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COVID-19 Testing Strategy for India

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Executive Summary

The rapidly spreading COVID-19 can be contained only with rapid, accurate testing and isolation of infected individuals. Various types of tests are available, but in India only select tests have been approved for diagnostic purposes.

Testing can however be done for purposes beyond diagnosis. Purposes include community testing for preparation of healthcare measures or surveillance of communities coming out of lockdowns. Hence, testing strategies should be determined by needs of the test.

Further, shortages of approved testing kits have been reported. Instead of having a centralised policy to determine testing strategies, local governments should be empowered to use available resources intelligently. Our main recommendations are:

1. Allow local governments to determine testing strategies based on available resources and density of cases. The Union government can recommend testing standards and share data available on testing strategies.

2. For community testing, waste water based testing or pooled PCR test may be useful.

3. For diagnostic testing, molecular diagnostic using RT-PCR is gold standard. Ramping up capacity is essential and should be done in parallel to exploring other testing methods.

4. In the absence of sufficient RT-PCR tests, rapid tests can be deployed after categorisation of patients based on their contact with a COVID-19 positive patient, exhibition of symptoms, and estimated period since infection.

An intelligent strategy can help increase coverage of testing through optimal usage of immunodiagnostic and RT-PCR kits. Immediate and local decision making to test all possible COVID-19 carriers is essential to stop the spread of the disease.

1. Introduction

Sars-CoV-2, the underlying virus causing COVID-19, has infected nearly 8 million globally and resulted in over 430,000 deaths[1]. However, these figures might be an under-representation of the impact of the disease. Shortage of testing kits has limited detection of the actual spread of the virus and the inability to exhaustively test for the virus has resulted in containment failure feeding the spread of the disease further.

Countries are scrambling to develop and manufacture new diagnostic kits at a massive scale. Real Time-Polymerase Chain Reaction (RT-PCR) is the gold standard technique for diagnosing COVID-19[2]. However, it is relatively expensive, cumbersome, and time-consuming to perform. Other testing kits which detect antibody or antigen are cheaper and faster, but also unreliable.

The major trade-off for choosing a testing kit is between the complexity of usage and reliability (sensitivity and specificity) of the results. This is particularly true for COVID-19 because in the absence of any proven medication or vaccine, accurate, rapid testing, and isolation remains the only way to contain the disease.

There are two principal challenges in exhaustively testing for COVID-19:

i. A shortage of cheap, reliable and rapid testing kits
ii. Identification of individuals for testing – a significant portion of the infected population shows mild to no symptoms and may not get tested[3].

In the absence of exhaustive testing, the disease will continue to spread as unaware asymptomatic and pre-symptomatic patients mingle with other healthy individuals.

Exhaustive testing remains the only way to contain the disease. It is important to note that the primary aim of diagnosis is to isolate the patient. COVID-19 specific therapeutic interventions are still being tested. Thus, the test may not always inform on the intervention given to the patient, but would be more effective on isolating and containing the spread of the disease. This document summarises the different kinds of testing kits available and proposes purpose-based strategies to increase testing coverage within India.

2. Types of testing

2.1 Indirect testing

Indirect testing techniques look for symptoms caused by COVID-19. However, since these are not unique to COVID-19, these techniques can only be used as an indicative measure of illness but not for confirmatory diagnostic purposes. These testing approaches can be used for triage purposes, to categorise individuals into high-risk and low-risk suspects.

2.1.1 Thermal Detection

Thermal screening detects increased temperature in individuals. However, this does not directly detect COVID-19 infection. Further there are many other conditions that can cause a rise in body temperature. Asymptomatic and pre-symptomatic patients, though infected, would escape thermal detection as they will not display a raised body temperature. Thus thermal screening is a cheap but an ineffective way for identifying COVID-19 positive individuals.

2.1.2 Clinical Diagnosis

China briefly approved the use of chest CT findings of viral pneumonia as evidence of *clinical diagnosis* of COVID-19 infection[4]. However, clinical diagnosis in the absence of a confirmatory test is not acceptable in India.

2.1.3 Symptomatic Diagnosis

Other characteristic symptoms of COVID-19 including loss of smell, fever, congested chest can be used to indicate suspects infected with COVID-19.

2.2 Direct testing

Direct testing techniques detect either viral particles or the body's reaction to the virus.

