Mini Review

Challenges in the diagnosis of SARS-CoV-2 (COVID-19) infection

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Volume 6 Issue 3 - 2021

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Received: May 23, 2021 | **Published:** July 12, 2021

A new viral outbreak, sustained by a member of the Coronaviridae family that has been finally defined as a severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) has recently emerged in Wuhan, China at the end of 2019.[1] The outbreak of the novel coronavirus disease (COVID-19) quickly spread all over China and to almost all over the countries of the world.[2,3] Like other coronaviruses, SARS-CoV-2 is an enveloped virus with a positive-sense, single-stranded RNA genome, containing four main structural proteins known as Spike (S, which contains the receptor-binding domain, known as RBD), Envelope (E), Membrane (M), and Nucleocapsid (N), along with additional genes such as ORF1a/b, ORF3a, ORF6, ORF7a/b, ORF8, and ORF10, which encode accessory proteins.[3,4]

WHO currently defines a "confirmed case" of COVID-19 as the patient who has received laboratory confirmation of SARS-CoV-2 infection, regardless of the presence of clinical signs and symptoms.

The etiological diagnosis of COVID-19 is only feasible by detecting nucleic acid content (i.e., RNA) of SARS-CoV-2 in the biological samples, which is an almost logical result of this clear connotation.[5,6] Despite the fact that the SARS-CoV-2 nucleic acid real-time polymerase chain reaction (PCR) test has become the gold standard for diagnosing SARS-CoV-2 infection thoroughout the world. However, these real-time PCR test kits have a number of drawbacks. Aside from the sample collection and transportation limitations, as well as kit results, the overall positive rate of RT-PCR for throat swab samples was estimated to be between 30% and 60% at first presentation. There are two types of SARS–CoV-2 experiments: those that detect the virus itself and those that detect the host's reaction to the virus. While the virus can be cultured, this is a dangerous procedure that is not done in clinical laboratories on a regular basis.[5-7]

Most tests used at this time for direct detection of COVID-19 are to identify the viral RNA through nucleic acid amplification (NAAT) techniques, usually employing RT-PCR.[2,3] The tests that detect viral RNA are dependent on viral RNA being present in the sample collected ftom the patient.[8] However, these detection methods heavily depend on the presence of the viral genome in sufficient amounts at the site of sample collection that can be amplified.[7] The swabs obtained from the nasopharynx and/or oropharynx are the most common sample forms being examined, with the former being slightly more sensitive than the latter; if both are obtained, the two swabs may be combined and tested simultaneously in a single reaction to save reagents. After processing, the swabs are placed in a liquid to release virus/viral RNA into the solution. The RNA of the virus is then extracted from the solution and amplified.[9,10]

It is also worth noting that viral RNA is not the same as a live virus, so finding the viral RNA does not always imply that the virus can be spread from that patient. In the event of an acute illness, the viral RNA-based techniques are the best tests available. It is important to remember that the consistency of the sample has an impact on the accuracy of the test, so the sample must be collected properly (and safely).[9,11]

COVID-19 testing helps to classify infected patients, and is useful for individual patient control as well as the implementation of the prevention measures to avoid the spread of the virus in health care facilities and the general public. Current RNA-based diagnostic tests are mostly qualitative, and while they may be calibrated to include viral loads, there is currently no systematic process in place. It is pertinent to cite that there is no set threshold for interpreting the viral loads, which can vary depending on the host.[1,10] Even though tests are now available, high demand has resulted in supply chain issues that have jeopardized their availability; these issues include the nasopharyngeal swabs, RNA extraction reagents and instruments, and PCR reagents and instruments.[4]

Serological testing is conventionally defined as a diagnostic procedure used for identifying the presence of an immune response against an infectious agent. To put this in the context of COVID-19, serology testing encompasses the identification (by qualitative assays) and/or measurement (using quantitative assays) of different classes of immunoglobulins (IgA, IgM, IgG) against SARS-CoV-2 for establishing whether a person has been infected by SARS-CoV-2, and has then developed antibodies which, if possessing neutralizing effects, may prevent future re-infection.[12]

The development of an antibody response to infection can be host-dependent and take time. In the case of COVID-19, early studies suggest that the majority of the patients seroconvert between7 and 11 days post-exposure to the virus, although some patients may develop antibodies sooner.[13] Antibody tests for COVID-19 may facilitate contact tracking. RNA-based techniques can help with this as well; serologic surveillance at the local, regional, state, and national levels; and the identification of those who have already had the virus and thus may be immune.[14] Assuming there is protective immunity, serologic information may be used to guide return-to-work decisions, as part of de-escalation strategies (lifting lock-down measures). Serologic testing may also be useful to identify individuals who may be a source for (currently experimental) therapeutic or prophylactic neutralizing antibodies.[13] Antibody testing can also be used in research studies to

assess the sensitivity of PCR assays for detecting infection. It can also be used retrospectively to determine the true extent of the pandemic and aids in the estimation of statistics, such as the case fatality rate. Finally, serologic testing may be used to identify viral RNA-negative patients who present late in their illness. The cross-reactivity of COVID-19 antibodies with antibodies developed against other coronaviruses could pose a problem in developing reliable serological tests.[15]

As the number of COVID-19 tests available grows, new challenges emerge, such as the need to better understand variability in sensitivity and specificity, as well as optimize assays from their original design (e.g., multiple targets to a single target) to reduce reagent use while maintaining performance.[6] The last point can be resolved by sequencing the evolved virus regularly to look for changes in primer and probe binding regions that could influence the performance of tests based on the viral RNA detection; periodic sequencing can also help monitor viral evolution. Furthermore, as the number of tests performed increases, reducing the time it takes for results to be available will become increasingly important to better control both the patients and healthcare staff.[16]

It is mentioned that SARS-CoV-2 causes infections both in humans as well as in animals.[2] Therefore, it is highly imperative that animals with signs or infections that resemble COVID-19 should be reported to national authorities and then to the Office International de Epizooties (OIE) with its headquater at Paris, France. National and regional veterinary laboratories in some countries are assisting with COVID-19 diagnosis by examining the human samples. For the prevention of COVID-19 infections, veterinarians should remain concentrated, aware, and in close contact with public health officials.[17] The importance of public health veterinaraian in global health has been emphasized earlier by Pal.[18]

It is emphazied to conduct further studies to develop a very simple, sensitive, specific, and low cost test kit that can be easily used at home and also in primary health centres located at the rural areas of many developing countries of the world.

Acknowledgments

The authors are very thankful to Prof. Dr. R. K. Narayan for his suggestions during the preparation of manuscript and Anubha Priyabandhu for computer help.

Author's contribution

All the authors contributed equally. They read the final version, and approved it for the publication.

Conflicts of interest

The authors declare that they do not have conflict of interest.

Source of financial grant

There was no financial support for this manuscript.

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