



## COVID-19 mRNA vaccine safety, immunogenicity, and effectiveness in a hospital setting: confronting the challenge

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In an article published in this issue of the Journal, Ponticelli and colleagues investigated the immune response and safety to BNT162b2 mRNA COVID-19 vaccine among healthcare workers (HCWs) in Italy [1]. In detail, the study captured data on vaccine immunogenicity, effectiveness, and safety over 3 months from vaccination (plus a passive surveillance of incident SARS-CoV-2 infections, over a further 3 months), contributing to the evidence on global vaccination campaign impact [2, 3].

In our view, this study has several important strengths. First, its real-world data are of paramount importance, especially because long-term surveillance (for both safety and efficacy) of the new mRNA vaccines is still underway. Another added value of this work is target population surveyed—hospital staff—which have been among the first to be vaccinated, and are at higher risk of infection because of their professional exposure. Moreover, having enrolled a closed cohort, such as professionals of a single hospital, this study can ensure the possibility of follow-up over longer

period, which could be hardly carried out in other contexts [4].

However, a notable weakness of the work by Ponticelli and colleagues, as acknowledged by the authors, is the duration of follow-up itself (three months plus other three of passive surveillance) which was not long enough to evaluate the possible and predictable loss of effectiveness over a longer time span. This is particularly true with regard to the potential impact of SARS-CoV-2 variants, seasonality of virus waves and the exposure to a higher number of COVID-19 patients in specific periods of the calendar year, as well as other factors that might influence the protection offered by the vaccine [1, 5].

Authors also observed that in the cohort of HCWs who underwent serology testing, 82.5% had a good serological response within 2 weeks from vaccination. Such a result is consistent with literature so far available and confirms the importance of timely vaccination, especially in high-risk settings such as hospitals [6]. On this point, longitudinal sero-surveys to assess the dynamics of vaccine-induced immunological response, in terms of level and time-trend, are extremely important [4]. A protective antibody threshold below which the risk of break-through infections increases is yet to be known and, although a low antibody level is likely to keep offering protection by virtue of the immune memory, continuous monitoring of antibody levels should serve as reference to decide the need for a booster dose [4]. In light of this, we would like to encourage Ponticelli and colleagues to extend the follow-up period in a future study.

As previously mentioned, the study also collected data on COVID-19 vaccine adverse events following immunization (AEFI). From an epidemiological standpoint, the risk of AEFIs was higher among persons who were already infected with COVID-19, but this association was no longer significant at the second dose, in line with previous reports [2, 3]. Moreover, Ponticelli and colleagues also found differences among sexes. Indeed, also other epidemiological studies found similar differences in AEFI among men and women,

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both considering the general population or even HCWs [2, 3]. In this regard, it is worth mentioning a cross-sectional study recently published by Ripabelli, also enrolling HCWs, found that age under 55 years was a predictor for AEFIs [7], supporting findings from Ponticelli and colleagues. Further research should explore possible factors other than age and sex, which might influence AEFIs occurrence, including health status and comorbidities.

In our view, this is an interesting aspect, and scientists should focus even more on sex and age differences both in terms of disease predisposition and survival, since global trends suggesting increased female survival have been reported, including in Italy [8]. Sex differences in terms of pharmacological response is also important to investigate for the existing repurposed drugs as well as other emerging drugs.

Data on both efficacy and safety are important for the safe roll-out of COVID-19 vaccination campaigns and should be extensively communicated not only within the scientific community but also to policy-makers and general public. Indeed, even if they are important to stimulate a scientific debate and foster new research questions, they are also relevant for policy-makers, public health experts and general public. Nowadays, many European and other countries started administering the third dose of COVID-19 vaccine. In light of this, having real-world and timely data would serve policy-makers in planning effective and costly benefit vaccination strategy [4, 9]. Public health experts will largely benefit in setting priorities and identifying correct target population, understanding how to implement vaccination campaign and how and what to communicate to the general public [9–11]. Lastly, a transparent, timely and updated communication would largely improve the trust of general public toward health institutions and authorities, hopefully reducing doubts and hesitancy, and improving vaccination acceptance [12, 13].

In light of the surge of virulent variants, and the reduction of effectiveness and immunities observed in some countries [5], that are causing new epidemic waves, this commentary aims at generating further discussion and debate on the need to focus efforts in enhancing studies on long-term immunological response to and safety of COVID-19 vaccinations. Indeed, the existing body of evidence collected so far has been providing strong confirmation of short and medium-term efficacy and safety of COVID-19 vaccines that confirmed vaccination as an essential tool for the control of the SARS-CoV-2 pandemic [1, 5–9]. However, questions as such as how long the protection obtained after vaccination lasts, as well as whether there are differences among age groups or sexes in vaccine effectiveness and safety, and best vaccination schedule for a life-long protection still need to be answered.

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## Declarations

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