2.2.1 Real Time-Polymerase Chain Reaction (RT-PCR)

RT-PCR detects the genome of the virus and is considered as the gold standard for COVID-19 diagnosis. The RT-PCR test detects live viral infection. It works by amplifying and detecting the nucleic acid present in the virus. However, conventional RT-PCR tests require access to specialised equipment and training. A variant test in the form a chip-based battery operated RT-PCR test is available. TrueNat machines which can run and

analyse these tests are easier to handle and can be used in rural or remote areas as a replacement for conventional RT-PCR testing[5].

2.2.2 Real Time-Loop Mediated amplification of viral nucleic acid (RT-LAMP)

RT-LAMP functions on a similar principle as RT-PCR, however the mechanism for amplifying the nucleic acid is different. RT-LAMP test is rapid, accurate, and cost effective that can be set up with minimal expertise and instrumentation.

In India, the Sree Chitra Tirunal Institute of Medical Sciences & Technology has developed a LAMP based kit, known as GeneLAMP-N SARS-CoV. However, this kit did not pass an evaluation by ICMR[6]. CSIR is developing another RT-LAMP kit along with Reliance Industries Limited[7].

2.2.3 CRISPR-Cas based detection

A novel technique which also detects viral nucleic acid using CRISPR based technology. This mode of testing is still under development[8].

2.2.4 Antigen testing

Rapid antigen testing kits detect the presence of the antigen (viral particles) in the sample. These kits are relatively cheaper and give rapid results. Hence, they can be used as point-of-care diagnostic kit. However, antigen kits do not have the same sensitivity as RT-PCR testing and are more likely to give false negatives. In India, ICMR has developed its own antigen kit and has also approved an antigen kit developed by SD Biosensor for use[9].

2.2.5 Antibody testing

The antibody testing technique detects antibodies present in an individual's body in response to a viral infection. Antibody testing kits are also rapid tests and cheaper as compared to RT-PCR tests. India has several antibody tests commercially available, but they have not been approved for diagnostic purposes[10]. Antibodies are generated in response to the virus and linger on even after the viral infection is over. Hence, interpreting a result of an antibody test is difficult – a positive antibody test does not mean the person may be carrying the virus at the time of the test. Hence its use in diagnosis is limited.

2.3 Community level testing

2.3.1 Wastewater testing

Testing wastewater from sewage treatment plants has been previously employed to study the presence of pathogens at a community level. The technique has been used in Australia and is being optimised by laboratories for detection of COVID-19[11]. This technique does not identify infected people

directly but could be used to gauge the proportion of infected people in a community.

2.3.2 Pooled RT-PCR testing

Pooled testing is an approach to combine samples derived from more than one individual into a single RT-PCR test. This approach reduces the cost to testing and resources used for testing everyone. However, if the RT-PCR gives a positive result, this approach cannot accurately determine which of the samples is infected. In this case, an individual RT-PCR needs to be run on all samples. Hence pooled testing is recommended in areas of low prevalence, where the likelihood of positive samples is low.

3. Parameters for Assessing a Testing Kit/Approach

3.1 Sensitivity

Sensitivity of a kit determines how many times the kit will correctly identify a positive sample. A 100% sensitive kit will be accurate at picking up the presence of the virus all positive samples, while not identifying the virus in any negative kit. Sensitivity is a crucial parameter, particularly when testing is being done to diagnose a suspected patient. False positive reports can lead to healthy individuals being quarantined or exposed to other positive patients. False negative results can lead to carriers of the disease being allowed to mingle with other healthy individuals. In terms of sensitivity, RT-PCR is the most reliable test and hence is considered as a gold standard for diagnosis of COVID-19 around the world.

3.2 Specificity

Specificity of the kit indicates its ability to identify the Sars-CoV-2 virus that causes COVID-19. Since there is a huge spectrum of viral and antibody structures, some kits/techniques may unintentionally detect other viruses/antibodies as COVID-19. In such incidences, a patient suffering from some other disease might get confused as a COVID-19 patient. RT-PCR is again the most specific test available for diagnostic purposes.

3.3 Complexity to set up and use

Various parameters feed into the complexity of a test:

- Cost to set up, requirement of specialised equipment, etc.
- Requirement of specialised training for performing the test
- Time to run the test and get the result
- Access to test components, kits, etc.

