Longitudinal monitoring of anti-SARS-CoV-2 RBD IgG antibodies after BNT162b2 vaccination in healthcare workers

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To the Editor,

Nearly two years after the origin of the ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, the race to develop and distribute effective coronavirus diseases 2019 (COVID-19) vaccines continues. Recent evidence suggests that the clinical efficacy of the COVID-19 vaccines currently cleared by EMA (European Medicines Agency) is as high as 80-100% shortly after administration (1), though a significant decline of efficacy after several months, especially in preventing symptomatic COVID-19 illness, has been recently demonstrated (2). This evidence leads the way to using additional vaccine boosters, usually to be administered 6 months after completing a standard vaccination cycle (3), and is supported by reliable laboratory data, demonstrating that vaccine efficacy depends on anti-SARS-CoV-2 neutralizing antibody levels (1), whose values tend to naturally wane over time (4,5). This study was hence aimed to provide further insights on the kinetics of anti-SARS-CoV-2 IgG neutralizing antibodies elicited by COVID-19 vaccination in healthcare workers and their potential correlation with vaccine efficacy.

We initially enrolled 100 healthcare workers of the Hospital of Peschiera del Garda (Italy), all SARS-CoV-2 seronegative, who voluntarily received COVID-19 vaccination with Pfizer/BioNTech BNT162b2 (Comirnaty, Pfizer Inc., New York, NY, US; 30 µg in two doses, 3 weeks apart). Serum samples were collected before all subjects received the first and second BNT162b2 vaccination, and then 1, 3 and 6 months after the second BNT162b2 dose. Serum values of anti-SARS-CoV-2 RBD (receptor binding domain) IgG antibodies were measured with ACCESS SARS-CoV-2 IgG II (Beckman Coulter Inc., Brea, CA, US). This method is a paramagnetic particle, chemiluminescent immunoassay, excellently correlated with a surrogate virus neutralization test ($r=0.96$; $p<0.001$), and with sensitivity and specificity for detecting previous SARS-CoV-2 infections, both approaching 100% (6). Results of measurements were reported in terms of antibodies units (AU)/mL (this method is not traceable to the World Health Organization standard), expressed as median and interquartile range (IQR). Effectiveness of BNT162b2 vaccination in eliciting a significant and durable humoral response in our population was defined as an anti-SARS-CoV-2 RBD IgG antibodies level ≥10 AU/mL, in keeping with manufacturer's recommendations. Further technical and analytical characteristics of this assay are reported elsewhere (7). All our study subjects provided a written informed consent for undergoing BNT162b2 vaccination and long-term serological monitoring. The study was performed in accordance with the Helsinki Declaration and approved by the Ethics Committee of the Provinces of Verona and Rovigo (59 COVIDCESC; November 3, 2021).

The final study population included 86 SARS-CoV-2 baseline seronegative subjects, with a median age of 45 years (IQR 31-53 years; 47.7% males), while 14 subjects were lost to follow-up over the 6-month study period.

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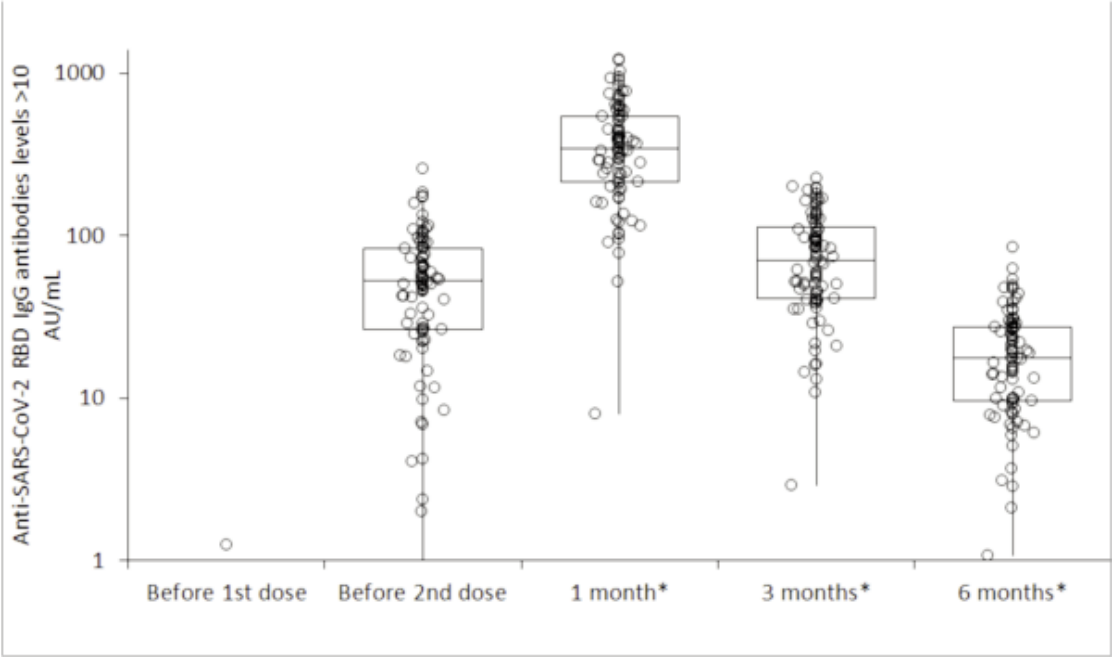

Figure 1
Longitudinal monitoring of anti-SARS-CoV-2 RBD (receptor binding domain) IgG serum levels in seronegative healthcare workers undergoing BNT162b2 mRNA-based vaccine administration. The dashed line delineates the manufacturer's recommended threshold of antibodies positivity (i.e., ≥10 AU/mL).

