ABSTRACT

COVID-19 is a pandemic, highly contagious infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The World Health Organization has declared the ongoing outbreak a global public health emergency. This disease has spread rapidly and affected millions of people worldwide. Currently, there are no specific clinical signs or symptoms of SARS that can be used to differentiate it from other causes of community- or hospital-acquired viral pneumonia. Accurate diagnosis of cases holds the key to managing any pandemic through identification, isolation, and treatment of patients while defining the epidemiology of the pathogen. Because an increasing number of asymptomatic individuals must be tested for COVID-19, a safe and efficient screening system is required. The diagnosis of suspected cases is presently confirmed by nucleic acid assays with real-time PCR using respiratory samples. On the other side, serological tests are comparatively easier to perform, but their utility may be limited by their ease of performance and the fact that antibodies appear later in the disease course. This review is aimed at summarizing the currently available information on different methods used for screening and diagnosing COVID-19 infections.

INTRODUCTION

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) is a novel virus that caused the first major pandemic disease in the family Coronaviridae. Many coronavirus infections in the past 20 years were not regarded as highly pathogenic to human beings until the outbreaks of SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) (Zhong et al., 2003; Drosten et al., 2003; Fouchier et al., 2003). At the end of 2019, the China Office of the WHO (World Health Organization) reported a cluster of pneumonia cases in Wuhan City, China, and the causative pathogen was identified as Novel Coronavirus (nCoV 2019); the WHO named this disease COVID-19 (Wu et al., 2020; Zhou et al., 2020; Wang et al., 2020).

COVID-19 is an extremely infectious disease. Coronaviruses are enveloped RNA viruses belonging to the Coronaviridae family and the order Nidovirales, which contain approximately 27–32 kilobytes of positive-sense single-stranded RNA. This subfamily consists of four genera: Alpha coronavirus, Beta coronavirus, Gamma coronavirus, and Delta coronavirus, on the basis of their phylogenetic relationships and genomic structures. These subfamilies are broadly distributed and cause infections in humans and other mammals. Alpha and beta coronaviruses infect only mammals. Gamma and delta coronaviruses infect birds, but some of them can also infect mammals. Although the source of the beta coronavirus 2019 SARS-CoV-2 is unknown, initial cases have been linked to the South Hunan seafood market. The infected people may have severe symptoms in the respiratory and digestive organs. Like other coronaviruses, the SARS-CoV-2 has at least six open reading frames (ORFs) and many other accessory genes. There are two open reading frames (ORFs) at the 5’ terminal two-thirds of the genome, ORF1a and ORF2. These ORF encode two polyproteins, namely pp1a and pp1ab, which are further cleaved into 11 and 16 proteins, respectively. Nucleocapsid (N), membrane protein (M), envelope protein (E), and spike (S) are among the structural proteins found at 3’ terminals. In the case of COVID-19, the spike protein appears to be the primary protein interacting with host cells. Hence, the spike protein is likely the protein to which antibodies are raised, but this is not clear at this time. These viruses also contain some accessory proteins, which aid in virus replication. The S gene aids SARS-CoV-2 in host specificity and receptor binding, and some virion may also contain hemagglutinin esterase (HE) protein. (Cui, J., et al., 2019; Huang C. et al., 2020 and Miller et al., 2016)

Clinical manifestations of COVID-19 infection include fever and cough as primary clinical manifestations, as well as shortness of breath and myalgia. Some patients have serious complications such as acute respiratory distress syndrome (ARDS) and cytokine storm, which may lead to death. (Malik et al., 2020). It has the capacity for human-to-human transmission. The lack of awareness in hospital infection control and international air travel facilitated the rapid global dissemination of this agent. The collection of appropriate specimens is very crucial for the detection of most of the infected cases of COVID-19. Nasopharyngeal swabs are typically collected, but we may miss the detection in some cases; therefore, lower respiratory tract specimens such as sputum and bronchoalveolar lavage (BAL) may be an alternative choice. Therefore, there is an urgent need to have an...
accurate, rapid, readily available, and reliable diagnostic test for SARS-CoV-2 infection. Various immunological, nucleic acid, and amplification diagnostic tests have been developed and are widely available to date. Various integrated point-of-care molecular devices are currently under development, and some are available to provide accurate and fast diagnostic services for SARS-CoV-2 infections. (Löflhelholz et al., 2020).

In view of the present crisis of the COVID-19 pandemic, fast and reliable testing strategies are imperative. In this review, we attempt to learn more about the current diagnostic methods for SARS and Cov-2 infections. The different methods used for screening and sample collection will also be discussed.

Screening and Specimen collection of patients with COVID-19 pneumonia.

Accurate diagnoses of cases hold the key to managing any pandemic through identification, isolation, and treatment of patients while defining the epidemiology of the pathogen. Because an increasing number of asymptomatic symptomatic individuals must be tested for COVID-19, a safe and efficient screening system is required. Presently, no specific clinical signs or symptoms of COVID-19 can be used to differentiate it from other causes of community- or hospital-acquired pneumonia. In order to decide if a patient should be tested, WHO published case definitions for surveillance but encouraged countries to adapt these depending on their local epidemiological situation and other factors. (WHO 2020). A suspect case is defined as (i) a patient with acute respiratory illness (fever and at least one sign or symptom of respiratory disease, such as cough or shortness of breath) and a history of travel to or residence in a location reporting community transmission of COVID-19 disease within 14 days of the onset of symptoms (ii) a patient with severe acute respiratory illness (fever and at least one sign or symptom of respiratory disease, e.g., cough, shortness of breath, and requiring hospitalization) and in the absence of an alternative diagnosis that fully explains the clinical presentation. As per the WHO guidelines, a “probable case” is a suspect case for whom testing for the SARS-CoV-2 is inconclusive or for whom testing could not be performed for any reason. WHO further defines a “contact” as a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case: (i) face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 min. (ii) direct physical contact with a probable or confirmed case. (iii) direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment. For confirmed asymptomatic cases, the period of contact is measured as the 2 days before the intubation procedure or before and after the 14 days after the date on which the sample was taken, which led to confirmation. (Venter, M., & Richter, 2020).

