

# Antibody in SARS-CoV-2 Infection: Helpful in Combating COVID-19?

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## ABSTRACT

Coronavirus disease 2019 (COVID-19) is a fast-moving pandemic affecting almost the whole of the world. The disease is rapidly rising with a sharply increasing curve. Since this is a novel virus and its properties are not well understood, investigating the pathophysiology, diagnostic values, and immune response of the body is the need of the hour today. The clinical practice needs to be put in the right direction while following the right laboratory and management strategies. Analysis by molecular diagnostic tests and immunodiagnostic tests are complementary to each other in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The role of antibody estimation in COVID-19 infection needs to be explored so that it can be used in understanding the seroprevalence, surveillance, and containment policies. Its utility in ascertaining the asymptomatic patients and susceptible individuals cannot be denied. It is yet to be confirmed that antibody response confers immunity to SARS-CoV-2. The methodology of estimation of antibodies is also an important aspect as sensitivity and specificity play an important role.

**Keywords:** Antibody, Coronavirus disease 2019, Immunity, Seroprevalence, Severe acute respiratory syndrome coronavirus 2.

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## INTRODUCTION

The coronavirus disease 2019 (COVID-19) disease has become a worldwide pandemic. It has affected 37.6 million confirmed cases worldwide, including 1.08 million deaths, as reported to WHO and affected 7.12 million in India as of October 12, 2020. Its first case among humans was reported in December 2019 in Wuhan China<sup>1</sup> and is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease COVID-19 is characterized by high infectivity is still growing at an alarming rate, the diagnosis and management of which is a challenge for governments all over the world. Molecular testing for the diagnosis of COVID-19 has been the main focus in the past few months. To move further now to “flatten the COVID-19 curve”, we need large-scale testing in the community to identify the extent of infection and immunity to inform the containment strategy. Definite COVID-19 diagnosis entails SARS-CoV-2 detection by nucleic acid amplification technology (NAAT).<sup>2-4</sup> But instead of estimating the virus directly, we can identify the presence of antibodies in case the body's immune system has encountered the virus. These types of tests have important public health applications in the current coronavirus disease (COVID-19) response.

## Overview of SARS-CoV-2

Severe acute respiratory syndrome coronavirus 2 is an enveloped, single-stranded RNA virus of the family Coronaviridae, genus Betacoronaviruses. All coronaviruses share similarities in the organization and expression of their genome with a size of ~30 kb that encodes for multiple structural proteins comprising 4 structural proteins, such as, the spike (S), the envelope (E), the membrane (M), and the nucleocapsid (N), as well as 16 non-structural proteins.<sup>5</sup> They cause disease with symptoms ranging from those of a mild common cold to more severe ones, such as, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19. Other coronaviruses are known to infect humans include 229E, NL63, OC43, and HKU1 are known to be ubiquitous and present as cold or flu-like symptoms.<sup>6,7</sup>

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Severe acute respiratory syndrome coronavirus 2 is transmitted person-to-person primarily via respiratory droplets, but also indirect transmission through contaminated surfaces is possible.<sup>8-10</sup> Severe acute respiratory syndrome coronavirus 2 can be isolated from respiratory samples obtained via naso/oropharyngeal swabs or from sputum. The virus accesses host cells via the angiotensin-converting enzyme 2 (ACE2), which is the most abundant in the lungs.<sup>11,12</sup> The interval during which an individual with COVID-19 is infectious has not yet been clearly established. The incubation period for COVID-19 is thought to range from 2 to 14 days following exposure, with most cases showing symptoms approximately 4 to 5 days after exposure.<sup>1,13,14</sup> Those infected may exhibit symptoms including fever, cough, fatigue, sputum production, loss of smell, and shortness of breath.<sup>15,16</sup>

## Immune Response in COVID-19

Antibodies are blood proteins produced by the immune system to fight foreign invaders like viruses and may help to ward off future attacks by those same invaders. Serum immunoglobulin (Ig)G, IgM, and IgA responses to SARS-CoV have been reported in patients after primary SARS infection.<sup>17</sup> Like infections with

other pathogens, SARS-CoV-2 infection elicits the development of IgM and IgG antibodies, which are the most useful for assessing antibody response because little is known about IgA response in the blood. Total antibodies are the levels of the most sensitive and earliest serological markers of which begin to increase from the second week of symptom onset.<sup>18</sup> In addition, the development of neutralizing antibodies can also be assessed. Neutralizing antibodies inhibit viral replication *in vitro*, and as with many infectious diseases, their presence correlates with immunity to future infection, at least temporarily. These IgGs reached a peak in serum during the convalescent phase and diminished after recovery.<sup>19</sup> Neutralizing IgGs have been reported in SARS-CoV-2 infection leading to the neutralization of the SARS-CoV-2.<sup>20</sup>

