Optimizing effectiveness of COVID-19 vaccination: will laboratory stewardship play a role?

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To the Editor,

We read with interest the editorial by Lippi et al. [1] about the important contribution that laboratory medicine may presently provide to enhance the real-world optimization of the effectiveness of COVID-19 vaccination. The growing flourishing of new variants and the approval for the use of new vaccines makes it mandatory to evaluate the effectiveness of vaccination protection over time. Actually, the European Medical Agency has approved five vaccines for prevention of symptomatic COVID-19, the last on December 20. Two of the vaccines are messenger RNA (mRNA)–based vaccines encoding the spike protein antigen of SARS-CoV-2 encapsulated in lipid nanoparticles, Comirnaty (BioNTech/Pfizer) and COVID-19 mRNA-1273 vaccine (Moderna). A third vaccine is a recombinant chimpanzee adenoviral vector (ChAdOx1-S) encoding the spike glycoprotein of SARS-CoV-2, ChAdOx1 nCoV-19 COVID-19 vaccine (Vaxzevria; AstraZeneca). The fourth is a recombinant adenovirus type 26 vector (Ad26.COV2.S) encoding the SARS-CoV-2 spike glycoprotein, the Janssen COVID-19 Vaccine. The fifth a protein-based vaccine (Novavax).

COVID-19 vaccines induce both virus-specific antibodies and T cell responses, but it is the neutralizing antibodies (nAbs) that interfere with the entry of SARS-CoV-2 into host cells that are considered to be key for host protection. However, SARS-CoV-2 nAbs elicited by vaccination (or natural infection) might become insufficient for host protection owing to declining titres over time [2] and/or the emergence of viral escape variants [3,4]. Conversely, compared with nAbs, SARS-CoV-2-specific memory T cells are maintained for a relatively long time. Moreover, there is increasing evidence that SARS-CoV-2 VOCs rarely escape memory T cell responses elicited by SARS-CoV-2 vaccination or natural infection [5].

Defining the correlates of protection necessary to manage the COVID-19 pandemic requires the analysis of both antibody and T cell parameters, but the complexity of traditional tests limits virus-specific T cell measurements. The assessment is essentially based on laboratory tests, and encompasses SARS-CoV-2 serological immunoassays, as surrogate measures of humoral immunity and neutralizing antibodies, interferon-gamma release assays, as surrogate tests aimed at deciphering and monitoring cellular immunity, along with flow cytometry techniques for assessing the presence and number of memory B cells.

Measuring the level of protection conferred by anti-SARS-CoV-2 (trimeric) spike or RBD (receptor binding domain) antibodies (especially total and IgG) is a suitable and reliable approach for predicting biological protection against the risk of infection and severe coronavirus disease 2019 (COVID-19) illness. Khoury et al. [6] underscored that the anti-SARS-CoV-2 neutralization level significantly predicts overall immune protection and may guide approval decisions for mRNA COVID-19 vaccines and other COVID-19 vaccines. The same measurements also indicated that higher antibody responses correlated with higher estimated vaccine efficacy against symptomatic COVID-19 [2]. Furthermore, the antibody level associated with 80% vaccine efficacy against symptomatic infection with majority Alpha (B.1.1.7) variant of SARS-CoV-2 was achieved with 264 binding antibody units (BAU)/mL for anti-spike IgG and 506 BAU/mL for anti-spike and anti-RBD antibodies [7]. However, the antigen (either spike or RBD) and epitopes of the prototype SARS-CoV-2 coated in some immunoassays may no longer reflect the sequence of circulating variants. Consequently, anti-SARS-CoV-2 antibodies elicited by highly mutated SARS-CoV-2 variants may no longer be efficiently recognized by the currently available commercial immunoassays. Therefore, as reported by Lippi et al. [8] about the new variants and their impact on serological assays, it is important
initiate validation studies to ensure that the currently available commercial immunoassays for detecting anti-SARS-CoV-2 spike and RBD antibodies are still capable of predicting neutralizing activity against emerging and highly-mutated SARS-CoV-2 variants [8].

Conversely, major efforts are still needed to better standardize laboratory tests for investigating cellular immunity and evaluating their overall utility in clinical practice. It is crucial to assess the levels of protection generated by natural infection or SARS-CoV-2 vaccines, mainly in individuals professionally exposed and in vulnerable groups. Measuring T-cell responses may complement antibody tests currently in use as correlates of protection. There are a good number of studies demonstrating T-cell responses to SARS-CoV-2 using techniques [9] widely applied to measure responses to other viral infections. These techniques include variations of the ELISPOT-assay which measure mainly IFN-γ production and intracellular-cytokine-staining (iCS) by flow cytometry. Activation-induced markers, also by flow cytometry, can be a sensitive technique. However, they have limitations in the applicability compared with whole blood interferon-Gamma-Release-immuno-Assay (IGRA) to using them in a clinical laboratory.

A possible rapid and simple alternative to these methods is the direct addition of stimulatory antigens to whole blood that induce the secretion of cytokines (usually IFN-γ) in plasma, which is subsequently quantified using two detection methods: CLIA (Liason, Quantiferon® Gold Plus) or ELISA (Quantiferon® Human IFN-γ SARS-CoV-2, Qiagen®). This assay has also been shown to measure the presence of SARS-CoV-2–specific T cells in asymptomatic and symptomatic SARS-CoV-2–infected patients [10]. On December 2, Qiagen has obtained CE mark for its QuantiFeron® assay, which can assess T-cell responses to Covid-19. The SARS-CoV-2 assay is designed to detect interferon-γ (IFN-γ) produced by CD4+ and CD8+ T cells in response to a SARS-CoV-2 peptide cocktail (Ag1 and Ag2) in the blood. The new in vitro diagnostic test has the ability to detect T-cell responses to Covid-19 early in the course of infection or after vaccination.

There is now an open debate on the distribution of COVID-19 vaccines among different settings and countries, with the need to set a delicate balance between the use of additional boosters (for preventing waning of immunity in those who have already been vaccinated or with previous COVID) that are too close together which could trigger unexpected collateral effect.

The emergence and rapid rise to global predominance of the variant, together with the recent emergence of the Omicron variant, remind us that variants of concern are likely to continue to evolve and challenge existing vaccines that depend primarily on humoral immune responses.

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