Specific and real-time diagnostic tests should be performed not only for the identification of potential cases but also for contacts who need to be quarantined and guided on epidemiological questions around the infection. Selection of the relevant specimen and knowledge of the incubation period, viremia, and shedding period are important criteria in diagnosing individual cases and defining transmissibility to inform the extent of isolation periods for patients. Nucleic acid testing (reverse transcriptase PCR) is recommended for the diagnosis of acute cases. Serological assays have an important role in answering epidemiological questions, including determining the exposure rate and accessing community spreads, but are not relevant for accurate diagnoses of acute cases. Only laboratory confirmation can be used to make an etiological diagnosis and differentiate atypical pneumonia from other causes. Proper collection of samples is the most important step in the laboratory diagnosis of infectious diseases. A specimen that is not collected correctly may lead to a negative result.

As per the Center for Disease Control and Prevention (CDC) recommendations, the upper respiratory specimen should be collected for RT-PCR-based testing of COVID-19, and especially the nasopharyngeal exudate is the preferred choice (CDC, 2020). Within a week from the onset of symptoms, patients with COVID-19 usually possess high viral loads in their upper and lower respiratory tracts. (Zhou et al., 2020). A nasopharyngeal swab and/or an oropharyngeal swab are often recommended for screening or diagnosing early infections. Nasopharyngeal swabs usually reach the correct area to be tested in the nasal cavity that has yielded the highest viral loads for the diagnosis of COVID-19 (Li et al., 2020; Yu et al., 2020). A recent study revealed that samples of bronchoalveolar lavage fluid yielded the highest SARS-CoV-2 RNA rate, although this study did not compare or evaluate results from nasopharyngeal swabs (Wang et al., 2020). Patients who present with severe pneumonia and acute respiratory distress syndrome may require emergent intubation as well as respiratory isolation in a negative-pressure room. A nasopharyngeal swab or bronchoalveolar lavage (BAL) has been used for collecting lower respiratory tract specimens as they have yielded the highest viral loads for the diagnosis of COVID-19 (Li et al., 2020; Yu et al., 2020).
molecular testing. While collecting specimens, health care professionals should follow WHO infection prevention and control guidelines and wear personal protective equipment (PPE) such as gloves, gowns, eye protection, and N95 masks (WHO 2020). All specimens collected for laboratory investigations are regarded as potentially infectious.

Testing of specimens from multiple sites (e.g., upper and lower respiratory tracts) may improve the sensitivity of the RT-PCR and reduce false-negative test results, especially during the second week of illness. For asymptomatic patients and patients with mild symptoms, the collection of both nasopharyngeal swabs and oropharyngeal swabs is recommended; these should be placed together in the same viral transport medium (VTM) to increase the sensitivity (WHO 2020, CDC 2020). Additional clinical specimens can be collected as the COVID-19 virus has been detected in blood, urine, and stool. In the case of deceased patients, the collection of autopsy material, including lung tissue, is also considered. (Kaijin et al., 2020).

As serological assays become available retrospectively in recovered patients, paired serum (acute and convalescent) can be useful in defining cases (Zhang et al., 2020; ShiX et al., 2005; Ding Y. et al., 2004). Several studies reported the detection of higher viral loads in older patients. However, the viral load did not positively correlate with disease severity (Tsang et al., 2020; Pung et al., 2020; Wang et al., 2020). Since SARS-CoV-2 and most other respiratory viruses are RNA-based, care should be taken to select extraction and inactivation protocols that will not damage RNA. A recent study suggests that heat inactivation at 56 °C for 30 min may result in false negatives for samples with low viral loads (Pan et al., 2020). Specimens for virus detection should reach the laboratory as soon as possible after collection. Correct handling of specimens during transportation is essential. Specimens that can be delivered to the laboratory can be stored and shipped at 2–8 °C. When there is likely to be a delay in specimens reaching the laboratory, the use of viral transport medium (VTM) is strongly recommended in the laboratory biosafety guidance related to the novel coronavirus (2019-nCoV). (Guidance on regulations for the transport of infectious substances, 2019–2020) The primary container should be sealed with a screw cap. The container should be made of plastic that has a low risk of breakage. Patient information should be recorded on the specimen container using two or more identifiers (e.g., name, patient number), along with the necessary information for testing requests.

The outer surface of the primary container should be disinfected using appropriate disinfectants, such as 70% ethanol. The container should be packed in a zipper bag and placed in a secondary container before transportation. The secondary container should be sealed and shock-resistant, and it should be labelled to indicate that it contains infectious substances. When transporting specimens to a laboratory within the same institution, the specimens should be transported in person; the pneumatic tube system should not be used. A separate route should be used for transportation. The personnel transporting the specimen should be trained in spill decontamination procedures in case of specimen leakage. Specimens may be frozen to -20°C or, ideally, -70°C and shipped on dry ice if further delays are expected. It is important to avoid repeated freezing and thawing of specimens (Kwon et al., 2020; Korea Center for Disease Control and Prevention, 2020; CDC, 2020). WHO documents a summary of the optimum sample collection procedures and storage, which are similar to those for influenza. The specimen collection and storage temperature protocol to investigate emerging acute respiratory diseases is summarized in Table 1.

### Table 1: The specimen collection and storage protocol to investigate non-seasonal influenza and other emerging acute respiratory diseases

<table>
<thead>
<tr>
<th>Specimen types</th>
<th>Collection material</th>
<th>Storage temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngeal and oropharyngeal swabs</td>
<td>Dacron or polyester flocked swabs</td>
<td>2-8°C</td>
</tr>
<tr>
<td>Sputum</td>
<td>Sterile container</td>
<td>2-8°C</td>
</tr>
<tr>
<td>Bronchoalveolar lavage</td>
<td>Sterile container</td>
<td>2-8°C</td>
</tr>
<tr>
<td>Nasopharyngeal or nasal aspirates or washes</td>
<td>Sterile container</td>
<td>2-8°C</td>
</tr>
<tr>
<td>Tissue from biopsy or autopsy, including lung tissue</td>
<td>Sterile container with saline or VTM</td>
<td>2-8°C</td>
</tr>
<tr>
<td>Serum</td>
<td>Serum separator tubes</td>
<td>2-8°C</td>
</tr>
<tr>
<td>Whole blood</td>
<td>Collection tube</td>
<td>2-8°C</td>
</tr>
<tr>
<td>Stool</td>
<td>Stool container</td>
<td>2-8°C</td>
</tr>
<tr>
<td>Urine</td>
<td>Urine collection container</td>
<td>2-8°C</td>
</tr>
</tbody>
</table>

### Surveillance and Sampling Strategies

Individual case definition mechanisms (2.1), as mentioned above, help choose whether a patient should be tested or not. However, a pandemic like COVID-19 necessitates robust surveillance systems at local and global levels, which are required to strengthen the effective implementation of control measures. The aim of these surveillance systems is to limit the spread of disease, enable public health authorities to manage the risk, and thereby enable economic and social activity to resume to the extent possible. Surveillance is also necessary to predict the longer-term trends of COVID-19
transmission and the changes ahead (WHO 2020). A “case sample” is considered a subset of individuals from a larger population. Sampling is simply stated as selecting a portion of the infected population that will actually collect evidence from the research area under surveillance. Samples are used to make inferences about populations. (Landreneau, K. J., et al., 2009).

