EDITORIAL
INFECTIOUS DISEASE

The value of serology testing to manage SARS-CoV-2 infections

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Validated serology tests are a good complement for the SARS-CoV-2 RNA test, allow rapid epidemiological control and reveal immune status before and after vaccination. https://bit.ly/3eKAc6h

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The figures presented in the World Health Organization's latest report on the current status of the coronavirus disease 2019 (COVID-19) pandemic and the COVID-19 dashboard of the Johns Hopkins University of Medicine are quite similar: respectively, 6,416,828 and 6,656,827 cases worldwide, and 382 867 and 391 571 deaths [1, 2].

The origin of the pandemic is believed to have been a wet market in Wuhan, China, where the new strain of coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) was initially extracted from several patients' lower respiratory tract samples in December 2019 [3]. These patients presented with symptoms of severe pneumonia, including fever, fatigue, dry cough and respiratory distress in 29% of cases [4, 5].

The evidence shows that virus transmission can occur during the incubation period, which is officially estimated to be between 2 and 14 days [6, 7]. However, a case with an incubation period of 27 days was reported on 22 February by the local government of Hubei province, and high sputum viral loads were found during the recovery phase in a patient with pneumonia caused by COVID-19 [8].

The range of rapid diagnostic methods available to control the pandemic is growing. However, their usefulness remains questionable, given the lack of official validation of their performance in terms of sensitivity and specificity: only a limited number of assays have received emergency use authorisation from the US Food and Drug Administration [9].

Rapid PCR tests to diagnose the disease and to avoid its spread, and serological assays to determine the production of antibodies, are two important tools in managing this pandemic. Unfortunately, the sensitivity of PCR methods is no higher than 70%, which may potentially lead to underdiagnosis of COVID-19, especially in less severe or asymptomatic cases. Serological tests are fundamental to determine the acquired immunity of patients who have had the disease and to establish the level of immunity in the general population.

Serology assays overcome two important limitations of SARS-CoV-2 PCR-based techniques. The first is that they can be manipulated in a biosafety level 2 laboratory, whereas the detection of viral load requires a

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biosafety level 3 environment, in addition to higher protection measures during sample procurement. Secondly, sampling issues are less important in serology assays. Finally, in SARS-CoV-2 PCR-based techniques, the type of respiratory specimen and the sampling method may have a strong influence on the test's sensitivity.

In this issue of the *European Respiratory Journal*, Bin Lou *et al.* [10] present interesting data on SARS-CoV-2 assessed using PCR and on seroconversion dynamics in a cohort of 80 patients from the First Affiliated Hospital of Zhejiang University in China. The authors measured cumulative levels of antibodies (Ab), IgM and IgG at different time points ranging from 5 to 30 days after the onset of symptoms or after exposure (in only 45 patients). The fact that three different serology assays were used (two in the case of IgG) and the study of the seroconversion dynamics after the onset (0–7, 8–14 or 15–29 days) offer an interesting picture of immune response to SARS-CoV-2, clustered according to short *versus* long incubation periods and the development of critical *versus* non-critical illness. Critically ill *versus* non-critically ill patients did not differ with regard to time to seroconversion after exposure. The seroconversion time correlated inversely with the incubation period.

Using deep sputum instead of swabs, Bin Lou *et al.* [10] found the highest sensitivity of ELISA in the 15–29 days period for Ab (100%), IgM (97%) and IgG (93%). Overall, these results indicate that viral load decreased as antibody response was enhanced. Indeed, these authors found that the RNA test sensitivity was very high (100%) during the first 7 days of onset but decreased at 8–14 days (to 90%) and at 15–29 days (to 70%). Similar findings by other authors suggest that monitoring the dynamics of COVID-19 infection combining serological tests and high throughput assays would be better than using the RNA test alone [11].

Thus, serology tests seem more useful for studying seroconversion dynamics and for providing relevant epidemiological data during the mid-long term of the disease course rather than at early stages. The cumulative seroconversion showed that Ab, IgM and IgG reached 100% at 15, 18 and 20 days post-exposure or 16, 21 and 29 days after onset of symptoms, respectively. Since the quarantine period is established at 14 days, Bin Lou *et al.* [10] suggest that serology tests could be performed before and after de-isolation to monitor antibodies and reduce the risk of spread.

Nevertheless, the data presented by Bin Lou *et al.* [10] are representative of hospitalised patients and include not levels of antibodies but the cumulative seroconversion dynamics. Yong *et al.* [12] reported three clusters of COVID-19 identified in Singapore by active case-finding and confirmed by RT-PCR: a member of church A met a member of church B at a family gathering and SARS-CoV2 was spread by community transmission. This study suggested that serological testing can play a crucial role in identifying convalescent cases or people with milder disease who might have been missed by other surveillance methods. However, there is a need for more extensive studies in non-hospitalised patients. From the information provided up to now it remains unclear whether a negative serological test (IgG) reflects a lack of active immune response or is a false-negative.

High-sensitivity serology assays may be useful for the rapid identification of a large number of infected patients and asymptomatic carriers, and for preventing virus transmission and ensuring timely treatment of patients [13]. However, in a study quantifying antibodies against the new coronavirus by luminex in health workers, García-Basteiro *et al.* [14] obtained a higher dynamic range with a specificity of 100% in IgM, IgG and receptor-binding domain and a sensitivity of 97% in both Igs. Interestingly, they reported that asymptomatic patients had lower levels of antibodies than mild-severe cases. In addition, in agreement with Bin Lou *et al.* [10], they found that seroconversion occurred between 2 and 3 weeks after symptom onset.

Serology testing is a useful tool which may have several more applications in the future. Serology tests can be useful for complementing RNA tests, for the rapid identification of cases and for recommending quarantine or defining clusters. It is also a good method for containing and identifying the route of transmission in order to control the spread of the pandemic and to facilitate epidemiological studies. Serology assay may also be useful to check immune status after vaccination. Finally, serology tests can identify plasma donors for therapeutic approaches involving plasmapheresis. Their usefulness in asymptomatic and mild patients remains unclear, because several studies report that these patients present the lowest levels of antibodies. Further studies are now required to determine the dynamics of antibody levels in severe COVID-19 presentation, its complications, and its associated mortality. Finally, there is still a need to establish the levels of antibodies that confer protection against reinfection, and also how long this protection may last.

Conflict of interest: None declared.

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