### Kinetics of COVID Antibody

Although IgM and IgG are positive even as early as the fourth day after symptom onset, levels increase moderately in the second and third week of illness.<sup>21</sup> Other studies have reported seroconversion as early as within 5 days after symptom onset for IgM<sup>22</sup> and within 5–7 days for IgG.<sup>22,23</sup> Maximum seroconversion occurs at 2 to 3 weeks for IgM,<sup>22–26</sup> at 3 to 6 weeks for IgG,<sup>22–24,27</sup> and at 2 weeks for total antibodies.<sup>25,28</sup> Whereas IgM seems to vanish around week 6 to 7,<sup>26,29</sup> high IgG seropositivity is seen at that time.<sup>22,26,29</sup> Levels and chronological order of IgM and IgG antibody appearance are highly variable,<sup>23–25,30</sup> supporting the detection of both antibodies simultaneously as antibodies in some persons can be detected within the first week of illness onset. Severe acute respiratory syndrome coronavirus 2 infections are somewhat unusual because IgM and IgG antibodies arise nearly simultaneously in serum within 2 to 3 weeks after illness onset. Thus, the detection of IgM without IgG is uncommon. How long IgM and IgG antibodies remain detectable following infection is not known (Fig. 1).

### SARS-CoV-2 Testing: Objectivity of Laboratory Tests Available

There are two ways to detect the presence of a virus, directly or indirectly, i.e., current infection or previous infection. Detecting viral RNA by reverse transcriptase polymerase chain reaction (RT-PCR) technique, indicating active viral infection in the body, is being used to diagnose cases of COVID-19 and is an essential part of contact tracing and testing. On the contrary, antibody tests or serological assays are time-tested methods to find out the presence of the virus

in the body indirectly. Nucleic acid amplification technology and antigen tests help diagnose COVID-19, whereas antibody testing helps to identify individuals exposed to the virus and determine the prevalence of infection and immunity in a population.

Antibody testing is gaining impetus now and is now broadly available. It can play an important role in identifying groups at higher risk for infection. Unlike viral direct detection methods, such as, nucleic acid amplification or antigen detection tests that can detect acutely infected persons, antibody tests help to determine:

- Whether the individual being tested was ever infected — even if that person never showed symptoms (target the asymptomatic population).
- Waning or past SARS-CoV-2 virus infection indirectly, by measuring the host humoral immune response to the virus.
- The proportion of a population previously infected with SARS-CoV-2 and provide information about populations that may be immune and potentially protected.
- Demographic and geographic patterns of serological test results can help in determining the communities who have experienced a higher infection rate and therefore may have higher rates of herd immunity.
- Serological test results may assist to locate potentially infected persons and determine potential donors of blood for convalescent plasma as a possible treatment for those who are seriously ill from COVID-19.
- Serological methods have been developed and will have important public health and clinical uses to monitor and respond to the COVID-19 pandemic and thus might help to decide on the application, enforcement, or relaxation of containment measures.<sup>31</sup>

At this point of peak of worldwide pandemic antibody testing is the right tool to understand the seroprevalence, extent of virus spread in households, communities, and specific settings, and the proportion of the population still susceptible to infection. In an individual, they help determine previous exposure and potential immunity. This may help already immune healthcare workers (HCW) and other workforce to return to work. Can serology help identify donors for convalescent plasma therapy and non-immune individuals who would benefit from vaccine administration? This question needs to be answered in the coming days.

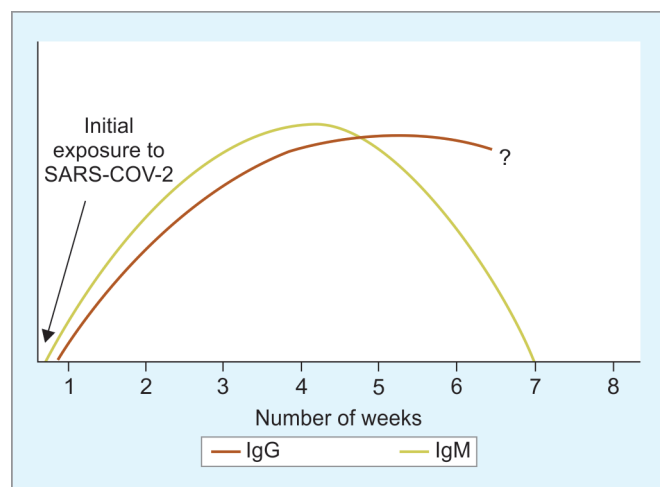


Fig. 1: Kinetics of COVID antibody

### Antibodies vs Molecular Testing

Epidemiological studies are much needed in the times of the corona pandemic to choose measures for public health and containment. Along with the exploration of serial viral load, reliable data are the need of the hour for knowing the profile of serum antibody responses to guide antiviral treatment, infection control, epidemiological measures, and vaccination.