There are two types of sampling methods employed in epidemiological surveillance:

**Probability Sampling**
This includes some form of random selection in choosing the elements. Greater confidence can be placed in the representativeness of probability samples. This type of sampling involves a selection process in which each element in the population has an equal and independent chance of being selected.

- Simple random sampling: in a simple random sample, every member of the population has an equal chance of being selected.
- Stratified random sampling: this method is appropriate when the population has mixed characteristics (like age, demography, etc.) and you want to ensure that every characteristic is proportionally represented in the sample.
- Cluster sampling: cluster sampling also involves dividing the population into subgroups, but each subgroup should have similar characteristics to the whole sample. Instead of sampling individuals from each subgroup, entire subgroups are randomly selected.
- Systematic Sampling: This is similar to simple random sampling, but it is usually slightly easier to conduct. Every member of the population is listed with a number, but instead of randomly generating numbers, individuals are chosen at regular intervals for sampling.

**Non-probability Sampling**
The elements that make up the sample are selected by nonrandom methods. This type of sampling is less likely than probability sampling to produce representative samples. Even though this is true, researchers can and do use non-probability samples. The three main methods are:

- Convenience Sampling: A convenience sample includes the individuals who happen to be most accessible to the researcher.
- Quota sampling is primarily motivated by ease of access. Instead of the researcher choosing participants and directly contacting them, people volunteer themselves (e.g., by responding to a public online survey).
- Purposive Sampling: This type of sampling involves the researcher using their judgement to select a sample that is most useful for the purposes of the research.

Any COVID-19 surveillance system placed should be geographically comprehensive and include all people and communities at risk. Surveillance for vulnerable or high-risk populations should be enhanced. This will require a combination of surveillance systems, including contact tracing, in the entire health care system, at the community level, as well as in closed residential settings and for vulnerable groups. Surveillance at the primary care level is needed to detect cases and clusters in the community. Where possible, testing facilities are made available at primary care clinics. A complementary option is to establish dedicated COVID-19 community testing facilities. Patients with probable and confirmed COVID-19 cases are notified within 24 hours of identification. Fast data reporting and analysis are critical to detecting new cases and clusters. Therefore, only the minimum number of data variables are to be collected (e.g., age, sex, date of illness onset, date of sample taken, test result, location of testing site, etc.). Data reporting to local or national public health authorities is done on a daily basis. Patients with probable or confirmed COVID-19 diagnoses in hospitals are notified within 24 hours of identification. All COVID-19 deaths are reported within 24 hours of the death. The minimum essential data from hospital settings includes: age, sex/ gender, and place of residence; date of onset; date of sample collection; date of admission; laboratory test result; severity on admission: admitted to the intensive care unit (ICU); treated with ventilation, if the case is a health care worker; outcome (discharge or death); etc. Existing sentinel surveillance of influenza-like illness (ILI) or acute respiratory infections (ARI) is useful to monitor trends in community transmission of the COVID-19 virus and to ensure that other priority respiratory diseases are being detected. Integration of COVID-19 with the Global Influenza Surveillance and Response System (GISRS) is described in operational considerations for COVID-19 surveillance using GISRS. Virologic sentinel surveillance of COVID-19 is conducted using clinical specimens obtained through sentinel surveillance of ILI, ARI, and SARI (Severe Acute Respiratory Infection). Integrated epidemiological and virological surveillance will play a significant role in monitoring the spread and evolution of COVID-19 virus, understanding the cocirculation of COVID-19 virus with influenza and other respiratory viruses, and subsequent interpretation of respiratory epidemiological and disease observations in relation to COVID-19, as well as supporting the update of diagnostic tests. Infections in health workers should, at a minimum, be systematically integrated into the national surveillance system. Dedicated enhanced surveillance for some high-risk groups is necessary to ensure the prompt detection of cases and clusters, faster than through primary care or hospital-based surveillance. People who live in closed environments, such as prisons, or residential facilities, such as retirement communities or care homes for persons with disabilities, can be especially vulnerable because they may not be able to seek help themselves. Vulnerable groups may also live in settings where the probability of transmission is higher than in the general population or have health conditions or predisposing factors that increase their risk of severe illness. Enhanced surveillance includes the use of active case finding, such as...
through daily screening of signs and symptoms, including daily temperature monitoring, and daily zero reporting for all individuals in high-risk groups under surveillance. While surveillance systems will typically capture the number of COVID-19 cases, it is also important to collect information on the total number of laboratory tests conducted for the COVID-19 virus. Data on the number of tests conducted for SARS-CoV-2 are collected from all relevant laboratories. Knowing the testing denominator can indicate the level of surveillance activity, and the proportion of positive tests can indicate the intensity of transmission among symptomatic individuals. Presently, reverse transcriptase polymerase chain reaction (RT-PCR) testing (explained in 2.3) is the most common and reliable laboratory diagnostic method. If other diagnostic methods are used, the number of tests conducted and cases confirmed by different laboratory diagnostic methods need to be recorded.

It is widely accepted that a large fraction of COVID-19 cases goes undetected. However, this is subject to significant ascertainment bias because tests are typically ordered only from symptomatic cases, whereas a large proportion of infected people may show little to no symptoms (Mizumoto et al., 2020). Non-symptomatic infections can still shed the SARS-CoV-2 virus and are therefore detectable by RT-PCR-based tests. It is therefore possible to test randomly selected individuals to estimate the true disease prevalence in a population. Recent technical advances have enabled high-throughput PCR, in which multiple samples are pooled into one tube. Combining probes from several individuals and testing them together reduces the total amount of testing needed. This method is known as “pooling” or “group testing.” The main idea is that when samples from several people are mixed together and tested, the test will report negative when everyone is healthy and positive when at least one is positive (Abdalhamid et al., 2020). The other ideas include using ten-fold fewer tests (Verdun et al., 2021) and clearing 20 times the number of people from isolation with the same number of tests (Gollier and Gossner, 2020).

