Journal of Infection 85 (2022) e125–e126

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Letter to the Editor

Impact of SARS-CoV-2 Omicron variants on serum neutralization in a cohort of healthcare workers vaccinated with BNT162b2

Letter to the editor

Dear editor,

Despite all the forces put in place to counter the Coronavirus Disease 2019 (COVID-19) pandemic and despite the progress made, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and its variants of concern (VOCs) continue to spread causing considerable issues. Nowadays, the most widespread variants belong to the Omicron sublineages.[1]

In July 2021, we published in this Journal partial results of our study on serum neutralization activity of three different cohorts on different SARS-CoV-2 VOCs.[2] One of the cohorts was a group of healthcare workers (HCW) of Perugia Hospital vaccinated with BNT162b2 (Comirnaty® - BioNTech/Pfizer). This cohort was enrolled for a prospective observational study that lasted 1 year and was approved by the Ethics Committee of the Umbria Region (protocol number 20686/21/OV) and it was conducted in accordance with the Declaration of Helsinki. Here, we present the complete results of the study.

Samples of vaccinated subjects were withdrawn before the first dose of BNT162b2 (T0), right before the second one (T1), after 14–21 days (T2), 3 months (T3) and 6 months (T4) from the second dose. Furthermore, the serum neutralizing activity was also checked after 14–21 days from the third vaccine injection (T5). Neutralizing antibodies (NT-Abs) titers against SARS-CoV-2 were evaluated as previously described.[2] Strains of SARS-CoV-2 identified as 20A.EU1, B.1.617.2, BA.1, BA.2 and BA.5 were used. Identification was performed as previously described.[3]

This cohort was composed of 108 HCWs vaccinated with the BNT162b2 COVID-19 mRNA vaccine.

Demographic and clinical characteristics are summarized in Table 1. The mean age was 44.7 ± 10.1 years and 18.1% were male. All subjects were tested for SARS-CoV-2 antibodies before vaccination. Ninety-one subjects had no SARS-CoV-2 infection, either before or within 21 days from completed vaccination.

Six subjects had asymptomatic SARS-CoV-2 infection before vaccination. Six subjects had mild or asymptomatic SARS-CoV-2 infection between the first and second vaccine dose. Four subjects were lost to follow-up at different time points. Another participant had an anaphylactic reaction to the first dose of the vaccine and did not undergo the second one. Consequently, these 17 patients were analyzed separately.

The NT-Abs over time trend showed a peak immediately after the second dose (T2), a progressive reduction up to six months (T3-T4) and a second peak, even higher, after the third dose (T5). These findings confirmed what is already known in the literature.[4]

Table 1
Demographics, comorbidities, and clinical presentation.

	Healthcare workers
No.	91
Age, median (IQR) [range], years	46.3 (36.3–53.3) [28.0–69.1]
Sex:	
Male, No. (%)	16/91 (17.6%)
Comorbidities:	
Autoimmune disease, N/tot (%)	4/91 (4.4)
Diabetes, N/tot (%)	1/91 (1.1)
Hypertension, N/tot (%)	9/91 (9,9)
Malignancy, N/tot (%)	0/91 (0.0)
Chronic kidney disease, N/tot (%)	0/91 (0.0)
Chronic liver disease, N/tot (%)	0/91 (0.0)
COPD or chronic lung disease, N/tot (%)	0/91 (0.0)
Chronic ischaemic heart disease, N/tot (%)	0/91 (0.0)
Cerebrovascular disease, N/tot (%)	0/91 (0.0)
Dyslipidaemia, N/tot (%)	1/91 (1.1)
Obesity, N/tot (%)	0/91 (0.0)
N comorbidity, median (IQR)	0 (0–1)
BMI, mean (SD)	23.6 (4.5)
History of adverse drugs reactions, N/tot (%)	4/91 (4.4%)
History of adverse vaccines reactions, N/tot (%)	0/91
Smoke, N/tot (%)	34/91 (37.4)
Polypharmacy, N/tot (%)	14/91 (15.4)
Chronic steroid therapy, N/tot (%)	0/91 (0.0)
History of SARS-Cov2 infection, N/tot (%)	0/91 (0.0)
T cell, mean (SD)	1683.7 (823.7)
CD4, mean (SD)	944.4 (483.3)
CD4%, mean (SD)	32.5 (12.1)
CD8, mean (SD)	533.1 (294.0)
CD8%, mean (SD)	17.5 (6.6)
CD4/CD8, mean (SD)	1.9 (0.8)
Days from second vaccine dose, median (IQR)	16 (15–18)
Death, N/tot%	0/90 (0.0)

Footnotes: IQR, interquartile range; SD, standard deviation; tot, total.

