Editorial

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Kinetics and biological characteristics of humoral response developing after SARS-CoV-2 infection: implications for vaccination

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With the ongoing coronavirus disease 2019 (COVID-19) pandemic outbreak unremittingly spreading all around the world, and a plausible future characterized by a condition of endemic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1], widespread vaccination against this new coronavirus is currently regarded as one of the most effective strategies for mitigating the paramount adverse consequences of COVID-19 on people, healthcare, societies and economies [2].

The recent availability of different types of vaccines, especially the two RNA-based BNT162b2 [3] and mRNA-1273 [4] licensed by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) between the end of 2020 and the beginning of 2021, is disclosing a brighter perspective in the fight against COVID-19. Despite vaccination of at least 60–70% of the worldwide population would be probably needed to reach diffuse and durable herd immunity [5], the unprecedented haste that has allowed to rapidly develop and distribute SARS-CoV-2 vaccines is counterbalanced by some objective difficulties to provide a sufficient amount of doses for vaccinating not only the entire worldwide population, but especially professional categories at higher risk of SARS-CoV-2 infection such as the

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Tommaso Trenti, Department of Laboratory Medicine and Pathology, Unità Sanitaria Locale, Modena, Italy healthcare workers, who were the most strongly hit by the first wave of the pandemic outbreak in many worldwide countries [6].

The compelling need to identify population subsets to which vaccination shall be prioritized thus apparently collides with indications provided by many healthcare organizations. The US Centers for Disease Control and Prevention (CDC), for example, claim that mRNA COVID-19 vaccines are supposed to be safe even in people with clinical evidence of prior SARS-CoV-2 infection, so that widespread vaccination shall be pursued irrespective of a positive history of prior symptomatic or asymptomatic SARS-CoV-2 infection [7]. The CDC also state that viral testing aimed at diagnosing an acute SARS-CoV-2 infection, along with serologic testing for defining presence of anti-SARS-CoV-2 antibodies titer, are not recommended before vaccination. This generic indication has been actually endorsed by many governments and healthcare authorities, so that vaccination campaigns are carried out without establishing the possible presence (and eventual level) of anti-SARS-CoV-2 antibodies, on the premise that natural immunity from COVID-19 may not be durable and protective, and that vaccination would not carry clinical risks in people who already bear anti-SARS-CoV-2 antibodies [8]. This last claim is especially weird, as patients with prior known COVID-19 infection have been almost excluded from phase III vaccine trials, so that the risk of developing adverse effects, including antibody-dependent enhancement (ADE) and/or immune complex reactions, cannot be clearly ruled out in this patient population.

Despite the fact that the vital questions on how long humoral immunity will last and protect the population from recurrent SARS-CoV-2 infections remains mostly unanswered so far [9], evidence is accumulating that the strategy of widespread vaccination, including people who have recently recovered from fully asymptomatic, mildly symptomatic or even severely symptomatic SARS-CoV-2 infection, may be plagued by some biological and clinical

drawbacks. A recent article, published by Dan and colleagues in the journal Science [10], has provided evidence that the circulating immune memory to SARS-CoV-2 appears to endure for up to six months in patients with previous SARS-CoV-2 infection. In particular immunoglobulins(Ig)G targeting the SARS-CoV-2 spike protein were found relatively stable over time (half-life, 140 days; 95% CI, 20-240 days), with SARS-CoV-2 spike-specific memory B cells being even more abundant six months after SARS-CoV-2 infection than in earlier period. Notably, the rate of patients maintaining seropositivity for SARS-CoV-2 spike IgG was found to be as high as 90% between 6 and 8 months post-infection. The assessment of anti-SARS-CoV-2 spike IgA, a class of antibodies highly expressed at mucosal surface, and hence supposed to provide efficient protection against (re-)infection [11], revealed an even longer half-life compared to IgG (210 days; 95% CI, 126-703 days).