However, their efficiency is highly dependent on the frequency of positive samples, which varies significantly across regions and even within regions as testing criteria and conditions change. Two possible optimized pooling strategies are currently employed for diagnostic SARS-CoV-2 testing on large scales; both address dynamic conditions. In the first, an estimate of the target frequency determines the initial pool size, and any subsequent pools found positive are re- pooled at half size and tested again. The second method is a simpler approach of optimized one-time pooling followed by individual tests on positive pools. These strategies are convenient, and they offer a significant reduction in the number of materials, equipment, and time needed to test large numbers of samples. (Shani et al., 2020). On the other hand, a pool testing strategy could potentially increase worldwide testing capacity many times over, thus boosting a country’s capacity to test mildly to asymptotically affected individuals. This strategy proposes that instead of individually testing patients with low clinical suspicion of SARS-CoV-2 infections, samples are pooled together in what is called a “minipool” and then tested together, running a single RT-PCR for all the unified samples. Preliminary results showed that there is no dilution and no decrease in test sensitivity when minipools of five samples each are used. Since the RT-PCR looks directly at the viral RNA, a negative result in a pool test is reliable. Thus, the infection was discarded in all the patients included in the pooled sample.

**Nucleic Acid Amplification Assay**

SARS-CoV-2 is a single-stranded, positive-sense RNA virus. The availability of sequence data has facilitated the design of primers and probes needed for the development of SARS-CoV-2-specific testing. Routine confirmation of cases of COVID-19 is based on the detection of unique sequences of virus RNA by real-time reverse transcription polymerase chain reaction (RT-PCR), with confirmation by nucleic acid sequencing when necessary. The majority of molecular diagnostic tests have utilized real-time RT-PCR technology targeting different SARS-CoV-2 genomic regions, including the ORF1b or ORF8 regions and the nucleocapsid (N), spike (S) protein, RNA-dependent RNA polymerase (RdRP), or envelope (E) genes. The most widely used method of COVID-19 diagnostics is a reverse transcription quantitative polymerase chain reaction (RT-qPCR) assay to detect the presence of SARS-CoV-2 RNA in patient samples, typically nasopharyngeal swabs. RNA extraction is a major bottleneck in current COVID-19 testing. (Shen et al., 2020; Smyrlaki et al., 2020). Because of its high sensitivity and specificity, polymerase chain reaction (PCR) is regarded as the gold standard test for the molecular diagnosis of viral and bacterial infections. Isothermal nucleic acid amplification, including transcription-mediated amplification and CRISPR-based methodologies, is considered a promising alternative assay due to its fundamental advantage in quick procedure time at constant temperature without thermocycler operations. As such, real-time reverse transcriptase-PCR (RT-PCR) is of great interest today for the detection of SARS-CoV-2 due to its benefits as a specific and simple qualitative assay. Furthermore, real-time RT-PCR has sufficient sensitivity to aid us in early infection diagnosis. Therefore, the “criterion-referenced” real-time RT-PCR assay can be considered as the main method to be applied to detect the causative agent of COVID-19, i.e., SARS-CoV-2 (Carter et al., 2020; Shen et al., 2020; Wan et al., 2016; Noh et al., 2017; etc).

**Reverse Transcription-Polymerase Chain Reaction (RT-PCR)**

In acute respiratory infections, RT-PCR is routinely used to detect causative viruses from respiratory secretions in nucleic acid testing assays. The real-time reverse
transcription (PCR) method is one of the best and most accurate laboratory methods for detecting, tracking, and studying the coronavirus. Real-time RT-PCR is a method by which the presence of specific target genetic material can be detected (Sethuraman et al., 2020). This reaction relies on small DNA sequence primers designed to specifically recognize complementary sequences on the viral RNA genome and the reverse transcriptase to generate a short complementary DNA copy (cDNA) of the viral RNA. In real-time RT-PCR, the amplification of DNA is monitored in real time as the PCR reaction progresses. This is done using a fluorescent dye or a sequence-specific DNA probe labelled with a fluorescent molecule until the viral cDNA can be detected. Coronavirus have a number of molecular targets within their positive-sense, single-stranded RNA genome that can be used for PCR assays (Corman et al., 2020). These include genes encoding structural proteins, including envelope glycoproteins spike (S), envelope (E), transmembrane (M), helicase (Hel), and nucleocapsid (N) (Chan et al., 2020). In addition to the genes that encode structural proteins, there are species-specific accessory genes that are required for viral replication, like RNA-dependent RNA polymerase (RdRp), hemagglutinin esterase (HE), and open reading frames ORF1a and ORF1b (Corman et al., 2020; Lan et al., 2020). The assay includes at least two molecular targets to avoid potential cross-reaction with other endemicle coronaviruses as well as potential genetic drift of SARS-CoV-2. In the United States, the CDC recommends two nucleocapsid protein targets (N1 and N2) (Holshue et al., 2020), while the WHO recommends first-line screening with an E gene assay followed by a confirmatory assay using the RdRp gene (Corman et al., 2020). RT-PCR has traditionally been carried out as a one-step or two-step procedure. One-step real-time RT-PCR uses a single tube containing the necessary primers to run the entire RT-PCR reaction. Two-step real-time RT-PCR involves more than one tube to run the separate reverse transcription and amplification reactions but offers greater flexibility and higher sensitivity than the one-step procedure. (VanGuilder, H. D., et al., 2008; Wong et al., 2005).

