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Editorial

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Available Laboratory Tests for Diagnosis of Covid 19

Rajeev Shah[1]*, Reena Mehta[2], Aarjav R Shah[3], Sudesh Kamat[4] and Ajay Choudhary[5]

[1]Head & Professor, Microbiology Department Pacific Medical College, Udaipur.

[2]Expert in Genetics & Cancer/Expert in DNA Technology, University of New South Wales, Australia.

[3]Shreenathji Clinic, Mumbai.

[4]Embryologist, Bloom IVF Department, Lilavati Hospital, Mumbai

[5]Tutor, Microbiology Department, Pacific Medical College, Udaipur.

***Corresponding Author:** Rajeev Shah, Head & Professor, Microbiology Department Pacific Medical College, Udaipur.

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For the infectious virus like corona, laboratory testing becomes key point or very crucial in identifying both symptomatic as well as asymptomatic patients, firstly to treat them and secondly to isolate them, to prevent spread of infections to others. The Covid 19 infection is highly infectious, more over till moment not a single effective treatment nor any vaccine is invented, so to minimize the rate of transmission along with morbidity and mortality, the most important thing one can do is the breaking the chain of transmission, or in other words preventing the spread of infection by separating Covid 19 infected population by isolation and quarantine of infected population from non-infected population. So, for this purpose some early, cheap, rapid and reliable diagnostic screening laboratory test becomes urgently to be invented. Thus with this early rapid screening test infected population could be detected earlier and then isolating them would break chain of transmission of infection which in turn stop spread of Covid 19 infection. This could be achieved only by quarantining or isolating the Covid 19 positive patients, after laboratory diagnosis of Covid 19, either at homes or in hospitals, depending upon clinical condition of the patients. Thus to identify Covid 19 patients, requires early, rapid, cheap and accurate testing methods.

The diagnosis of viral diseases in laboratory can be done mainly by following methods.

1. Detecting virus particles in specimen taken from the appropriate site.
2. Detecting Antibody by serological procedure by detecting specific anti-viral antibodies (rise in antibody titre or presence of IgM antibody)/detection of presence of a cell-mediated immune response.
3. Detecting viral antigens (Ag) in blood or body fluids by serological procedure.
4. Detecting viral nucleic acids in the blood or body cells of a patient by PCR.
5. Culture of infectious virus from appropriate clinical specimen from appropriate site.
6. Examination of cells by cytological or histological procedures from the site of the infection in those viral infections in which a characteristic viral cytopathic effect (CPE) is observed.

Today, following three tests are available for laboratory diagnosis of Covid 19 infections.

1. RT- PCR (Reverse Transcription Polymerase Chain Reaction)
2. Isothermal nucleic acid amplification Test.
3. Serological Test Detecting Antibody (both IgM and IgG)

1. RT-PCR

From very beginning Polymerase Chain Reaction testing method which detect viral nucleic acid was available for covid 19 viral infection was available but it was too costly, too much time consuming and laborious. It also requires special room with negative pressure.

With simple PCR method only DNA can be detected, but Covid 19 is RNA virus, so it requires reverse transcriptase PCR (RT-PCR). The sensitivity of this test is about 61%, and oral or throat swabs are to be taken and these swabs are to be transported to PCR laboratory within 72 hours in viral transport medium under 40C temperature. As RT PCR is very popular, every one knows too much, it is not needed to discuss about in detail.

2. Isothermal Nucleic Acid Amplication

Loop-mediated isothermal amplification (LAMP) is a single-tube technique for the amplification of DNA and a low-cost alternative to detect certain diseases. Reverse Transcription Loop-mediated Isothermal Amplification (RT-LAMP) combines LAMP with a reverse transcription step to allow the detection of RNA.

LAMP is an isothermal nucleic acid amplification technique. In contrast to the polymerase chain reaction (PCR) technology, in which the reaction is carried out with a series of alternating temperature steps or cycles, isothermal amplification is carried out at a constant temperature, and does not require a thermal cycler.

On 27 March 2020, the FDA issued an Emergency Use Authorization for a test by Abbott Laboratories, called ID NOW COVID-19, that uses isothermal nucleic acid amplification technology instead of PCR. The assay amplifies a unique region of the virus's RdRp gene; the resulting copies are then detected with "fluorescently-labeled molecular beacons". The test kit uses the company's "toaster-size" ID NOW device which costs $12,000-$15,000. The device can be used in laboratories or in patient care settings, and provides results in 13 minutes or less. There are currently about 18,000 ID NOW devices in the U.S. and Abbott expects to ramp up manufacturing to deliver 50,000 ID NOW COVID-19 test kits per day.

In a study conducted by the Cleveland Clinic, the ID NOW COVID-19 test detected the virus only in 85.2% of the samples that contained it. According to the director of the study a test should be at least 95% reliable. Abbott said that the issue could have been caused by storing the samples in a special solution instead of inserting them directly into the testing machine.