Altogether these data are in keeping with many previous findings, which converge to suggest that humoral [12] and B-cell memory [13] immunity against SARS-CoV-2 would last for not less than 4-6 months after an active infection, especially in subjects who have developed moderate to severe illness. Concerning the question as to whether this immunity would be protective against either (re-)infection or virus transmission, the results of a recent study carried out by Kim et al. provide important clues on this matter [14]. The authors studied a cohort of ferrets, which were first infected with SARS-CoV-2 to boost neutralizing antibodies. The animals were then divided in five different groups based on to their neutralizing antibodies titers, and were subjected to a second infection with a heterologous SARS-CoV-2 strain. Importantly, ferrets with moderate to high antibodies titers (i.e., from 1:20 to 1:160) not only were protected from reinfection, but were also unable to transmit the virus to other uninfected animals. These findings are supportive of evidence provided by the recently published BNT162b2 [3] and mRNA-1273 [4] trials, that development of anti-SARS-CoV-2 immunity would be nearly 95% efficient against development of COVID-19, coupled with comparable efficient protection against the risk of SARS-CoV-2 infection. Similar findings have been reported in a large seroprevalence survey, involving over 12,500 healthcare workers [15], which proved that a prior SARS-CoV-2 infection may be capable to generate such a humoral immune response that will reduce by nearly 10-fold the risk of a second SARS-CoV-2 nucleic acid amplification test (NAAT) positive results (adjusted incidence rate ratio, 0.11; 95% CI, 0.03-0.44).

Several lines of evidence attest that logistic challenges of producing, delivering and administrating SARS-CoV-2 vaccines are still daunting, and will remain so for long [2],

thus jeopardizing the rapid establishment of a solid heard immunity, effective for limiting both the circulation of the virus within the community and the infection of fragile individuals, who are at higher risk of developing severe. even lethal, forms of this illness. Moreover, although the cost of vaccines will gradually decline over time in parallel with development, approval and commercialization of new formulations, the predicted expenditure needed for vaccinating several billions of people worldwide is colossal.

In this virtually enigmatic scenario, we strongly believe that SARS-CoV-2 vaccination shall follow straightforward prioritisation, where people who are less likely to be infected, re-infected and/or develop more aggressive COVID-19 illness shall be deferred until more vulnerable parts of the population have acquired a sufficient degree of protective immunity. This consideration paves the way to some (non-mutually exclusive) options, whereby we ad interim recommend that:

- (1) Anti-SARS-CoV-2 antibodies (anti-spike, preferably anti-receptor binding domain (RBD) IgG and eventually IgA) titer shall be assessed before vaccination, so that SARS-CoV-2 vaccine administration can be prioritized to seronegative individuals. Only immunoassays with well-demonstrated correlation between SARS-CoV-2 antibodies and neutralization activity shall be used [16].
- Whenever the assessment of anti-SARS-CoV-2 antibodies is impossible or unfeasible, SARS-CoV-2 vaccination shall be deferred in subjects with molecular diagnosis of recent (i.e., <3 months) infection, at least until higher risk categories of seronegative subjects have completed the vaccination cycle, or the virus has accumulated mutations such that it can be supposed that natural immunity may have become inefficient.
- Immunoassays that provide quantitative measurements shall be preferred over those generating only semi-quantitative or qualitative results [17], whilst fully automated techniques are advisable for supporting large volumes of tests.
- (4) Anti-SARS-CoV-2 antibodies (anti-spike, preferably anti-receptor binding domain (RBD) IgG and eventually IgA) titer shall be monitored for up to 6-8 months, preferably starting 1-2 weeks after the last dose of the vaccine (if >1 dose is planned), using always the same assay. This would allow to timely identify lack of seropositivity or seronegativization, thus enabling to guide the clinical decision making for possible SARS-CoV-2 revaccination or administration of new therapies such as those based on SARS-CoV-2 monoclonal antibodies.
- (5) Antibodies assessment and monitoring, before and after vaccination, are necessary in patients with immunodeficiencies and cancer.

The performance characteristics (both analytical and diagnostic) of each specific test shall then be validated and/or verified by laboratory medicine professionals in collaboration with health care institutions and in vitro diagnostic companies, since only laboratory experts have such adequate skill and competency for validating the test for the intended use according to its specific performance characteristics. The laboratory professionals shall also be involved in selecting the most suitable test according to the aforementioned criteria, as well as in identifying reliable diagnostic algorithms for SARS-CoV-2 diagnostics (for example, for test repetition or orthogonal testing). When feasible and clinically advisable, assessment of cellular immunity may also be an option.

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