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# Serology Testing for SARS-CoV-2: Benefits and Challenges

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## Editorial

As COVID-19 was declared as a pandemic by the World Health Organization (WHO) in March 2020, it is an emerging need to discuss different aspects of this pandemic. In any pandemic, valid and rapid laboratory diagnostic tests are critically important for early diagnosis, which will increase the rate of successful treatment and more importantly prevent the spread of the disease.

The reverse transcription-polymerase chain reaction (RT-PCR) and serologic testing are the two common diagnostic laboratory tests that can be used for infectious diseases such as COVID-19 infection. The genetic information of the SARS-CoV-2 virus has been known soon after the outbreak of the COVID-19, therefore the RT-PCR kit was immediately developed and validated. The RT-PCR kit is an approved diagnostic test and is clinically available for COVID-19 diagnosis. It also has Food and Drug administration (FDA) approval for at-home- sample collection. The sample collection is the only challenge for this test, which may cause a high rate of false-negative results.

Designing and developing serological tests for SARS-CoV-2 has also begun immediately after the first reports of COVID-19. The IgM and IgG kits have been developed based on the knowledge of the SARS-CoV-2 antigens. However, there are several technical challenges in producing these kits. Before a serology kit is approved for clinical use, it needs to go through a long procedure from designing and development to feasibility and validation, which takes place in licensed laboratories and commercial manufacturers. Then the preliminary evaluation, verification, maintenance, and launch will be done in clinical laboratories. If the test successfully passes all the steps and then the authorized organizations approve the documented data, the kit will be available for the clinical uses. However, there are several unanswered questions for the SARS-CoV-2 serological tests:

1. When does the seroconversion for SARS-CoV-2 occur? There are different reports for the seroconversion upon SARS-CoV-2 infection, which varied based on gender, age, the severity of the disease, and the underlying medical conditions (1,2). However, what is certain is that the chance to detect the IgG in the first two weeks of the onset of symptoms is low. Some reports showed the IgG seroconversion may even happen before IgM seroconversion (1).
2. Do all the patients produce antibodies? There are reports that have confirmed some of the COVID-19 patients did not produce antibodies, therefore their serology tests were negative. These individuals are probably at risk for SARS-CoV-2 reinfection. (2). However, these observations could be due to the low detection limit of the serological kits. If this hypothesis is correct the low level of the antibody may not have enough protective effect against the SARS-CoV-2 infection.
3. Are the individuals with the positive serological test at the risk of the reinfection? There is some evidence that showed the serological test of some individuals was positive while their RT-PCR was also positive. In these cases, there is a probability that produced antibodies did not have a Neutralization effect, therefore, the antibodies do not have a protective effect (3).
4. What is the level of the antibody, which can prevent the COVID-19 reinfection? Unfortunately, there has not been enough research done on this matter. Currently, there is not a precise model for the production of the antibodies and their protective effects in SARS-CoV-2 infection (4-6).
5. Does the positive SARS-CoV-2 serological test certainly mean that the individual has been infected? There is evidence that confirmed the cross-reactions between SARS-CoV-2 and other coronaviruses and even between SARS-CoV-2 and other respiratory viruses (7).
6. Can the SARS-CoV-2 serological tests be used as screening tests? Although the positive SARS-CoV-2 serological tests confirm the past infection, it cannot be used for the screening.

Therefore, the SARS-CoV-2 serological tests have some limitations and need to be improved based on the clinical studies to develop laboratory kits with higher validity. But this does not mean that these tests cannot be

used before overcoming all their limitations. Despite all the limitations, the SARS-CoV-2 serological tests could be beneficial at this special pandemic. Hence, FDA issued some of these serological tests, which provided the technical documentation, for the Emergency Use Authorization (EUA).

The other important question is how these tests can be beneficial. Despite all the limitations, SARS-CoV-2 serological tests have several applications:

1. Application in public health: These tests are critically beneficial for detecting the past SARS-CoV-2 infection for health care and essential workers. Given that the chance of the reinfection in short term is low if the IgG is positive and the RT-PCR is negative, these workers can go back to work with a low risk of transmission to others.

Besides, the serological tests can be used to determine the Herd immunity if they are widely tested in the community. Ultimately, it can be helpful to estimate the risk of transmission to the other people in the community (2).

2. Application in treatment: The Convalescent plasma treatment is one of the treatments that was approved by the FDA on April 25th, 2020. In this treatment, the plasma of the individuals who have recovered from COVID-19 will be used for the severe SARS-CoV-2 infection. This treatment was inspired by the successful treatment for the SARS infection in 2003. It is also predicted that this treatment can also be used for preventing the infection for the individual at a high risk of infection and Post-exposure prophylaxis. Therefore, the SARS-CoV-2 serological tests are the key to this treatment.
3. Application in determining the vaccine effectiveness: The serological tests are a vital part of the vaccine development and monitoring its effectiveness (2).
4. Application in designing the return-to-work protocol: Governors use various methods to design the protocol for the return-to-work and to the normal life in the community. But at least in the case of health workers and people in the frontline, the serological test plays a determining role.

Currently, the SARS-CoV-2 serological tests are available in ELISA and Lateral flow immunochromatography methods. In both methods, the antibodies against one of the two main surface proteins of SARS-CoV-2 are detected. In some kits, the S1 subunit of Spike protein is the target for the detection. S1 subunit is specific for each strain of the Coronavirus (8). The main molecular mechanism of the cell injury may be mediated by the S1 subunit. This subunit has high immunogenicity and a high affinity to Angiotensin-converting enzyme 2 (ACE2). Using the S1 subunit to design the SARS-CoV-2 serological tests increase their specificity and sensitivity. In spite that these serological tests were issued by FDA and showed high specificity and sensitivity in preliminary studies, there are not enough documents for FDA approval. The Center for Disease Control (CDC) also developed a SARS-CoV-2 serological kit with a specificity of more than 99% and sensitivity of 96%, but still, this test does not have permission to be used as a diagnostic test (6).

Also, a point-of-care serological test was developed that has lower specificity and sensitivity compared to the ELISA. The WHO does not recommend this test as a diagnostic tool, however, encourages scientists to improve this test for the epidemiological studies. Currently, there is no SARS-CoV-2 serological kit for the in-home-use by patients and all these tests are only available in the clinical laboratories.

In conclusion, laboratory medicine professionals are responsible to inform health care providers about the limitations of the SARS-CoV-2 serological tests, which may cause uncertainty in interpretation. It is recommended that the results obtained from serological tests should be considered together with other clinical information and imaging diagnostic tests.

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