If we talk of the robust underlying technology for NAAT which has excellent specificity, its outcome directly depends on the viral load acquired during sampling. The sampling method, the time point of infection, individual patient, patient's position, as well as sample preparation time may lead to variations in results. Subsequently, a non-negligible proportion of infected individuals by screenings may be missed<sup>24,32,33</sup> which may lead to continuous viral spread. Moreover, the method is costly and needs high expertise to do. It directly detects SARS-CoV-2 RNA in nasopharyngeal or oropharyngeal swab or bronchoalveolar fluid,

etc. The beneficiary in this is the individual so that transmission can be prevented.<sup>34</sup>

Serological methods detect and/or measure the amount of antibodies to SARS-CoV-2. Detection of the immune response can be by a qualitative method that would detect antibody or a quantitative method that would allow you to calculate the amount of antibodies present in the sample. This can be useful to monitor immune status over time, as is done for other infectious diseases. The beneficiary in this may be HCW or for public health so that susceptible individuals and individuals with neutralizing antibodies can be identified for surveillance.<sup>34</sup>

### Antibody Testing

There are three major categories of serological test methods available or in development for SARS-CoV-2: namely, rapid test immunoassays and virus-neutralizing tests.<sup>35,36</sup> Of these, laboratory-based immunoassays are best in terms of reliability of methodology, shorter turn-around time means giving results very fast, easy sampling method (blood), and better specificity and sensitivity. Blood samples are easy to collect and are routinely handled and processed in laboratories. Coronavirus disease 2019 assay would be another serology test on the immunoassay analyzers that routinely perform various serology tests in laboratories. Also, trained staff for operating the analyzers is already available.

### Targets for SARS-CoV-2 Antibody Diagnosis

For COVID-19, a specific protein from the SARS-CoV-2 virus is used as the target antigen to detect any antibodies in patient serum that can recognize the specific viral protein. The two major antigenic targets of the SARS-CoV-2 virus against which antibodies are detected are spike glycoprotein (S) and nucleocapsid phosphoprotein (N). The protein target determines cross-reactivity and specificity because N is more conserved across coronaviruses than S.<sup>37</sup>

Currently available tests target antibodies to 1 of 2 viral surface proteins; nucleoprotein (N protein) or spike protein (S protein).<sup>38</sup> Several assays use the S1 subunit of the spike protein, which incorporates the binding domain for ACE2 receptor because it is highly immunogenic. Antibodies that bind to the spike protein are likely to be neutralizing antibodies because they would prevent the virus from invading human cells. In contrast, non-neutralizing antibodies also bind to SARS-CoV-2 but do not prevent it from entering cells.

### Serology and HCW

Healthcare workers who are a backbone of the health services are at high risk to acquire SARS-CoV-2 infection from patients or other fellow HCW during this period of the active pandemic of COVID-19. Nevertheless, they too can be contagious to highly vulnerable patients especially non-COVID patients visiting the hospital seeking healthcare. Testing antibodies to SARS-CoV-2 can give a clearer picture as to the status of immunity at the point of testing. Antibody development in humans correlates with a marked decrease in viral load in the respiratory tract.<sup>39</sup> It cannot be the basis for the diagnosis of COVID-19 infection but instead detect evidence of viral infection at some time point in the past. It suggests that the presence of antibodies may decrease a person's infectiousness and offer some level of protection from reinfection. However, definitive data are lacking, and it remains uncertain whether individuals with antibodies (neutralizing or total) are protected against reinfection

with SARS-CoV-2, and if so, what concentration of antibodies is needed to confer protection.