As can be seen from Fig. 1, before vaccination (T0) no one had NT-Abs against SARS-CoV-2, at T1 the median NT-Abs titer was 10 (IQR <10–10), at T2 80 (IQR 40–80), at T3 20 (IQR 20–40), and at T4 10 (IQR 10–20) against 20A.EU1 strain. Furthermore, 73 serums were collected after 14–21 days from the third dose (T5) and at this time-point, the NT-Abs median titer was 160 (IQR 120–340) against 20A.EU1 strain. The T5 NT-Abs titer was 2.8-fold higher than T2 (after the second dose) ($p < 0.0001$). This difference is also maintained when T2 and T5 samples were tested with B.1.617.2 strain with an NT-Abs titer 2.5-fold higher at T5 compared to T2 ($p < 0.0001$).

Several studies demonstrated that 2-dose mRNA vaccines provided high protection against symptomatic infection by delta variant and moderate protection against the Omicron ones, but the effectiveness wanes over time. The mRNA booster dose provides additional protection against the Omicron variant.[5,6]

In our study, we demonstrated a correlation between these clinical-epidemiological data and the serum neutralization activity.

https://doi.org/10.1016/j.jinf.2022.08.023

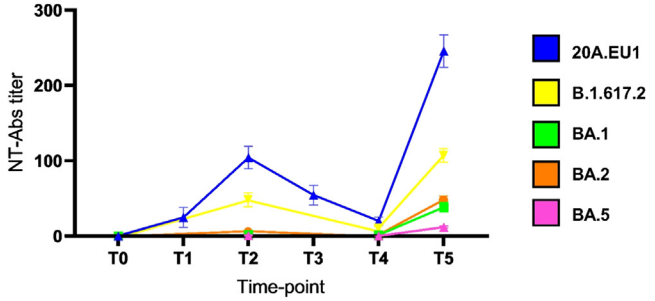

Fig. 1. Vaccine-elicited serum neutralization activity: neutralizing antibodies (NT-Abs) titer decay curve for different SARS-CoV-2 variants. Time-points: before the first dose of BNT162b2 (T0), right before the second one (T1), after 14–21 days (T2), 3 months (T3) and 6 months (T4) from the second dose, after 14–21 days from the third vaccine injection (T5).

At the T2, the NT-Abs titer was significantly lower for the Omicron strains (BA.1, BA.2 and BA.5 median NT-Abs <10, interquartile, IQR 0–7.5) compared to 20A.EU1 strains (80, IQR 40–80) and B.1.617.2 (40, IQR 20–40) (p <0.05), while there was no significant difference among the Omicron variants. At T4 time point, a significant reduction in NT-Abs titer was observed and a significant difference was confirmed for the 20A.EU1 and B.1.617.2 strains compared to the Omicron variants. At T5, the differences highlighted at the previous time-points were confirmed, moreover, a significant reduction in the titer was observed on the BA.5 variant (10, IQR 0–20) compared to the BA.1 (20, IQR 10–40) and BA.2 (40, IQR 20–80) (p = 0.002). Furthermore, for 34.2% (25/73) of subjects, the serum neutralization assay showed a titer <10 for the BA.5 variant after the third vaccine dose.

Other studies, also demonstrated that neutralisation efficiency against BA.5 is lowest among all Omicron variants, even among people infected with BA.1 following three or four vaccine doses.[7,8]

Poor data are available on the efficiency of the fourth dose against Omicron variants. Cohen et al. performed a multicenter cohort study (4-dose group versus 3-dose group) during the first month of the 4-dose vaccination campaign. They demonstrated that the fourth BNT162b2 vaccine dose resulted in a reduced Omicron 1 breakthrough infection rate compared to the 3-dose group.[9]

In conclusion, the study showed that the NT-Abs titer progressively decreases over time, starting from the second dose of vaccine and then showing a higher peak after the booster dose. Furthermore, the Omicron variants have shown the ability to evade, even if not totally, the humoral immunity obtained through vaccination. In particular, the resistance of the BA.5 variant could partly explain the peak of infections recently encountered in Italy and in the world.

Ethical statements

The Vero E6 cell line was kindly provided by Istituto Zooprofilattico Sperimentale di Brescia, Brescia, Italy.

This research was approved by the Ethics Committee of the Umbria Region, protocol number 20686/21/OV.