Positive test results from a single sample must be confirmed by a repeat test detecting a different region of the SARS-CoV-2 genome on the same sample. If possible, another repeat sample should also be tested to exclude false positive results due to amplicon carryover. Since the viral load in nasopharyngeal aspirate usually peaks on the 10th day after the onset of symptoms, suspected SARS cases must have the tests repeated as the disease evolves to avoid false-negative results. Stool specimens should be sent for testing on a regular basis, as a high percentage of patients develop diarrhoea and shed virus during the second week of illness. Viral load determination of nasopharyngeal specimens or serum upon presentation might have clinical value as it is an important prognostic factor. Any treatment regimen would benefit from long-term monitoring of viral load. (Cheng et al., 2004; Peiris et al., 2003; Chan K. et al., 2004; Chu et al., 2020; etc.). Apart from sensitivity issues, RT-PCR has some other drawbacks, such as possible biological safety hazards that may occur during transport and sample processing, nucleic acid extraction, and the requirement of sophisticated laboratory equipment like biosafety cabinets. Technical expertise, along with sample transportation, which is inevitable, makes the overall process time-consuming. All these drawbacks could make the process less useful in case of a health emergency or global outbreak situation. Moreover, in PCR, we are able to detect not only the target virus, but it can also perform co-detection of several other respiratory viruses, which leads to an increase in false positive or negative results (Cho et al., 2014).

**Isothermal nucleic acid amplification**

Isothermal nucleic acid amplification is an alternative strategy that allows amplification at a constant temperature and eliminates the need for a thermal cycler. Therefore, several methods based on this principle have been developed. Isothermal amplification techniques are conducted at a single temperature and do not need specialized laboratory equipment to provide similar analytical sensitivities to PCR. Isothermal amplification techniques can be multiplexed during the amplification or readout stage. This is done by using polymeric beads encoded with unique optical signatures like organic fluorescent molecules for each gene. Multiplexing increases the amount of information gained from a single test and improves clinical sensitivity and specificity. Loop-Mediated Isothermal Amplification (LAMP) is a relatively new molecular amplification point-of-care technique that is widely used for COVID-19 diagnosis. The technique is based on the synthesis of target DNA at a constant temperature of 60–65°C using a specially designed primer and DNA polymerase that has strand displacement activity instead of heat denaturation as in other PCR techniques. This novel technique can amplify any genomic material with high efficiency and in a shorter amount of time. RT-LAMP has been developed as a rapid and cost-effective testing alternative for SARS-CoV-2. It requires a set of four primers specific for the target gene or region to enhance the sensitivity and combines LAMP with a reverse transcription step to allow for the detection of RNA. Photometry can be used to detect the amplification product by measuring the turbidity caused by magnesim pyrophosphate precipitate in the solution as a byproduct of amplification.

The reaction can be followed in real time either by measuring the turbidity or by fluorescence using intercalating dyes. Since real-time RT-LAMP diagnostic testing requires only heating and visual inspection, its simplicity and sensitivity make it a promising candidate for virus detection. The RT-LAMP test uses reverse transcriptase to convert the viral RNA to cDNA, which
is subsequently amplified by the DNA-dependent DNA polymerase for rapid colorimetric detection with a DNA-binding dye.

LAMP has been shown to be effective at detecting viral RNA in cell lysates at levels of approximately 480 RNA copies without interference, providing an alternative to RT-PCR for rapid and simple detection of SARS-CoV-2 RNA. (Notomi et al., 2000; Thai et al., 2004). Transcription-Mediated Amplification (TMA) is a patented single-tube, isothermal amplification technology modelled after retroviral replication that can be used to amplify specific regions of either RNA or DNA much more efficiently than RT-PCR. It uses a retroviral reverse transcriptase and T7 RNA polymerase and has been used for the detection of nucleic acids from multiple pathogens. The initial steps involve hybridization of the viral RNA target to a specific capture probe and an additional oligonucleotide containing a T7 promoter primer, which are captured onto magnetic microparticles. Then, the captured RNA target hybridized to the T7 promoter primer is reverse transcribed into a complementary cDNA. The RNAc activity of the reverse transcriptase subsequently degrades the target RNA strand from the hybrid RNA cDNA duplex, leaving a single-stranded cDNA, which includes the T7 promoter. An additional primer is used to generate double-stranded DNA, which is subsequently transcribed into RNA amplicons by T7 RNA polymerase. These new RNA amplicons then reenter the TMA process, allowing this exponential amplification to generate billions of RNA amplicons. The detection process involves the use of single-stranded nucleic acid pyrotechnics that hybridize specifically to the RNA amplicon in real time. Each torch is conjugated to a fluorophore and a quencher. When the torch hybridizes with the RNA amplicon, the fluorophore is able to emit a signal upon excitation. (Kacian et al., 1999) Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) represents a family of nucleic acid sequences found in prokaryotic organisms, such as bacteria. These sequences can be recognized and cut by a set of bacterial enzymes called CRISPR-associated enzymes. Certain enzymes in these families can be programmed to target and cut viral RNA sequences.

The CRISPR-based methods do not require complex instrumentation and can be read using paper strips to detect the presence of the SARS-CoV-2 virus without loss of sensitivity or specificity. These tests are both low-cost and can be performed in as little as an hour. These tests have great potential for point-of-care diagnosis. (Zhang et al., 2020; Broughton et al., 2020). The rolling circle amplification (RCA) method has attracted considerable attention in nucleic acid determination. In isothermal conditions, RCA is capable of a 109-fold signal amplification of each circle within 90 minutes. An efficient assay for the detection of SARS-CoV-2 by RCA has been set up in both liquid and solid phases and has yielded preliminary results on a small number of clinical respiratory specimens. The main advantage of RCA is that it can be performed under isothermal conditions with minimal reagents and avoids the generation of false-positive results, which are frequently encountered in PCR-based assays. (Chapin et al., 2011, Xu et al., 2019, Wang et al., 2005, etc.).

**Cartridge Based Nucleic Acid Amplification test (CB-NAAT) and True NAAT**

Unlike traditional RT-PCR tests, the sample preparation in CB-NAAT tests is automated, and the results are available within half an hour. The test uses nose- or throat-swab samples, which are collected from patients and dipped in a solution that inactivates the virus. A few drops of the solution are then placed on a cartridge. On inserting this cartridge into a machine, a preprogrammed reaction is initiated, which extracts the nucleic acids or the genetic material from the samples. This has to be followed by RT-PCR. The purified nucleic acid is added into a microtube containing freeze-dried RT-PCR reagents and allowed to stand for a minute, then applied to a microchip and then inserted into another machine, where the reverse transcription and PCR take place. The advantage of this test is that it is quick and portable. This allows the easy setup of mobile testing centers or kiosks in containment zones instead of having to transport samples to labs. True NAT is an indigenously developed, portable version of CB-NAAT, also known as the GeneXpert test. Both of these tests were originally designed to screen for tuberculosis.

