time of infection of the matched-BK), and on type of antibody decrease kinetics.

Analytical procedure

Neutralizing antibodies: A pseudovirus-neutralization test (pVNT) was used to assess the neutralization potency of BNT162b2-elicited antibodies against the Omicron BA.1 variant. The antibody titer is determined as the dilution of serum at which 50% of the infectivity is inhibited (IC50) as determined by a non-linear sigmoid regression model. A sample with a titer of less than 1/20 was considered negative. More details about the method have been described elsewhere [29, 30].

Binding antibodies: Binding antibodies against the RBD of the S1 subunit of the SARS-CoV-2 spike protein were measured by the Elecsys Anti-SARS-CoV-2 S assay that measured total antibodies (Roche Diagnostics, Machelen, Belgium) with a positivity cut-off of 0.8 BAU/mL. An automatic dilution of 1/100 at >250 BAU/mL was performed by the analyzer to extend the measurement domain up to 25,000 BAU/mL. Additionally, total antibodies against the SARS-CoV-2 NCP were measured using the Elecsys Anti-SARS-CoV-2 assay (Roche Diagnostics). Results above 0.165 cut-off index were considered positive, as reported elsewhere [31]. Binding antibodies were analyzed on a cobas e 801 analytical unit (Roche Diagnostics).

Statistical analysis

Median and interquartile ranges (IQR) were used for demographic data while geometric mean titers (GMT) and 95% confidence intervals (95% CI) were used to present binding and neutralizing antibodies. The between-group difference was evaluated using a Wilcoxon matched-pairs signed rank test. In order to evaluate the antibody level just before the infection in BK cases, a kinetic model for each participant was computed to interpolate the most precise antibody level just before the infection (i.e., 10 days before the positive RT-qPCR). Based on the antibody decrease pattern of each participant, a simple linear regression or a non-linear regression (i.e., one-phase decay) was modeled to permit the retrieve of the expected antibody level at the corresponding timepoint. The matched-control of each BK case, having the same sex and age, was also selected to have a similar antibody kinetic model (simple linear or non-linear regression). The antibody level of each control was also interpolated to match the exact same timing of infection as the BK case. Ratio of cases to controls have also been computed to document on the difference between these groups and their respective measurand at key time points. Data analysis was performed using GraphPad Prism 9.4.1 (San Diego, CA, USA). A p-value <0.05 was considered significant.

Results

Twenty-four participants that developed a BK infection after the booster were identified. Most developed mild symptoms (88%) while few were asymptomatic (12%). Among these, 6 (25%) were men and 18 (75%) were women, and 7 (29%) developed a SARS-CoV-2 before the primary vaccination. The median age of the BK group was 43.0 years (interquartile range (IQR): 37.0–52.8; min–max: 23–63 years). The median BK infection time after the booster administration was 106 days (IQR: 66.0–132 days, min–max: 46.0–156 days). Seven participants (29.2%) developed a BK infection before day 90 and 17 (70.8%) after 90 days. The GMT of anti-NCP before the breakthrough infection was 0.163 (95% CI: 0.083–0.083) and significantly increase to 16.39 (95% CI: 7.98–33.69) after the breakthrough infection ($p<0.0001$). The control group was also composed of 24 individuals (6 men and 18 women). Among these, 10 (42%) developed a SARS-CoV-2 before the primary vaccination. The median age of 44.0 years (IQR: 38.3–53.0; min–max: 25–61 years) was not

significantly different compared to the BK group (p=0.51). Contrary to the increase of anti-NCP observed in BK participants, the GMT of anti-NCP remained quite stable over time (0.711 [95% CI: 0.203–2.50] to 0.64 [95% CI: 0.196–2.12]; p=0.1226). Each BK case was matched against a control that had the same sex, age, and timing since the booster administration (Supplementary Figure 1). None of the BK or controls developed a BK infection between the primary vaccination and the booster dose.

In the BK cases, we observed a GMT of neutralizing antibodies of 26.6 (95% CI=18.0–39.3) that was significantly lower compared to the control group considering all data (59.5; 95% CI=32.3–110; p=0.0042). The difference was more pronounced if considering the participants that developed a BK infection before day 90 (46.5 [95% CI=18.2–119] vs. 381 [95% CI=285–509]; p=0.0156). After 90 days, the difference was no longer significant (21.1 [95% CI=14.0–31.9] vs. 27.7 [95% CI=17.2–44.6]; p=0.3028) (Figure 1). The kinetics of neutralizing antibodies also differed from the two groups (Figure 2).