**After the second vaccine dose*

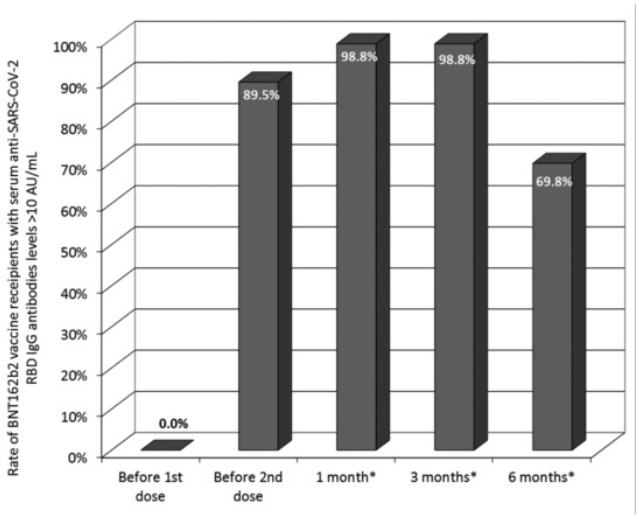

Figure 2
Rate of BNT162b2 vaccine recipients displaying with anti-SARS-CoV-2 RBD (receptor binding domain) IgG serum levels ≥10 AU/mL, which corresponds to the antibodies positivity threshold defined by the manufacturer.

**After the second vaccine dose*

The results of anti-SARS-CoV-2 RBD IgG antibodies up to 6 months after completing the 2nd BNT162b2 vaccine dose is reported in Figure 1, showing that the serum levels of these antibodies reached a peak of 344.4 AU/mL (IQR, 216.7-542.2 AU/mL) 1 months after the second vaccine dose, but then declined to 70.6 AU/mL (IQR, 41.8-112.0 AU/mL) and further to 17.6 AU/mL (IQR, 9.7-27.3 AU/mL) at 3 and 6 months after the second vaccine dose, respectively. Such reductions correspond to a median decrease from the peak of -79.3% (IQR, -76.5 – -82.6%) and

-95.3% (IQR, -93.3 – -96.4%) at 3 and 6 months after the second vaccine dose, respectively. The overall rate of BNT162b2 vaccine recipients displaying serum anti-SARS-CoV-2 RBD IgG antibodies levels above the 10 AU/mL threshold is shown in Figure 2. Briefly, the rate increased from 0/86 (0%) at baseline (all subjects were SARS-CoV-2 seronegative), to 77/86 (89.5%) and 85/86 (98.8%) after the first and second BNT162b2 vaccine doses, remained stable up to 3 months after the second vaccine dose (85/86; 98.8%), but then declined to 60/86 (69.8%) when anti-SARS-CoV-2 RBD IgG antibodies were assayed 6 months after the second vaccine dose. Notably, it is not surprising that the only subject who remained seronegative (i.e., anti-SARS-CoV-2 RBD IgG antibodies levels <10 AU/mL) throughout the study period was a 70-year old man, since vaccine reactogenicity is reportedly lower in older male people (8,9).

In keeping with previous evidence from other countries, populations and settings (4,5), the results of this study on Italian healthcare workers who underwent administration of BNT162b2 mRNA-based COVID-19 vaccine suggest that humoral immunity and, more specifically, the serum levels of anti-SARS-CoV-2 RBD IgG antibodies, displayed a dramatic decay 6 months after vaccination, with values 95,3% lower than those measured at the peak, with nearly 30% of subjects displaying antibodies levels below the recommended threshold of positivity (i.e., <10 AU/mL). This data suggests that nearly one-third of BNT162b2 vaccine recipients have an insufficient value of serum anti-SARS-CoV-2 RBD IgG antibodies at 6 months post-vaccination. Intuitively, this finding goes hand in hand with the evidence that the rate of breakthrough SARS-CoV-2 infections in COVID-19 vaccine recipients increases over time and is strongly correlated with the level of anti-SARS-CoV-2 RBD IgG antibodies (10), as well as provides additional support to the importance of SARS-CoV-2 serologic monitoring before administration of vaccine boosters. This strategy would allow to timely identify those in whom the neutralizing antibodies have waned faster, have become more vulnerable to infection and disease, and shall hence be prioritized for receiving additional vaccine boosters in the future (8,9).

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CONFLICT OF INTEREST

None.

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