**IMMUNOLOGICAL ASSAYS**

Immunological tests measure the antibodies generated by the host body's immune response against the virus infection (antibody test) or the proteins of COVID-19 virus present in the respiratory specimens (antigen test). When a virus enters the human body, it triggers an immune response that results in the production of an antibody against the virus; detecting such an antibody in an infected person is extremely useful regardless of whether the person has symptoms. Antibody tests are blood-based tests that can be used to identify whether people have been exposed to a particular pathogen. The serum includes antibodies to specific components of pathogens, called antigens. These antigens are recognized by the immune system as foreign and are targeted by the immune response. These types of tests are often used in viral infections to see if the patient has an immune response to a pathogen of interest, such as SARS-CoV-2. The role of serological assays to detect IgG, IgA, or IgM anti-SARS-CoV-2 antibodies in serum, plasma, or capillary blood provides a clear picture of the outbreak size in each country and helps to assess the degree of immunization. (Okba et al., 2020). Serological testing for COVID-19 is particularly attractive because of the relatively short time to diagnosis and the ability to test for an active immune response against the virus. Serological tests have variable sensitivity and specificity. Research has demonstrated that the spike
(S) and nucleocapsid (N) proteins are the primary viral antigens against which antibodies are raised. (Chan et al., 2009; Kumar et al., 2020). These antigens are the most commonly used in serological tests. During infection, several types of antibodies are raised against the virus. IgM antibodies emerge first, after 5 days of post-symptom onset. IgG antibodies typically emerge after 10 days of post-symptom onset. Many serology tests detect both IgG and IgM simultaneously, which increases the specificity of the test. IgA antibodies may also increase during infection and are typically found in mucous. While serological tests are now widely available, the correlates of immunity are still poorly understood.

The presence of antibodies only indicates a previous SARS-CoV-2 infection. The results of serological tests can then be used to estimate the true spread of the virus through a population, even if individuals were asymptomatic or were never diagnosed. The presence of antibodies does not indicate that an individual is protected from reinfection since there is limited understanding of the levels and persistence of antibodies necessary for protective immunity. Therefore, serological tests cannot inform an individual of their immunity to reinfection (Yu et al., 2020). However, the test results may also help in choosing convalescent plasma, which can be used as a promising treatment option for COVID-19-infected individuals.

**Antibody Tests**

The determination of SARS-CoV-2 exposure relies largely on the detection of either IgM or IgG antibodies that are specific for various viral antigens, including the spike glycoprotein (S1 and S2 subunits) and nucleocapsid protein. The methodology for these determinations includes the traditional enzyme-linked immunosorbent assay (ELISA), immunochromatographic lateral flow assay, neutralization bioassay, and specific luminescent immunoassays. Each of these formats brings advantages (speed, multiplexing, automation) and disadvantages (trained personnel, dedicated laboratory requirements, etc.). Rapid antigen tests, which use antibodies to detect the presence of viral antigen(s) in serological samples, are complementary to these. Major diagnostic companies are currently focusing on the development of high-throughput serology tests.

- **Enzyme-linked immunosorbent assays (ELISA):** A faster serological test performed in a laboratory that provides a readout of antigen-antibody interactions. Essentially, patient antibodies are “sandwiched” between the viral protein of interest and reporter antibodies so that any active patient antibodies are detected. A serological assay was developed using an ELISA kit that was developed for detecting IgM or IgG antibodies against the N proteins of SARS-CoV-2. For IgM detection, ELISA plates were previously coated with mouse and anti-human antibodies. This test can be qualitative or quantitative and is generally a lab-based test that is obtainable within a few hours. These tests usually use whole blood, plasma, or serum samples from patients. The test relies on a plate that is coated with a viral protein of interest, such as spike protein. Patient samples are then incubated with the protein, and if the patient has antibodies to the viral protein, they bind together. The bound antibody-protein complex can then be detected with another wash of antibodies that produce a colored or fluorescent-based readout. (Liu et al., 2020). ELISA is speedy, has the ability to test multiple samples, and is adaptable to automation for increased throughput, but can be variable in sensitivity and is suitable for point-of-care determinations.

  - **Lateral flow assays (LFAs):** Lateral flow assays (LFAs), also called rapid diagnostic tests (RDTs), display a colorimetric, qualitative readout of the presence of antibodies. These are often used in point-of-care settings. The patient sample is passed through a membrane on which the target antigen is anchored. If the sample contains antibodies specific to that antigen, they form a complex that results in a colored band on the strip. These are similar to pregnancy tests. This is facilitated by a recombinant antigen present on immunochromatographic paper, on which the test sera are applied, and antigen antibody binding is detected visually by a color change on a membrane. The results can be obtained within 15–20 minutes. The test is inexpensive and requires no trained personnel, but it provides only qualitative results. When used in conjunction with rapid antigen tests, where anti-SARS-CoV2 antibodies are used in place of immobilized viral antigen, they allow for a more direct assessment of ongoing infection.

  - **Neutralization assays:** determine an antibody’s ability to prevent virus infection of cultured cells and the cytopathic effects of viral replication. For this assay, patient samples of whole blood, serum, or plasma are diluted and added at decreasing concentrations to the cell cultures. If neutralizing antibodies are present, their levels can be measured by determining the threshold at which they are able to prevent viral replication in the infected cell cultures. The time to results for neutralization assays is typically 3–5 days, but recent advances have reduced this to hours. This type of testing requires cell culture facilities, and in the case of the SARS coronavirus, Biosafety Level 3 (BSL3) laboratories are required. Despite these limitations, the determination of neutralizing antibodies is important in the short term for the therapeutic application of convalescent plasma and in the long term for vaccine development.

  - **Luminescent immunoassay:** This test shows whether a patient has antibodies to a pathogen by displaying a fluorescent signal when patient antibodies interact with virus proteins. Luminescent immunoassays comprise methods that lower the limits of detection for antibody-based reagents. Generally, they involve chemiluminescence and fluorescence. For SARS-CoV-2, two-step chemiluminescent immunoassays for the detection of IgG and IgM SARS-CoV-2 antibodies in human serum or plasma have been demonstrated. Samples react with paramagnetic microparticles coated...
with SARS-CoV-2-specific antigens (recombinant N- and S-proteins), and alkaline phosphate-labeled antihuman IgG or IgM monoclonal antibodies are added to the reaction mixture, resulting in a chemiluminescent emission, measured as relative light units (RLU) by a photomultiplier built into the system. After 25 minutes, the first results were generated (Nuccetelli et al., 2020).