The difference between BK and controls was less obvious considering the measurement of binding antibodies. A significant difference was only found considering all data (6.950 [95% CI=5.101–9.470] vs. 11.395 [95% CI=8.627–15.050]) (p=0.0301). If considering the participants that developed a BK infection before or after 90 days, no significant difference was identified (Figure 1). Regarding the kinetics, there is a tendency for higher titers in controls, although 95% intervals of the regression models were overlapping (Figure 2).

Ratio of cases to controls were lower considering the neutralizing antibody titers of all participants as compared to binding IgG (0.45 [95% CI=0.24–0.84] vs. 0.61 [95% CI=0.42–0.89]) but this difference was non-significant (p=0.64). The difference was however significant for the samples collected <90 days after the booster (0.12 [95% CI=0.04–0.36] vs. 0.64 [95% CI=0.30–1.38]; p=0.02). After 90 days, ratios increased (0.76 [95% CI=0.40–1.47] vs. 0.60 [95% CI=0.37–0.97]) and were non-significantly different (p=0.37).

Discussion

In our study, we found that BK cases presented lower levels of neutralizing and binding antibodies in the peri-infection period as compared to matched-controls that did not develop a BK infection. The difference was mostly noticeable considering neutralizing antibodies, especially in subjects that developed a BK infection before 90 days.

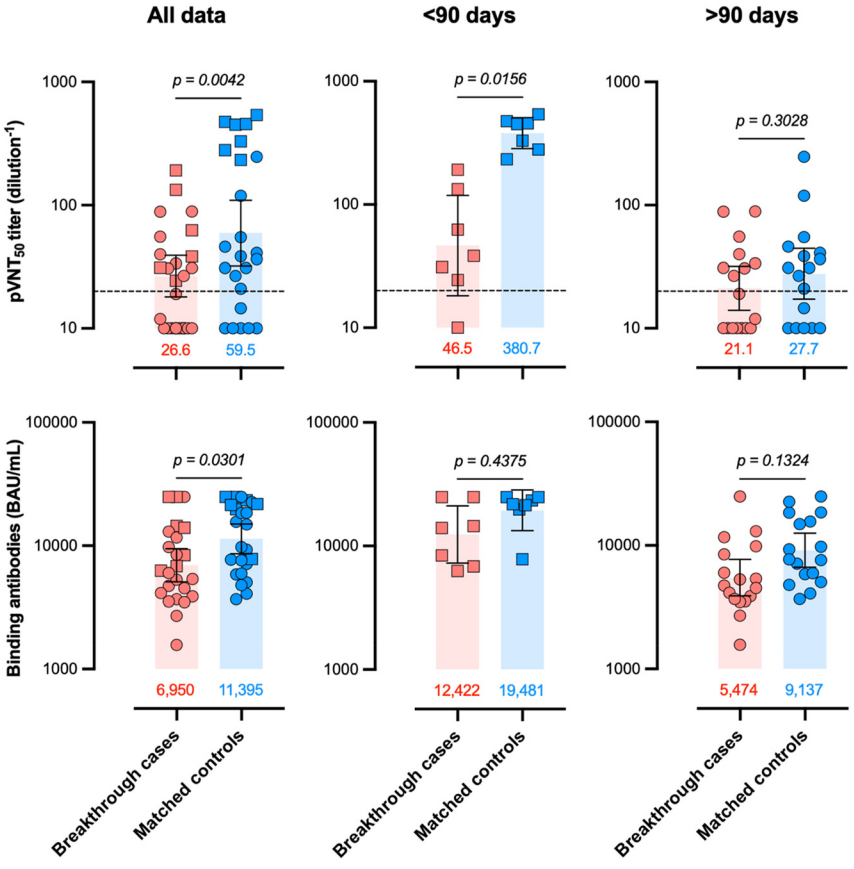

Figure 1: Neutralizing and binding antibody titers among breakthrough cases and matched-controls. Geometric means and 95% CI are represented. Breakthrough cases are represented in red and controls in blue. Samples collected before 90 days since the booster administration are represented with a "square" and samples collected after 90 days with a "dot". The positivity cut-off for neutralizing antibodies corresponds to a dilution titer of 1/20.

