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Letter to the Editor

Serological testing for SARS-CoV-2: Advancements and future challenges

Dear Editor,

It is with great interest, that we read the letter by Lippi and Plebani [1] commenting on our review article recently published in EJIM [2]. To our view both articles converge on the position that serological testing for SARS-CoV-2 is a valuable tool for influencing public health policies, accounting for both general population surveys (post-infection and/or vaccination) and surveys in specialized settings, such as hospitals and nursing homes. We fully agree that the surge of still evolving variants e.g., Omicron variant necessitates the development of updated immunoassays, particularly in cases where Spike or RBD are employed as target antigens, allowing for the accurate detection of emerging variants. In addition, novel assays must demonstrate concordance between overall humoral response and neutralizing antibody capacity. To this end multiple efforts are under way e.g., involving multiplex flow cytometric assays [3,4] and low-volume antibody assays that are cost-effective and could be used for seroprevalence studies in low and middle-income countries [5].

It is indeed a responsibility for laboratory scientists to continuously access the reliability of commercially available assays and feed-back to the industry. Nevertheless, as discussed in our review, assays against the N-protein still seem reliable for population-level seroprevalence studies as demonstrated in a recent cross-sectional study in all 50 US States. It was shown, that seroprevalence increased from 8% in November 2020 to 58,2% in February 2022 and most importantly the spread of Omicron variant was captured in the data [6]. This was also depicted in another study from Geneva, where total antibody seroprevalence was 93.8%, including 72.4% for infection-induced antibodies [7]. Finally, data from another study from Mexico, testing the pre-vaccination (and pre-Omicron) nationwide baseline found a comparable diagnostic accuracy of SARS-CoV-2 spike RBD and N-specific IgG tests [8].

Lippi and Plebani also raise the point that both natural and vaccine-induced immunity progressively diminishes. We note that repeated vaccination and/or infection with different SARS-CoV-2 variants trains the immune system resulting e.g., post-vaccination in the development of durable memory B- and T-cells which mature and increase in numbers despite the decline of antibody titers from peak levels [9]. As a result, the decrease of antibodies titers in the circulation does not necessarily means waning of immunity against the antigen used in the anti-SARS-CoV-2 prototype vaccines (i.e., Wuhan-Hu-1 S protein) or the SARS-CoV-2 strain that caused the infection but rather reflects the evolutionary leaps of the S protein e.g., in the Omicron variant [10].

Nonetheless, the accuracy in measurement of antibodies titers and circulating T-cell activity in the blood and (if possible) in the mucosa is an important issue and should be considered when any serological survey is conducted keeping also in mind the existing standardization or harmonization issues, as also pointed out by Lippi and Plebani [11]. Undoubtedly, standardization and harmonization of binding assays needs improvement especially for longitudinal analyses. Since the beginning of the pandemic, a major goal was to achieve herd immunity, a state where the rate of virus transmission among the infected, vaccinated or none of both would rapidly decrease. Accurate serosurveys are one of the means to determine whether such a state exists, or whether new variants will continuously move the goalposts.

In any case, as discussed in our article, serological testing, apart from epidemiology, has proven particularly helpful to dissect immune responses in patients treated with immunotherapies or in other biological fluids such as CSF [2]. As in all biological or biomarker testing, constant validation is needed to ensure reliability and reproducibility of results.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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