### Recent Development in the Field of COVID-19 Testing

A recent study in *Nature Medicine* brings much-needed clarity, along with renewed enthusiasm, to efforts to develop and implement widescale antibody testing for SARS-CoV-2.<sup>40</sup> Information influencing serological recommendations is rapidly evolving on daily basis, particularly evidence of whether positive serological tests indicate protective immunity or decreased transmissibility among those recently ill. Therefore, the specific aim at this stage is to test with accuracy and capacity to meet the needs of such large-scale testing in both government and private sectors. Standardized immunodiagnostic serology assays would fulfill these demands. High specificity is a compelling need for antibody tests for COVID-19 so as not to incorrectly designate a susceptible individual as immune to COVID-19.

### DISCUSSION

Nearly all immune-competent individuals will develop an immune response following SARS-CoV-2 infection. Nevertheless, serological assays do not replace molecular methods, such as, RT-PCR as the primary tool for the accurate diagnosis of acute or active infection despite their importance in clinical laboratory and practice. Antibody testing is the right tool to understand seroprevalence, the extent of virus spread in households, communities, and specific settings, and the proportion of the population still susceptible to infection. It generates crucial intelligence on the rate of asymptomatic infections and the mortality attributable to COVID-19 in the population. As we move ahead on the epidemic curve and as more information becomes available, the determination of herd immunity through serosurveillance is vital in the present scenario. Serological testing will support the continued efforts of patient contact tracing and donors for convalescent plasma therapy.

Serological assays for SARS-CoV-2 now have Emergency Use Authorization (EUA) by the U.S. Food and Drug Administration (FDA), which has independently reviewed their performance. Currently, there is no identified advantage of assays whether they test for IgG, IgM, and IgG, or total antibody. It is important to minimize false-positive test results by choosing an assay with high specificity and by testing populations and individuals with an elevated likelihood of previous exposure to SARS-CoV-2. For serology methods to be used effectively for both population-level studies and individual use, scientists need more data on the performance characteristics of these tests and the human immune response to SARS-CoV-2 infection.

Specifically, antibodies may not develop until 1 to 2 weeks post-symptom onset which means serological tests may not detect current SARS-CoV-2 infections and therefore cannot be used as a tool to diagnose current COVID-19.<sup>35,41</sup> It cannot replace the gold standard test, i.e., RT-PCR but can be used as a surrogate tool along with other factors like clinical history, symptoms, time of presentation of symptoms, and previous RT-PCR report if any to reaching on the diagnosis of COVID-19 in absence of RT-PCR report or a negative RT-PCR report. To understand seroprevalence, i.e., the spread of disease and identifying asymptomatic carriers the Indian Council of Medical Research (ICMR) has also supported the use of antibody tests by enzyme linked immuno sorbent assay (ELISA) and chemiluminescence immunoassay (CLIA) for epidemiological studies and surveillance.<sup>42</sup>



## CONCLUSION

We conclude and propose that a positive report of antibodies present in a person signifies exposure to SARS-CoV-2 and subsequent development of immunity in person. On the contrary, a negative report cannot be simply interpreted as non-exposure to the SARS-CoV-2 virus. It should be deduced in conjunction with other factors like RT-PCR reports and signs and symptoms present. In case of a negative antibody test with a history of symptoms in past, repeat testing after a period of 7 to 10 days may be beneficial. Detection of antibodies after this period is suggestive of decreased infectiousness and that some degree of immunity from future infection has developed. However, the absence of detectable levels of antibodies even after 2 to 3 weeks after the diagnostically proven infection by RT-PCR technique also has to be addressed. Possibility of nevertheless, additional data are needed to validate the facts and modify public health recommendations based on serological test results. Antibody testing strategies are needed to understanding the epidemiology of COVID-19 as well as exploit the results for faster returning to normalcy.

Determining the herd immunity and identifying the potentially immune population is now the main target before us. Also, recurrence of COVID-19 illness appears to be very uncommon, suggesting that the presence of antibodies could confer at least short-term immunity to infection with SARS-CoV-2.

Is antibody response in terms of antibody levels in SARS-CoV-2 infection depends upon the severity of disease and the viral load? And are IgG and IgM antibodies present in asymptomatic individuals who tested positive for SARS-CoV-2; these findings need to be confirmed in larger studies. Most importantly, antibody titers that can protect against reinfection as well as intransience of the antibodies induced by SARS-CoV-2 are yet unknown.

Despite appearing to be a promising investigative tool, the main lacuna of antibody testing for COVID-19 is the paucity of literature on seroconversion of antibodies and pathogenesis of the development of COVID-19 worldwide as it is a novel disease. It has become a necessity of this pandemic time as it can be used as a testing tool for a large population especially as a screening measure with good specificity and sensitivity. It is a cost-effective, convenient, fast, and easily available test modality in comparison to viral detection methodology RT-PCR.

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