**Antigen Detection Assays**

Antigen detection with monoclonal antibodies or monospecific polyclonal antibodies against the protein was found to be a sensitive and specific test for the diagnosis of SARS (Kumar et al., 2020). In a large study with sera collected from 317 SARS patients at different time points of illness, the detection of SARS-N antigen was performed using a panel of three monoclonal antibodies. Over 80% of SARS cases were discovered within the first 7 days of illness. As serum antibody levels started to rise at day 7, the sensitivity of the serum antigen assay progressively decreased to 0% at day 21 (Chan et al., 2004, Hsueh et al., 2003).

**RAPID ASSAY METHODS**

Rapid tests are non-automated, primarily qualitative (but also quantitative in some cases), and used for in vitro diagnostics. These tests can provide results within 10–30 min, so their results are considered instant as compared to the molecular tests, which generally take 4–6 h. Moreover, these tests are user-friendly, so they won’t require any extensive training or expertise to operate and can be used either in a hospital environment or in the field without any difficulty. The manifestation of the COVID-19 infection is highly nonspecific, including respiratory symptoms such as fever, cough, dyspnea, and viral pneumonia (Huang et al., 2020). Thus, extensive diagnostic tests specific to this infection are urgently required to confirm suspected cases, screen patients, and conduct virus surveillance. Rapid tests are used to diagnose patients without sending samples to centralized facilities, thereby enabling communities without laboratory infrastructure to detect infected patients. In this, a point-of-care (PoC) device, i.e., a rapid, robust, and cost-efficient device that can be used onsite and, in the field, and which does not necessarily require a trained technician to operate (Nguyen et al., 2018), LAMP assays (explained in 2.3.2) in PoC devices have high specificity and sensitivity and are simple to perform; hence, soon after their initial development, they became an enormously popular isothermal amplification method in molecular biology, with applications in pathogen detection. LAMP uses strand-displacement polymerases instead of heat denaturation to generate a single-stranded template; hence, it has the advantage. LAMP technology is proven to be more stable and more sensitive in detection compared to PCR (Francois et al., 2011). Lateral flow antigen detection (explained in 2.4.1) for SARS-CoV-2 is another point-of-care approach under development for diagnosing COVID-19. In commercial lateral flow assays, a paper-like membrane strip is coated with gold nanoparticle-antibody conjugate, and capture antibodies are used. These assays have previously demonstrated reliable clinical sensitivity (57%), specificity (100%), and accuracy (69) for IgM and 81%, 100%, and 86% for IgG, respectively. A test that detected both IgM and IgG yielded a clinical sensitivity of 82% (Xiang et al., 2020). However, lateral flow assays do not directly confirm virus presence; instead, they provide serological evidence of recent infections (Li et al., 2020). Microarray assays have been used for rapid, high-throughput detection of SARS-CoV-2 nucleic acids. They rely on the generation of cDNA from viral RNA using reverse transcription and the subsequent labelling of cDNA with specific probes loaded into the wells of microarray trays. The microarray assay has proven useful in identifying mutations associated with SARS-CoV-2 and has been used to detect up to 24 single nucleotide polymorphisms (SNP) associated with mutations in the spike (S) gene of SARS-CoV-2 with 100% accuracy. The ability to detect different emergent strains of SARS-CoV-2 may become necessary as the COVID-19 pandemic evolves, and microarray assays provide a platform for rapid detection of those strains as a result of mutational variations. A next-generation shotgun metagenomics sequencing platform has been developed by Illumina with the ability not only to detect the presence of multiple strains of coronaviruses but also to comprehensively examine multiple pathogenic organisms present in a complex sample.

Chest CT images from patients with COVID-19 typically demonstrate bilateral, peripheral ground glass opacities. Because this chest CT imaging pattern is nonspecific and overlaps with other infections, the diagnostic value of chest CT imaging for COVID-19 may be low and dependent upon other interpretations. Given the variability in chest imaging findings, a chest radiograph or CT alone is not recommended for the diagnosis of COVID-19. The American College of Radiology also does not recommend CT for screening or as a first-line test for the diagnosis of COVID-19. Lymphopenia is the most common laboratory finding in COVID-19 and is found in as many as 83% of hospitalized patients. (Huang et al., 2020) Lymphopenia, neutrophilia, elevated serum alanine aminotransferase and aspartate aminotransferase levels, elevated lactate dehydrogenase, high CRP, and high ferritin levels may be associated with greater illness severity (Chen et al., 2020). Patients with critical illness had high plasma levels of inflammatory markers, suggesting potential immune dysregulation (Wang et al., 2020).