3. Serology Tests

Rapid diagnostic test (RDT): This is typically a qualitative (positive or negative) lateral flow assay that is small, portable, and can be used at point of care (POC). These tests may use blood samples from a finger prick, saliva samples, or nasal swab fluids. RDTs are often similar to pregnancy tests, in that the test shows the user colored lines to indicate positive or negative results. In the context of COVID-19, these tests most frequently test for patient antibodies (IgG and IgM), or viral antigen. In some cases, it can be beneficial to measure baseline (before infection) of IgG and IgM titers.

Enzyme-linked immunosorbent assay (ELISA): This test can be qualitative or quantitative and is generally a lab-based test. 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 color or fluorescent-based readout. In the context of COVID-19, these tests most frequently test for patient antibodies (IgG and IgM).

Neutralization assay: This test relies on patient antibodies to prevent viral infection of cells in a lab setting. Neutralization assays can tell researchers if a patient has antibodies that are active and effective against the virus, even if they have already cleared the infection. These tests require whole blood, serum, or plasma samples from the patient. Neutralization assays depend on cell culture, a lab-based method of culturing cells that allow SARS-CoV-2 growth (like VeroE6 cells). When virus and cells are grown with decreasing concentrations of patient antibodies, researchers can visualize and quantify how many antibodies in the patient serum are able to block virus replication. This blocking action can happen through the antibody binding to an important cell entry protein on the virus, for example.

Chemiluminescent immunoassay: This test is typically quantitative, lab-based, and uses whole blood, plasma, or serum samples from patients. A variation of this test can use magnetic, protein-coated microparticles, known as a chemiluminescent microparticle immunoassay. The test relies on mixing patient samples with a known viral protein, buffer reagents, and specific enzyme-labeled antibodies that allow a light-based, luminescent read-out. Any antibodies in the patient sample that react to the viral protein will form a complex. Then, (secondary) enzyme-labeled antibodies are added that bind to these complexes. This binding induces a chemical reaction that produces light. The amount of light (radiance) emitted from each sample is then be used to calculate the number of antibodies present in a patient sample. This test can look for multiple types of antibodies, including IgG, IgM, and IgA.

Type of test	Time to results	What it tells us	What it cannot tell us
Rapid diagnostic test (RDT)	10-30 minutes	The presence or absence (qualitative) of antibodies against the virus present in patient serum.	The amount of antibodies in the patient serum, or if these antibodies are able to inhibit virus growth
Enzyme linked immunosorbent assay (ELISA)	2-5 hours	The presence or absence (quantitative) of antibodies against the virus present in patient serum.	If the antibodies are able to inhibit virus growth.
Neutralization assay	3-5 days	The presence of active antibodies in patient serum that are able to inhibit virus growth ex vivo, in a cell culture system.	It may miss antibodies to viral proteins that are not involved in replication.
Chemiluminescent immunoassay	1-2 hours	The presence or absence (quantitative) of antibodies against the virus present in the patient serum.	If the antibodies are able to inhibit virus growth.

As of 24 April, six tests had been approved for diagnosis in the United States, all under FDA Emergency Use Authorization (EUA). The tests are listed and described at the Johns Hopkins Center for Health Security. Other tests have been approved in other countries.

In the United States, as of 28 April, Quest Diagnostics made a COVID-19 antibody test available for purchase to the general public through the Quest Direct service. Cost of the test is approximately US$130. The test requires the individual to visit a Quest Diagnostics location for a blood draw. Results are available days later.

A number of countries are beginning large scale surveys of their populations using these tests. A study in California conducted antibody testing in one county and estimated that the number of corona viruses cases was between 2.5 and 4.2% of the population, or 50 to 85 times higher than the number of confirmed cases.

In late March 2020, a number of companies received European approvals for their test kits. The testing capacity is several hundred samples within hours. The antibodies are usually detectable 14 days after the onset of the infection.

Among all above three laboratory tests, easier and cheapest test is Serology tests-Antibody detection test which need only finger needle prick one or two drops of blood. This test is rapid, cheap and convenient to be performed but as it detects only antibody, it become positive at very late stage of infection. Antibody in Covid 19 generally become detectable only fifteen days after infection. So here invention of some serological antigen detection test becomes necessary, which can detect Covid 19 infection earlier than antibody detection tests. When it is compared with HIV, it has been found that usually antibody to HIV are detected, so long window period of about 12 weeks is seen. But with the invention 4th generation, tests which even detect p24 antigen along with antibody it can be reduced to about four weeks.

Thus economical rapid screening tests are required to identify infected population detection earlier and then isolating them would break chain of transmission of infection which may help in stopping spread of Covid 19 infection, till moment no effective treatment nor vaccine is invented.

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