RT-PCR is the most complex of the individual testing approaches available. It requires access to specialised equipment and the test itself takes about 2-3 hours to give a result. RT-LAMP is relatively simpler to use, but still depends

on access to specialised machinery in a laboratory. The antibody and antigen testing kits are rapid and can be used at point-of-care.

The trade-off while assessing a testing kit is between specificity-sensitivity and ease of use. RT-PCR continues to be the most trusted testing approach despite it being cumbersome and time-consuming because it is the most sensitive and specific test to be validated till now.

4. Reasons for Testing

Testing can be done for different purposes:

4.1 Diagnostic

Testing can be used to accurately identify patients infected with the virus. This is essential to isolate infected individuals and contain the disease. A challenge to diagnostic testing is that a significant number of infected individuals are asymptomatic. Recently, ICMR has allowed RT-PCR based testing of asymptomatic contacts of COVID-19 positive patients. It is important that both asymptomatic and symptomatic contacts are assessed. A third category of patients are pre-symptomatic. These are patients who have been infected but are yet to develop symptoms. At early infection stage, there is no way to distinguish between asymptomatic and pre-symptomatic patients. Both categories of patients are capable of transmitting the disease to others.

4.2 Testing for community surveillance

Community surveillance is important to assess the presence of COVID-19 in a community. This is important particularly when opening up locked down or understanding to what extent the disease has spread in a community. When opening up a containment zone after a decrease in number of cases, community testing can help ensure there are no missed cases.

4.3 Herd Immunity studies

Sero-prevalence studies study the presence of antibodies in communities to understand how exposed they are to the virus. For well-studied diseases, sero-prevalence studies can be used to predict herd immunity levels. In case of COVID-19 infection, antibody-based immunity is still under-studied. It is unknown if and for how long antibodies to COVID-19 can protect against the virus.

4.4 Preparation for a possible outbreak

Routine surveillance of communities can help predict an oncoming outbreak. An early identification of the extent of spread can help divert resources, ramp up capacities and prepare healthcare measures to manage the outbreak. The

Takshashila Institution's document on preparing for the second wave details measures needed for such an adversity[12].