Conflict of Interest

All authors declare no conflicts of interest.

Disclaimers

Nothing to declare.

Acknowledgments

Thanks to the healthcare workers of Santa Maria della Misericordia Hospital that spontaneously participated to this study, once again their contribute was crucial.

References

1. European Centre for Disease Prevention and Control. Variants of interest and concern in the EU/EEA. Available at https://www.ecdc.europa.eu/en/news-events/epidemiological-update-sars-cov-2-omicron-sub-lineages-ba4-and-ba5 2022.
2. Anna Gidari, Samuele Sabbatini, Sabrina Bastianelli, Sara Pierucci, Chiara Busti, Claudia Monari, et al. Cross-neutralization of SARS-CoV-2 B1.1.7 and P.1 variants in vaccinated, convalescent and P.1 infected. *J Infect* 2021;**83**(4). doi:10.1016/j.jinf.2021.07.019.
3. Anna Gidari, Samuele Sabbatini, Elisabetta Schiaroli, Sabrina Bastianelli, Sara Pierucci, Chiara Busti, et al. The combination of molnupiravir with nirmatrelvir or GC376 has a synergic role in the inhibition of SARS-CoV-2 replication *in vitro*. *Microorganisms* 2022;**10** Jul 21. doi:10.3390/microorganisms10071475.
4. Antonietta Isgrò Maria, Giusy Trillò, Luigi Russo, Lucia Tornesello Anna, Luigi Buonaguro, Lina Tornesello Maria, et al. Bimodal antibody-titer decline following BNT162b2 mRNA anti-SARS-CoV-2 vaccination in healthcare workers of the INT - IRCCS "Fondazione Pascale" cancer center (Naples, Italy). *Infect Agent Cancer* 2022;**17** Jul 28. doi:10.1186/s13027-022-00451-1.
5. Takeshi Arashiro, Yuzo Arima, Hirokazu Muraoka, Akihiro Sato, Kunihiro Oba, Yuki Uehara, et al. COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection during Delta-dominant and Omicron-dominant periods in Japan: a multi-center prospective case-control study (FASCINATE study). *Clin Infect Dis* 2022 Aug 3ciac. doi:10.1093/cid/ciac635.
6. Yuntao Zou, Doudou Huang, Qian Jiang, Yanglin Guo, Chider Chen. The vaccine efficacy against the SARS-CoV-2 Omicron: a systemic review and meta-analysis. *Front Public Health* 2022;**10** Jul 13. doi:10.3389/fpubh.2022.940956.
7. Limor Kliker, Neta Zuckerman, Nofar Atari, Noam Barda, Noam Gilboa, Ital Nemet, et al. COVID-19 vaccination and BA.1 breakthrough infection induce neutralising antibodies which are less efficient against BA.4 and BA.5 Omicron variants, Israel, March to June 2022. *Euro Surveill* 2022;**7**(30) pii=. doi:10.2807/1560-7917.ES.2022.27.30.2200559.
8. Jasmin Quandt, Alexander Muik, Nadine Salisch, Bonny Gaby Lui, Sebastian Lutz, Kimberly Kruger, et al. Omicron BA.1 breakthrough infection drives cross-variant neutralization and memory B cell formation against conserved epitopes. *Sci Immunol* 2022 Jun 2eabq. doi:10.1126/sciimmunol.abq2427.
9. Cohen Matan J, Jonatan Oster, Moses Allon E, Avishay Spitzer, Shmuel BenensonIsraeli-Hospital 4th Vaccine Working Group Association of receiving a fourth dose of the BNT162b vaccine with SARS-CoV-2 infection among health care workers in Israel. *JAMA Netw Open* 2022;**5**(8) Aug 1. doi:10.1001/jamanetworkopen.2022.24657i.

Anna Gidari*, Elisabetta Schiaroli
Department of Medicine and Surgery, Clinic of Infectious Diseases, "Santa Maria della Misericordia" Hospital, University of Perugia, Piazzale Lucio Severi 1, Perugia 06132, Italy

Samuele Sabbatini
Department of Medicine and Surgery, Medical Microbiology Section, University of Perugia, Perugia, Italy

Sabrina Bastianelli, Sara Pierucci, Chiara Busti, Daniela Francisci
Department of Medicine and Surgery, Clinic of Infectious Diseases, "Santa Maria della Misericordia" Hospital, University of Perugia, Piazzale Lucio Severi 1, Perugia 06132, Italy

*Corresponding author.
E-mail address: anna.gidari@studenti.unipg.it (A. Gidari)