Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Travel Medicine and Infectious Disease 41 (2021) 102046

Contents lists available at ScienceDirect

Travel Medicine and Infectious Disease

journal homepage: www.elsevier.com/locate/tmaid

Correspondence

Serologic aspects of COVID-19: Recommendations for use in the clinical setting

Dear Editor

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) is a new zoonotic coronavirus that was detected in humans in December 2019, in Wuhan, China [1]. SARS-CoV-2 uses its spike (S) protein to bind to the SARS-CoV-1 receptor, ACE2, to enter the cell, a process that is facilitated by the priming of the serine protease TMPRSS2 [2]. Making a diagnosis of COVID-19 infection may require clinical presentation, radiology, and laboratory testing. In COVID-19 patients, SARS-CoV-2 virus was detected in urine, blood, anal, and oropharyngeal swabs, suggesting the virus is invading multi-organs and is not restricted to the respiratory system [3]. Proper sampling technique is essential for obtaining an adequate specimen.

The WHO and United States Centers for Disease Control and Prevention (CDC) continues to recommends Nucleic acid testing (NAAT) as the method of choice for the detection of viral RNA from respiratory tract specimens. Reverse-transcriptase polymerase chain reaction (RT-PCR) is a widely used method. Other testing platforms have been developed, such as a CRISPR–Cas12-based assay, but have not yet been approved for clinical use. Some concerns exist regarding the performance of molecular based assays including false-negative rates, long turn-around-time, complexity, expense, risk of specimen contamination, and technical issues.

The role of antibody testing in the diagnosis of acute viral respiratory infections is usually restricted to epidemiological studies as seroconversion may take up to two weeks to develop in all patients. Rapid diagnosis is essential for the timely management of COVID-19, and for that research groups and industry are developing molecular-based and protein-detection (antigen/antibody) assays, including point-of-care (POC) rapid diagnostic tests (RDTs).

Several assay methods, both in-house and commercial, have been developed to detect antibodies against SARS-CoV-2, including enzyme-linked immunosorbent assay (ELISA), magnetic chemiluminescence enzyme immunoassay (MCLIA), colloidal gold-based immunochromatographic (ICG) strip assay, chemiluminescence enzyme immunoassay (CLIA), immunofluorescence assay (IFA), Western blotting, and lateral flow immunoassay (LFIA).

Serologic analyses might have a role in diagnosing COVID-19 in symptomatic patients who test negative by RT-PCR assays. In surveillance studies of COVID-19, Long et al. observed that 4.3% (7/164) of close contacts of infected patients testing positive for IgG and/or IgM antibodies but were negative by RT-PCR [4].

The timing of seroconversion differs in the studies depending on reference to the onset of symptoms or exposure to the virus ranging between 5 to 11 days post exposure. Long et al. reported a median of 13 days post onset for both IgG and IgM; and all patients who could be followed serologically achieved seroconversion by day 20 after onset of symptoms [4]. Seroconversion occurs in three forms: IgM seroconversion followed by IgG, IgG seroconversion followed by IgM, and synchronous conversion (IgM and IgG).

Understanding the value of serologic testing for COVID-19 is inextricably linked to the antigenic determinants of the virus. Given that the SARS-CoV-2 S protein shares moderate sequence homology with S proteins of other CoVs (compared the N protein), this would theoretically render it a better target for antibody detection. Indeed, based on neutralization studies anti-S protein antibodies correlated with neutralization assay. Using the receptor binding domain (RBD) of SARS-CoV-2 as a source of antigen for serologic testing, combined with molecular analyses, an enhanced sensitivity might be achieved compared with nucleic acid testing alone.

Kohmer et al. evaluated sensitivity and specificity of six commercially available, four high-throughput immunoassays and two manual assays, using different recombinant SARS-CoV-2 antigens [5]. Their results clearly favored assays that utilize both S and N proteins which gave the highest sensitivity (89%) compared to S or N proteins alone (67–78%). All assays demonstrated high specificity (97–100%).

The choice of assay will also be relevant regarding testing for a monoclonal, oligoclonal or polyclonal response to the virus. As there is the possibility of virus mutation, a polyclonal response might be the desired outcome, and thus multiplex serologic assays would need to be developed for determining multiple antibody specificities.

Laboratories must make sure that assay used have received certification for in vitro diagnostic use (e.g, CE, FDA). Sensitivity and specificity of the assays is influenced by manufacturing techniques, choice of antigen(s), timing of patient specimens and quality control procedures. The utility of the assays regarding assessment of immune status or efficacy of future vaccines will depend on whether antibodies can neutralize the virus *in vivo*.

Ong et al. (2020) tested six different rapid assays for the detection of SARS-COV2 antibodies and found them to have very low sensitivity (10–55%), the kit with highest sensitivity was further tested in 228 confirmed COVID19 positive cases. Overall, test sensitivity was 43% and specificity of 98% [6]. Sensitivity was increased when tested in patients with at least one week of symptoms or with high CRP. This study suggests that rapid tests are of very low-test sensitivity, negative results cannot exclude infection thus rapid assays are not useful as diagnostic systems to replace molecular testing.

To summarize, there is a definite role for antibody testing in SARS-CoV-2 infection. We need better understanding of the available commercial assays, in terms of sensitivity and specificity and limitations. Table 1 provides recommendations based on the current knowledge from available studies. IgA specific antibodies appear to correlate with disease severity and persist longer than IgM. We recommend RT-PCR testing, and in symptomatic patients and their contacts with negative RT-PCR results, serum IgA, IgM and IgG, with assays that use S and N

https://doi.org/10.1016/j.tmaid.2021.102046
Received 9 August 2020; Received in revised form 16 March 2021; Accepted 26 March 2021
Available online 31 March 2021

Table 1
Recommendations.

-A disclaimer should accompany serology results that contain:
○Sensitivity and specificity of the test
○Molecular testing is the gold standard for diagnosis
○Positive IgA and/or IgM suggest recent infection with SARS-CoV-2
○Increasing IgG titers suggest recent infection
○ Positive SARS-COV-2 serology does not mean immunity to infection/reinfection
-Sensitivity of automated immunoassays is higher than ELISA based assays and rapid tests.
-IgA is a better marker for recent infection, as it stays much longer than specific antibodies, after recent infection.
-In symptomatic cases who are negative by RT-PCR, serology can be used as supplementary testing but not replacement to the RT-PCR assays.
-Serology assays would be useful tools to study the epidemiology of COVID-19 in the society.
- Assays that utilize both S and N proteins are recommended as they give higher test sensitivity.

antigens.

Financial resources

None.

Declaration of competing interest

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

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