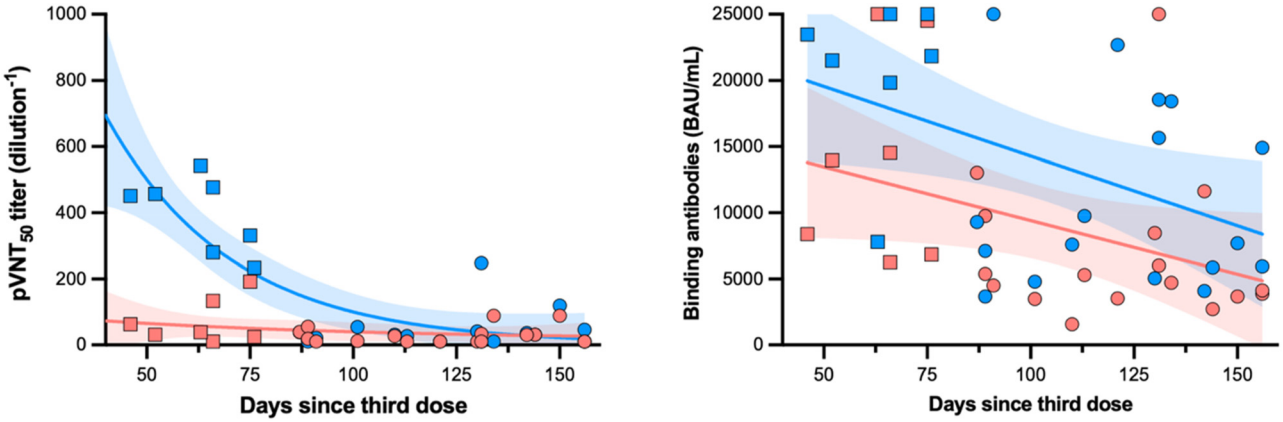

Figure 2: Kinetics of neutralizing and binding antibody titers among breakthrough cases and matched-controls. The kinetics are represented with its 95% CI. Breakthrough cases are represented in red and controls in blue. Samples collected before 90 days since the booster administration are represented with a "square" and samples collected after 90 days with a "dot".

Since the levels of antibodies is correlated to the VE, some previous studies already hypothesized lower levels of antibodies in peri-infection BK samples compared to controls [23]. In the study of Bergwerk et al., lower levels of neutralizing antibodies and binding IgG (Beckman Coulter) were observed in a cohort of 22 Alpha BK cases compared to a matched control group (192.8 vs. 533.7 AU and 11.2 vs. 21.8 AU, respectively). Antibodies were measured the day of the BK diagnosis and the median time of BK since the second BNT162b2 vaccine dose was 36 days. Torres et al. found similar conclusions with the detection of binding antibodies (Roche diagnostics) at 3 months being associated with a lower risk of Delta BK [32]. Our group also published about significantly lower binding total antibody levels (Roche Diagnostics) in 16 Omicron BK cases as compared to controls [33]. All cases developed a SARS-CoV-2 infection less than 90 days after the homologous BNT162b2 booster [33]. Two other studies concluded about the absence of difference [34, 35]. The first included 33 Omicron BK cases and measured neutralizing and total binding antibodies (Roche Diagnostics) at around the time of infection [34]. The second included around 50 Delta BK and measured binding IgG levels (Siemens Healthcare) [35]. Interestingly, the median time of BK infection in both studies was 105 days and 10–24 weeks after vaccination with BNT162b2. These results are consistent with ours showing that the difference between BK cases and controls was no more observed for late BK infection (i.e., >90 days). We also showed that the proportion of cases to ratio was lower considering the measurement of neutralizing compared to binding antibodies, mostly for samples collected >90 days (0.12 vs. 0.64). This observation is similar to that of Bergwerk et al. (0.35 vs. 0.65) [22].

As the neutralizing antibodies correlate with the level of protection against re-infection, our results suggests that about 3 months (90 days) after the booster, the effectiveness of this protection strongly decreases. The probability of having a BK infection after 90 days would therefore depend more on the prevalence of the disease, on the variant in circulation and on the application of sanitary measures by the population.

In addition to be a predictor of the risk of BK infection, increased levels of antibodies (Roche Diagnostics) measured in serum collected within 7 days of symptom onset or diagnosis of Omicron infected vaccinated subjects were associated with a decrease in the occurrence of fever, hypoxia, CRP elevation, and lymphopenia [36]. Patients with higher antibody levels also had lower viral loads obtained by PCR than those with lower antibody levels [22, 36].

The study of Brada et al. focused on the pre-vaccination levels of binding IgG as a predictor of subsequent BK infection. They found that binding IgG levels over 700 BAU/mL (Abbott Laboratories) was associated with a 35% reduced risk of infection in the six months following vaccination. In our study, BK did not have lower neutralizing or binding antibody levels compared to the matched-control group before the administration of the booster dose (data not known) [37].

In conclusion, our results showed that subjects that developed an Omicron BK infection had lower levels of neutralizing and binding antibodies. The difference against controls that did not develop a BK infection was mostly noticeable considering neutralizing antibodies, especially for BK infection occurring within 3 months after the booster administration.

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Competing interests: Authors state no conflict of interest.
Informed consent: Informed consent was obtained from all individuals included in this study.
Ethical approval: The study was approved by a central ethical committee (approval number: 2020-006149-21).

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