This review summarizes various diagnostic methods used for the identification of COVID-19 infections. While RT-PCR has been the dominant technique for detection of viral RNA, other nucleic acid assays, including isothermal amplification assays, hybridization microarray assays, amplicon-based metagenomics sequencing, and the cutting-edge CRISPR-related technologies, are also under development or have resulted in approved tests. A comparative account of different diagnostic methods...
<table>
<thead>
<tr>
<th>Method</th>
<th>Working Principle</th>
<th>Advantage</th>
<th>Time Required</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Next generation sequencing (NGS)</td>
<td>Whole-genome sequencing, shotgun metagenomics etc.</td>
<td>Highly sensitive and specific, could provide all related information; can identify novel strain. Helps to examine multiple pathogenic organisms present in a complex sample.</td>
<td>1-2 days</td>
<td>Require high expertise &amp; cost. Highly sophisticated Lab required.</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>Specific primer-probe based detection</td>
<td>Fast results, higher sensitivity, well established methodology in viral diagnostics.</td>
<td>3-4 hrs.</td>
<td>High cost due to expensive consumables. Expensive lab equipment. RNA extraction is highly tedious and sensitive.</td>
</tr>
<tr>
<td>Isothermal nucleic acid amplification</td>
<td>Synthesis of target DNA at constant temperature of 60-65°C using specially designed primer</td>
<td>No thermal cycler required. Can be easily detected by color change or turbidity</td>
<td>1-2 hrs.</td>
<td>Too sensitive, highly prone to false positive results due to carry-over or cross contamination</td>
</tr>
<tr>
<td>LAMP</td>
<td>More than two sets of specific primers pair-based detection.</td>
<td>Highly repeatable and accurate. No thermal cycler required</td>
<td>1 hr.</td>
<td>Primer designing is complex</td>
</tr>
<tr>
<td>CB NAAT/ True NAAT</td>
<td>Cartridge Based Nucleic Acid Amplification and detection</td>
<td>Automated sample preparation, pre-programmed reaction. Can be used in a PoC devices</td>
<td>15–30 min</td>
<td></td>
</tr>
<tr>
<td>CRISPR based methods</td>
<td>Enzymes programmed to target and cut viral RNA sequences</td>
<td>Low-cost, do not require complex instrumentation, can be read using paper strips</td>
<td>15–30 min</td>
<td>Not properly standardized for SARS Cov2 detection</td>
</tr>
<tr>
<td>Serological (traditional)</td>
<td>Antigen/Antibodies IgG/IgM/ELISA etc.</td>
<td>Sensitive and specific. useful for choosing the convalescent plasma therapy.</td>
<td>4-6 hrs.</td>
<td>Samples taken after 3-4 days of infection.</td>
</tr>
<tr>
<td>Rapid Serological (traditional)</td>
<td>Antigen/Antibodies IgG/IgM</td>
<td>Convenient, can be used in a PoC devices</td>
<td>15-30 min</td>
<td>Samples taken after 3-4 days of infection.</td>
</tr>
<tr>
<td>Lateral flow assay</td>
<td>colorimetric, qualitative detection of the presence of antibodies</td>
<td>Inexpensive and convenient, can be used in a PoC devices</td>
<td>10-15 min</td>
<td>Nature of the sample affects capillary action, (e.g, blood clotting) pre-treat ment is required.</td>
</tr>
<tr>
<td>Luminescent immune assay</td>
<td>Chemiluminescence or fluorescent labelled antibody or antigen</td>
<td>Highly sensitive, Quantitative</td>
<td>1-2 hrs.</td>
<td>Closed analytical systems required for detection</td>
</tr>
<tr>
<td>Microarray</td>
<td>rapid high-throughput detection of viral RNA using cDNA</td>
<td>Highly sensitive, longer target sequences can be detected</td>
<td>1 hr.</td>
<td>Fabrication of cDNA micro array is labor intensive.</td>
</tr>
<tr>
<td>CT scan</td>
<td>Computerized tomography of Chest images</td>
<td>Enhance sensitivity of detection if findings combined with RT-PCR results</td>
<td>1 hr.</td>
<td>Indistinguishability from other viral pneumonia other chest complications</td>
</tr>
<tr>
<td>Biochemical tests</td>
<td>Blood counts, Lymphopenia, elevated serum enzyme levels, high</td>
<td>Could support routine symptomatic treatment regimens of COVID 19</td>
<td>1-24 hrs</td>
<td>Not conclusive evidence for COVID 19 infections</td>
</tr>
</tbody>
</table>
available for COVID-19 is given in table 1. The urgent need for accurate and rapid diagnosis of SARS-CoV-2 infection remains critical as global healthcare systems continue to operate during the course of the COVID-19 pandemic. In particular, serological and immunological testing of infected asymptomatic and symptomatic individuals, and their close contacts, is expected to be in high demand.

CONCLUSION
The COVID-19 pandemic, caused by the SARS-CoV-2, has resulted in over 17 million confirmed cases and over 7 lakh deaths worldwide in less than six months. The living and working conditions of billions of people worldwide have been significantly disrupted due to different forms of social distancing and lockdowns in many cities. The widespread availability of accurate and rapid testing procedures is extremely valuable in unravelling the complex dynamics involved in SARS-CoV-2 infection and immunity. One of the many challenges in containing the spread of COVID-19 is the inability to identify asymptomatic cases that result in the virus spreading to close contacts. Thus, the global outbreak of COVID-19 has emphasized the importance of the laboratory diagnosis of human coronavirus infections in order to limit the spread as well as appropriately treat those patients who have serious complications. WHO has published a uniform case definition for surveillance and testing for COVID-19 infections. However, the focus on implementing the most reliable diagnostic tools varies in different places. Since COVID-19 is a new nosological entity, there are no data as of yet that would enable the determination of standards for the interpretation of specific diagnostic tests. As with any other infectious disease, the accuracy of each method depends on the method of collecting the material, the quality of the sample, and the equipment applied. Although RT-PCR testing plays a crucial role in accurately detecting SARS-CoV-2 on a case-by-case basis, it also has inherent problems that limit its utility. Current obstacles to the widespread use of RT-PCR testing include a shortage of testing kits and an extended processing period of several hours before results are obtained. Moreover, the results of real-time RT-PCR tests must be cautiously interpreted. A combination of real-time RT-PCR and clinical features, especially CT images, could facilitate interpretation of specific diagnostic tests. As with any other infectious disease, the accuracy of each method depends on the method of collecting the material, the quality of the sample, and the equipment applied. Although RT-PCR testing plays a crucial role in accurately detecting SARS-CoV-2 on a case-by-case basis, it also has inherent problems that limit its utility. Current obstacles to the widespread use of RT-PCR testing include a shortage of testing kits and an extended processing period of several hours before results are obtained. Moreover, the results of real-time RT-PCR tests must be cautiously interpreted. A combination of real-time RT-PCR and clinical features, especially CT images, could facilitate better disease management. Proper sampling procedures, good laboratory practice standards, and using high-quality extraction and a real-time RT-PCR kit could improve the approach and reduce inaccurate results. Loop-Mediated Isothermal Amplification (LAMP) is a relatively new, convenient molecular amplification point-of-care technique that is widely used for COVID-19 diagnosis. The technique does require sophisticated laboratory equipment to provide similar analytical sensitivity to RT-PCR. Serological testing for COVID-19 is particularly attractive because of the relatively short time to diagnosis and the ability to test for an active immune response against the virus. A lot remains to be understood regarding the value of serological testing in COVID-19 diagnosis and monitoring. The results of serological tests can then be used to estimate the true spread of the virus through a population, even if individuals were asymptomatic or were never diagnosed. More comprehensive evaluations of the performance of serology tests are rapidly under way. Considerations for the use of serology methods for COVID-19 require the correct and appropriate interpretation of the results and understanding the strengths and limitations of such tests.

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