Internal and Emergency Medicine (2022) 17:311–312
https://doi.org/10.1007/s11739-021-02907-5

CE - LETTER TO THE EDITOR

Response to BNT162b2 mRNA COVID-19 vaccine among healthcare workers in Italy: a 3-month follow-up: comment

Cristina Serraino[1] · Remo Melchio[1] · Marco Badinella Martini[1] · Laura Gerbaudo[2] · Luigi Fenoglio[1]

Received: 30 November 2021 / Accepted: 6 December 2021 / Published online: 10 January 2022

Dear Editor,

We have read the study by Ponticelli et al. [1] with great interest and we congratulate them for the very useful reported data. We agree with them on the importance of obtaining up-to-date and real-world data on the efficacy and safety of COVID-19 vaccination. We therefore would like to share and compare the data we have collected on vaccination with BNT162b2 mRNA COVID-19 of healthcare workers (HCWs) at AO Santa Croce & Carle, a teaching hospital in the North-West of Italy.

From 27th December 2020 and for the following 3 months, 2059 HCWs were vaccinated in our hospital as follows (Table 1): 1717 HCWs (440 males and 1277 females) who were not previously infected and 342 HCWs (100 males and 242 females) with a documented history of SARS-CoV-2 infection (mean duration between infection and vaccination of 119.5 days). The mean age of vaccinated HCWs was 43.1 ± 11.7 years. Serum samples were obtained 21 days after administration of the first single dose from HCWs who were previously infected, if the infection was contracted less than 6 months earlier, and 21 days after administration of the second dose from HCWs who were not previously infected and from those who were infected more than 6 months earlier. The reference cut-off to attest to the antibody reactivity was > 1 U/mL. In line with Ponticelli et al. [1] we found a positive antibody response rate (99.8%) among HCWs 21 days after having performed the second vaccination dose. We observed similar findings (99.7%) for those who were previously infected within six months and were therefore vaccinated with a single dose with antibody control 21 days later (Table 1). We also observed a difference in the levels of neutralizing antibody between samples from previously infected participants (median: 161 U/mL, IQR: 106–339) and those who were not previously infected (median: 86 U/mL, IQR: 45–123) ($p < 0.0001$). More specifically, in the previously infected group we also observed a difference in the levels of neutralizing antibody between samples from those infected more than 6 months earlier who received two vaccine doses (median: 270 U/mL, IQR: 149–500), and those who were infected more recently and received one vaccine dose (median: 146 U/mL, IQR: 103–263) ($p < 0.0001$). Therefore HCWs with previous COVID-19 infection had significantly higher neutralizing antibody titers after administration of a single dose of mRNA-vaccine compared to uninfected HCWs who received two doses of the vaccine. These interesting data were in line with those of Ponticelli et al. [1] and other studies [2] which showed that the level of antibodies induced by the vaccine was significantly high after 2 weeks from the single dose of SARS-CoV-2 mRNA vaccine in HCWs with pre-existing immunity, thus reinforcing the hypothesis that the previous SARS-CoV-2 infection can be considered an analogue of immune priming. Recently infected HCWs, who were vaccinated with only one dose, were categorized into two groups according to the time elapsed from infection to vaccination: up to 2 months (85 HCWs) and more than 2 months (77 HCWs). The two groups differed with respect to the levels of neutralizing antibody, with median values ranging from 134 U/mL (IQR: 101–202) in participants vaccinated 1–2 months after infection to 160 U/mL (118–325) in those vaccinated more than 2 months after infection ($p = 0.03$). Interestingly, our findings indicated that the booster response was more efficacious when the vaccine was administered more than 2 months after SARS-CoV-2 infection. Similar findings were described by other authors who identified a more efficacious response when the vaccine was administered more than 3 months following infection [3]. Currently, insufficient information is available to draw

✉ Marco Badinella Martini
marco.badinella.martini@gmail.com

[1] Department of Internal Medicine, Santa Croce e Carle" Hospital, Via Michele Coppino 26, Cuneo, Italy

[2] Occupational Health Service, "Santa Croce e Carle" Hospital, Cuneo, Italy

Table 1 Baseline characteristics of vaccinated HCWs

Total vaccinated HCWs, *N* (%)	2059
Age, mean ± SD	43.1 ± 11.7
Sex (male), *N* (%)	540 (26.2)
HCWs with previous SARS-CoV-2 infection, *N* (%)	342 (13.6)
HCWs with reactivity (> 1 U/mL) after 21 days from second dose of vaccine, *N* (%)	1713 (99.8)
HCWs with SARS-CoV-2 infection within the previous six months with reactivity (> 1 U/mL) after 21 days from single dose of vaccine, *N* (%)	341 (99.7)

SARS-CoV-2 Severe Acute Respiratory Syndrome-CoronaVirus 2; *HCWs* HealthCare Workers; *SD* Standard Deviation, *N* number

a definitive conclusion regarding the optimal timing of a single vaccine dose after infection. At 3 months from the start of vaccination, we also observed an incidence rate of Sars-CoV2 infection among vaccinated HCWS of 0.8% (14 HCWs), slightly lower than Ponticelli et al. [1] but still in line with the data of other studies [4]. These HCWs had only mild symptoms and had a neutralizing antibody titer of 83 U/mL (IQR: 36–115).

We fully agree with Ponticelli et al. [1] that accurate real-world information on adverse events after immunization (AEFI) are critical to ensuring vaccine safety and promoting the vaccination campaign. Unfortunately, we did not have detailed data on the AEFI of HCWs in our hospital. However, the only data in our possession attested to the complete absence of potentially lethal AEFI, determining visits to the emergency room or hospitalization. We also agree on the potential "notoriety bias" of their study, resulting in over-reporting by some AEFI among HCWS. In fact we believe that this may also be due to media pressure and concern, widespread among HCWs, for COVID-19 vaccine [5].

Despite the great efforts that have been made, however big questions still remain for the future. For example, it is currently unclear whether a time-dependent decrease in neutralizing antibody levels can lead to a decrease in the immune response or what the optimal time window is needed to maximize efficacy and safety in previously infected individuals. Only through the constant collection and observation of future data we will be able to give answers to these numerous questions.

Declarations

Conflict of interest All authors declare that they have no conflict of interest.

Ethics approval All performed procedures in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the ethic committee of AO Santa Croce e Carle, Cuneo.

Informed consent All participants provided written informed consent before data collection, including agreeing for the results to be published.

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