5. Strategies for Testing

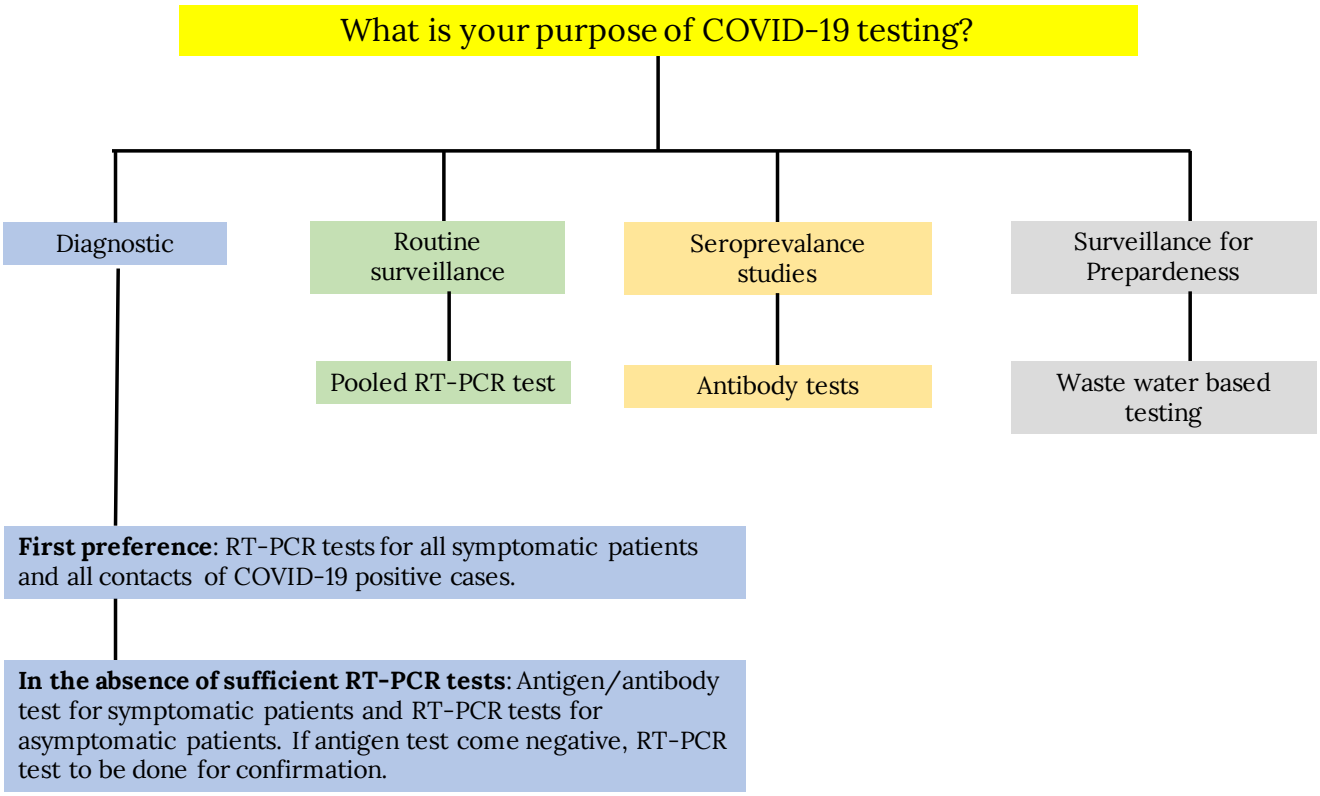

Figure 1: Mapping test type to purpose of COVID-19 testing

Testing strategies are dependent on the purpose of testing and availability of resources. A blanket testing policy can result in the squandering or concentration of resources at select hotspots. Thus, we propose that decisions for testing strategies be decentralised and taken at a local level. The Union government can set standards for testing and testing kits.

5.1 Community based testing:

For community-based testing, wastewater-based testing or pooled testing can be used. Waster water-based testing is yet to be optimised but it would be very effective tool in predicting an oncoming outbreak and prepare for the same.

In Takashashila Institution's advisory on pooled testing, we have recommended that a threshold population be initially tested by conventional RT-PCR in metropolitan areas or other areas with prior cases[13]. In other areas, pooled testing can be prioritised based on travel history and case

history of the community. Pooled testing can also be used in routine surveillance of employees in business parks.

5.2 Diagnostic testing:

For diagnostic testing, RT-PCR is the preferred technique; however, it is cumbersome and expensive. The newly developed antibody and antigen tests are as of yet unreliable and can give misleading results. Hence for diagnostic testing we recommend the following strategy:

Scenario where sufficient RT-PCR kits are available:
The preferred action point is to ramp up testing capacity using RT-PCR kits to cater to all testing demand within reasonable time. Strategies to ramp up testing have been detailed in Takshashila's policy advisory on improving testing capacity[14]. If sufficient RT-PCR testing capacity is available, all samples should be checked using this technique. For low-risk individuals, pooled testing can also be employed.

Scenario where sufficient RT-PCR kits are unavailable:
If sufficient RT-PCR kits are unavailable, antibody/antigen kits can be used. Both antibody and antigen kits are unlikely to pick up early infection. Therefore, their use in pre-symptomatic/asymptomatic cases is limited. However, they may be tried as a first test for symptomatic patients. For triaging, symptomatic contacts of previously identified COVID-19 contacts can be prioritised for the antigen test. If symptomatic patients test negative, a confirmatory RT-PCR test can be done.

Interpreting an antigen/antibody test result from an asymptomatic person is difficult and therefore, RT-PCR tests can be used for such contacts. However, we have currently not comprehensively studied how many asymptomatic contacts might actually be carrying the disease. Local level study of how many contacts carry the disease and can be correctly diagnosed using immunodiagnostic studies can help design better use of testing resources.

If in a certain population, all asymptomatic persons are actually healthy, using RT-PCR tests on them will improper use of resources. However, if in a certain population a significant number of other asymptomatic persons are actually carrying the disease, this population needs to be exhaustively tested using RT-PCR analysis. Hence, the decision to allocate resources should be

done at the local level after a base level of research on the spread of the disease in that area.

6. Conclusion

A blanket policy for testing is likely to squander valuable resources. A decentralised approach can help local authorities make better decisions to use their resources and test more widely. Accurate and early testing of asymptomatic, pre-symptomatic and symptomatic individuals is necessary to contain the spread of the disease. Community testing is essential to understand healthcare requirements for the future.

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